CLINICAL

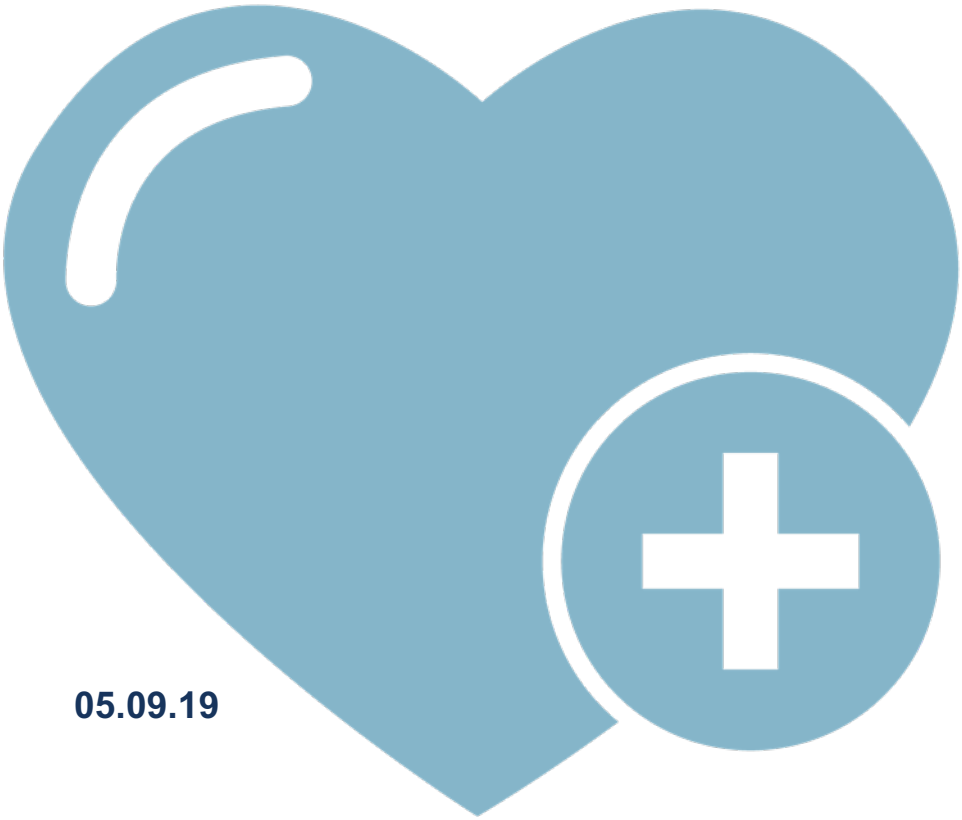
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

Pancreatic Islets and Parathyroid Gland Co-transplantation for Treatment of Diabetes in the Intra-Muscular Site

Application Number: CLIN2-11437 (Revised Application)	Review Date: 25 April 2019

Clinical Trial Stage Project Proposal (CLIN2)



05.09.19

Pancreatic Islets and Parathyroid Gland Co-transplantation for Treatment of Diabetes in the Intra-Muscular Site

APPLICATION NUMBER: CLIN2-11437 (Revised application)

REVIEW DATE: 25 April 2019

PROGRAM ANNOUNCEMENT: CLIN2 Clinical Trial Stage Projects

Therapeutic Candidate or Device

Human pancreatic islets and parathyroid gland combination graft

Indication

Patients with established Type 1 diabetes

Therapeutic Mechanism

Pancreatic islet transplantation has become a more viable approach to treat patients with established Type 1 diabetes. However, widespread application has been limited by several barriers, most importantly, poor islet survival and an inability to monitor islets after transplant. Co-transplantation of parathyroid tissue with pancreatic islets leads to dramatic improvement in islet survival and function after intramuscular transplant, which enables easy access and monitoring.

Unmet Medical Need

The ability to restore long-term normal blood glucose levels with islets from a single donor, using a low morbidity procedure, in a retrievable site that can be non-invasively monitored has not been attainable previously. This trial is aimed at addressing this critical unmet need.

Project Objective

Phase 1/2a trial completed

Major Proposed Activities

Perform phase 1/2a safety and efficacy trial of pancreatic islet and parathyroid co-transplantation in the muscle of patients with Type 1 diabetes

Perform safety analysis and efficacy assessment of islet and parathyroid grafts in a novel intramuscular islet transplant site

Perform exploratory studies on islet engraftment mechanisms and immunologic monitoring of pancreatic islet and parathyroid grafts

Funds Requested

$11,083,012 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 13 GWG members

Votes for Score 2 = 2 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

This resubmission proposes intramuscular co-transplantation of parathyroid gland and islet cells for type 1 diabetes. Overall, reviewers thought the applicants provided a detailed response to concerns from the prior review and the new data provided support the rationale. The review panel also considered whether the proposal offered a sufficient value proposition in light of three key concerns. First, the therapy targets a small patient population. Second, the expected advancement of pluripotent stem cell (PSC)-derived cell transplants could well replace the proposed donor islet transplantation approach. Finally, current U.S. regulatory barriers for islet transplantation could be a significant risk for the commercialization of the project.

