Submitted to CRATER - Conference on Recent Advances in Translational Eye Research 2025

Development of new rabies virus vectors with modified tropism toward retinal cells

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Vision is essential throughout human life, and its loss is one of the most feared limitations. According to the World Health Organization, at least 2.2 billion people suffer from visual impairment or blindness. Retinal degeneration diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP), comprise a large number of ocular diseases that are characterized by the progressive loss of photoreceptor cells. Therefore, there is a need to explore new and effective therapeutic approaches for treating retinal degenerative diseases. Among promising methods has emerged the use of Rabies virus (RV), a (-)RNA rhabdovirus known for its ability to infect neurons through retrograde transport (from postsynaptic to presynaptic cells) and carry large cargos. However, RV's lack of cell-type specificity makes it difficult to control the targeting of specific cells and the delivery of therapeutic genes. To address this, our project aims to modify the tropism of a G-deleted Rabies virus (RVΔG) by pseudotyping it with chimeric proteins designed to bind selectively to receptors found only on selected cell types within the retina. We hypothesize that this targeted approach will allow us to precisely infect different retinal cells. The first step will involve creating a lentivirus expressing the chimeric glycoproteins, which will be used to transduce BHK-21 cells for stable line generation. Next, we will produce a pseudotyped RV and inject it into the mouse eyes. The specificity of the virus will be confirmed by immunostaining assays. Furthermore, we will develop a protocol for pseudotyped RV infection of organotypic culture of porcine retina explants. The project aims to enhance our understanding of pseudotyping techniques and their potential applications in gene therapy for retinal degenerative diseases.