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| Development of the retinal neuro-vascular unit from human pluripotent stem cells as a model system to study retinal diseases**Katerina Apostolidi**1,2#, **Maria Markou**1, **Sofia Bellou**1,4, **Theodore Fotsis**1,3, **Carol Murphy**1\*,and **Eleni Bagli**1\*1 Biomedical Research Institute, Foundation of Research and Technology-Hellas, University Campus, 45110 Ioannina, Greece2 Department of Biological Applications and Technology, University of Ioannina, 45110 Ioannina, Greece3 Laboratory of Biological Chemistry, Medical School, University of Ioannina, 45110 Ioannina, Greece4 Confocal Laser Scanning Microscopy Unit, Network of Research Supporting Laboratories, University of Ioannina, Ioannina, 45110, Greece# Presenting author: Aikaterini Apostolidi, email: a.apostolidi@uoi.gr\* Corresponding author: Carol Murphy, email: carol\_murphy@bri.forth.gr |

abstract

The retinal neurovascular unit (rNVU) describes the set of interactions and functional coupling between the neural and vascular component of the retina [1]. rNVU is responsible for the development of the retinal blood barrier (RBB) as well as the maintenance of the homeostasis of the neuroretinal barrier [2]. It has been shown that the dysfunction of the rNVU plays a crucial role in the pathophysiology of diseases, such as diabetic retinopathy and age-related macular degeneration, which are major causes of blindness nowadays [3-5]. In vitro retinal model development has gained momentum due to the inadequacy of animal models in replicating the structure and function of the human retina. Human embryonic and induced pluripotent stem cell(hESC and hiPSC)-derived retinal organoids(ROs) have demonstrated diverse applications, such as investigating human retinogenesis, modeling diseases and drug discovery. While multiple protocols have been established to generate ROs aligning with fundamental principles of forebrain and eye development, these ROs lack vascularization and thus their maturation is impaired [6]. Our work is focused on the generation of human vascularized hESC/hiPSC-derived ROs. We have already generated and extensively characterized endothelial(ECs) and mural(MCs) cells derived from hPSCs. In addition, we have also generated and characterised hESC/hiPSCs-derived Retinal Pigment Epithelium(RPE) and-ROs using a sequential step strategy, mimicking the spatio-temporal development of the retina in vivo. Our plan is to generate an innovative humanized in vitro retinal model (retina-on-a chip,ROC). Specifically, we will develop for the first time in the literature a three-dimensional tissue construct consisting of RPE cells, neural cells(ROs) and vessels, all derived from hPSCs in the relevant anatomical layout within a microfluidic system, in order to develop the main blood-retinal-barrier (BRB) and achieve the dynamic interaction of the different cell types. The final tissue construct will afford an innovative system to study the molecular mechanisms that govern retinal diseases. Specifically, our in vitro retinal NeuroVascular unit (rNVU) serves as a platform to elucidate the pathophysiology of Retinitis Pigmentosa(RP)(an inherited disease causing blindness) using patient-derived hiPSCs with a PRPF31 mutation, known to be responsible for RP development.

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