

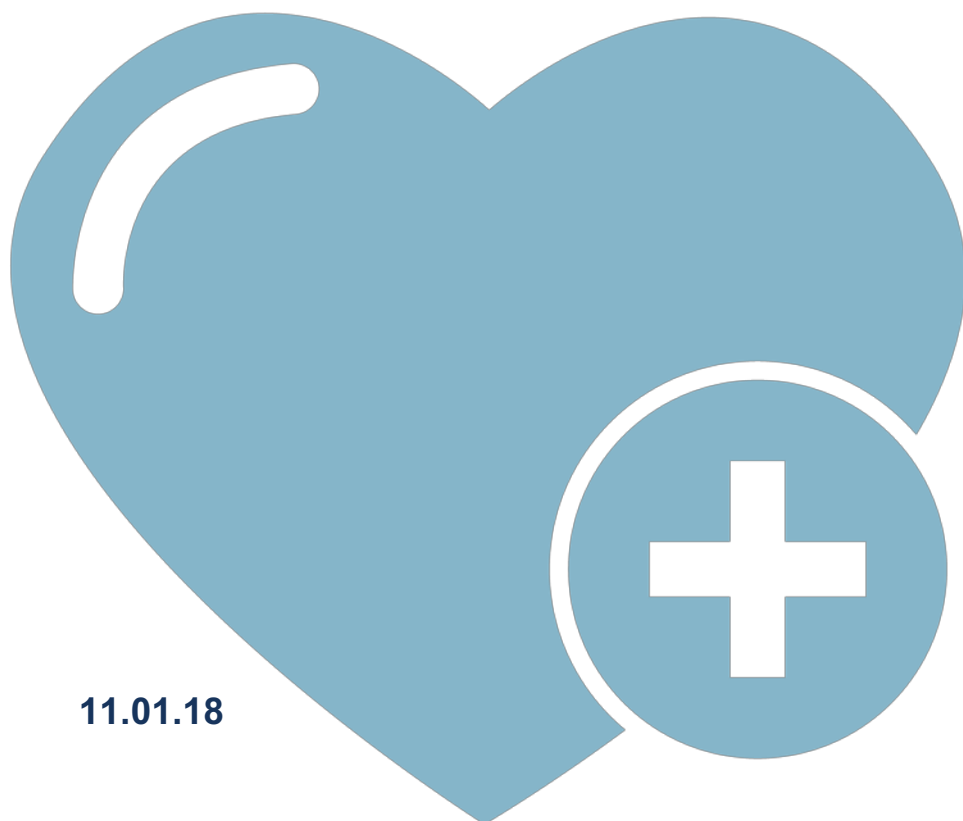
Grants Working Group Public Review Summary

Placental Mesenchymal Stem Cell Augmentation of Fetal
Myelomeningocele Repair

Application Number: CLIN1-11404

Review Date: 25 October 2018

Late Stage Preclinical Project Proposal (CLIN1)



11.01.18

Placental Mesenchymal Stem Cell Augmentation of Fetal Myelomeningocele Repair

APPLICATION NUMBER: CLIN1-11404

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Allogeneic Placenta-derived Mesenchymal Stem Cells Seeded on Extracellular Matrix (PMSC-ECM)

Indication

Myelomeningocele (MMC) - or Spina Bifida - diagnosed prenatally

Therapeutic Mechanism

Placenta-derived mesenchymal stem cells (PMSCs) act by a paracrine mechanism, secreting a variety of growth factors, cytokines, and extracellular vesicles. This secretory profile is unique to PMSCs and is responsible for protecting motor neurons from apoptosis, which occurs due to chemical and mechanical trauma when motor neurons are exposed to the intrauterine environment. PMSC treatment increases the density of motor neurons in the spinal cord, leading to improved motor function.

Unmet Medical Need

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.

Project Objective

IND filing, Phase 1/2 trial start-up activities

Major Proposed Activities

Manufacture product to supply the proposed studies and clinical trial

Assess safety of the therapeutic PMSC product

Assess efficacy using clinical-grade product

Funds Requested

\$5,666,077 (\$0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 15 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.

Review Overview

Overall, the reviewers were very enthusiastic about the proposed stem cell-device combination product for spina bifida. The value proposition of a one-time treatment that would be additive to the current standard of care in-utero surgery for a lifelong condition that incurs high medical costs was very appealing. The proposed activities align with what is needed for a successful IND filing at the end of the project. In addition, the applicant team is highly experienced in the field and is well-positioned to execute the project on-time. The GWG voted unanimously to recommend the application for funding.

