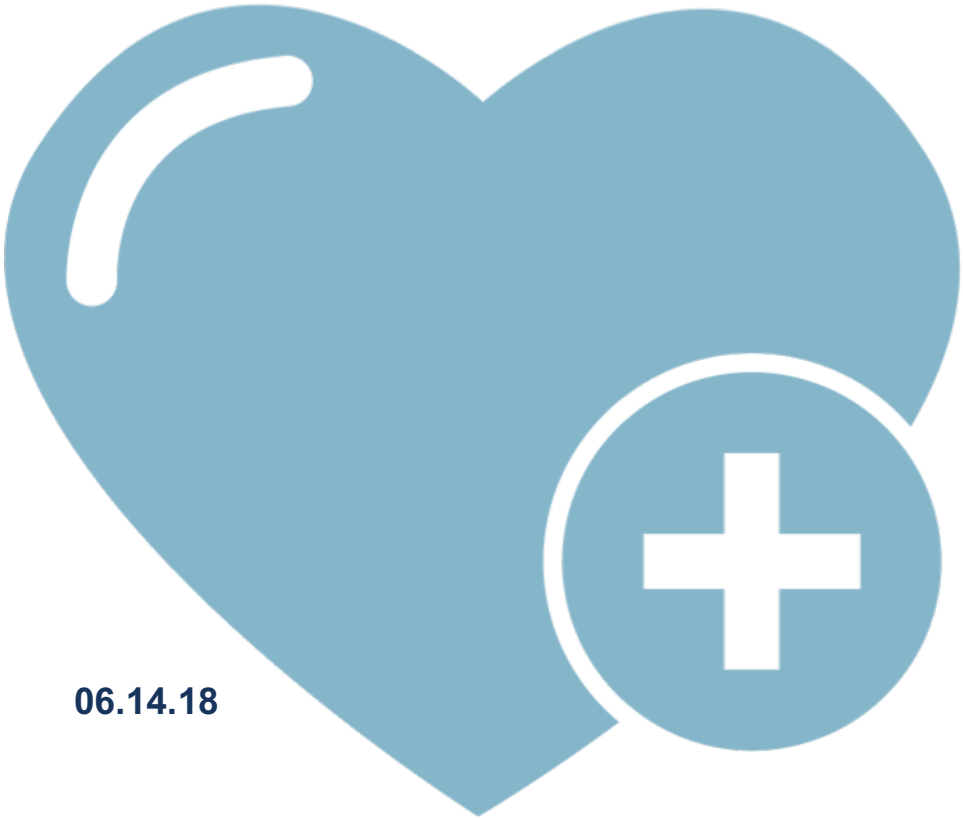
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

MRI Guided Delivery of Neural Progenitor Cells Secreting GDNF for the Treatment of Parkinson's disease

Application Number: CLIN1-11059	Review Date: 31 May 2018

Late Stage Preclinical Project Proposal (CLIN1)



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MRI Guided Delivery of Neural Progenitor Cells Secreting GDNF for the Treatment of Parkinson's disease

APPLICATION NUMBER: CLIN1-11059

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

A neural progenitor cell line transfected with glial cell line derived neurotrophic factor (GDNF)

Indication

Mid-stage Parkinson's disease (UPDRS stage III or lower)

Therapeutic Mechanism

Degeneration of dopaminergic neurons that project from the substantia nigra to the striatum causes the primary motor symptoms of Parkinson's disease. The cells will be transplanted into the putamen, and are expected undergo limited migration to areas of degeneration, induce sprouting of dopaminergic terminals and protect dopamine cell bodies. The cells can mature into astrocytes that may provide additional protection of degenerating regions through secretion of supportive factors.

Unmet Medical Need

Current treatments provide symptomatic relief of Parkinson's disease (PD), but become less effective over time as they have no effect on the disease process. The cells are expected to slow the disease progression by inducing sprouting of dopaminergic terminals and protecting dopaminergic cells.

Project Objective

Complete pre-clinical studies, and file an IND.

Major Proposed Activities

Manufacture cells to supply the proposed clinical trial

Demonstrate long-term lack of tumorigenicity and safety in rats

Demonstrate safety and tolerability of cells in aged MPTP lesioned large animal model of Parkinson's disease

Funds Requested

$5,811,340 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 GWG members

Votes for Score 2 = 6 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

There is a clear unmet need for new treatments for Parkinson's disease. Currently available treatments only target symptoms and do not slow or halt disease progression. Reviewers thought that the proposed therapy has the potential to improve the underlying physiology of the disease, and that the combined cell and gene therapy effects could significantly improve patient outcomes compared to the current standard of care. While there have been mixed results in prior clinical trials that deliver GDNF, several of them had flaws in the study design which may have negatively impacted the results. Thus, the reviewers thought that the continuous delivery of GDNF by cells in the proposed therapy may overcome the limitations from previous studies, and they agreed that the overall approach was sound. There were minor concerns with the proposed time points for the animal study, cell viability using the proposed cell delivery method, and imaging contrast agent, but overall the reviewers thought that the strength of the team and current proposed plan would enable the project to move forward to an IND. They recommended the project for funding.

