

Red light-triggered anti-angiogenic and photodynamic combination therapy of age-related macular degeneration

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Choroidal neovascularization (CNV) is the key pathological event of wet age-related macular degeneration (wAMD), which would result in permanent vision loss. Anti-angiogenic therapy with intravitreal anti-vascular endothelial growth factor (VEGF) agents has become the standard treatment for wAMD. However, several limitations remain, including the safety concerns of monthly intravitreal administration and insufficient efficacy for neovascular occlusion¹. Herein, we report a novel and minimally-invasive approach to achieve anti-angiogenic and photodynamic combination therapy of wAMD by intravenous administration of photoactivatable nanoparticles (Di-DAS-VER NPs). The nanoparticles composed of reactive oxygen species (ROS)-sensitive dasatinib (DAS) prodrug and photosensitizer verteporfin (VER) exhibit negligible *in vitro* toxicity in the dark, while showing potent photodynamic (PDT) and anti-angiogenic effect upon red-light irradiation at 690 nm. Therefore, red-light irradiation to the mouse eye could trigger the intraocular release of anti-angiogenic DAS, accompanied by selective neo-vessels occlusion. Notably, Di-DAS-VER NPs achieved remarkable CNV suppression with minimized systemic toxicity in a laser-induced CNV mouse model. By integrating a photoactivation process with combinational therapeutics into a simple nanosystem, this study enables an effective intravenous therapy for wAMD.

(1) Gao, Y.; Yu, T.; Zhang, Y.; Dang, G. Anti-VEGF Monotherapy Versus Photodynamic Therapy and Anti-VEGF Combination Treatment for Neovascular Age-Related Macular Degeneration: A Meta-Analysis. *Invest Ophthalmol Vis Sci* **2018**, 59 (10), 4307-4317. DOI: 10.1167/iovs.17-23747.