APP #	TITLE	BUDGET REQ	FUND	SCORE	1	2	3	Product Type	Approach
SEPTEMBER CYCLE - CLIN APPLICATIONS									
CLIN2-12095	A Phase I Clinical Trial for a Lentiviral Gene Therapy Targeting the TCIRG1 Gene for Infantile Malignant Osteopetrosis (IMO)	**$3,728,485**	**Y**	**1**	13	1	0	Cell and gene therapy	Autologous cell therapy that corrects gene in patient HSCs
CLIN2-12090	Anti-HIV duoCAR-T cell therapy for HIV infection	**$8,970,732**	**Y**	**1**	12	2	0	Cell and gene therapy	Autologous CAR T cell therapy that targets and kills HIV-infected T cells
OCTOBER CYCLE - CLIN APPLICATIONS									
CLIN2-12129	The CuRe Trial: Cellular Therapy for In Utero Myelomeningocele Repair	**$8,996,474**	**Y**	**1**	14	0	0	Cell therapy	In utero administration of placental-derived mesenchymal stem cells to protect motor neuron damage
CLIN2-12153	Phase I Study of IL13Rα2-Targeting CAR T Cells After Lymphodepletion for Children with Refractory or Recurrent Malignant Brain Tumors	**$8,996,500**		**2**	2	13	0	Cell and gene therapy	Autologous CAR T cell therapy engineered to target IL13Rα2-expressing brain tumor cells
CLIN2-12139	Phase 1b/2a trial and manufacturing development of ART352-L, an endogenous stem cell reactivation therapy to enhance bone autograft osteogenesis	**$5,979,859**		**2**	0	15	0	Biologic	A biologic formulation that stimulates growth (osteogenesis) in bone grafts
CLIN2-12149	Phase 1 Clinical Development of IO-202, A First-in-Class Antibody Targeting LILRB4, for the Treatment of AML with Monocytic Differentiation and CMML	**$6,000,000**		**2**	0	11	3	Biologic	A monoclonal antibody that targets AML tumor cells

Application #	CLIN2-12095
Title (as written by the applicant)	A Phase I Clinical Trial for a Lentiviral Gene Therapy Targeting the TCIRG1 Gene for Infantile Malignant Osteopetrosis (IMO)
Therapeutic Candidate (as written by the applicant)	The therapeutic candidate is an ex-vivo autologous gene therapy approach for Infantile Malignant Osteopetrosis (IMO).
Indication (as written by the applicant)	The target clinical indication is Infantile Malignant Osteopetrosis (IMO), a pediatric, autosomal recessive rare disease.
Unmet Medical Need (as written by the applicant)	Children with severe IMO face morbid conditions such as hematologic and/or neurologic deficits that worsen over time. There is a high chance of death in the first decade of life without successful allogeneic HSCT. This gene therapy will treat the underlying TCIRG1 mutation in IMO patients.
Major Proposed Activities (as written by the applicant)	• Patient recruitment, screening, and support (by various CROs) on their clinical journey • Enrollment of patients • Cell processing
Funds Requested	$3,728,485
GWG Recommendation	Tier 1: Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 1

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

Scoring Count	14
Votes for Score 1 (exceptional merit and warrants funding)	13
Votes for Score 2 (needs improvement)	1
Votes for Score 3 (sufficiently flawed that it does not warrant 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: 11	• Infantile Malignant Osteopetrosis (IMO) is an extremely rare, life-threatening genetic disorder that almost exclusively affects children. IMO results from mutations in the TCIRG1 gene which impairs osteoclast function and causes defective bone resorption. There is a significant unmet medical need for this disease. However, it should be noted that this is an ultra-rare disease with a very small patient population. • There is an unmet medical need which can only be treated with an allogeneic stem cell transplant which is problematic in patients as young as 1 month of age. Symptoms may be insidious and slightly delayed but often inexorably progress with life altering and life ending complications so that the therapeutic window is limited and narrow since symptoms may not be reversible once they develop. • Although a very rare, ultra-orphan indication. It may have deep impact but not very broad impact.

	• Yes, this is a dreadful disease. • Rare disease warranting the approach. • Allogeneic hematopoietic stem cell transplant may be equally effective and less expensive, but yet this therapy provides a good alternative to this treatment as not all cases will have good matches for stem cell transplant. • Allogeneic transplants, the standard of care, are definitely suboptimal and improvement is needed. • Treatment options for malignant osteopetrosis in kids represent a significant unmet medical need. Proposed treatment is a very good alternative of the standard hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT may not be an option due to lack of donor. It is also associated with significant side effects (such as GVHD and infections). • The proposed treatment offers a sufficient value proposition because it is potentially (i) curative and (ii) may be cheaper over a course of many years of treatment. • There is an enormous number of CROs which have been engaged (12 in total), which will ensure reproducible high quality reagents and data capture and assays for gene correction that are validated but will unfortunately dramatically increase the cost of therapy for each of the two children proposed. The applicant is requesting approximately two thirds of the cost from CIRM. • Rare disease with potentially curative therapy. • Excellent team with skills to deliver this. • For very small patient population. • If successful, the proposed product-candidate will have very small market because malignant osteopetrosis is an extremely rare pediatric disease.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 11	• Yes. Questions regarding hematopoietic mobilization in infants and adequate apheresis feasibillity. Safety of myeloablative busulfan in infants and adequate supportive care. GFR too high inclusion cutoff. • Much of the preclinical and IND enabling studies have already been done. • Pre-clinical data is solid, but how effective will it be, since a multi-genetic disease. • The rationale and pre-clinical proof of concept studies are clear. • The program has received a letter to proceed from the FDA. The IND has been cleared. • The scientific rationale is sound. • The proposal includes significant pre-clinical and pre-IND data for transition to clinical trial.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 9	• Networking with patient groups and with advocacy networks have been well developed already to insure referral and early diagnoses of patients. • The rational plan for the phase 2 registration study has been developed and all of the pieces are in place and this approach has already been vetted by the FDA. • The project is well planned. The IND has been cleared by FDA already and the study is ongoing. • FDA has approved the trial and the first patient should be enrolled in the next several months. • Only two patients are treated for a cost of ~$2.5M per patient. There is an unmet medical need but the authors do not provide a balanced view of an effective and much cheaper alternative, allogeneic stem cell transplant. The outcomes as quoted in recent studies suggest an overall survival of over 90%. Although there is risk of GvHD these infants can be conditioned with reduced conditioning regimens which is not the case in this study. • There are some concerns with whether the proposed conditioning, mobilization, and apheresis regimens are feasible. • A significant issue relates to the need for a backup stem cell graft. Will these be cords that are purchased or identified in advance? This would need to be defined. Secondly, if unrelated grafts are considered there would need to be a better defined way of having them immediately available if graft failure occurs.

