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Development of ○○○ inhibitor as a novel therapy for Aged-Macular degeneration

Gachon University

Disease Area	**Ophthalmology**
Product Type	Small molecule
Indication	Wet-AMD
Target	Undisclosed
Mechanism of Action	1) Binds directly to target protein, inhibiting its enzymatic activity 2) Induces target protein degradation in a proteasome-dependent manner 3) Inhibits AKT activation in human retinal microvascular endothelial cells (HRMEC) by blocking the specific receptor-mediated signaling 4) Inhibits proliferation, migration, and tube formation of HRMEC
Competitiveness	1) Novel target molecule for wet-AMD 2) The most potent inhibitor of target protein reported to date 3) Dual function of inhibiting retinal vascular cell proliferation and blocking immune cell activation 4) Overcomes problems with existing antibody therapies (e.g., unresponsiveness, fibrosis, and eye injection) through development of novel small molecules
Development Stage	**Hit**
Route of Administration	1) Intravitreal or eye drop 2) Oral administration
Key Data	1) Target binding affinity: KD = 663 nM 2) Enzyme inhibition: 64 % inh. at 3 μM, 100% inh. at 10 μM 3) Proteasome-dependent target protein degradation: at 0.1-1 μM 4) Inhibition of HRMEC proliferation: IC_{50} = 1.392 μM 5) Cytotoxicity: RPE proliferation IC_{50} > 100 μM 6) In vivo activity: Significant reduction of retinal lesion in Laser-induced CNV model 7) Plasma stability: ~ 100% remaining upto 250 min (mouse, rat, and human) 8) Microsomal stability: 71.3% remaining at 60 min (human) 9) PAMPA: 15.74±1.78 (10^{-6}cm/sec)