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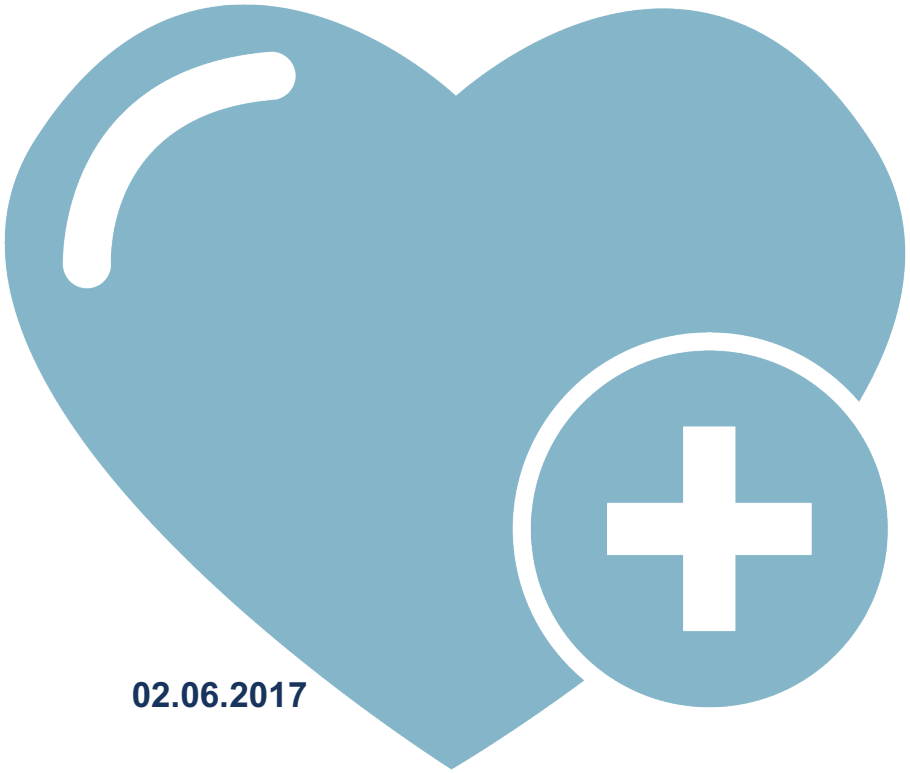
Grants Working Group Public Review Summary

IND-Enabling Studies Using Human ESC-Derived MEF2CA-Programmed A9 Neural Progenitor Cells for Parkinson's Disease

Application Number: CLIN1-09759	Review Date: 31 January 2017

Late Stage Preclinical Project Proposal (CLIN1)



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IND-Enabling Studies Using Human ESC-Derived MEF2CA-Programmed A9 Neural Progenitor Cells for Parkinson's Disease

APPLICATION NUMBER: CLIN1-09759

REVIEW DATE: 31 January 2017

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

Human ESC-derived neural progenitors expressing MEF2C (MEF2CA-hNPC)

Indication

Moderate to Severe Parkinson's disease (PD), where L-DOPA or other treatments are no longer effective

Therapeutic Mechanism

Transplantation of MEF2CA-hNPCs that become dopaminergic (DA) neurons and replace the primary cell type lost in PD, thus stopping or slowing progression of PD.

Unmet Medical Need

Currently there is no cure for PD, which affects approximately one million people in the US and about ten million worldwide. This work aims at developing a potentially curative cell replacement therapy.

Project Objective

Filing of IND with the FDA

Major Proposed Activities

Manufacturing of cGMP qualified Stem Cell Bank for GLP studies

Preclinical dose-response efficacy studies, and toxicity/safety evaluations of MEF2CA-hNPCs in PD rats.

Prepare and file IND with the FDA

Funds Requested

$4,817,184 ($0 Co-funding)

Recommendation

Score: 3

Votes for Score 1 = 0 GWG members

Votes for Score 2 = 0 GWG members

Votes for Score 3 = 13 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

While cellular therapy holds great potential to impact the urgent unmet medical need in Parkinson's disease (PD), reviewers did not think the application included sufficient proof-of-concept data with this product to justify initiation of late stage preclinical IND-enabling studies. Further, the reviewers thought the application reflected the team's lack of late stage preclinical and clinical development experience. Therefore, this application was not recommended 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.

- Parkinson's disease (PD) represents a clear and urgent unmet medical need, and an efficacious cellular therapy holds promise to fulfill this unmet need.

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

- Reviewers did not think sufficient evidence was presented to support that the therapeutic candidate is likely to improve the standard of care for PD patients.

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

- While cellular therapy in general could offer a sufficient, impactful, and practical value proposition for PD patients and health care providers, the potential benefit of this therapeutic was not sufficiently demonstrated to support a strong value proposition at this time.
- The applicant seems to misuse the term "disease modifying", which would require the therapeutic to alter disease pathogenesis, in describing the value proposition. Instead, this product, if efficacious, would provide a disease treatment effect (i.e. replacement of dying cells). Therefore, some of the impact described in the application is inaccurately stated.

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 data presented in the application did not convince reviewers that the proposed cellular product is likely to have the described advantages over other cell-based treatment or provide the described benefit to patients.
- While it is possible the behavioral data may meet minimal regulatory criteria to enter the clinic, provided behavioral data was both not very convincing and not of a sufficient duration to convince reviewers that a long-term benefit can be realized with this cell product. Reviewers, therefore, did not think it appropriate to move forward with expensive preclinical IND-enabling studies until the applicant has stronger proof-of-concept data.

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

- The applicant needs to acquire stronger proof-of-concept data before advancing development of this therapeutic candidate.

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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 proposed plan addressed most of the concerns raised by the FDA, though some reviewers did express concern that the applicant might not be accurately interpreting some of the regulatory comments.
- There was no mention of the quality control plan or how this would be developed.
- Safety risks seem manageable, and the preclinical plan accounts for these risks.
- The clinical plan does not adequately address safety concerns and suggests a lack of experience on the part of the applicant.
- The applicant does not adequately account for potential differences in the functional behavior of the research grade cell line verses the GMP grade cell line.
- Reviewers were unclear what screening of the cell line has already occurred regarding its genetic content and/or oncogenic potential.
- The proposed period to look at graft-induced functional recovery is insufficient according to standards in the field for demonstrating functional recovery.
- Graft-induced dyskinesia (GID) does not occur spontaneously in the proposed animal model (as it does in patients), and reviewers did not think GID concerns were sufficiently addressed.
- It is unclear if animals in the safety studies will be immunosuppressed, and if not, how quickly grafts will be rejected. If grafts are rejected in a matter of weeks, the safety questions will not be able to be adequately answered.

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

- The program needs input from individuals with more experience in preclinical and clinical development as well as with individuals familiar with the standards in the PD field before reviewers would consider it well-constructed.

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

- While the timeline reflects urgency, moving forward with IND-enabling studies without strong proof-of-concept data is not commensurate with CIRM's mission.

Is the project feasible?

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

- Manufacturing is likely to be more challenging than anticipated by the applicant.
- The required components and team is in place to carry out the proposed work.

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.

- Reviewers thought some of the language and terminology in the application

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reflected a lack of regulatory and preclinical and clinical development experience by the team.

- The team is scientifically strong and has extensive experience managing scientific teams and projects.

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

- Contingency plans seem adequate.

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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: Do Not Fund and Do Not Allow Reapplication for 6 months (CIRM concurs with the GWG recommendation).