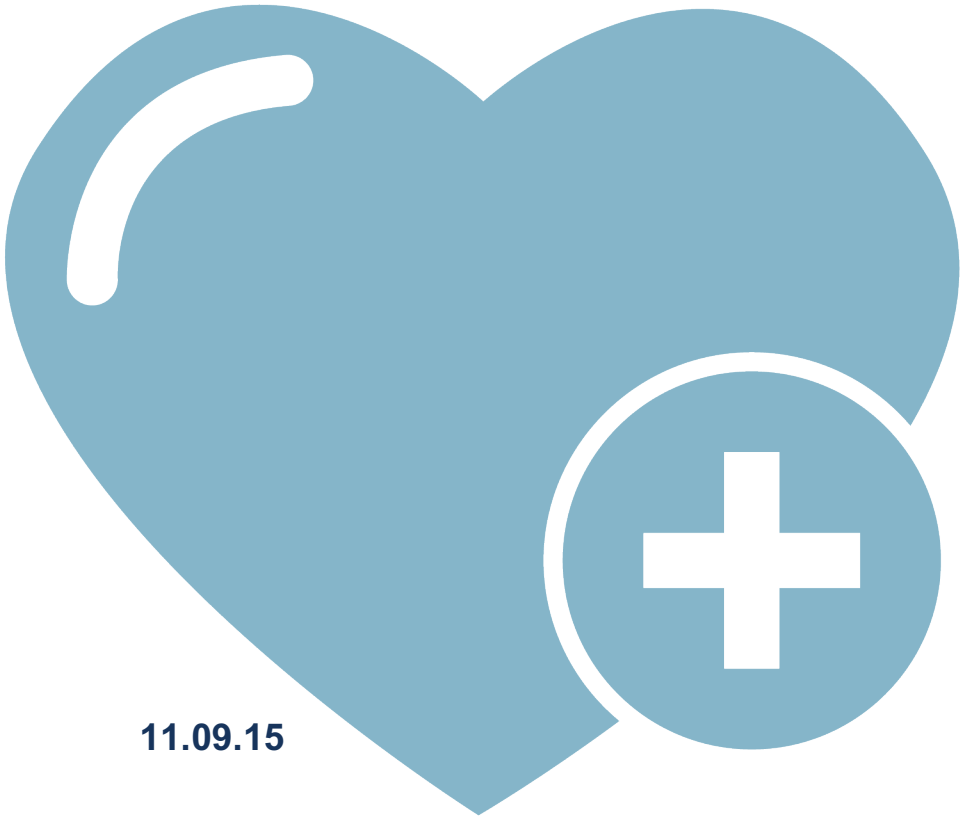
CLINICAL

Grants Working Group Public Review Summary

Human PSC-derived dopaminergic neurons for cell therapy for Parkinson's disease

Application Number: CLIN1-08295	Review Date: October 27,2015

Late Stage Preclinical Project Proposal (CLIN1)



11.09.15

CLINICAL

Human PSC-derived dopaminergic neurons for cell therapy for Parkinson's disease

APPLICATION NUMBER: CLIN1-08295

REVIEW DATE: October 27, 2015

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate

The therapeutic candidate is "dopaminergic neurons" derived from human pluripotent stem cells (PSC) for the treatment of Parkinson's disease (PD).

Indication

Patients with a diagnosis of PD who are not adequately treated with conventional therapy.

Unmet Medical Need

Current treatments for PD do not restore the population of dopamine neurons. As the disease progresses, the efficacy of current therapies declines. The lack of treatments targeting the neurodegenerative process has justified the development of new therapeutic approaches, such as the cell therapy proposed here.

Major Proposed Activities

Manufacture product to support IND: Develop the technology required to manufacture the needed cells for therapeutic use.

Complete preclinical safety and efficacy studies: Test the cells using approved methods to show that the cells are safe and effective.

Submission of IND: Design a Phase I clinical trial to show that the cell product is safe to use in human and can be developed further.

Funds Requested

$6.8M ($0 Co-funding)

Recommendation

Score: 3

Votes for Score 1 = 0 GWG members

Votes for Score 2 = 0 GWG members

Votes for Score 3 = 12 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.

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

Review Overview

While the review panel expressed great enthusiasm regarding the use of stem cell therapies to treat Parkinson's disease (PD), reviewers agreed that additional work in product characterization and understanding the potential safety and efficacy is necessary before this product should enter late stage preclinical research as defined under the CLIN1 program announcement.

