UNIVERSITY OF CALIFORNIA, LOS ANGELES

UCLA

BERKELEY · DAVIS · IRVINE · LOS ANGELES · RIVERSIDE · SAN DIEGO · SAN FRANCISCO

SANTA BARBARA · SANTA CRUZ

JULES STEIN EYE INSTITUTE
UCLA SCHOOL OF MEDICINE
CENTER FOR THE HEALTH SCIENCES
100 STEIN PLAZA
LOS ANGELES, CALIFORNIA 90095-7008
U.S.A.

June 19, 2022

Application and Review Subcommittee (ARS)/
Independent Citizens Oversight Committee (ICOC)
California Institute for Regenerative Medicine

Re: DISC2-13475
"*Developing gene therapy for dominant optic atrophy (DOA) using human pluripotent stem cell-derived retinal organoids*"

Dear members of ARS /ICOC,

Our DISC2 application has proposed to use stem cell-derived mini human retinas to produce retinal ganglion cells. These cells are essential for vision as their axons constitute the optic nerve connecting the eye to the brain. Our goal is to establish a disease model in the dish for the inherited optic nerve disease, dominant optic atrophy. This disease commonly begins to impact patients during childhood. Using stem cell-derived retinal neurons, we will develop a gene therapy for this vision impairing disease.

The scientific reviewers recognized the merits of the proposal, including:

- the use of advanced stem cell technology to overcome the scarcity of disease-affected cells, since the entire human retina contains less than 1% of retinal ganglion cells;
- the development and testing of a novel stem cell gene therapy directly on the disease afflicted cell type for the first time;
- the strong preliminary data to support the feasibility of the research.

Here, I would like to address a concern raised by some reviewers regarding development of a gene augmentation therapy for dominant optic atrophy.

- As understood by the reviewers, dominant optic atrophy caused by OPA1 gene mutations may be due to haploinsufficiency (the loss of one copy of the gene) or dominant-negative (a bad copy of the gene interfering with the non-mutated normal gene function). Either way, the disease can have a dominant inherited pattern.

- Since OPA1 is a large gene (>100kb) and mutations are found throughout the entire gene, most patients likely suffer from haploinsufficiency. So, a gene supplement approach makes sense for the majority of dominant optic atrophy patients.

- A gene supplement approach may also make sense for patients carrying dominant-negative OPA1 mutations, since increase the level of the normal gene would likely lessen or “dilute out” the detrimental effect of the defective mutant.

- Our proposal anticipates and addresses this issue noted by the scientific reviewers since we will test the gene therapy in both patients’ iPSCs and CRISPR-edited hESCs. Therefore, we will be able to provide a clear answer that distinguishes between the two underlying mechanisms, and even test efficacy for both.

Our proposed research is novel and significant:

- This will be the first time this optic nerve disease will be studied using stem cell-derived authentic human retinal cells.

- Our research will establish an important human stem cell-based platform to study other major blinding diseases involving optic nerve damage. For example, this platform will facilitate the development of new treatments for glaucoma, a common blinding condition in aging population.

- Moreover, the proposed gene therapy for dominant optic atrophy is also relevant to other neurological diseases such as Parkinson’s and Charcot-Marie-Tooth. Progress in our stem cell gene therapy will shed light on treating other neurodegenerative and ageing related diseases.

In summary, our DISC2 proposal is a direct response to the CIRM Strategic Plan calling for the full use of stem cell technology to establish novel research platforms that may be high risk but will have high impact in the field of regenerative medicine.

We appreciate the consideration of the CIRM ARS /ICOC for funding our DISC2 application.

Sincerely,

Xian-Jie Yang, PhD

Professor of Ophthalmology
UCLA School of Medicine