In the end, the reviewers thought the study would provide important information on a possible alternative transplantation site that is more easily accessible, and the parathyroid gland could provide improved engraftment. If efficacious, the proposed therapy could lead to US regulatory approval for islet transplantation and clear the commercialization path for this and future diabetes treatments in a field that needs innovation. Overall, the enthusiasm from clinical experts for the potential of a new approach outweighed commercialization concerns and the panel recommended the application for funding.

Review Summary

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

YES	15	NO	0

Reviewers considered the following:

a) Whether the proposed treatment fulfills an unmet medical need.

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

c) 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.

d) 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?

Summary of Reviewers' Comments:

- Current islet transplantation is hampered by major islet loss after infusion and procedure-related risks. An alternative islet transplantation site with better engraftment and survival would be beneficial.
- There was significant debate between reviewers about the value proposition. Disease area experts thought that the possibility of improvement of islet transplantation with this method would be valuable for the diabetes field. Although it is likely only a small number of patients would be impacted by this product due to a limited supply of donor islet cells and the immunosuppression necessary, the potential benefit could outweigh the risks, if effective. Product development experts thought that the overall value proposition of the trial was low, as the applicants see the trial as part of a development path for future stem cell-derived products that could be placed in intramuscular parathyroid grafts. Therefore, the studies proposed would likely need to be repeated in the future with the new stem cell-derived islets.
- Biological licensure for islet transplantation is a current barrier to this therapy in the U.S. Disease area experts thought that success in the proposed trial would be important to secure the

necessary regulatory approval for islet transplantation in the US. Product development experts were concerned that the current regulatory barrier to commercialization of the proposed therapy was a significant risk.

2. Is the rationale sound?

YES	15	NO	0

Reviewers considered the following:

a) 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.

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

Summary of Reviewers' Comments:

- In the initial review of the application, reviewers noted that the provided preclinical data didn't convincingly support the rationale for the proposed approach. A substantial amount of unpublished data was added to justify the use of parathyroid gland co-transplantation. The new data on parathyroid related factors and the beneficial use of the PTG in islet engraftment support this line of islet-PTG co-transplantation research.
    - The update is broadly consistent with their rationale and proposed MOA for PTG and islet co-transplantation. In particular, they have more clearly delineated the theoretical roles of supportive factors and angiogenic factors during the early post-transplant period and started to identify both types of factors made by PTG.
    - The applicants put forward a good rationale why an intramuscular site should be investigated. The new data show good islet survival in the intramuscular transplant site, and the graft can also be readily retrieved for analysis from muscle.
    - There are some aspects of the MOA that remain unclear and may be useful to investigate for future dosing and potency assays. These would not be directly addressed by the proposed trial but could be answered in a separate study.
    - The applicants conducted an in vitro study looking at the effect of various immune suppressive drugs on the secretion of multiple molecules from PTG tissue, showing minimal apparent impact of immune suppression. However, long-term support of islet function by PTG under conditions of clinical immunosuppression is still unclear.

3. Is the project well planned and designed?

YES	15	NO	0

Reviewers considered the following:

a) 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.

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

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

Summary of Reviewers' Comments:

- Reviewers generally agreed the phase 1/2a trial is well-designed. The timeline is feasible to recruit proposed number of subjects with type 1 diabetes, to transplant those subjects, and to evaluate the relevant outcome parameters.
- Reviewers expressed concern regarding two unknown variables: a novel transplantation site and co-transplantation with parathyroid tissue. At the end of the study it will not be clear which of these two factors made the major contribution for the success or failure of the product.
- It is not clear when the applicants will consider the treatment strategy a success. Insulin independence is the primary objective. However, in many islet transplantation centers the main objective is not insulin independence, it is stability of glycemic control and absence of severe hypoglycemic events. Clear criteria for further therapeutic development are needed.
- The potential for a future stem cell-derived insulin-producing cell replacement is a consideration. As PSC-derived insulin-producing cells will be present in unlimited numbers, the issue of stimulating engraftment is likely to be less important. Cell death would have much less consequence with PSC-derived cells than with the limited number of donor islets currently used in islet transplantation. It is also unclear whether an intramuscular site is the best site for safety. Open scaffolds and the perimuscular region are other alternatives.

4. Is the project feasible?

YES	15	NO	0

Reviewers considered the following:

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

b) 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.

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

Summary of Reviewers' Comments:

- Generally, reviewers agreed the project time line is appropriate to obtain sufficient data and the possible risks were adequately addressed.
- Reviewers recommend the addition of an endocrinologist to monitor for hyperparathyroidism as

the team expertise is heavily surgical.

- There was extended discussion regarding possible regulatory barriers to the multi-tissue product. Concerns were raised regarding whether the project would lead to a commercially viable product for a sufficient number of patients. Some reviewers thought that clear efficacy of the proposed therapy would lead to regulatory success, while others disagreed.

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).