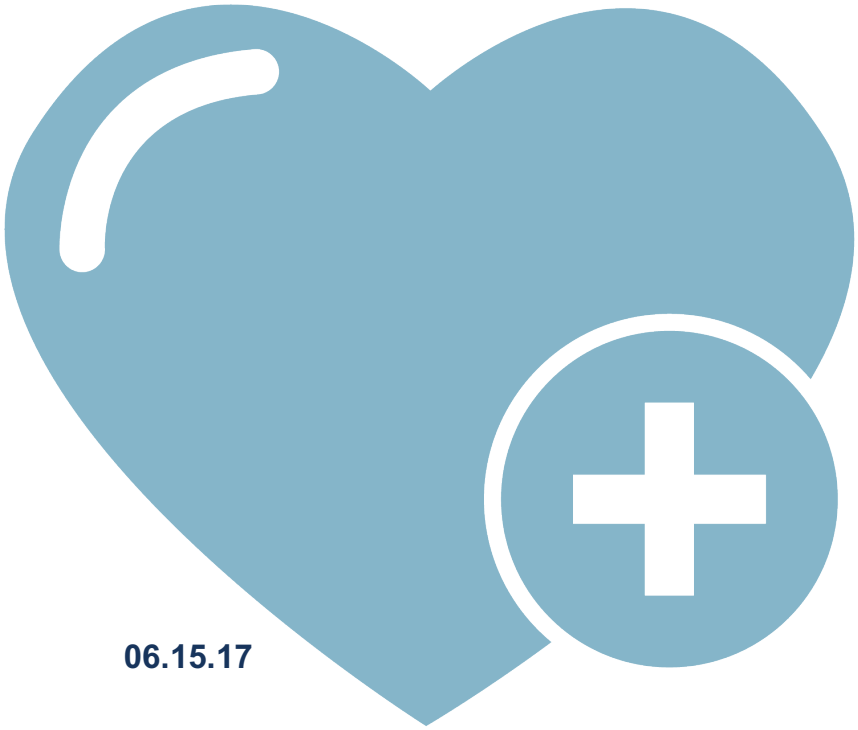
CLINICAL

Grants Working Group Public Review Summary

Intraparenchymal NR1 Stem Cell Therapy for Chronic Subcortical Ischemic Stroke

Application Number: CLIN1-09433	Review Date: 30 May 2017

Late Stage Preclinical Project Proposal (CLIN1)



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Public Review Summary

Intraparenchymal NR1 Stem Cell Therapy for Chronic Subcortical Ischemic Stroke

APPLICATION NUMBER: CLIN1-09433

REVIEW DATE: 30 May 2017

PROGRAM ANNOUNCEMENT: CLIN1 Late Stage Preclinical Projects

Therapeutic Candidate or Device

A human embryonic derived, non-genetically modified neural stem cell (NR1), originally derived from the Wi-Cell H-9 line.

Indication

Patients with chronic motor deficits, from 6 months to 5 years after stroke.

Therapeutic Mechanism

The proposed therapeutic mechanism of action of NR1 neural stem cells is the secretion of factors that enhance the brain's own ability to heal itself after stroke, including the creation of new blood vessels to replace those that were injured beyond repair, and modulation the immune system.

Unmet Medical Need

Stroke is the leading cause of adult disability. There is no medical therapy that promotes stroke recovery, establishing this as a major unmet medical need.

Project Objective

To prepare and submit an IND application.

Major Proposed Activities

Completion of ongoing in vitro work.

Animal selection for and carrying out GLP toxicology and biodistribution studies of the transplanted NR1 cells into the rodent brain.

Pre-IND activities leading to submission of the IND.

Funds Requested

$5,300,000 ($0 Co-funding)

Recommendation

Score: 1

Votes for Score 1 = 9 GWG members

Votes for Score 2 = 1 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.

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Review Overview

Chronic motor deficits following stroke are a major unmet medical need and there are different cell based approaches being developed for this indication. The reviewers thought that the applicants, by following the STAIR and STEPS guidelines, had generated robust preclinical data on their NR1 cell candidate. The reviewers generally accepted the proposed paracrine mechanism of action but were not convinced that the data supported immunomodulatory activity of the cells. Reviewers thought that the candidate warranted further development and that the project was well planned. Reviewers also thought that the team was well qualified to conduct the preclinical and clinical development of the candidate. Therefore, reviewers recommended the project 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.

- Chronic stroke is a major unmet medical need.
- The proposed treatment holds modest promise to address this unmet medical need.

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

- Currently, the only treatment option is physical rehabilitation. This approach, if successful, could provide improvement in motor outcomes.

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

- Even modest improvements in motor outcomes can have meaningful improvements in the quality of life of these patients.
- Deployment may be limited to specialized centers due to delivery method.

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 proof of concept and mechanism of action of NR1 cells was demonstrated in multiple animal models, and in multiple labs in accordance with STAIR and STEPS guidelines.
- The preclinical data supports a paracrine mechanism of action of the NR1 cells.
- Some reviewers expressed concern about the lack of a dose response in the preclinical studies.
- Reviewers thought that the preclinical data did not support the immunomodulation mechanism of action and, in particular, the microglial polarization hypothesis.

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

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- While there are several cell-based treatments being studied for this indication by other groups, the preclinical data supports continued development of the NR1 therapeutic candidate.

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 program is meticulously planned.
- The applicant has incorporated FDA recommendations into the design of the IND enabling studies.
- Some reviewers believed that the potency assay development was premature at this stage of the project.

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

- The manufacturing processes are well-developed and appropriate for IND enabling studies.
- The NR1 candidate is very well-characterized.

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

- The project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission.

Is the project feasible?

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

- The study timelines are well-defined and reasonable.

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 team developed the product and has participated in clinical trials with similar products for stroke.

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

- The team identified appropriate cell production, product safety and device related risks and has a contingency plan to manage these risks and potential delays.

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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: Fund (CIRM concurs with the GWG recommendation).