Application #	CLIN1-12865
Title	Late-Stage Pre-Clinical Development of a CAR-T cell for the Treatment of ROR1+ Hematological Malignancies
Therapeutic Candidate (as written by the applicant)	We are developing ROR1 Chimeric Antigen Receptor (CAR) modified T cells for the treatment of hematological and solid tumor cancers.
Indication (as written by the applicant)	The target for our therapy is patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and acute lymphoblastic leukemia (ALL).
Unmet Medical Need (as written by the applicant)	The CAR-T cell therapy that we are developing will be used to treat patients with difficult to treat hematological malignancies that are resistant to standard chemotherapies, have few therapeutic options, dire prognoses and represent a tremendous, global unmet medical need.
Major Proposed Activities (as written by the applicant)	• Produce a clinical grade GMP lentiviral vector required to produce the patient modified CAR-T cells. • Complete technology transfer to advance our research grade cell production process into a clinical grade GMP facility. • Complete regulatory documents for submission to regulatory authorities including the IRB and FDA prior to phase 1 clinical study initiation.
Funds Requested	$4,130,260
GWG Recommendation	***Tier 1: warrants funding***
Process Vote	All GWG members unanimously affirmed that "The review was scientifically rigorous, there was sufficient time for all viewpoints to be heard, and the scores reflect the recommendation of the GWG." Patient advocate members unanimously affirmed that "The review was carried out in a fair manner and was free from undue bias."

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.

Highest	1
Lowest	2
Count	14
Votes for Tier 1	9
Votes for Tier 2	5
Votes for Tier 3	0

- A score of "1" means that the application has exceptional merit and warrants funding;
- A score of "2" means that the application needs improvement and does not warrant funding at this time but could be resubmitted to address areas for improvement;
- A score of "3" means that the application is sufficiently flawed that it does not warrant funding, and the same project should not be resubmitted for review for at least six months after the date of the GWG's recommendation.

KEY QUESTIONS AND COMMENTS

Proposals were evaluated and scored based on the key questions shown below, which are also described in the PA/RFA. Following the panel's discussion and scoring of the application, the 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: 12	• Yes. The successful development of a ROR1 targeted immune effector therapy could save thousands of lives. • The application uses CAR-T expressing an antibody to ROR1 to addresses an unmet need in oncology: applying CAR-T technology to target solid tumors, with an initial focus for clinical development in patients with hematological malignancies. • In response to the prior critique, the applicant has adequately addressed some of the prior requests, including an expanded rationale justifying the indicated hematological malignancies and plans for expanding to solid tumor cancers. • In response to the prior critique, the applicant has adequately elaborated on the biology and rationale for going after ROR1 within the context of a CAR-T therapy. • The clinical plan to initially target patients with B cell hematological malignancies is appropriate given the preclinical data. ROR1 is widely expressed on hematological and solid tumor malignancies and generally absent/low on normal tissues making this antigen an attractive target for CAR-T. • A significant proportion of patients with CD19+ hematological malignancies fail to achieve durable responses with current anti-CD19 CAR-T therapies. CAR-T targeting ROR1 may represent and alternative, additive, or synergistic therapy for these patients. • Patients whose disease has progressed after anti-CD19 CAR-T would be eligible for ROR1 CAR-T. • While anti-ROR1 CART may be effective in solid tumors, preclinical data supplied by the applicant indicate lower activity against ROR1+ prostate cancer than hematological malignancies. • The process of manufacturing and distributing CAR-T remains prohibitively expensive and the proposed technology and clinical development plan will not lead to any improvements in manufacturing efficiency. The applicant has described a modest simplification of the logistics of ROR1 CAR-T manufacturing.
No: 0	*none*
GWG Votes	**Is the rationale sound?**
Yes: 12	• In response to questions related to ROR1 expression, pre-clinical, and tissue cross reactivity studies, the applicants have adequately addressed these issues. • Yes, the proposal is supported by the clinical activity of the antibody. • Preclinical data support the feasibility of ROR1 CAR-T and their cytotoxicity against ROR1 cancer cells, including B-cell malignancies. • Feasibility of manufacturing ROR1 CAR-T from two CLL patients is shown. • Anti-ROR1 CAR-T have significant anti-tumor activity in mice with human cells. • While clinical trials of an anti-ROR1 antibody have not shown significant toxicities, the side effects of an anti-ROR1 CAR-T are unknown. Other CAR-T directed against solid tumors have had unexpected and fatal side effects in early phase human clinical trials. The toxicity profile of anti-ROR1 CAR-T cannot be established from pre-clinical studies in mice models, but a lack of toxicity in large animal models is reassuring. • The safety profile of ROR1 CAR-T in humans is unknown, but risk of the proposal is mitigated by phase 1 data of the antibody in 300 patients with B cell malignancies who have been enrolled on phase 1/2 trials to-date. Additional clinical trials using antibody being performed by another organization will add additional information regarding the off-target toxicity and safety of the antibody.
No: 0	*none*
GWG Votes	**Is the proposal well planned and designed?**
Yes: 11	• The applicants have been very responsive to the previous CIRM review. • Improved feasibility in both manufacturing and clinical design. • The plans for technology transfer of anti-ROR1 CAR-T with lentivirus production by another

