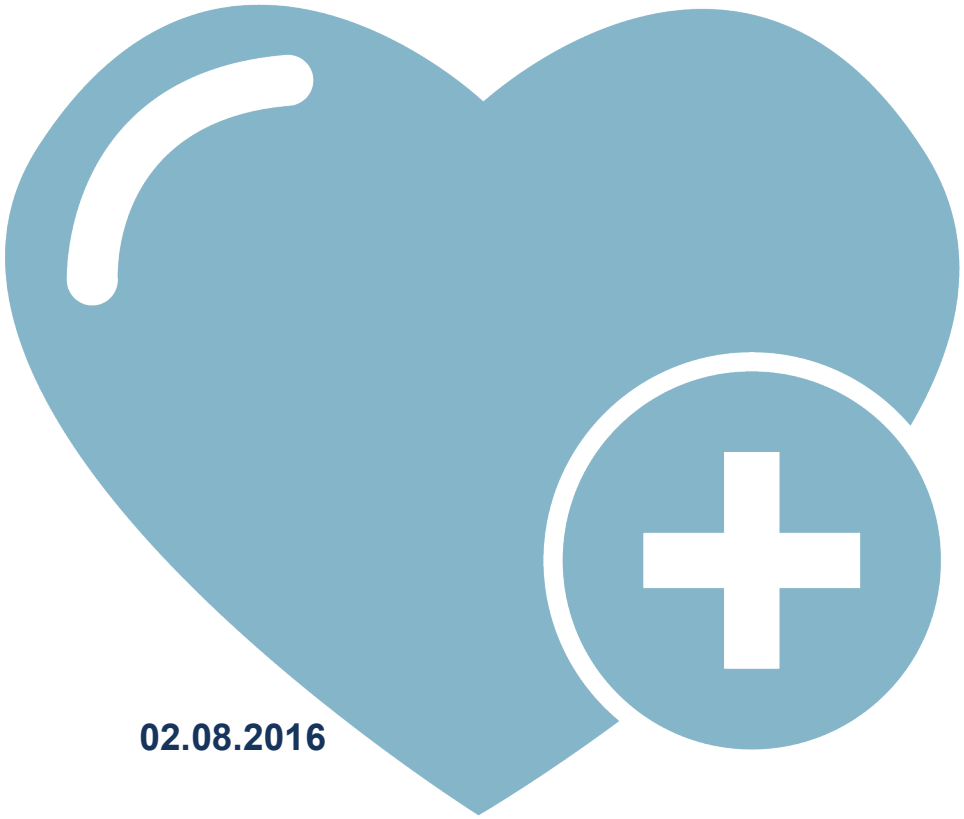
CLINICAL

Grants Working Group Public Review Summary

Development of AB-110: genetically-modified endothelial cells plus expanded cord blood hematopoietic stem cell combination as a transplantation therapy for hematologic malignancies

Application Number: CLIN1-08342 (Revised Application)	Review Date: January 26, 2016

Late Stage Preclinical Project Proposal (CLIN1)



02.08.2016

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Development of AB-110: genetically-modified endothelial cells plus expanded cord blood hematopoietic stem cell combination as a transplantation therapy for hematologic malignancies

APPLICATION NUMBER: CLIN1-08342 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

CD34+ cord blood-derived hematopoietic stem and progenitor cells co-cultured and co-infused with genetically modified endothelial cells

Indication

Life-threatening high-risk hematologic malignancies including leukemia and lymphoma

Unmet Medical Need

For life threatening high risk blood cancer, cord blood stem and progenitor cells for transplantation can be obtained rapidly and can provide a chance of cure; however, the cord blood units are small and have low cell dose, which prolongs recovery with a high chance for serious complications, even death.

Major Proposed Activities

Develop and validate the GMP process for manufacturing the AB-110 product in a closed system bioreactor

Complete assessment of the safety of the E-CEL HUVEC component of AB-110 in both rodents and nonhuman primates as recommended by the US FDA

Prepare and file an IND application to advance the product into clinical studies

Funds Requested

$3,797,117 ($844,638 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 4 GWG members

Votes for Score 3 = 0 GWG members

- 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.

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Review Overview

While noting some weaknesses, particularly related to manufacturing the product and the clinical protocol, reviewers were impressed by the applicant's responses to the review recommendations from the original review and thought the team understands the weaknesses and will work to overcome them. Given the potential impact of this proposal, compelling scientific rationale, and the belief that this team will be successful under the CIRM 2.0 system to achieve the goals of the project, reviewers recommended this project for funding.

Review Summary

Does the project hold the necessary significance and potential for impact?

a) Consider whether the proposed treatment fulfills an unmet medical need.

- Improving outcomes following cord blood (CB) transplantation is an unmet medical need.
- Rapid recovery of absolute neutrophil count (ANC) and platelets (PLT) following CB transplant could decrease the treatment related mortality (TRM) score, and, therefore, TRMs and associated morbidities. This approach has the potential to have such an impact.
- Developing platform technologies for improving engraftment of hematopoietic stem cells (HSC) is of high impact. This technology is relatively novel with potential to positively impact engraftment in other types of HSC transplants, including for HSC gene therapy products, which might be where the future of this product lies.

b) Consider whether the approach is likely to provide an improvement over the standard of care for the intended patient population.

- If the product leads to rapid recovery of ANC and PLT following CB transplant, this approach is likely to provide an improvement over current standard of care.

c) Consider whether the proposed treatment offers a sufficient, impactful, and practical value proposition for patients and/or health care providers.

