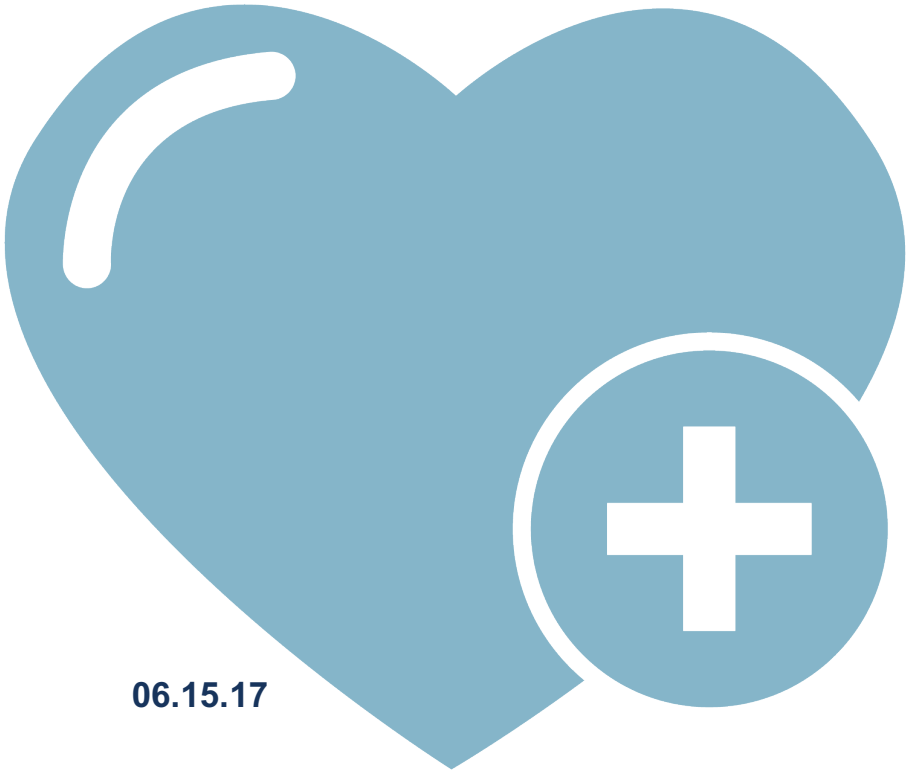
CLINICAL

Grants Working Group Public Review Summary

In Utero Hematopoietic Stem Cell Transplantation for the Treatment of Fetuses with Alpha Thalassemia Major

Application Number: CLIN2-09183 (Revised Application)	Review Date: 30 May 2017

Clinical Trial Stage Project Proposal (CLIN2)



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CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

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In Utero Hematopoietic Stem Cell Transplantation for the Treatment of Fetuses with Alpha Thalassemia Major

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Maternal bone marrow-derived CD34+ hematopoietic stem cells.

Indication

Fetal alpha thalassemia major

Therapeutic Mechanism

This strategy that takes advantage of existing tolerance between the mother and fetus during pregnancy, so that maternal cells can be transplanted into a fetus without conditioning or immunosuppression. Survivors of alpha thalassemia need chronic blood transfusions or a stem cell transplant after birth, both of which have significant morbidity; if successful, in utero transplantation could result in a definitive cure, or allow postnatal boost transplant with decreased morbidity.

Unmet Medical Need

Alpha thalassemia major is almost always fatal in utero, and rare survivors need costly and morbid chronic care. There is an unmet clinical need to develop a therapy that would be life-saving, yet avoid the chronic disease burden of current survivors.

Project Objective

Phase 1 trial completed.

Major Proposed Activities

Manufacture maternal bone marrow stem cells.

Establish the safety of in utero transplantation in fetuses with ATM

Establish the feasibility of maternal bone marrow harvest and in utero transplantation.

Funds Requested

$12,131,817 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 12 GWG members

Votes for Score 2 = 0 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 for at least six months after the date of the GWG’s recommendation.

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Review Overview

This is a revised application that previously received a score of "2". In the initial review of this application, reviewers strongly supported the approach as a potential cure for an unmet clinical need in fetal alpha thalassemia major. Reviewers thought that there was strong preclinical data to support progression to testing safety of the approach in humans. Reviewers thought that the team was uniquely qualified and experienced to perform the proposed studies. However, reviewers expressed concern about whether approach would be transferrable to other centers, whether the proposed doses would pose risk of GvHD, whether the proposed procedures posed a safety risk to patients, and whether there were appropriate plans for treating patients with low levels of cell engraftment. The applicant addressed these concerns in the revision. Thus, reviewers recommended this application 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.

- Fetal alpha thalassemia major (ATM) represents a clear unmet clinical need due to low survival rates and lack of effective treatments.
- The current standard medical approach for an ATM pregnancy is termination or *in utero* blood transfusion. The rare survivors still require monthly transfusions.

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

- If effective, this approach would provide a cure or, at the least, ameliorate the disease.
- If successful, the fetal transplant approach could be extended to other blood disorders.

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

- Families already facing the psychological burden of an ATM pregnancy also face an enormous economic burden.
- This therapy will avoid post-natal therapy shortcomings and could achieve a definitive treatment before birth.
- Treatment could also reduce the incidence of pregnancy complications.
- Value is decreased if only low level chimerism is achieved but it could facilitate post-natal transplantation.

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 rationale is sound and based on vast and solid preliminary data in small and large animal models.
- Clinical outcomes of *in utero* transplantation in other indications have been poor to date.

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

- Overall, the data supports testing of in utero transplantation of maternal stem cells in human fetuses with ATM.

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 therapeutic candidate.

- The clinical study has an active IND and is very well planned and designed to show safety of the approach.
- It is unclear whether this approach can be transferred to other centers.

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

- The program has a strong team, appropriate infrastructure and expertise in all relevant fields to execute the clinical study.
- The program has appropriate oversight and monitoring committees.
- The program has adequate manufacturing plans.

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

- The project plan and timeline are reasonable given the rare nature of the disease and anticipated challenges with patient recruitment.

Is the project feasible?

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

- Patient accrual will be challenging but the PI has a plan to receive patients from other centers.

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 uniquely qualified and experienced to perform this trial.
- The fetal center has experience conducting similar trials and has the appropriate resources and equipment to perform this trial.
- Advisory boards and oversight committees will provide recommendations as an interim evaluation.

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

- The applicant has identified appropriate risks with respect to patient enrollment and low engraftment efficiency and has provided a strong 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).