Review Summary

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

YES	**15**	**NO**	**0**

a) Consider whether the proposed treatment fulfills an unmet medical need.

- Parkinson's disease (PD) is a debilitating neurodegenerative disease that afflicts approximately one million North Americans. The incidence of PD increases greatly with age. If successful, this proposal will minimize patient suffering and reduce the socioeconomic burden imposed on our aging population.

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

- Current therapies do not address the underlying pathophysiology in PD, leaving patients with debilitating refractory signs and symptoms in later disease. A cell-based approach may well overcome this limitation and is being pursued by several groups worldwide.
- If GDNF cell therapy works in humans, it could improve how PD is treated in certain patient populations.

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 proposed treatment would be a one-time surgical intervention, which has significant value if found to be effective.
- Some reviewers had concerns about the risks to the patient of an invasive surgical procedure and immunosuppression (IS) regimen.
- Accessibility of the therapy may be limited as it requires specialized expertise.

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	15	NO	0

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.

- Extensive data in scientific literature with similar products and therapeutic approaches (including by the applicant) support the proposed approach.
- Previous attempts to provide a GDNF-based therapy in humans with PD have led to mixed results. However, reviewers agree that certain studies have suffered from methodological issues and therefore should not have a strong impact on whether to pursue this line of research.
- Reviewers thought it was a strength of the proposal that the investigators are currently studying the same cell product in a related indication in the clinic.

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

- Overall, the current data support development of the product. The investigators have now completed studies of the therapy that have led to a detailed characterization of the cells' properties and support the rationale for its testing in PD.
- There is good preliminary evidence from several years of research by the applicants showing that the NPCs do not continue to divide at a high rate after intracerebral grafting, suggesting that the risk for tumor formation is low.

Is the project well planned and designed?

YES	11	NO	4

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 series of experiments described in this proposal will enable filing of an IND. The GLP toxicity and tumorigenicity studies are well designed and are based upon FDA pre-IND meeting feedback.
- Some reviewers expressed concern that the current time points proposed in the animal models may not yield interpretable data for cell survival and persistence. While acknowledging the FDA request for the longer studies, there is concern that if cells do not persist to 9 months in the rodent study, then the 3-month time point would be critical. A 6-month time point is recommended, if feasible.
- There was concern from some reviewers regarding the size of the cannula system, which is in clinical use but has not been approved or tested for use in cell delivery. Local tissue damage by the cannula at the target sites could potentially reduce the survival of injected cells. Earlier studies suggest that neuronal transplants survive poorly if the outer diameter is too large (greater than around 1-1.5 mm). Whether this also applies to the proposed cell product is not known. Other reviewers thought that the use of an already available delivery device would streamline the development process.
- Some reviewers felt the value of including the contrast agent to guide the injection in real time is questionable as the ceramic cannula is MRI compatible and the applicants state the distribution of the contrast agent would not be indicative of cell graft volume. It was also unclear how the injection parameters would be changed in real time if the spread of the agent indicated a

suboptimal location.

- Reviewers disagreed on whether using an immunosuppression regimen in the large animal study that differs from what would be used in human patients will adversely impact the project and future clinical development. There was some concern that the proposed clinical immunosuppression could have a negative effect on the cell therapy and that it would not be adequately modeled in the current large animal study design. However, some reviewers acknowledged that immunosuppression regimens are optimized specifically for each species and noted that the useful data from the animal model would be cell distribution and persistence.

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

- The proposed toxicology and tumorigenicity studies are required for IND filing. The other proposed studies are also justified including the large animal study to demonstrate surgical technique with the selected catheter.
- Some reviewers had concerns that there is some redundancy in using two animal models of PD for the pharmacology data, given the current regulatory landscape for cell therapies and the applicant's experience with the cell product in other indications.
- The large animal study is comprehensive, and it is unclear if all doses and 6-month duration is necessary for IND filing if the FDA is concerned with cell distribution and safety. Reviewers recommended an earlier time point to evaluate safety of the delivery device and administration procedure.

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 aggressive but in line with CIRM's mission.

Is the project feasible?

YES	**15**	**NO**	**0**

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

- While the timeline is ambitious, the proposal has a reasonable likelihood of success based primarily on the applicant's previous experience with the cell product.

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 lead investigators and their teams are very strong and highly qualified for the project.
- The team has access to all the necessary resources and already has detailed plans for production of the cells and which CROs shall perform the proposed studies.

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

- Overall the team has good contingency plans in place, which address manufacturing failure, incompatibility with the intended delivery device, and failure to obtain data from the planned animal studies.

- It is unclear if the cell product will persist in animal studies for the entire 6-9 months study duration. Some reviewers recommend that the applicant consider additional earlier scheduled time points to mitigate risk of generating data that are difficult to interpret.

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).