	• A data safety monitoring plan and committee should be defined and established.
	• Budget appears a bit inflated for the proposed study.
	• Yes. Potential manufacturing cost inflation.
	• The overall request for this grant is divided into the following categories:
	  • 1) Enrollment and dosing of 2 patients in the Phase 1 at the clinical site
	  • 2) Costs to support pharmacovigilance, site management, clinical data collection, database lock
	  • 3) Drug product manufacture and release
	  • 4) Patient travel and accommodations
	  • 5) Safety and preliminary efficacy assessment requiring various tools and developed/qualified assays

No: 1	• The mobilization in very young babies with IMO could be problematic.
GWG Votes	Is the proposal feasible?
Yes: 9	• Strong and experienced team who have been involved in other clinical stem cell gene therapy protocols and the treatment of children with other inherited diseases. The team is capable and has the requisite experience to enable success. • Excellent team and many things are well considered (eg. travel support, family care). • The decision to work with the collaborator is a strength; the collaborator is an established leader in the field with impeccable credentials and a depth of experience which will markedly enhance the success of this project. • Yes. Backup is an allogenic transplant, and the plan to provide well matched units suggests a potential delay in therapy. • Maybe. Depends critically on mobilization. • Potential risk, mostly related to collection and manufacturing are well described in the proposal. Mitigation strategy and contingency plan is present. • Multiple CMOs/CROs, used by the sponsor are also well qualified and experienced to perform different steps of the proposed work. However, so many CMO/CRO players complicates management of the trial and will contribute to very high cost. • The coordinated management of reagents and tests coming from 12 different CROs represents a logistical challenge. • Manufacture complete. • The timing seems reasonable for the project. • The proposed timeline looks reasonable. The clinical team is well qualified and have experience with previous similar clinical trials.
No: 2	• The major concern about proposal is whether you can mobilize cells in a 1 month old from the IMO marrow. If 3 bouts of apheresis are needed, how do you know the cells harvested on first day will be viable by day three when sending to manufacturing for modification? If the therapy fails what delay would there be before receiving allogeneic transplant? What is the risk the patient will deteriorate in the interim and come to harm? • I think feasibility is really the question here. I don't know if it is but I think it is a worthwhile question to investigate even just to better understand the disease itself.

Application #	CLIN2-12090
Title (as written by the applicant)	Anti-HIV duoCAR-T cell therapy for HIV infection
Therapeutic Candidate (as written by the applicant)	HIV-specific CAR-T cells
Indication (as written by the applicant)	Management of HIV infection
Unmet Medical Need (as written by the applicant)	Many people are not able to access and adhere to long-term antiretroviral therapy. This approach will address the needs to those who are not able to respond to current approaches, which we estimate to be up to 50% of those affected by HIV globally.
Major Proposed Activities (as written by the applicant)	• Manufacture of the CAR vector • Completion of a phase I/IIa dose-escalation clinical trial • Optimize the development process to make the product affordable and scalable
Funds Requested	$8,970,732
GWG Recommendation	Tier 1: Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 1

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

Scoring Count	14
Votes for Score 1 (exceptional merit and warrants funding)	12
Votes for Score 2 (needs improvement)	2
Votes for Score 3 (sufficiently flawed that it does not warrant 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: 13	• HIV has no curative therapy and current treatments are difficult to maintain in the affected population for logistical and financial reasons. • The proposal develops a new dual-specific envelope-targeted CAR T cell therapy for HIV. There is a well-designed and planned clinical protocol, with an open IND and a regulatory plan. • The plans to make lentiviral vectors with stable packing lines would also be transformative for the field -- this is a major blockage for multiple gene and cell therapies, so the impact could even extend beyond this proposal. • The plan for distributed manufacturing of cell products is also very admirable and a strength, and is particularly encouraging that they have already entered into discussion with FDA about it.

