Development of a Simultaneous Combination Therapy for Alternative Multidimensional Etiologies of Subretinal Angiogenesis

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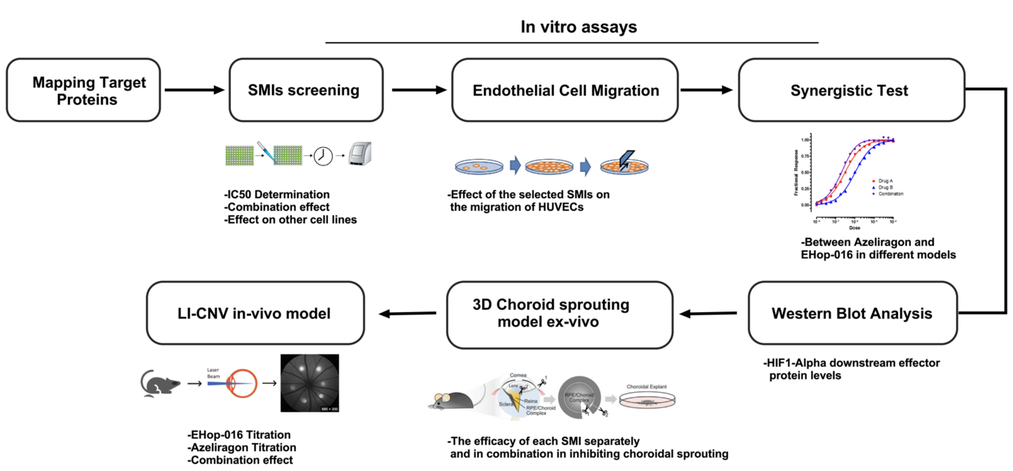
INTRODUCTION

Retinal vascular diseases are the leading causes of visual impairment and blindness. Neovascularization of the retina and choroid are the final complications of these diseases, producing abnormal vessels with increased permeability and bleeding tendencies, leading to retinal edema, atrophy, and potentially vision-threatening consequences. We aim to develop a novel combination therapy for multidimensional blocking of downstream key proteins involved simultaneously in various signal pathways of retinal vascular diseases.

METHODS

A comprehensive literature review identified key proteins, Rac1 and RAGE, as mediators in retinal vascular diseases. Small molecule inhibitors (SMIs) targeting these proteins were screened in-vitro using WST-1 proliferation and migration assays on HUVECs. A 3D choroid sprouting model validated the anti-angiogenic effect ex-vivo, and a laser-induced CNV model was used to mimic wAMD, in-vivo



RESULTS

We identified selective SMIs for two non-VEGF targets: Azeliragon for RAGE and Ehop-016 for Rac1. Both inhibited HUVEC proliferation and migration in vitro, and their combination produced a significant synergistic effect (Synergy Score >14.96). The combined inhibition demonstrated a strong anti-angiogenic effect in a 3D choroid sprouting model (0.41±0.13). It effectively reduced choroidal neovascularization (CNV) in vivo in a laser-induced mouse model, showing results comparable to Aflibercept treatment.

RESULTS

Figure 1: Dose-response curve of SMIs combination effect on HUVECs' proliferation