Review Summary

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

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

- Parkinson's disease (PD) represents a huge unmet medical need. However, it is not clear that the product under development in this proposal has the potential to fulfill that unmet medical need.

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

- A stem cell therapy has the potential to be disease modifying, which would greatly improve the standard of care for PD patients.

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

- Assuming an appropriate risk-benefit profile, stem cell therapies could provide a sufficient and impactful value proposition.
- The key advantage to the proposed product is differentiation without antibody selection and cryopreservation without apparent loss of viability or engraftment potential, both of which improve the value proposition of this product.

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 preclinical data package was considered insufficient to justify the proposed project. It is not clear that the product includes the right type of A9 dopaminergic (DA) neuron or that the cells are growing fibers post transplantation and that synaptic activity is occurring, both of which are crucial for efficacy. Though data was provided, it is not convincing.
- The product is not adequately characterized to justify moving into late stage preclinical IND-enabling research or manufacturing under Good Manufacturing Practice (GMP).
- The target range for cell survival of the graft is 10% to 100%, yet the data indicates survival is lower than 10% and it is unclear what percent of surviving cells are A9 DA neurons.
- Reviewers did not think the safety data in the application satisfactorily supported the statements made regarding the preclinical safety profile of the product. Examples of reviewer concerns include:
    - The applicant states that dyskinesia does not occur. However, dyskinesia is not observable in the selected animal models so it is

unclear how the applicant could support this assertion.

- The applicant states serotonergic neurons are not represented in the product. However, only 20% of the product is DA neurons and the rest is not fully characterized, so this claim is not well substantiated by the data provided in the application.
- Pilot tumorgenicity assays included undifferentiated and spiking studies but data from those studies, which should have produced tumors in a functional assay, were not clearly presented.

- The animal model data should include a much wider array of behavioral assessments and proof of concept studies with head-to-head comparisons of products generated using other differentiation protocols and with fetal-derived cell products.

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

- Reviewers did not think the data provided in the application supports moving forward with this product.
- Reviewers were not convinced that the applicant has identified the right product to move into IND-enabling preclinical research. Reviewers strongly encourage the team to continue working to better characterize the product and obtain quality data supporting initial safety and efficacy before moving forward to preclinical IND-enabling research and GMP manufacture.
- Reviewers suggested the project may be better suited to an earlier stage award and encouraged the team to carefully consider feedback in any earlier stage application.

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 intended dose for the proposed clinical trial is not clearly described, and the target product profile (TPP) lists a large target range for cell survival following transplantation. Sufficient justification for the acceptability of such a large range was lacking (i.e., that the high end of 100% is achievable and the low end of 10% is sufficient for needed biologic activity).
- The applicant currently has GMP product, yet is proposing contracting for additional GMP product and assembly of a Drug Master File (DMF). Reviewers were not convinced this was a necessary expense for success of the project at this stage.
- Reviewers would like to see additional animal models utilized to generate supporting data. Although the animal model is reasonable, engraftment, biodistribution, efficacy, and immunosuppression data is needed for the IND filing, and the data would be more robust with additional animal models.
- The plan for immunosuppression is not well supported by the data and sufficient experiments to support the immunosuppression plan are not proposed.
- Reviewers recommend large animal studies to understand cell distribution of the product using the novel delivery device.

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

- It is not clear whether the focus of the applicant is an embryonic (ESC) or

induced pluripotent stem cell (iPSC) derived product. The applicant's use of the term "pluripotent" seemed ambiguous at times. From a regulatory and drug development standpoint, ESCs cannot be leveraged to develop an iPSC product.

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

- The timelines certainly represent an urgency commensurate with CIRM's mission, but may be unrealistic, which 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.

- Timelines are aggressive, but feasible.
- With the current plan and data package, it seems unlikely an open IND could be achieved in 2 years.

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 encouraged the incorporation of PD experts with knowledge of cell therapy drug development and/or clinical trial design into the team.
- The proposed project manager brings excellent expertise to the team. However, he/she may not be an appropriate choice for project manager as he/she does not specifically have project management experience and likely does not have sufficient time to devote to this type of role on project.
- Reviewers encouraged the team to identify recognized leaders in the field who have not previously been involved with the team for the proposed advisory boards. Additionally, it seems highly unlikely that some proposed members will agree to serve on the committee, particularly members of the Food and Drug Administration (FDA).

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

- The contingency plans do not seem sufficient.

CIRM 2.0

CALIFORNIA'S STEM CELL AGENCY

Public Review Summary

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 (CIRM concurs with the GWG recommendation).