	• The distributed manufacturing is an important advance which will serve the field well. The focus to drive down the cost of lentiviral vector production is important for many therapies well beyond this study. • The addition of distributed manufacturing is exciting and I believe really fulfills the larger mission of CIRM. • Plan for distributed manufacturing, including partnerships established and attempting this regulatory strategy, is innovative and exciting with potential for great impact; anticipate challenges, but worthy pursuit. • Very strong and important for HIV and more generally for regulatory pathways for CAR-T cell development. • Potential impact to reduce cost of CAR therapy in general. • I laud the efforts to reduce cost but wouldn't underestimate the obstacles that FDA will put in front of that effort closer to phase 3/BLA submission. • I am particularly impressed with their intellectual property plan and collaboration for manufacturing. It is apparent that the population suffering from HIV infection need a different model of therapeutics than what the biotech/pharma industry has developed for cancer. Their plan to have royalty-free licenses and distributed manufacturing at low cost is a strength and aligns with the scientific and medical mission. They did not address whether the places that have high HIV populations (i.e. countries in Africa) will have the infrastructure and equipment to manufacture CAR-T cells, receive and store CAR-T cells in liquid nitrogen, or administer CAR-T cells and the attendant monitoring. However, I recognize that this is a futuristic goal and not an immediate concern during the grant period. • To be able to remove folks from a lifetime of antiviral drugs would be huge. • Potential to cure HIV infection. • This offers a cure for HIV instead of maintenance on anti-retroviral strategies chronically. • Being delivered at centers where disease burden lies in US. • HIV remains a major public health issue around the world, including the U.S. and California. A few case reports exist of patients becoming completely cured after a stem cell transplant. Other than these case reports, there is no broadly accessible functional cure for HIV. The applicants have recently developed duoCAR-T cells as a novel approach for the treatment and potential cure of HIV-1 infection. ◦ Their pre-clinical studies have demonstrated (1) potent inhibition of broad strains of HIV-1 replication in vitro; (2) protection of CD4+ duoCAR-T cells from infection by broad HIV strains in vitro; (3) elimination of HIV-1 infected cells in humanized mice; and (4) protection of the CD4+ cell compartment from HIV-mediated killing in humanized mice. • Would seem to make more sense to look for activity in patients with persistent viremia despite ART.
No: 0	*none*
GWG Votes	Is the rationale sound?

Yes:
13
	• Overall, yes, the project is innovative and yet sound. There is feasibility data in vitro and in animal models and also in large scale manufacturing that supports the project. The dual-targeting CAR whereby the T cells also become resistant to HIV infection is innovative and sound, given the prior data with the CD4+ CARs where the T cells became susceptible to HIV infection.
	• Their preclinical studies have shown that anti-HIV duoCAR-T cells can eliminate broad strains of HIV and protect CAR expressing primary CD4+ T cells from infection.
	  ◦ Similarly, they have shown elimination of HIV infected cells and protection of CD4+ T cells in humanized animal models.
	  ◦ Collectively, these data indicate that anti-HIV duoCAR-T cells could potentially cure patients from HIV infection by killing HIV infected cells and persisting long term in the body to survey and kill any remaining HIV infected cell that tries to produce virus.
	  ◦ Their approach for manufacturing, including the rationale for using a technology based platform, is sound and has a high probability of success.
	• The pre-clinical data is solid. Appears to be sustained knockdown of the virus and perseverance of the CARs.
	• Yes, in general the rationale is sound.
	• Not clear if cells have activity against wild-type patient isolates; would want to see transduction and activity in cells/virus from patient; important to rule out inhibitory effect of

	autologous serum from patient; not clear why these cells would have greater activity than prior mono-CAR T cells given the noted long-term survival of those cells. ● Consider doing work on apheresis product from HIV patients. ● Points raised about lack of data for wild type virus and impact of antibody are important to clarify before funding. ● There is a question as to whether HIV patient sera would compete with the CARs. Because the patient is on ART at the time of T cell collection, is the transduction efficiency affected? I would think that reverse transcriptase inhibitors would also block lentivirus transduction of T cells. The section on "successful manufacture of CAR-T cells for use in human clinical trials using the technology" really did not address these questions for HIV patients, since those trials are in patients with lymphoma and using a different vector. Therefore there is no feasibility data shown here for LV transduction of HIV patient CAR-T cells using the technology (though prior literature may address this issue). The information on viral copy number and transduction efficiency from lymphoma patients may or may not be generalizable to HIV CARs.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 13	● Overall the project is well designed and planned. The IND is open. The investigators have carefully thought out the eligibility of the study population, when CD4 T cell counts still allow for manufacturing, and then endpoints (viral load) and when ART therapy will be resumed. The commercial plan is more about developing the next generation of CMC reagents than a phase III protocol, but I think this is clever and what the field needs: affordable vector manufacturing with a packaging line, and distributed cell manufacturing that needs to be a pathway cleared with meaningful and frequent discussions with FDA and other regulatory authorities. The exosome aim is innovative and adds a scientific angle even if not exactly a commercial plan. The investigative team is clearly aligned and equipped to have come up with this thorough and detailed proposal and plan. ● The project is well planned and designed. ● The budget is appropriate for the planned activities. ● The de-centralized approach is well designed. ● Great to see partnership with IQVIA (and specific personnel within IQVIA); good partners for this innovative (and challenging) regulatory strategy; applaud plan and efforts. ● Yes, although the manufacturing data is based on lymphoma cell studies. ● Applicant should consider a clinical focus on treatment of resistant patients. ● The protocol need some work around the DMC and safety monitoring. ● Excellent group. ● Outstanding team.
No: 0	*none*
GWG Votes	Is the proposal feasible?
Yes: 13	● The intended objectives are feasible for this group, likely within the proposed time line, though some of it will depend on patient enrollment. This is a difficult time in that both a rare patient population and an intense phase I trial are colliding with the restrictions of COVID and climate emergencies. It may be a tough time to recruit a lot of patients for a trial that will be intense, but the investigators have addressed this. ● Yes, although again the current data is not based in HIV and one cannot be certain that in vitro studies will exhibit similar biological activity in people. ● Yes, excellent team. ● The investigators have the manufacturing expertise and clinical expertise to achieve the objectives. ● Impressive partnerships with collaborating partners. ● Commercial development to reduce cost and improve efficiency of vectors that might be relevant to other diseases. Developing a pathway for CAR manufacture. ● Site is well situated for study and corporate/foundation collaborations are excellent. ● I have concerns about the number of visits required for the patients. I am not sure if that is practical right now and if there will be issues with compliance.
No: 0	*none*

