BMP, TGFbeta, and Wnt-signalling inhibitor COCO treatment of retinal organoids leads to generation of cone photoreceptors

Sabine Lovejoy [1], Justin Belair-Hickey [2], Haiyang Huang [2], Connor Bowers [3], Derek van der Kooy [1,2,3]
1: Institute of Medical Science, 2: Department of Molecular Genetics 3: Department of Anatomy; University of Toronto

Temerty Medicine

VISION SCIENCE RESEARCH PROGRAM

Introduction

Retinal organoids are a powerful tool to investigate retinal development, and photoreceptor loss ex vivo[1]. Development of cone photoreceptors occurs in the absence of instructing factors that bias cell fate to another lineage[2].

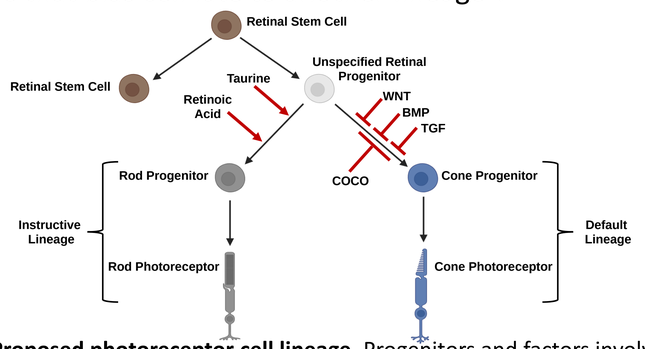

Fig 1. Proposed photoreceptor cell lineage. Progenitors and factors involved, including COCO, a cone-inducing factor.

Objective/Hypothesis

We aim to: Determine the effect of COCO on photoreceptor cell fate in retinal organoids, and hypothesize that COCO's blockage of alternate cell fates will lead to a population of cones within our model

Methods

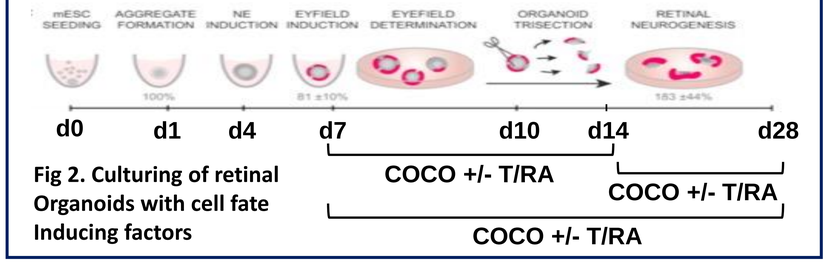

Fig 2. Culturing of retinal Organoids with cell fate Inducing factors

Cone marker gene expression increases post-COCO treatment

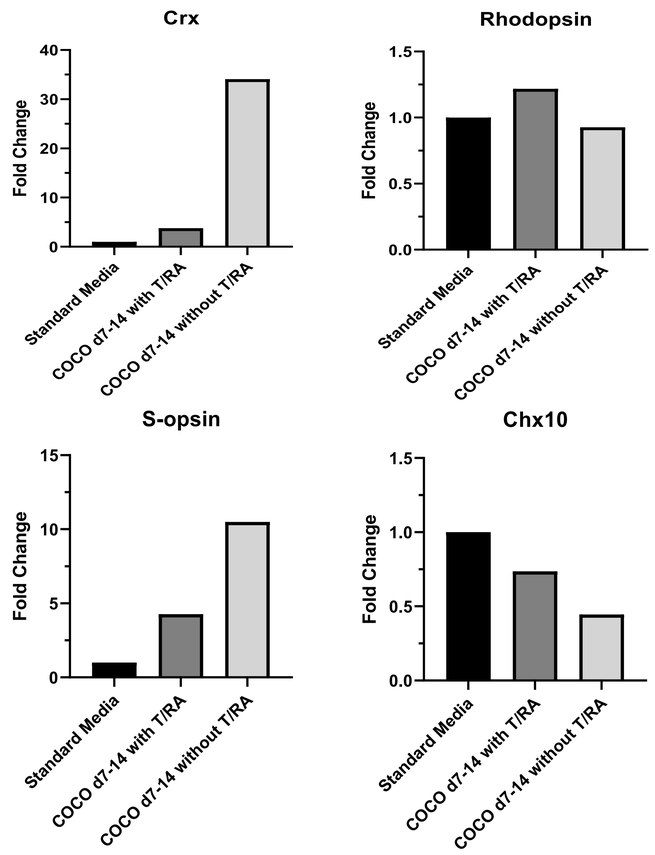

Fig 3. Comparison of cone and rod marker gene products across treatments. Gene product of cone markers Crx and S-opsin (left) increases significantly when COCO is administered in the absence of taurine and retinoic acid. Rod marker Rhodopsin is unaffected, and retinal progenitor gene Chx10 decreases in COCO-only conditions

Prolonged COCO may be detrimental

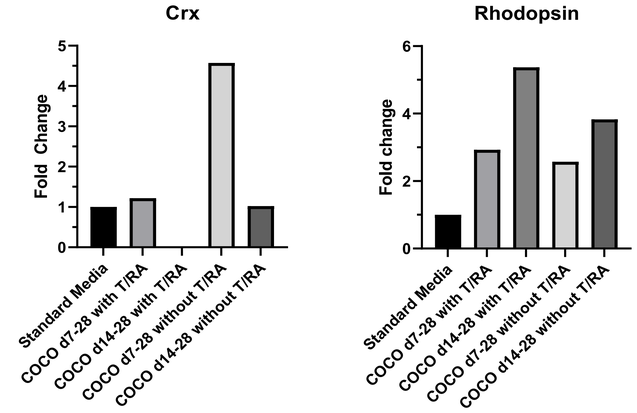

Fig 4. Comparison of primary cone and rod marker gene products in expanded timeline. Long-term COCO leads to overall decrease in cone gene marker product, but has no significant effect on rhodopsin gene product.

Conclusion

Administration of COCO to retinal organoids produces an increase in proliferation and differentiation towards a cone fate for up to 14 days of culture, at which expression of cone marker genes decline.

Future Directions

We plan to apply our model of treatment to human retinal organoids in service of developing clinical applications of transplant for the alleviation of low vision

References

1: Eiraku et al. *Nature* 472, no. 7341 (April 7, 2011): 51–56.
2: Khalili et al. *Stem Cell Research* 33 (December 2018): 215–27.