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IND enabling study of transplanting clinical grade neural progenitor cells for the treatment of retinal degeneration

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Statement of the problem: Age related macular degeneration (AMD) is the major cause of blindness with huge financial and social impact. Unfortunately, treatment is still very limited. Advance in stem cell biology offers real promise to save vision. Current stem cell-based therapies in clinical trials to treat AMD aim to replace retinal pigment epithelium (RPE). However, reported efficacies have been inconsistent, often poor, and the mechanisms of retinal protection remain poorly defined. RPE replacement strategy is complexed by several factors. Grafting early on is prohibited by diseased RPE cells still occupying Bruch's membrane (BM), whereas the problem with grafting too late is that insufficient numbers of functional photoreceptors remain. The co-dependency between RPE and photoreceptors leaves a narrow window of time in which interventions have the best chance of success. Another important consideration for RPE cell grafts is that BM undergoes progressive degeneration in AMD. Studies have clearly demonstrated that healthy RPE fails to resurface BM in both animal experiments and clinical trials.

An alternative cell type that does not require attachment to BM, preserves vision, and reduces the burden of aging RPE cells may be a viable option for treating AMD.

Methodology & Theoretical Orientation: Clinical grade NPCs were injected into the sub retinal space of rodent model for retinal degeneration to validate its efficacy and large animal model-Yucatan mini pig to test the feasibility of delivering viable NPCs. At several time points, visual function was examined by electro retinography (ERG and optokinetic response (OKR); retinal lamination and graft distribution was evaluated by spectral domain optimal coherence tomography (SD-OCT). Histological correlation with visual function was performed.

Findings: NPCs survived for long term, migrated extensively in the sub retinal space and offered dramatic preservation of photoreceptors. NPCs preserved RPE cell integrity, self-assembled as a layer in graft-secreted extracellular matrix (ECM) that did not require attachment to BM while offering vision preservation. NPCs reduced the burden of RPE cells by phagocytizing and degrading

Photoreceptor outer segments. NPCs were successfully delivered to the sub retinal space of Yucatan mini pig in the setting similar to human clinic; visual function was not affected by sub retinal injection of NPCs as measured by ERG. Retinal detachment due to the initial sub retinal injection was quickly reattached as revealed by SD-OCT.

Conclusion & Significance: As an alternative cell type to RPE cells, NPCs offer dramatic photoreceptor and vision preservation without needing to the attachment to the BM. NPCs survive for long term and migrate extensively from injection site. NPCs can be successfully delivered to large animal model without affecting retinal function. NPCs hold real potential for preserving existing retinal anatomy and function.

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