Application #	CLIN2-12129
Title (as written by the applicant)	The CuRe Trial: Cellular Therapy for In Utero Myelomeningocele Repair
Therapeutic Candidate (as written by the applicant)	Allogeneic Placenta-derived Mesenchymal Stem Cells Seeded on Cook Biodesign® Dural Graft Extracellular Matrix (PMSC-ECM)
Indication (as written by the applicant)	Myelomeningocele (MMC) -or Spina Bifida -diagnosed prenatally
Unmet Medical Need (as written by the applicant)	The current standard of care in utero surgery, while promising, still leaves 58% of patients unable to walk independently. There is an extraordinary need for a therapy that prevents or lessens the severity of the devastating and costly lifelong disabilities associated with the disease.
Major Proposed Activities (as written by the applicant)	• Enrollment of 6 patients to demonstrate safety and preliminary efficacy of PMSC-ECM product • FDA-compliant manufacturing and testing studies of the PMSC-ECM product
Funds Requested	$8,996,474
GWG Recommendation	Tier 1: Exceptional merit and warrants funding, if funds are available

SCORING DATA

Final Score: 1

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

Score Count	14
Votes for Score 1 (exceptional merit and warrants funding)	14
Votes for Score 2 (needs improvement)	0
Votes for Score 3 (sufficiently flawed and does not warrant 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: 13	• This cell product has the potential to improve outcomes for fetuses undergoing in-utero MMC repair, and thus could address a significant unmet medical need since many of these patients have major neurological disability despite in-utero repair. • Standard of care for a select group of patients with MMC is in utero repair. However, despite prenatal repair and improvement over outcomes following postnatal repair, a large number of patients (55%) undergoing in utero repair continue to have paralysis as well as bowel and bladder dysfunction. Based on a significant number of preclincial studies, there is good reason to believe that the proposed treatment will significantly improve outcomes following in utero MMC repair and address the unmet need. • This is highly significant. • Highly significant medical need. • Yes. If this MSC based cell therapy is safe and improves neurological outcomes, it would make a big impact.

	• If successful, the proposed treatment will significantly improve the current standard of care. • If successful, the proposed treatment will reduce long-term chronic health issues in patients with MMCs and thus significantly reduce health care costs and resource utilization.
No: 0	*none*
GWG Votes	Is the rationale sound?
Yes: 13	• Yes, the rationale is sound and there is a strong scientific premise. • Use of MSCs is a rational approach for the treatment of this disease. • The rationale for the proposed studies is strong. The applicants have developed a robust pre-clinical data package and have strong proof of concept data in at least 2 animal models (rat and sheep). • Morbidity caused by MMC results from a 2-hit hypothesis including the damage to the exposed spinal cord associated with neuron damage and inflammation. Through multiple preclinical studies, the group has demonstrated that the PMSC-ECM can reduce inflammation and provide neuron regenerative factors. Thus the scientific rationale is strong and well founded. • Given the safety/efficacy results from the animal studies and experience with producing this cell/matrix technology, this product appears ready to be tested in the Phase 1 study that would be funded by the CIRM grant. • The proposed study is based on a recently FDA approved product.
No: 0	*none*
GWG Votes	Is the proposal well planned and designed?
Yes: 12	• The Phase 1 study is well planned and designed. It adheres to the recommendations made by the FDA in the process of obtaining FDA approval for the PMSC-ECM product • The investigators have methodically developed this candidate and are now ready to test it rationally in the clinic. This is a well thought out and written plan. • The proposed study is well designed and is positioned to produce meaningful clinical data. • Very well-designed protocol, particularly now that a concurrent surgery-only control group has been added and the follow-up has been extended to 6 years of age. • Appropriate exclusion and inclusion criteria. Inclusion/exclusion criteria, secondary outcome measures and technique of repair will be based on the MOMs trial which has been established as the gold standard for in utero MMC repair. • Yes. This follows the MOMS trial in terms of planning and there is abundant pre-clinical data to support it. • Appreciate the incorporation of FDA feedback into the plan. • Excellent team with great track-record to-date. • Appropriate project timeline. One potential limitation is that patients 5-6 who are enrolled later in the study will not have as long a follow-up as earlier patients. The investigators acknowledge this and note that additional extra or intramural funding will be obtained to continue to follow these patients beyond the 3-year CIRM grant period. • Long-term follow up for tumorigenesis should be longer than the 3-year CIRM grant period. The investigators note that a 5-year follow-up will be done and additional extra or intramural funding will be obtained to continue to follow patients beyond the 3-year CIRM grant period. One would think that follow-up beyond 5 years will be necessary. • Although the Phase 2 study would not be funded through this application, would strongly recommend the Phase 2 be designed as a randomized, double-blind, controlled study in order to minimize bias in the assessments of both safety and efficacy outcomes.
No: 1	• I am fine with Phase 1 but I do not believe the Phase 2 trial is adequate and well controlled. Historical controls will be tough to implement here.
GWG Votes	Is the proposal feasible?
Yes: 13	• Project is completely feasible and the clinical site is one of the few institutions that can successfully do all stages of the proposed study (prenatal counseling, prenatal repair, short and long-term follow-ups of multiple outcome measures). They have demonstrated the feasibility of the trial.