- In CB transplantation, the cost of a dual cord transplant is becoming increasingly difficult to justify in a crowded marketplace that includes comparable and less expensive approaches such as haploidentical transplants. Therefore, new treatments must improve clinical outcomes and reduce costs to offer an impactful value proposition. In order to do both these things, the proposed treatment will need to both reduce TRMs and allow for use of single, smaller, better matched CB unit. The applicant seems to understand this and is targeting such improvements.
- If TRMs and morbidities are decreased by this approach, overall costs, such as those associated with number of days in the hospital, could be decreased. This would improve the value proposition of CB transplants to both providers and patients.
- The manufacturing procedure is incredibly complicated and the value proposition will be hampered by cost and complexity of manufacturing the final product. In cord blood transplant, the need is for a simple and rapid method that results in multilineage engraftment. Therefore, for this technology to be widely adopted by transplant providers, it is critical that the sponsor optimize a cost-effective, scalable manufacturing process. Steps are taken in this proposal to begin this process.

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Public Review Summary

Is the rationale sound?

a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether it is supported by the body of available data.

- The proposal is based on sound science and strong preclinical data that supports the technology's ability to positively impact engraftment.
- In the first review, data demonstrating short term recovery (which is critical for impact) was lacking. The applicant provided some data supporting short term recovery and indicated a focus on this moving forward.
- The proposal lacks some details such as transduction efficiencies achieved, multiplicity of infection (MOI), yields, etc.
- The applicants should carefully consider FDA comments regarding the inclusion of the E-cel population in the graft and evaluate its necessity.

b) Consider whether the data supports the continued development of the treatment at this stage.

- The preclinical data strongly support the potential for benefit to patients if the product is successfully developed and, therefore, support continued development of the treatment.
- It is of critical importance that the sponsor works throughout the development of this treatment to optimize a cost-effective and simplified manufacturing process. The sponsor seems to understand the importance of this and is proposing the first steps toward such a process.

Is the project well planned and designed?

a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and achieve meaningful outcomes to support further development of the treatment.

- Although reviewers thought it a good strategy to switch manufacturing to a bioreactor system, and the bioreactor is an excellent system for seeding the E-cels, there were concerns that sufficient comparability studies were not included in the project plan, and details of how the bioreactor will work are unclear. For example, reviewers were uncertain if adherence and cell contact will be maintained when there is media flow or how cells will be harvested and if an enzymatic step will be included.
- The original review noted serious concerns with the design of the Phase 1 trial. Although this application proposes preclinical IND-enabling activities only, clinical trial design is essential to understand potential impact and the strength of the proposed preclinical package. Reviewers noted the clinical protocol still needs improvement and had several recommendations (as listed below), but a major activity in this proposal is development of the clinical protocol. The applicant, in response to suggestions from the initial review, has appointed a clinical advisory board with excellent and experienced advisors, and reviewers were confident that a well-designed clinical trial would result.
    - The primary endpoint of the Phase 1 study should be safety (toxicity). A much larger study would be necessary to demonstrate improvement to the current standard of care (80% engraftment by day 42).
    - Increasing the homogeneity of the patient population and limiting variation in conditioning regimens is recommended to improve the ability to interpret clinical study outcomes.

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Public Review Summary

- The selected clinical efficacy endpoint does not give confidence that the approach will provide a clinical benefit and it is important to select an endpoint that, if met, will generate enthusiasm for the product.
- For the Phase 1 safety trial, reviewers recommended using a single clinical site and single manufacturer.
- The rationale for the timing of delivery of the graft is not clearly articulated and will be important to understand.

- FDA wants to see long term follow up and biodistribution with a treatment that exhibits long term persistence. As such, some of the proposed studies need modification. For example, the biodistribution study should be a minimum of 5-6 months and the imaging study should extend to 3-6 months in order to give a better understanding of how to succeed in the clinic.
- At the start of the trial, a master and working cell bank will be ready to go, which will benefit the trial.
- The trial design element to introduce unmanipulated cells with the manipulated product should give the manipulated graft a chance to engraft in the dual cord setting.

b) Consider whether this is a well-constructed, quality project.

- The applicants responded to reviewers concerns from the first review of this project with modifications to the data package, project plan and team composition, resulting in a quality project supported by a quality team.

c) Consider whether the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

- The timeline and plan demonstrate an urgency that is consistent with CIRM's mission, however, there are concerns with the feasibility of the proposed timelines.

Is the project feasible?

a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- In response to the original review and the need for a cost-effective and scalable manufacturing process, the applicant has proposed development of a bioreactor process to manufacture the final clinical product. Though this is an appropriate and welcome step, limited data was provided to support feasibility and comparability to the current system. It is not clear that the applicant has adequately budgeted time to complete the studies that will be necessary.
- The timeline has some inconsistencies, and it is likely that this will need to be reconsidered before launching the project. For example, some subtasks take longer than the total task.

b) Consider whether the proposed team is appropriately qualified and staffed and whether the team has access to all the necessary resources to conduct the proposed activities.

- The team is overly reliant on a single individual for success in developing an improved manufacturing process and to manufacture the product. The panel strongly recommended that the team consider redistributing manufacturing activities relating to development of the bioreactor process.
- The newly proposed Clinical Advisory Board is a significant improvement to the

application and includes individuals with appropriate qualifications and expertise.

c) **Consider whether the team has a viable contingency plan to manage risks and delays.**

- It is not clear the team fully understands the significance of switching to a new bioreactor platform and the need to repeat much of the previous non-bioreactor experimental test results in order to show comparability. This is not accounted for in the current project plan or in the contingency plan.

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CIRM Recommendation to Application Review Subcommittee

The CIRM recommendation to the Application Review Subcommittee is considered after the GWG review and did not affect the GWG outcome or summary. This section will be posted publicly.

RECOMMENDATION: Fund (CIRM concurs with the GWG recommendation).