

Project 3.2 Light-induced photoreceptor morphological changes – Towards objective and impartial diagnostics in ophthalmology

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Background:

Recently optoretinography (ORG) has emerged as a functional imaging system that can record optical signals generated by photoreceptors function. However, the molecular drivers of such changes are not identified, and thus the full diagnostic power of ORG can not be unleashed. In parallel, there is growing evidence that PDE6, a core enzyme in the phototransduction signal pathway known to be tethered to the photoreceptor disc, changes conformation during its activation/inactivation cycle and may drive the observed morphological change. It is only now possible to test the hypothesis that PDE6 is responsible for photoreceptor length changes through cryoEM tomography. The technique has the distinct advantage of allowing protein analysis in the cellular environment, we can assess the behaviour of PDE6 while it is attached to membranes. More than a mere curiosity, the complete characterization of the mechanism of this phenomenon may have implications for therapeutics, diagnostics, and the functional imaging of photoreceptor physiology, as only when fully characterized can a protein's potential be fully explored. With this project, we will test if PDE6 is the molecular driver of the morphological changes observed, including by ORG, on photoreceptors. Moreover, despite outstanding achievements in determining the

PDE6 structure, many aspects of its functionality remain poorly characterized.

Aim:

We seek to gather structural information on PDE6. We will use isolated rod outer segments and reconstitute isolated PDE6 in double vesicles of defined composition; we will instigate conformation changes of PDE6 with the aid of partner proteins and small molecules and track membrane distance changes with cryoET. In addition, this project will contribute towards objective and impartial diagnostics in ophthalmology.

Requirements:

- We expect applicants to have laboratory exposure to at least one of the following disciplines: biochemistry, structural biology, and molecular biology. Hands-on experience will be a plus.