	• The team, led by the PI, is a leading team in the field. Their involvement in the MOMs trial and subsequent in utero MMC repairs since the MOMs trial strongly supports their ability to complete the proposed studies within the suggested timeline. • Both the proposed timeline and the contingency plan for the Phase 1 appear reasonable. • The candidate should provide some benefit for patients. • Great team who is well equipped to conduct this work. A little on the pricey side, but in utero surgery is complex. • Strong team with extensive experience in this field. • The team has established multiple appropriate contingency plans to mitigate risks and delays.
No: 0	*none*

Application #	CLIN2-12153
Title (as written by the applicant)	Phase I Study of IL13Rα2-Targeting CAR T Cells After Lymphodepletion for Children with Refractory or Recurrent Malignant Brain Tumors
Therapeutic Candidate (as written by the applicant)	Autologous chimeric antigen receptor T cells derived from naive/memory T cells and engineered to target IL13Rα2 on pediatric malignant brain tumors.
Indication (as written by the applicant)	Recurrent/refractory malignant pediatric brain tumors that express the tumor-associated antigen IL13Rα2.
Unmet Medical Need (as written by the applicant)	This proposal addresses the critical unmet medical need for effective therapies to treat aggressive pediatric brain tumors, including glioblastoma, medulloblastoma, atypical teratoid/rhabdoid tumor, diffuse midline glioma, and others.
Major Proposed Activities (as written by the applicant)	• manufacture and release of IL13BBζ-Tn/mem CAR T cells • evaluate safety and feasibility of intraventricularly-delivered CAR T cells administered after lymphodepletion in pediatric patients • develop and establish methods and target populations for Phase 2 clinical trial
Funds Requested	$8,996,500
GWG Recommendation	Tier 2: Needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement

SCORING DATA

Final Score: 2

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

Score Count	15
Votes for Score 1 (exceptional merit and warrants funding)	2
Votes for Score 2 (needs improvement)	13
Votes for Score 3 (sufficiently flawed and does not warrant funding)	0

KEY QUESTIONS AND COMMENTS

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GWG Votes	Does the proposal have the necessary significance and potential for impact?
Yes: 13	• Pediatric neuromalignancies remain an area of very high unmet clinical need. Improved therapies for aggressive pediatric brain tumors are badly needed. • A lack of effecatious treatment options in pediatric brain tumors is a huge unmet medical need. Standard of care for many pediatric brain malignancies can only extend life post-diagnosis for a few months. The proposed CAR T cell therapy could improve survival of these patients significantly. • The proposed treatment addresses an area of unmet medical need and based on promising data in adults may provide therapeutic benefit in children. • There is a definite need for effective treatments for malignant brain tumors (pediatric and adult). Consequently, new, biologically sound and innovative treatments are critical. • The uniqueness of this protocol (compared to other similar protocols) is the use of lymphodepletion and its use of CAR T cells targeting malignant brain tumors in a pediatric population.

	• Good rationale and has potential to impact childhood glioblastoma. • High unmet need.

No:
1
	• A major strength of the application is the clinical implementation of a next-generation CAR T cell manufacturing pipeline in pediatric brain cancer patients, together with correlative studies to identify biomarkers of response, toxicity, efficacy.
	• Concerns include:
	  • Lack of preclinical data to support the thesis that a lack of naive/central memory T cells is a potential culprit in CAR-redirected patient T cells.
	  • Pre-clinical data that selected T cells outperform unselected T cells in the target patient population is needed.
	  • Manufacturing feasibility: Can sufficient selected cells be isolated from apheresis of these patients? There is concern that it will all be CD4 T cells since CD8 T cells are the first to lose their early memory state.
	  • Correlative studies should include an assessment of the tumor bed prior to (pathology specimens) and post-CAR T cell treatment to a) assess homing and b) tumor microenvironment changes.

GWG Votes	Is the rationale sound?

Yes:
11
	• CAR T cells targeting the IL-13RA is a sound rationale for targeting the tumor.
	• Use of the ventricular route for administration of CAR T cells into the brain is major strength of this proposal.
	• The rationale is sound for the most part but questions exist regarding underlying claims that "...lymphodepletion is critically important for maximizing efficacy of IL13BBζ-CAR T cells in our preclinical studies and is crucial for the efficacy of CD19-targeted CAR T cell therapy in patients with hematologic malignancies." While this might be true, heme malignancies may not have the same tumor microenvironment as brain tumors. If the tumor microenvironment serves as barrier to CAR T cell activity, how can lympodepletion unlock activity?
	• The rationale is scientifically sound, but there are some questions:
	  • Please provide data for IL13Rα2 expression on pediatric brain tumors.
	  • Biodistribution data in proposal refer to studies on Tcm populations. Since Tn/mem cells will be used in the clinical trial, please provide data or reference to trafficking of Tn/mem in the model of brain tumors.
	  • Please provide an explanation for the relevance of temozolomide, which was used in the mouse model, to Cy/Flu lymphodepletion which will be used in the trial.
	• Concern about heterogeneity in target expression in these tumors - should there be a threshold? Is it feasible to harvest enough autologous cells from these patients? Is there a risk of progression of the tumor while waiting to produce the cells?
	• Even though this study is early stage development (Phase 1), the manufacturing process is not optimized for industrial production at the large scale and adoption at point of care (for example, reformulation for multiple doses post-thaw). Many steps of the process are still using generation 1.0 tools and could be improved significantly. High cost of goods (~ $60k) may translate to very expensive commercial product (~ $300-400k) if marketed.