Review Summary

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

YES	14	NO	0
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a) Consider whether the proposed treatment fulfills an unmet medical need.

- Myelomeningocele (MMC), or spina bifida, is a rare disease resulting in lifelong lower limb paralysis as well as bowel and bladder impairments. It is the most common congenital cause of lifelong paralysis in the United States, and approximately four children a day are born with this devastating congenital defect.
- In utero surgical repair of MMC improves lower limb motor function in 20% more patients than standard postnatal repair suggesting a capacity for recovery in the regenerative fetal environment. Adding cell therapy could further improve these results.

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

- The development of in-utero surgery to repair the defect has resulted in improvements in motor function. However, over half of the patients are still unable to walk.
- Based on the robust *in vitro* and *in vivo* (both rat and sheep models) studies previously performed by this group it is reasonable to believe that the proposed approach is likely to provide an improvement over the standard of care.

c) Consider whether the proposed treatment offers a sufficient value proposition such that the value created by it supports its adoption by patients and/or health care providers.

- The healthcare costs for the disease are very high, and the lifelong burden on the patients and their families is significant. The proposed treatment is a relatively simple one-time administration of immobilized cells as an additional step during surgery. If successful, its value to both healthcare providers and patients would be very high.

c) If a Phase 3 Trial is proposed is the therapy for a pediatric or rare indication or, if not, is the project unlikely to receive funding from other sources?

- N/A

Is the rationale sound?

YES	14	NO	0
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a) Consider whether the proposed project is based on a sound scientific and/or clinical rationale, and whether the project plan is supported by the body of available data.

- The Management of Myelomeningocele clinical trial demonstrated the value of *in utero* surgical repair of MMS and provides strong clinical rationale for the proposed treatment.
- The scientific rationale for augmenting in utero surgical repair with implantation of the stem cell-device combination is sound and is supported by CIRM-funded preclinical data.
 - In a small animal model, application of PMSCs to the spinal cord decreased cell apoptosis.
 - In large animals, PMSCs increased motor neuron density in the spinal cord and these increases correlate with improved motor function in a dose-dependent manner.
- The applicants have demonstrated that PMSCs have improved functional activity in terms of cell expansion, secretory activity and wound healing capacity in comparison to bone marrow-derived MSC.
- Under prior CIRM funding the team translated the generation of PMSC to GMP manufacturing conditions.

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

- The preclinical data from previous CIRM-funded translational studies support the continued development of this promising treatment at this stage.

Is the project well planned and designed?

YES	14	NO	0
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a) Consider whether the project is appropriately planned and designed to meet the objective of the program announcement and to achieve meaningful outcomes to support further development of the therapeutic candidate.

- The project plan builds on advice from the FDA obtained at a Pre-IND meeting. The plan addresses many of the concerns raised by the FDA and should provide the data required for an IND filing at the end of the project.
- The investigators should consider whether pre-term placental tissue is really needed as the cell source. Collection of placental tissue at term will be more standard and reduce risks. It was unclear whether pre-term was a superior source of cells to placenta recovered at routine delivery.
- The animal safety studies propose doses equivalent to the highest human dose. It is unclear why the studies do not propose studying higher doses.
- Long-term safety studies are planned, but some longer-term functional studies are also suggested.
- Some additional work may be needed to understand the dose. The number of delivered cells may not be as precise as stated in the proposal. The number of cells attached and retained on the matrix will differ from what is seeded initially.

b) Consider whether the proposed experiments are essential and whether they create value that advances CIRM's mission.

- The proposed experiments are essential as many are based directly on the recommendations from a Pre-IND meeting with the FDA.

- The product is in line with the goals and mission of CIRM.

c) Consider whether the project timeline is appropriate to complete the essential work and whether it demonstrates an urgency that is commensurate with CIRM's mission.

- The timeline is sufficiently aggressive but realistic for the tasks to be achieved. There is a good body of preclinical information that display experience that will be invaluable in achieving the goals.

Is the project feasible?

YES	14	NO	0
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a) Consider whether the intended objectives are likely to be achieved within the proposed timeline.

- The studies are reasonable in scope for the 18-month timeline. The proposed models are already developed.

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.

- This is a highly qualified team that has made major improvements to the clinical treatment of this disease.

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

- The major risks are identified and focus primarily on manufacturing delays. The mitigation strategies proposed for each risk are sound and are covered financially. The risks cited are typical for most cellular therapies.



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).