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May 20, 2018

Re: TRAN1-10995

We thank the reviewers for their favorable critique which will move our previously CIRM-funded program (TR4-06648) closer to the clinic. Below, we addressed some reviewers' comments (in blue). We hope that the ICOC will support this promising research for California citizens as the Seiler lab only has funding until May of 2019, after which this expert team will no longer remain intact.

Significance and potential for impact: The reviewers acknowledged that treatment of RP is an unmet healthcare need, and that there could be an extension to other retinal diseases. We have already demonstrated disease-modifying activity up to ten months after transplantation in two animal models of retinal degeneration (two papers in press, one manuscript in preparation).

Rationale: Most reviewers supported the rationale, but there was some concern about how to demonstrate local paracrine effects and issues surrounding mixed cell tissue transplants. Experiments will be analyzed by functional testing and histology whether any correlation exists between improvement of visual function and transplant connectivity or the presence of any remaining host photoreceptors. Migration of cells inside the retinal will be investigated by human specific markers. The use of organoids could be better rationalized compared to use of purified photoreceptors. Transplantation of purified (dissociated) photoreceptor precursors has several issues: (1) Low number of cells integrating into the host retina. (2) Loss of cells over time. (3) More immunological issues than with sheet transplants. (4) Visual improvements after transplantation of dissociated photoreceptor precursors are due to cytoplasmic transfer to host cells rather than the activity of transplanted cells. (5) Such transplants require the presence of an intact host outer nuclear layer; i.e. this will not work in advanced retinal diseases.

Planning and Design: Reviewers generally thought that the proposal was designed well, but there was concern that the majority of the budget was for salary rather than technical projects. This impression is incorrect. The P.I., Dr. Seiler, will be actively performing experiments. The program manager was required by CIRM. In order to achieve a pre-IND meeting with the FDA, we require the advice of people that have experience with FDA applications. It is a strength of our application that our Center contains an Alpha stem cell clinic.

Some reviewers suggested to perform visual testing on the humanized rat model before and after transplantation, performing transplants in immunocompetent rats without immunosuppression, and give immuno-suppressive drugs to immunodeficient rats to assess impact of those drugs on RO engraftment separate from immune rejection. We will be glad to consult with CIRM scientific staff on these points.

Feasibility: Most reviewers thought that the proposal was feasible. There was some concern from a few reviewers that the budget involved too many senior people and too few technicians. Dr. Seiler, the PI, is will conduct transplants and analysis in all the experiments; 50% effort is more than justified. Co-I Dr. Browne will perform analysis of retina organoids, so his position is not administrative. Dr. Aramant will provide supporting work regarding instrumentation and surgery. Co-I Dr. Cummings will provide support with scientific analysis and FDA preparations. CIRM requires a program manager which we have at a 50%. Drs. Bota, Walsh and Inlay will serve as advisors with only 2% effort. The budget will support one Assistant Specialist and 3.6 technicians at UCI at various levels of expertise, with additional technical support at AIVITA. We will be glad to renegotiate any budget levels with CIRM if there is a positive funding decision.

I am looking forward to the discussion on May 24.
Sincerely

M. Seiler