	manufacturer are well designed. • The applicant has considered possible delays in the process of obtaining data on the feasibility of clinical scale, GMP-compliant ROR1 CAR-T and discussed appropriate mitigation strategies. • The deliverable from one year of CIRM funding will be an appropriate IND package to support a phase 1 clinical trial. • Specifics of the IND package include qualification of the lentivirus and demonstration that the GMP lab can manufacture anti-ROR1 CAR-T with three pilot non-GMP manufacturing runs and two GMP-compliant engineering runs. • The study design includes pharmacokinetic monitoring of the ROR1 CAR-T in vivo as well as anti-ROR1 antibodies. • The feasibility of manufacturing anti-ROR1 CAR-T from two elderly CLL patients is presented. • The concerns raised around manufacturing seem addressable in the course of this work. Some of the manufacturing concerns may place a burden of expectations on the work that may not be needed at a preclinical stage of development. • The applicants have a positive response to the previous review, but it is not always supported by data (e.g., on previous manufacturing runs). Manufacturing problems are apparently largely resolved, with reduced manufacturing time and removal of selection step. The impact of the removal of the selection step on proposed dose is not really addressed. • Applicants need to address impact of dropping positive selection step, and how that might impact dosage as presumably the % CAR+ cells is now much lower. • Still have concerns regarding manufacturing failure rates. • Do not understand applicant response regarding delayed expression of CAR after transduction.
No: 1	• The Gantt chart has been updated and reflects a well-planned and designed plan overall. • The manufacturing strategy remains unclear. The applicant states that they have completed over two dozen successful manufacturing runs at lab scale. That sounds good, but where is the actual data from the successful lab scale runs using the simplified process? • Why does the applicant expect a 25% CAR-T product failure rate if they have successfully manufactured products at lab scale using the simplified manufacturing process without affinity purification at a 14% failure rate? The overall plan is well structured and organized, but CMC remains a major unknown. The applicants present an incomplete data package. • Many of these issues can be easily resolved if the authors include a more comprehensive data package and a clearer discussion of the overall manufacturing strategy and experience from the representative lab scale process that has been generated to date.
GWG Votes	**Is the proposal feasible?**
Yes: 12	• Yes, overall, the project is feasible. • The applicants have and will generate good data on manufacturing feasibility. In their responses to CIRM reviews, they say they will drop the positive selection step at the beginning of the process, but it is not clear how much experience they have with this and how successful it will eventually be. • The planned 28-day manufacturing cycle has been shorted by elimination of the positive selection step, although specific details on the success and duration of manufacturing for all the products developed under this new procedure were not provided. • From a manufacturing perspective, the applicant adequately superficially addresses the potential concern around extended vein to vein time, manufacturing failures, and the use of an "affinity purification" step. Although the newly proposed manufacturing process is standard and is likely to produce sufficient cell numbers for the subjects enrolled in the trial, there is no actual data showing that the applicants have experience with this process. • The observed manufacturing failure rate has been less than 20%. The proposal clarifies that the expected manufacturing success rate is >75%. The manufacturing process is expected to be shortened, with the elimination of the positive selection step for CAR+ T cells. • The applicants claim they have successfully manufactured over two dozen lots of the ROR1 CAR-T product using the proposed simplified process, but they show no actual data.

	• It would be good for the authors to show that their proposed simplified manufacturing process is feasible, at least at lab scale. • Bridging therapies are permitted in the protocol. • Patients with prior treatment with anti-CD19 CAR-T are eligible. • The team has identified an alternative manufacturer of the lentivirus should the planned contract does not work out. • The one-year timeline is very tight with respect to manufacturing of the lentivirus and the generation of five CAR-T products. There is no allowance for any unexpected roadblocks or need to adjust the manufacturing plan.
No: 0	*none*
GWG Votes	**Does the project serve the needs of underserved communities?**
Yes: 12	• The applicant did a good job with this section. • The potential to treat patients with ROR1+ solid tumors is an attractive aspect of the anti-ROR1 CAR-T approach. • B cell ALL is represented in hispanics and the catchment area has a higher frequency of hispanics than the US population. Hispanics with B cell ALL have been accrued at high frequency to other clinical trials at the institution. • The description of the inclusive laboratory of the co-PI is reassuring, but this does not address underserved patient populations.
No: 0	*none*

DIVERSITY, EQUITY, AND INCLUSION IN RESEARCH

Following the panel's discussion of the application, the patient advocate members of the GWG were asked to indicate whether the application addressed diversity, equity and inclusion, and to provide brief comments. The responses were provided by multiple reviewers and compiled and edited by CIRM for clarity.

DEI Score: 9.5

Up to 7 patient advocate 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.

Score	Patient Advocate Votes	Has the applicant sufficiently addressed how they have or will incorporate perspectives from individuals with diverse experience and from underserved groups in the implementation of the proposed project?
9-10: Outstanding response	2	• Excellent presentation of community demographics. • Clear evidence of a commitment to DEI with regard to team members and trial participants. • DEI efforts appear to be both vertically and horizontally integrated throughout the organization. • Clearly articulated multi-departmental approach to recruiting a diverse participant population.
6-8: Responsive	0	*none*
3-5: Not fully responsive	0	*none*
0-2: Not responsive	0	*none*