DEPARTMENT OF OPHTHALMOLOGY
VITREORETINAL DISEASES AND SURGERY
BYERS EYE INSTITUTE AT STANFORD
STANFORD UNIVERSITY SCHOOL OF MEDICINE
2452 Watson Court, Palo Alto, CA 94303

Theodore Leng, MD, MS, FACS
Assistant Professor of Ophthalmology and, by Courtesy, of Anesthesiology, Perioperative and Pain Medicine
Director, Clinical and Translational Research; Director, Ophthalmic Diagnostics

Office: (650) 498-4264
Fax: (888) 565-2640
e-mail: tedleng@stanford.edu

October 11, 2018

Jonathan Thomas, PhD, JD
California Institute for Regenerative Medicine
Chair of the ICOC, Governing Board

Re: TRAN1-11300

Our team thanks the reviewers for their favorable review of our TRAN1 grant application (#11300) which will move our program closer to clinical implementation. Below, we have addressed some of the reviewers' comments (in blue). I hope that the ICOC will support this promising research for California citizens and the millions who are suffering from age-related macular degeneration (AMD).

Significance and Potential for Impact: The reviewers thought that the proposal was significant and would have a large impact.

Response: On behalf of the translational team, I thank the reviewers for their positive comments. I believe that our investigational product could have a significant impact on those suffering from dry AMD.

NeuBright is a purified banked allogeneic neural stem cell product developed to slow the progression or reverse dry AMD. This long-lasting self-renewing stem cell product is designed to be delivered in a one-time intervention with local immune suppression, an ideal therapy for the elderly patients of California. This redesigned cell suspension product will be delivered with a smaller surgical incision and provide a wider distribution of its retinal protective action. The NeuBright allogeneic stem cell product could bring a cost effective and simple AMD treatment option to Californians in the near future and fulfill CIRM's mission.

Rationale

Comment: Most reviewers supported the rationale, but one had concern about the small "n" in our animal studies. Work is needed to determine dose, timing, how often to repeat the therapy. It is unclear how the stage of the disease impacts the dosing and efficacy.

Response: A previous formulation of this stem cell line derived-product was tested in a Phase I/II trial showing long-term safety (up to 5 years post injection) and preliminary efficacy in patients. I was a principal investigator on this Phase I/II study and after my experience and feedback from the other clinical investigators, our team would like to propose changes to the manufacturing process, final formulation and cell dose to improve delivery of the cell product for optimal coverage area within the space under the retina to protect photoreceptors from degeneration and to potentially increase biological effect.

Since the cell line is the same as previously used, we have a large data set from RCS rat studies as the baseline for the cells' performance and thus, believe a large number of animals is not needed to demonstrate that the single cell suspension is comparable or better than the cells clusters for distribution within the subretinal space and protection of photoreceptors in the RCS rat model. A proof-of-principle study with the RCS rat model was carefully designed with sufficient numbers of animals that is statistically powered to bridge the previous formulation to the new final formulation.

The studies in non-human primates are to test the feasibility of the dose escalation and long-term local immunosuppression and is proposed with the minimum numbers of animals needed to obtain valid data for humane reasons. With robust preclinical data established prior to this proposal, I believe that the proposed animal studies will be sufficient to prepare a pre-IND meeting to obtain guidance from the FDA for any additional IND-enabling studies.

Comment: It is unclear what the viability of the product will be through the 38 gauge needle.

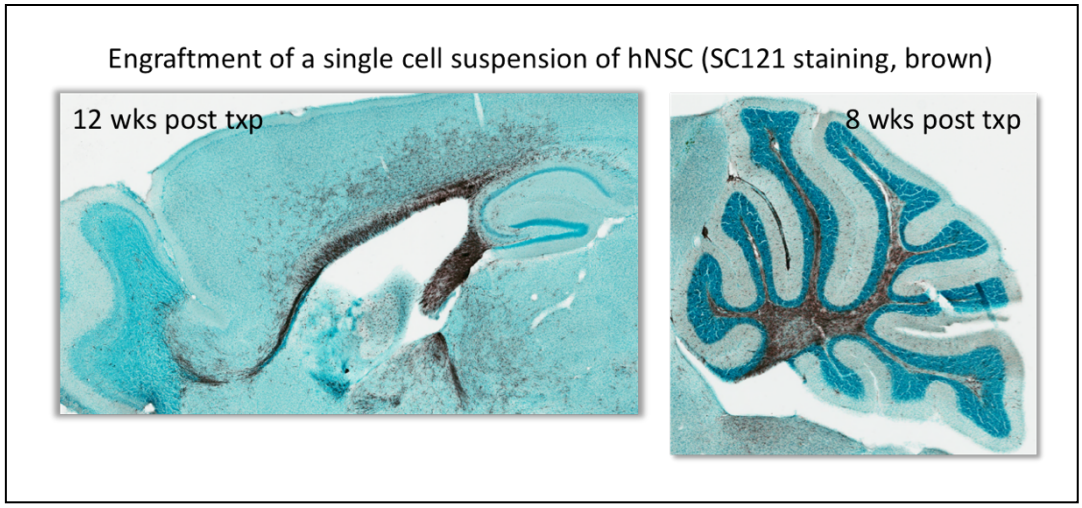
Response: This is a valid point; however, as a vitreo-retinal surgeon who has extensive experience in the surgical approach required for the proposed transplant, I believe that the safety of our patients would be greatly enhanced with the use of a smaller 38 gauge needle for cell delivery. Use of a smaller gauge needle will require us to test the single cell formulation of the product. The diameter of a 38 gauge needle is 100 microns, sufficiently wide enough for individual neural stem cells (which are ~ 8-16 microns) to pass through. In our proposal, we plan to evaluate and demonstrate the viability of the single cell product formulation with the specific 38 gauge needle we plan to use in clinical setting. This will be completed prior to executing the preclinical studies.

Planning and Design

Comment: The reviewers thought that the proposal was designed well, but there was concern with the idea to remove the cell clusters and create a single cell suspension. They correctly note that the old therapy seems to work, but it is unclear whether the single cells are better and that a little more data is needed. It was unclear whether the single cells will attach and work in the same way, or if they will they all leak out.

Response: The NeuBright neural stem cell product is different from retinal pigmented epithelium (RPE) and does not require the formation of a polarized sheet of cells for proper biological function. In prior animal studies, cells were delivered in small clusters of ~4-10 cells (<50u sphere size) and demonstrated product efficacy. The larger scale manufacturing parameters produced larger cells clusters of >100 microns.

Moreover, in previous studies, single cell formulations of neural stem cells were transplanted into the brains of immunodeficient mice and demonstrated robust human cell engraftment comparable to published studies with small cell clusters (Dever et al. International Society of Stem Cell Research, 2016, see figure below).



As a vitreo-retinal surgeon, I emphasize that a single cell formulation injected through a smaller diameter needle will facilitate a safer, more effective delivery that will be minimally invasive to elderly patients.

Feasibility: All of the reviewers thought that the proposal was feasible.

Response: We thank the reviewers for their positive comments.

We look forward to the discussion on October 18th.

Sincerely,

Theodore Leng, MD, MS
Director, Clinical and Translational Research
Byers Eye Institute at Stanford, Stanford University School of Medicine