No: 3	• They have treated over 60 adult patients. The product has demonstrated safety and some efficacy in adult patients. Yet, the applicants propose to test this product in pediatric patients. There is no clear rationale for moving to pediatric patients with malignant glioma. What is unique about pediatric patients and why do we think this will work in this context compared to the previous clinical experience? I suggest the sponsors start with their lymphodepletion + CAR T combination in the adults and then transition to pediatric patients. Alternatively, I suggest the authors aggregate and compile a more robust pre-clinical package to justify the use in pediatric patients. • Why the transition to pediatric patients, at the same time as the addition of lymphodepletion? • The proposal applicants provide a rationale for lymphodepletion based on their preclinical data in mouse glioma models. • Previous data indicates that IL13 receptors are highly variably expressed in gliomas. It would be important to define inclusion criteria based on expression (e.g., the percent tumor cells that express the receptor, etc.). • The variability in tumor types (despite being classified as Grade III or IV) could make drawing potent conclusions from the study difficult.

	• Differing tumor types may have different responses. Tumors that are not widely exposed (e.g., glioma) to the cerebrospinal fluid may not respond as well as those that are (e.g., medulloblastoma). • I was struck by the comments about the variability in tumor types and how to address heterogeneity. • Data supporting CAR T transport/trafficking from cerebrospinal fluid (where cells are delivered) to deep brain tumor would be important (perhaps from prior clinical trial data). • A preclinical study showing the superior potency of preselected cells is greater compared with unselected T cells is needed. • What is the manufacturing feasibility based on the assessment of selection-expressing cells in this patient group?
GWG Votes	Is the proposal well planned and designed?
Yes: 8	• The project is well designed. • The project is appropriately planned/designed and expected to yield meaningful outcomes with regards to feasibility and safety. Immunologic endpoints appear largely exploratory. Unclear what will be learned if trial is safe but not efficacious. • Some clarity regarding IL-13Ra testing is needed; is this a CLIA certified test? How long between results of test and initiation of trial? • The proposal is well planned from a correlative biomarker discovery perspective. • The clinical rationale is not clear for the pediatric population.
No: 6	• The group at the applicant institution has extensive experience with CAR T cell clinical trials. • Inclusion of patients to the age of 25 may not necessarily reflect a true pediatric population and could skew recruitment toward a more adult population. • I did not see proof of cell manufacturing data from blood or apheresis product, so it's unclear they can make the product. I did not see the scheme to make lentiviral vectors, so it is unclear what titer and specifications are attained. • Reviewers' comments about potential bio-distribution, tumor heterogeneity, heterogeneity of target expression and potential inclusion criteria for trial need to be addressed. • Without preliminary data to support the thesis that selection-expressing cells are more potent than unselected cells, and the lack of a manufacturing feasibility assessment I am somewhat reluctant to say "yes" here. • Some concerns from reviewers, but outweighed by the compelling need.
GWG Votes	Is the proposal feasible?
Yes: 12	• The project is feasible having been shown in adult patients and in adolescents. The team is uniquely qualified and has an active IND. There are some concerns about enrollment at a single institution. PNOC is listed as a consortia to enroll though phase 2 but not clear how this will be done and how efficacy will be measured across so many different diseases. • Single center for enrollment of pediatric malignant brain tumors (despite heterogeneous histologic mix) may be difficult. • If the investigators address concerns, then I think the candidate is clinically feasible. • The team proved a feasibility of similar projects (funded by CIRM) before. Proposed timeline looks appropriate. The team is very well qualified. • Please provide data for feasibility of sorting of Tn/mem from apheresis collections. • The proposal is feasible but with difficulty. Referrals will be important to enrollment.
No: 2	• It will be difficult to accrue enough pediatric patients in a single center trial. • Not sure if doable at one site.

Application #	CLIN2-12139
Title (as written by the applicant)	Phase 1b/2a trial and manufacturing development of an endogenous stem cell reactivation therapy to enhance bone autograft osteogenesis
Therapeutic Candidate (as written by the applicant)	A liposomal formulation of recombinant human WNT3A protein that is applied ex vivo to autologous bone grafts
Indication (as written by the applicant)	Degenerative spondylolisthesis, a degenerative disease of intervertebral discs
Unmet Medical Need (as written by the applicant)	Nearly 90% of individuals over 50 exhibit degenerative changes in their intervertebral discs. Spinal fusion with autograft increases spinal stability, but > 20% of those procedures fail due to reduced regenerative capacity of aged autograft. This product may address this need, restoring bone formation.
Major Proposed Activities (as written by the applicant)	• Initiate and complete Phase 1b/2a clinical trial of the product and submit Clinical Study report to FDA • Drug product GMP manufacturing to support future Phase 2b clinical studies
Funds Requested	$5,979,859
GWG Recommendation	Tier 2: ***Needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement***

SCORING DATA

Final Score: 2

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

Score Count	15
Votes for Score 1 (exceptional merit and warrants funding)	0
Votes for Score 2 (needs improvement)	15
Votes for Score 3 (sufficiently flawed and does not warrant 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: 11	• Lower back pain is a major cause of morbidity. • Autograft is the standard of care for spinal fusion. According to the applicant, nearly 90% of individuals over age 50 exhibit degenerative changes in their intervertebral discs. This degeneration could lead to symptomatic disease and could significantly impact quality of life. • The proposed treatment does address an unmet medical need in terms of improving the success rate of this type of bone graft as well as speeding recovery. The treatment could have a positive effect on reducing the cost of the treatment and recovery of these patients. • The indication is not a major unmet need, although the product could help some people if it works as proposed. The trial does, however, make sense as a way to enter a clinical development program for a broader spectrum of potential indications.

