**DISC2- 14089**

Project title: Chemically engineered photoreceptors for vision restoration in retinal degeneration associated blindness.

PI: Biraj Mahato (Assistant Professor, Children’s Hospital Los Angeles)

**Sub: Public comments to the ICOC and CIRM review office.**

Dear ICOC and CIRM review office,

Retinal degeneration is a leading cause of irreversible blindness affecting millions of people in US and no treatments are available to restore vision. My laboratory is involved in development of chemically induced cell-based therapy to restore vision in these patients. Here, I would like to draw ICOC’s attention on the reviewer’s feedback for this application. Reviewers indicated the following major points. (i) The efficiency of the process may be too low to support the proposed activities. (ii) Far too much work is planned, and the project is understaffed. /The project needs to be streamlined. (iii) ‘proof of concept data *in vivo* would give more confidence in the project’ (part of minority report). As a principal investigator of this application, I am ready to answer these criticisms at this stage of application. Please see below my responses to these critics.

**(i) The efficiency of the process may be too low to support the proposed activities.**

We already demonstrated that efficiency of our rod photoreceptor reprogramming process is 24.8% and we published this result in **Mahato et. al.,** ***Nature***, vol. 581, pages, 83–88 (2020) [Extended data Fig.8d]. Therefore, I am confident that my team can make required number of cells in larger cell culture plates to carry out the proposed studies. For example, fifteen 10cm tissue culture dish would be sufficient to inject CiPCs in 25-30 animals (200,000-300,000 cells/eye).

**(ii) Far too much work is planned, and the project is understaffed.** **/The project needs to be streamlined.**

I would work with a CIRM scientific officer to reduce some proposed experiments to streamline the project. Currently, I have one postdoc and two visiting research scholars in my lab to perform the proposed studies. I also perform bench work in the lab regularly and have requested salary support for one postdoc and one research specialist (senior position). Additionally, my collaborator and her project scientist at the University of California, Irvine, will perform proposed experiments. Altogether, total of 6 highly experienced and 2 junior level scientists will be involved to perform the proposed aims.

**(iii) ‘proof of concept data *in vivo* would give more confidence in the project’ (minority report).**

In a recent proof-of-concept study, we injected these chemically induced photoreceptor cells into the blind mice (*rd1*) eyes and performed pupil reflex studies 4 weeks after injection. Our results indicated improvement of pupil reflex in chemically engineered cell injected eyes compared to vehicle injected control eyes . Moreover, injected cells were survived in the inner nuclear layer (INL) of the retina at 4 weeks after injection. These exciting results indicated that these cells are functional and added confidence to this proposed study.

Altogether at this stage of application, as a PI of this proposal I can address all the major comments raised by the reviewers. Moreover, my application has preliminary data that are pointing to success, and the proposed studies are logical (also indicated in reviewer’s minority report). Therefore, I request ICOC and CIRM review office to consider this proposal for funding in this cycle.

Thank you.