**Use of Polypeptide-Based Nanoconjugates as a Combination Therapy Approach to treat Retinitis Pigmentosa**

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Inherited retinal dystrophies (IRDs) are a group of diseases which affect the retina causing a progressive loss of vision. Retinitis pigmentosa (RP), the main IRD, is the major genetic cause of blindness in developed countries, affecting about two million people. RP is mainly associated with photoreceptor (rods and cones) dysfunction and loss that, eventually leads to blindness. Studies in patients and animal models suggest that oxidative stress and inflammation contribute to its progressive and irreversible vision loss. It is a devastating diagnosis and one of the frontiers of ophthalmology. Although later advances have led to more effective design of clinical trials, we still lack treatments.

Recent advances in nanomedicine seek to curtail these limitations, overcoming ocular barriers by developing non-invasive or minimally invasive delivery modalities. Due to their intrinsic characteristics, polymer therapeutics, and polypeptide-based combination conjugates in particular, represent ideal delivery systems for the combination-based therapies required to address this pathology. Aiming to tackle the elevated oxidative stress and chronic neuroinflammation, we proposed the use of polypeptide-based combination therapy based on the blockage of both pathways.

We rationally designed and synthesized a family of single-drug conjugates, to be used in a combination regime at the adequate ratio, by using pH-responsive linkers and employing differing poly-L-glutamic acid architectures (linear and star-shaped) and varied drug loadings. In vivo instillation (eye drops) of our combination therapy in a murine model of RP, rd10 mice suggested a functional signature associated with neuroprotection. First, light avoidance behaviour tests revealed lower residence in the lighted area for the combination group, confirming the synergistic effect of the therapy which provides vision recovery. Aligned with this finding, electroretinography highlighted the improved effect of the combination therapy, which confirms a better functional evaluation of the photoreceptors and downstream associated retinal cells. Second, we observed an enhancement photoreceptor cell survival and the reduced migration of microglia due to the lower inflammation in treated animals. Collectively, we state that our nanoconjugates as combination therapy can be a major breakthrough in retina degenerative disorders-centered therapeutic strategies