	• Unclear if CIRM funding is justified given some concerns expressed that unmet patient need is limited and impact of CIRM funding may be limited. • Possibly, but this is not the indication to show that this is true, safety can be shown but efficacy is complicated by non-standardized interbody procedures. • Impactful.
No: 5	• It is unclear that the proposal addresses a significant unmet medical need. • I think the unmet medical need is relatively weak compared to other research funded by CIRM. Agree that it would be better studied in a more refractory population (RA, Osteoporosis, etc). • Back pain is important but most sufferers would not be candidates for this intervention. It may have impact separate from the spondylolisthesis cohort.
GWG Votes	Is the rationale sound?
Yes: 13	• The applicants have generated a body of pre-clinical data, which was partially funded by CIRM, that supports the rationale for this trial. • The scientific and therapeutic rationale are sound. The technology has been studied extensively for nearly 20 years. There are many publications that support the treatment. • The in vitro data demonstrating that the bone graft does take up the Wnt protein from the liposomal delivery system is impressive. The in vitro studies seem to demonstrate the effectiveness of the delivery system and its ability to be taken up by bone. The only question remaining is the demonstration that sufficient Wnt protein is available. • Rationale is sound. • Some concerns about how the amount of drug taken up by the cells will be made consistent.
No: 3	• Spondylolisthesis as a primary driver of the protocol isn't a sound rationale. • Such approaches have been problematic in the past - eg BMP2. The investigators do not address why their approach would be superior and safer. • Yes, scientifically. Clinically, no.
GWG Votes	Is the proposal well planned and designed?
Yes: 2	• The project is appropriately designed. The applicant has had many interactions with the FDA throughout the process, and the clinical hold issue was addressed relatively quickly. A number of changes were made to the clinical protocol as a result of those interactions. • There is no "control" group in the clinical study; i.e., there is no "placebo" or standard of care group of patients. All patients are getting the treatment. Perhaps the investigators can rely on historical data? • The proposal is well designed but lacks stopping rules.
No: 14	• The applicants should standardize the overall surgical procedure and graft preparation process to make for a better trial design. Overall, the major flaw of this study is the lack of a control arm with standard autograft. If the applicants redesign the study and include a control arm, I think it would merit funding. • Consider introducing a control group, particularly in this indication/patient population, and if early interim data from first in human study will be used to gate the Phase 2b study in parallel and FDA interactions to negotiate regulatory pathway to BLA. • Scientifically sound. Clinical trial is not optimized and needs procedure standardization and a control group. • Concerns regarding absence of a control group. • The points raised by the reviewers for the proposed trial are important (1) concurrent controls and maybe even a formulation placebo in this indication are needed (2) detailed instructions on surgical procedures to be used for each patient are needed. • There needs to be a control group, better governance around the DSMB, and definition and timing around stopping rules. • No standardization of the surgical fusion. • It would be a much better use of resources to include a control group. • Agree with concern from primary reviewers that clinical trial protocol requires revision. • Initiation of phase 2b in parallel to first in human testing is not advised; rather, team should consider gating later-stage clinical testing plans (and regulatory engagement) to a more thorough understanding of safety and bioactivity profiles first (i.e., proposal for early interim data to inform is problematic). • Governance around DSMB /stopping rules of concern. • The supply chain for the intervention is extremely complex and at risk.

	• Some of the nuts-and-bolts logistic questions raised by the reviewers (cold chain complexities and number of vials of product that need to be accessed to dose) deserve attention, but can be addressed at a later time.
GWG Votes	Is the proposal feasible?
Yes: 16	• The applicants have a deep history in this area and have outlined a study that is feasible. • The project is feasible. They seem to have their drug substance and drug product far enough along to have reliable product for the clinical study. • The team is qualified and well staffed. They are using very good CDMOs and other vendors. The responses to the issues raised by FDA were all excellent. The quality of their regulatory interactions are excellent. • Supply chain issues may be a problem. • The proposal is feasible if the above concerns are addressed. • Have some doubts they can revise the protocol in under six months. • Time line is aggressive.
No: 0	*none*

Application #	CLIN2-12149
Title (as written by the applicant)	Phase 1 Clinical Development of a First-in-Class Antibody Targeting LILRB4, for the Treatment of AML with Monocytic Differentiation and CMML
Therapeutic Candidate (as written by the applicant)	A first-in-class antibody targeting leukocyte immunoglobulin-like receptor B4 (LILRB4), an immune inhibitory receptor
Indication (as written by the applicant)	Acute myeloid leukemia (AML) with monocytic differentiation and chronic myelomonocytic leukemia (CMML)
Unmet Medical Need (as written by the applicant)	AML is the most common acute leukemia in adults. Nearly 20,000 new cases are expected in the U.S. in 2020. Despite advances in treatment, less than 30 percent of AML patients are alive five years after initial diagnosis. CMML is a malignant hematopoietic stem cell disorder with dismal survival.
Major Proposed Activities (as written by the applicant)	• Conduct a Phase 1 study to evaluate the product in relapsed/refractory patients with AML with monocytic differentiation and CMML.
Funds Requested	$6,000,000
GWG Recommendation	Tier 2: ***Needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement***

SCORING DATA

Final Score: 2

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

Score Count	14
Votes for Score 1 (exceptional merit and warrants funding)	0
Votes for Score 2 (needs improvement)	11
Votes for Score 3 (sufficiently flawed and does not warrant funding)	3

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: 11	• The proposal is to perform a phase 1 study of a naked antibody targeting LILRB4, in patients with relapsed/refractory monocytic AML or CMML. This is a population with dismal outcomes to current chemotherapy. Monocytic leukemias uncommonly have "targetable" mutations in IDH1, IDH2, or FLT3, and this limits application of newer therapeutics. Therefore, there is a therapeutic need, even if this is an uncommon disease. • The disease target, refractory monocytic AML, has a very high unmet need. The monoclonal antibody target is highly expressed in this population. • AML is an unmet medical need. LILRB4 is an innovative new target. • AML remains a disease with tremendous unmet medical need. There are no curative options for AML. If the proposal translates into the clinic, it could have impact.

