CLINICAL

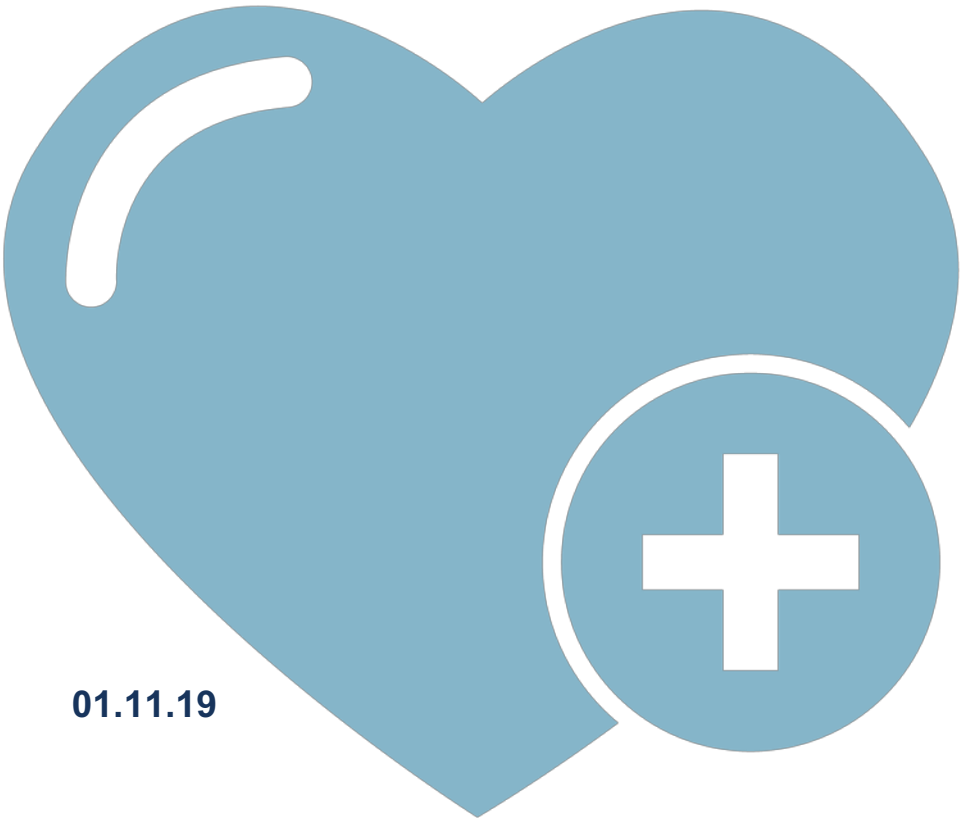
CIRM
CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

An hESC-derived hNSC Therapeutic for Huntington's Disease

Application Number: CLIN1-10953 (Revised Application)	Review Date: 20 December 2018

Late Stage Preclinical Project Proposal (CLIN1)



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APPLICATION NUMBER: CLIN1-10953 (Revised application)

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PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

A human neural stem cell product to prevent or delay disease symptoms for treatment of Huntington's Disease (HD).

Indication

Huntington's Disease is a progressive, degenerative brain disease that typically strikes in midlife with no existing disease modifying treatments.

Therapeutic Mechanism

Based on our pre-clinical studies, the human neural stem cells engraft and differentiate into neuronal populations, express the neurotrophic factor BDNF and reduce mutant Huntingtin protein accumulation. Further, host tissue forms synaptic contacts with transplanted cells and may provide new and functional connections to reduce the aberrant cortical excitability in HD. These molecular and histological improvements correlate with improvement in behavior and electrophysiological deficits.

Unmet Medical Need

No treatment currently exists that can slow or prevent the unrelenting progression of Huntington's Disease, a devastating brain disease, therefore a completely unmet medical need exists.

Project Objective

File an Investigational New Drug request with FDA.

Major Proposed Activities

Good Manufacturing Practice (GMP) manufacturing and characterization of the cell product to supply the first in human study.

Good laboratory practice (GLP) long term safety, biodistribution and tumorigenicity studies in HD modeled and Wt mice.

