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CALIFORNIA'S STEM CELL AGENCY

Grants Working Group Public Review Summary

IND-enabling Study of Subretinal Delivery of Human Neural Progenitor Cells for the Treatment of Retinitis Pigmentosa

Application Number: LSP1-08235

PA 15-01: Late Stage Preclinical Projects

Review Number: 2015-04

THERAPEUTIC CANDIDATE
Human neural progenitor cells (CNS10-NPC)

INDICATION
To stabilize disease progression and maintain ocular integrity and vision for retinitis pigmentosa (RP) patients

UNMET MEDICAL NEED
RP constitutes a group of inherited disorders of progressive retinal degeneration affecting over 1.5 million people worldwide. There are diverse genetic causes of RP including up to 200 different mutations and there is no curative treatment available. This approach may also be applied to the treatment of the more prevalent disease of age-related macular degeneration.

MAJOR PROPOSED ACTIVITIES
Starting with an existing Master Cell Bank, produce sufficient CNS10-NPCs for all preclinical studies and a Phase 1/2a clinical trial.

Complete IND-enabling preclinical studies to understand dosing, scale-up, toxicity, and tumorigenicity for using CNS10-NPCs for treatment of RP.

Obtain FDA regulatory approval to commence clinical trial with CNS10-NPC in RP subjects.

FUNDS REQUESTED
$4,954,514

RECOMMENDATION
Score: 1

Votes for Score 1 = 15 GWG members
Votes for Score 2 = 0 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.

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REVIEW OVERVIEW

Reviewers thought the strengths of the application were: 1) the clear unmet medical need; 2) the strong scientific rationale for development of this drug candidate in this indication; 3) the robust preliminary data supporting moving the candidate towards clinical testing; and 4) the sound and feasible IND-enabling experimental plan. Reviewers noted that the provided draft clinical protocol needs modification to ensure robust clinical data will be obtained from the intended clinical trial but thought the team to be capable of addressing this concern during the award period.

REVIEW SUMMARY

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

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

- RP is a significant unmet need, and the proposed therapy could delay progression of vision loss, which would be impactful.
- Preclinical data indicates a mechanism of action (MOA) supporting use of the drug candidate in other degenerative retinal diseases.

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

- A stem cell-based therapy could improve RP patient outcomes through beneficial effects that have potential to slow disease progression.
- Other approaches alone, such as gene therapy, are unlikely to address the medical need due to the varied genetic causes for RP.

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

- The proposed therapy could offer a high impact value proposition given the significant loss of productivity in the patient population.
- The true impact of a therapy cannot be known until the clinical effect is defined, but several features support a practical therapeutic value. These include that the intended clinical application uses a standard ophthalmologic procedure associated with minimal risk; the candidate is allogeneic and can be cryopreserved to support shipment and storage; and the preclinical data supports a single, or limited, administration of the cells.

- The proposed preclinical studies are designed to further inform the future clinical value of the therapeutic.
- Additional work to understand the MOA of the cells might bolster the impact of the therapy and support expansion to other indications of retinal degeneration.

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 candidate as proposed does not directly address the specific genetic defects that cause RP, but the preclinical data shows engraftment and migration of the cells with associated preservation of visual acuity, which provides a strong clinical rationale.

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

- The provided data establish abundant and strong support for continued development of this drug candidate.
- The proposed large animal model studies are likely to provide additional critical information for design of the intended clinical trial.

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 preclinical program is well planned and designed to support a successful IND application within two years.
- The proposed studies are based on FDA guidance and should inform selection of the clinical dose and immunosuppression protocol.
- The draft clinical protocol needs refinement under this award to ensure that robust clinical data can be obtained from the intended clinical trials. Specifically, the patient population and clinical endpoints should be further informed by the preclinical work and careful consideration by individuals with extensive ophthalmological clinical trial experience.
- The size and design of the proposed large animal study could limit interpretation of the data and, as this is a xenograft model, immunosuppression is critical and not sufficiently addressed. Consultation with experts in this area is recommended.

- Analytical method qualification and validation was thought to need improvement. Additional assays may be required for cell characterization and understanding MOA.

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

- The program is well-constructed and of high quality.
- The team will leverage existing defined manufacturing protocols and has a quality assurance program in place.
- The team has had productive interactions with FDA and has considered and mitigated various risks to the degree possible.

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

The project plan is ambitious, but feasible, as is consistent with CIRM's mission.

Is the project feasible?

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

- The proposed timelines are realistic for the proposed studies and feasible to complete within the proposed award period.
- It is likely that resources and time will need to be committed to get FDA concurrence with the clinical trial protocol and selected clinical endpoints. The team should address this challenge early to support timely progression to initiation of a clinical trial.

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.

- This is a well-qualified and experienced team.
- The investigators have a longstanding interest in cellular therapy for RP and are experienced both in eye disease and development of a similar cell-based product.
- Team members are gaining additional experience with IND filings that will be leveraged for this program.
- The applicant institution offers an outstanding clinical environment and appropriate infrastructure is in place.

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

- The team has identified and outlined various risks to the program and has viable contingency plans in place.
- The Center Director has indicated willingness to use discretionary funds to support this project, if needed.
- The team has been proactive in addressing concerns related to cell source material; but, additional attention to securing critical supplies and contracts for manufacturing the clinical product was encouraged.