NOVEL TOPICAL ANTIANGIOGENIC SRPK1 INHIBITORS IN THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION

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Age-related macular degeneration (AMD) is a disease of the central macula and the leading cause of blindness in people over 50 years of age. Exudative (wet) AMD is characterized by choroidal neovascularization (CNV), the leakage of blood and serous fluid from the neomicrovasculature beneath the retinal pigment epithelium (RPE), leading to the loss of photoreceptors, retinal detachment, macular scarring and visual loss. Current treatment regimens for AMD involve costly monthly intraocular injections, with non-specific and weakly potent humanized anti-vascular endothelial growth factor (VEGF) antibody therapies. Serine-rich protein kinase-1(SRPK1) has been identified as a regulator of pro-angiogenic VEGF splicing by phosphorylating serine-rich splicing factor-1 (SRSF1), which binds to VEGF pre-mRNA. A novel SR phosphorylation Inhibitor (SPHINX) compound that inhibits SRPK in the micromolar range and regulates VEGF gene splicing has been recently developed [1]. We have generated a novel low molecular weight derivative (SPHINX7) that has potencies in the 10^{-8}M range, is lipophilic, and inhibits angiogenesis in a CNV model as an eye-drop. These results indicate that more potent, topical SRPK inhibitors can act as anti-angiogenics and may be good therapeutic candidates.

[1] Gammons (2013). IOVS 54(8):5797-5806.