Investigational New Drug (IND) preparation, publishing and submission.

Funds Requested

$6,000,000 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 8 GWG members

Votes for Score 2 = 1 GWG members

Votes for Score 3 = 5 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 application proposing a cell therapy for Huntington's Disease (HD) was a resubmission that received a split vote from the panel. In general, the panel agreed there was evidence that the therapy showed an effect in multiple animal models. Though the mechanism was unclear, they agreed that it would be difficult to resolve this in preclinical studies and further revisions of the proposal would not be beneficial. Reviewers disagreed on whether the modest potential for a clinically meaningful benefit would be worth pursuing given the additional risk of surgery and immunosuppression in patients. Some thought that prior failures in trials with different cells, combined with ongoing clinical testing of promising, non-cellular approaches to HD, did not support further development of this therapy. Others thought that the proposed cell product is an improvement over previously tested cell therapy products and if a cell therapy for HD is to ever be pursued then this project provides the best opportunity to move the field forward. Therefore, the recommendation for further development of the project was supported by a majority of panelists who thought a cell therapy for HD is worth pursuing in an indication where no meaningful therapeutic treatments currently exist.

Review Summary

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

YES	10	NO	3

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

- HD currently has no treatments that alter disease progression in any meaningful way. The current application seeks to use neural stem cell transplantation to ameliorate disease progression. Given the lack of current treatment options for HD the proposed treatment addresses an unmet medical need.

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

- If the proposed therapy slows progression, it will represent an improvement over the standard of care for HD. While other studies have not led to significant and quantifiable benefit to patients, the proposed study uses a different cell type and cell source.

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.

- Reviewers disagreed on whether the treatment offers a significant value to the patients and caregivers.
    - Some reviewers thought the immunosuppression and surgical risk that is required for this cell therapy may outweigh any potential therapeutic benefits given that there are other less invasive treatment options being tested.
    - Others thought that despite the stated risks, any potential treatment for slowing down disease progression is worth pursuing as current alternative therapeutic approaches are still many years away from commercial use.

Is the rationale sound?

YES	7	NO	6

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.

- Reviewers agreed that there was evidence that the cells were producing brain-derived neurotrophic factor (BDNF) in the animal models. However, reviewers disagreed on whether the delivery of BDNF would have clinically meaningful benefit.
- Reviewers generally agreed that the evidence that cells are forming connections in the animal models was not convincing.
- Several concerns raised in the initial review regarding the animal models used, statistical analysis, and impact of the mutant protein on the implanted cells have been addressed by the applicant.

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

- Reviewers disagreed on this point. Some reviewers thought that continued development is not supported by the relatively modest benefit seen in the animal models, the risk to patients, and the low potential clinical benefit. Other reviewers acknowledged that it is a high-risk project and that the potential therapeutic effect would be modest but thought that the product is still worthy of clinical testing.

Is the project well planned and designed?

YES	11	NO	2

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.

- In the initial review, there were several manufacturing concerns raised that made it unclear whether there would be sufficient cell banks available to complete the preclinical and clinical studies. In the resubmission, there were significant changes in the manufacturing process that have largely addressed these concerns.
- In the initial review, there was concern that the dose and duration of the large animal study would not allow for sufficient safety data for clinical studies. In the resubmission, the large animal dose was increased to support a higher initial clinical dose.
- In the initial review, there were concerns that the cells were developed on mouse feeders, despite the cells being originally derived on human feeders. While the reviewers understand it may be difficult to address this, and that the product can still be used clinically, it remains a concern.

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

- In the initial review, there were concerns that one of the treatment groups for the tumorgenicity/toxicity study was not needed. In the resubmission, the applicant has removed the treatment group per FDA agreement.

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.

- Reviewers agree the timeline is reasonable.

Is the project feasible?

YES	12	NO	1

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

- In the initial review, there were concerns that the recruitment timeline was too short. In the resubmission, the enrollment has been extended.

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.

- In the initial review, there were concerns that strong project management would be needed to coordinate the scope of activities between multiple groups. In the resubmission, the applicant has clarified the roles of the project team.

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

- Overall, reviewers thought that the contingency plans were reasonable.

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).