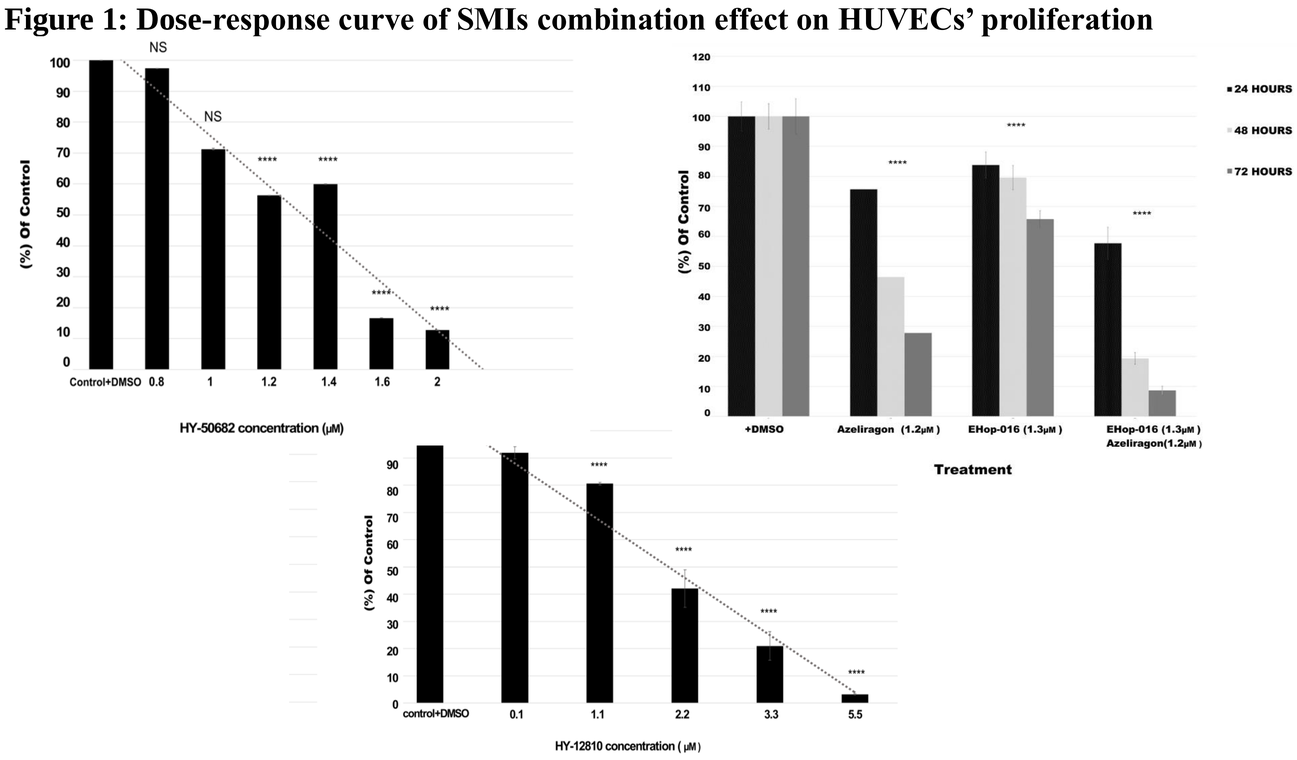


Figure 2: Synergistic interactions between Azeliragon and EHop-016 in different models: (A) ZIP, (B) Loewe

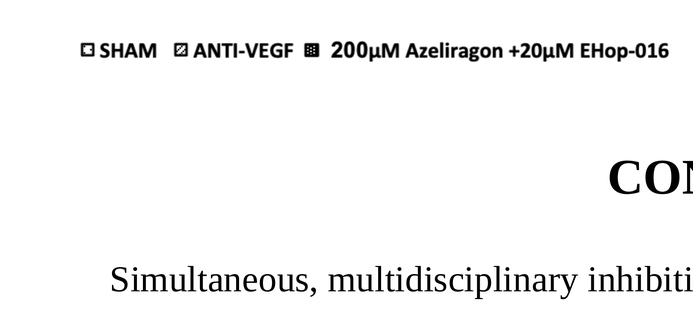


Figure 3: Inhibition of angiogenesis in 3D choroid sprouting model, *ex-vivo*

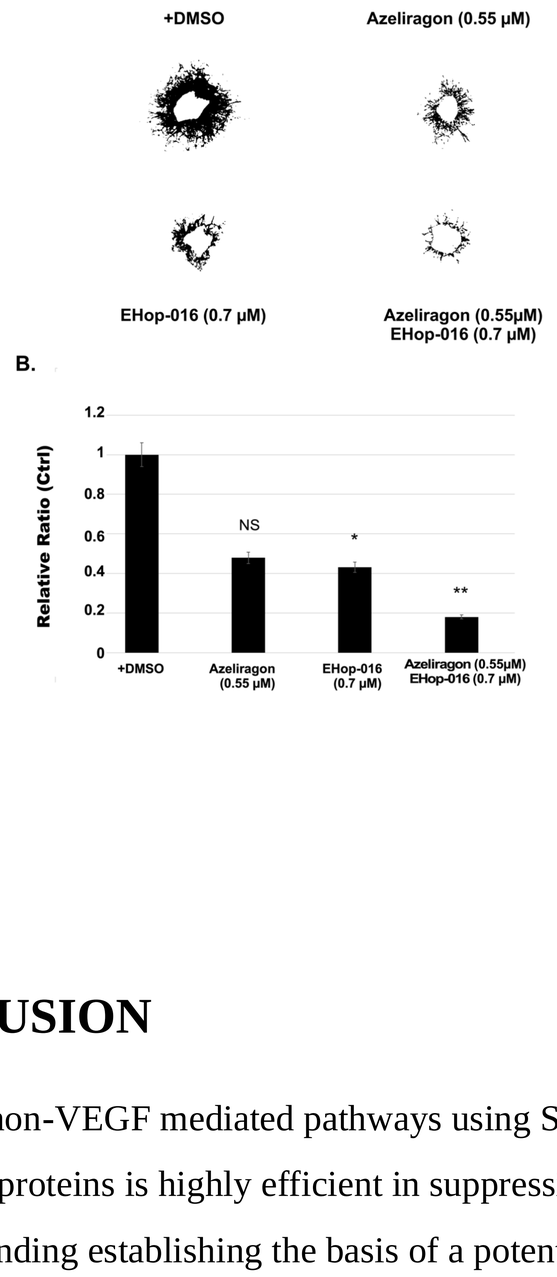
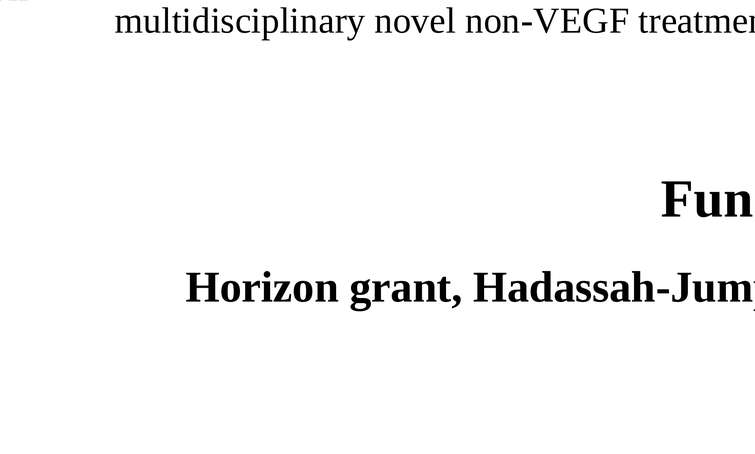


Figure 4: SMIs effect on a mouse model of LI-CNV



CONCLUSION

Simultaneous, multidisciplinary inhibition of non-VEGF mediated pathways using SMI combination therapy against Rac1 and RAGE proteins is highly efficient in suppressing experimental CNV formation, a preliminary finding establishing the basis of a potentially multidisciplinary novel non-VEGF treatment for various retinal vascular diseases.

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