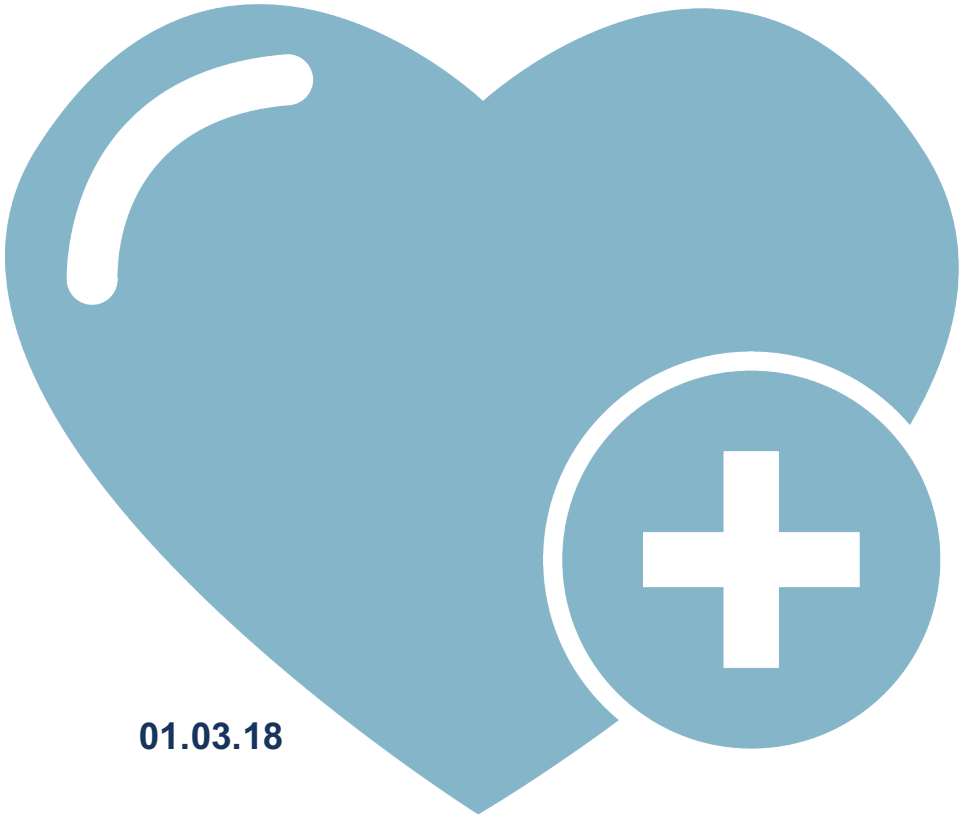
CLINICAL

Grants Working Group Public Review Summary

Cellular Immunotherapy for Induction of Immune Tolerance in HLA Matched Living Donor Kidney Transplant Recipients

Application Number: CLIN2-10411 (Revised Application)	Review Date: 19 December 2017

Clinical Trial Stage Project Proposal (CLIN2)



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Cellular Immunotherapy for Induction of Immune Tolerance in HLA Matched Living Donor Kidney Transplant Recipients

APPLICATION NUMBER: CLIN2-10411 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

MDR-101 is cellular therapy consisting of kidney donor-derived CD34+ HSCs and CD3+ T-cells.

Indication

Maintenance of kidney allograft function after withdrawal of post-transplant immunosuppressant (IS) drugs in HLA matched kidney transplants recipients.

Therapeutic Mechanism

Following infusion and engraftment of MDR-101, the progeny cells establish a state of mixed lympo-hematopoetic chimerism. This leads to a condition known as immune tolerance in which the transplanted kidney is no longer viewed as foreign by the recipient. This allows the gradual withdrawal of all immunosuppressive (IS) drugs that were previously required to prevent rejection of the transplanted kidney.

Unmet Medical Need

It is well established the current IS drugs are directly nephrotoxic and have increased risks of diabetes, heart disease, and cancers and contribute to increased transplant recipient morbidity and mortality and coincident transplant organ loss. Elimination of IS drugs should minimize these risks.

Project Objective

Completion of phase 3 study and BLA submission to FDA.