	• The clinical need is evident. The rationale supporting LSC targeting is relatively weak. The choice of patients for the clinical trial should be clarified. • Agree this is a high unmet need. • Unmet need, although a rare disease. • Is mono-therapy the only approach with this Ab? It could it be developed as a combination therapy approach. • In their description of competitive landscape they do not describe on-going clinical studies, which may be highly relevant in this disease space. The early compounds appear challenged by toxicity profiles and it is unclear if this represents a class effect or a surmountable problem. Therefore, alternative strategies may emerge in this disease space. • The applicants do not note that monocytic leukemia associated with MLL translocations is common in infant leukemias (age < 1 year), and that these patients have dismal outcomes. Their proposal will not enroll patients < 18 years of age, but this is also a relevant, at need, group of patients they could consider in future designs.
No: 2	• Significant doubt about potential for a significant clinical signal - what to do next? • There are doubts about the choice of patient population - CMML inclusion muddies the water.
GWG Votes	Is the rationale sound?
Yes: 10	• Target expressed in tumor. High unmet need. More and better preclinical models would help rationale. • LILRB4 is an interesting target for treatment of AML. Therefore targeting by an antibody is a viable approach. • The investigators plan to target LILRB4, which is over-expressed in a subset of AML patients. The investigators show that LILRB4 is over-expressed in a subset of patients. The animal models, however, are not predictive of clinical activity and do not reflect the actual disease biology. Short of clinical data, it is difficult to determine if the rationale is truly sound. • Preclinical data, especially xenograft data, is not at all strong. Very little evidence of a strong tumor killing effect. Impact on cancer stem cells as opposed to bulk tumor is also weak. • The rationale is modest. They have identified an antigen that is highly expressed in M5 AML and commonly expressed in M4 AML. It is not expressed in other forms of AML. They have generated an antibody against this antigen, completed clinical synthesis, and primate safety studies. They have assessed the antibody in preclinical studies. We do not find those results compelling. • Target is of interest, although expression on many cell types raises potential safety concerns. • Is cytokine release syndrome likely in these patients? What is the plan to communicate early/unexpected toxicity across sites? • It would be good to understand how they think about a development plan that may need to include another agent. • A single agent naked antibody seems unlikely to have a strong clinical effect in this setting, and supporters of their program should anticipate underwriting followup studies with combinations with azacytidine or other chemotherapy. These patients are unlikely to have robust T cell populations to activate, and if they do, these leukemias are at risk for CRS due to strong IL6 and interferon expression. • There is minimal evidence that this target is associated with “leukemic stem cells.” They demonstrate that nearly 100% of monocytic AML express this antigen. But leukemic stem cells are supposed to be rare. So it does not appear to be enriched in this population.
No: 3	• The preclinical studies supporting the rationale seem very weak. Similarly, it seems very unlikely that a naked antibody will be effective in this setting, and there are not preclinical data to strongly support the use of the antibody in combination with a specific drug. • The evidence supporting cancer stem cell inhibition is somewhat weak. • Weak stem cell rationale - sounds more like a differentiation marker.
GWG Votes	Is the proposal well planned and designed?
Yes: 5	• The phase 1 study seems well designed and the operational plan to include multiple sites is remarkable. However, based on lack of preclinical data to determine whether efficacy is likely with monotherapy versus requiring therapy in combination, and to suggest which combination therapy should be pursued, it is not possible to know whether this trial design

	is appropriate. If the trial needs to evaluate safety and efficacy of combination therapy, there needs to be a design determining how and when to incorporate combination therapy into the phase 1 study. ● There is concern that there isn't a threshold % of the leukemia cells expressing the target to allow recruitment - should this be an inclusion criteria - minimal expression? Is the drug likely to work if the target isn't expressed? ● Where is the DSMB? ● Have engaged major centers.
No: 8	● The clinical trial appears largely well planned. They have support from major medical centers to open the study and enroll patients. ● Relatively straightforward clinical study. However, doubts on specific correlative studies and how to proceed. ● The enrollment criteria are vague: “relapsed AML with myelomonocytic or monoblastic/monocytic differentiation or relapsed CMML”. It would seem that immunophenotypic criteria would be helpful. And a minimum expression of the target antigen would be necessary. Perhaps this may be better defined in the protocol. ● They do not define required performance status or what is meant by “adequate renal, hepatic, and cardiac function.” Again, this may be better defined in the protocol. ● Need to better define correlative studies and how they will be used to determine dose if efficacy is not seen. Restrict to M5 AML only. Add DMSB. ● Methods for the correlative studies for the trial should be described in detail. ● I think for the most part it is, but agree with the comments that the indication should be narrowed to exclude chronic disease. ● The investigators did not show strong evidence that targeting LILRB4 results in targeting the LSC population. More evidence is needed. ● The dose limiting toxicity algorithm is complex and difficult to understand. ● There is insufficient plan to monitor, detect, and treat CRS, should the antibody be active. ● Lack of a DSMB and clarity on dose limiting toxicity definitions are an issue.
GWG Votes	Is the proposal feasible?
Yes: 13	● The proposal is feasible based on the current data regarding the agent and approval from the FDA to move forward. ● The proposal is feasible. ● They have the GMP reagent. They have a broad group of major cancer centers prepared to participate. ● Overall the trial is well designed. The rationale for a monotherapy phase 1 study is not adequately supported by the preclinical data. ● The proposal is feasible if the above concerns are addressed. ● Good team, investigators. ● Experienced sites.
No: 0	*none*