Major Proposed Activities

cGMP manufacturing of MDR-101 product.

Demonstrate predictive value of donor mixed chimerism testing in recipients of HLA matched HSCs.

Demonstrate the ability to achieve durable immune tolerance.

Funds Requested

$18,763,585 ($18,763,585 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 11 GWG members

Votes for Score 2 = 1 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". Reliance on chronic immunosuppression and the risk of chronic graft rejection are major hurdles preventing long-term success of kidney transplants. Reviewers agreed that the proposed product, which is based on decades of preclinical and clinical data, represents a safe therapeutic solution for addressing this unmet medical need in HLA-matched kidney transplant recipients. Reviewers noted that the phase 3 study is appropriately designed to support filing of a Biologics License Application (BLA) and its design has the agreement of the FDA. In the initial review of the application, reviewers expressed concerns about project feasibility including clinical trial site support and about the viability and functionality of the product. Reviewers were satisfied with the applicant's response, which included additional information on site activation, letters of support from California sites and additional data on product manufacturing and characterization. Reviewers thought that the proposed project has a high likelihood of success and recommended the 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.

- The need for immunosuppression and risk of chronic rejection are the main hurdles preventing long-term success of kidney transplantation. The proposed treatment will achieve immune tolerance via mixed chimerism in HLA-matched kidney transplant recipients thereby reducing or eliminating the need for chronic immunosuppression.

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

- The proposed treatment will provide a significant improvement over the current standard of care by reducing or eliminating the need for chronic immunosuppression and by reducing the risk of chronic organ rejection.

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

- The proposed treatment has the potential to be safer and to have less side effects for HLA-matched kidney transplant recipients than the current standard of care.
- The proposed treatment, if successful in eliminating reliance on chronic immunosuppression, could result in cost savings for the healthcare system.

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?

- Reviewers noted that there is potential for obtaining orphan drug designation.

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Is the rationale sound?

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 project is based on sound scientific and clinical rationale and is supported by extensive pre-clinical and clinical data spanning four decades.
- The preliminary efficacy data from the phase 1/2 studies show good likelihood of achieving mixed chimerism and withdrawal of immunosuppression in transplant recipients.

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

- The safety and preliminary efficacy data from phase 1/2 studies strongly support continued development of the treatment in phase 3 studies.

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 to achieve meaningful outcomes to support further development of the therapeutic candidate.

- The applicant has obtained agreement on the phase 3 study design from the FDA via a special protocol assessment (SPA).
- The phase 3 study design is appropriately planned and designed to provide pivotal data for BLA filing.
- Reviewers noted that long-term follow up should also be performed on the donors.
- Some reviewers were unclear on what information the control group will contribute to the study endpoints.

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

- The design of the primary, secondary and informational endpoints should provide important information for BLA filing.
- The data collected from this phase 3 study will also inform on the potential of a wider indication for the proposed therapeutic approach.

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 project timeline demonstrates appropriate urgency.
- The project has an aggressive timeline and plans to recruit up to 40 trial sites to meet the accrual targets.

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Is the project feasible?

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

- In the initial review of the application, reviewers were concerned whether the applicant had appropriate support from the potential clinical sites and whether the sites were qualified to administer the therapy. Reviewers were satisfied with the applicant's response, which detailed site qualification criteria, activation status of the clinical sites, and letters of strong support from the California sites.
- In the initial review of the application, reviewers were concerned whether the cell therapy processing protocol would retain viability and functionality of the product. Reviewers were satisfied with the applicant's response, which detailed product characterization data including viability and cell functionality.
- In the initial review of the application, reviewers were concerned whether residual levels of the induction therapy agents in the transplant patients would adversely impact post-infusion functionality of the product. The reviewers noted that the applicant provided adequate additional data but did not directly address the concern regarding CD3+ T cell functionality.
- Some reviewers were unclear whether the induction therapy regimen would be standard across all sites or whether it would defer to standard practice at individual sites.

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 well qualified and has the access to necessary facilities and equipment. This application is built on decades of strong experimental and clinical work.

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

- The applicant identified risks associated with manufacturing and clinical trial execution and provided an adequate 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).