Mucus-Penetrating Particles of a Novel Receptor Tyrosine Kinase Inhibitor

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Abstract #1516

Summary of Key Findings

- K106 is a potent and selective VEGF signaling inhibitor
- K106 can be formulated as mucus-penetrating particles (MPP)
- K106 applied topically as MPP in animals reaches the back of the eye where it is pharmacologically active

Introduction and Objective

Neovascularization at the back of the eye is a key contributor to vision loss in diseases such as age-related macular degeneration (AMD). Vascular endothelial growth factor (VEGF) pathway blockade is a clinically proven treatment for AMD currently achieved through repeated intravitreal (IVT) injections of a biologic agent.[1] We have previously demonstrated mucus-penetrating particles (MPP) can enhance the exposure of a topically applied steroid.[2] The objective of this work was to design a novel receptor tyrosine kinase inhibitor (RTKi) that selectively blocks the VEGF pathway and can be delivered topically. The RTKi was formulated as MPP to avoid rapid clearance from the ocular surface by uniformly coating and penetrating the mucus barrier. This MPP formulation of the novel RTKi was tested in a vascular leakage model in rabbits.

Methods

K106 was synthesized and assayed for enzymatic affinity against VEGF, PDGF, EGF, FGF, and RET receptors. Cellular potency for KDR (VEGF-R2) and PDGFR-β were also determined. To study efficacy, 1% K106 MPP were topically administered to rabbits every 4 hours for 6 days with an IVT injection of VEGF on Day 3 and fluorescein angiography on Day 6. Ocular drug concentrations were measured on Day 6. To study tissue distribution in a larger species, 2% K106 MPP were topically administered to mini-pigs BID for 5 days.

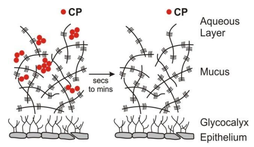
K106 Potency and Selectivity

K106 has an enzymatic affinity of 0.5 nM and a cellular potency of 0.2 nM for KDR and 13 nM for PDGFR-β. K106 is selective for KDR over RET, EGFR, and FGFR by 28, 680, and 188-fold, respectively.

	Kd (nM)	KDR Fold Selectivity
KDR (VEGFR-2)	0.5	--
FLT1 (VEGFR-1)	0.8	2
FLT4 (VEGFR-3)	6.2	12
PDGFRA	1.3	3
PDGFRB	0.2	0.4
EGFR	340	680
FGFR	94	188
RET	14	28
CDK5	>10000	--

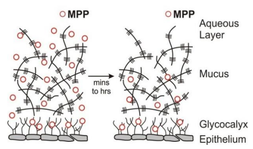
Mucus-Penetrating Particles

Conventional Particles (CP)

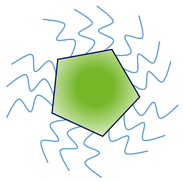


- Muco-adhesive particles are **rapidly cleared** from mucus through mucus turnover
- Particle aggregation and mucus adherence lead to **poor distribution**

Mucus-Penetrating Particles (MPP)



- Muco-inert particles penetrate through tear film mucus layer
- Mobility leads to **uniform distribution** across the mucosal epithelia

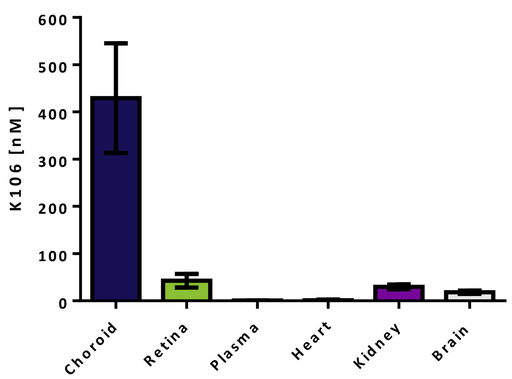


- Drug nanoparticle core; Drug loading ~100%
- All excipients have been in previously FDA-approved ophthalmics
- Stable aqueous nanosuspension (ready to use)
- Scalable manufacturing (sterile product)

K106 MPP Test Article	Z-ave Particle Size (nm)	PDI
Mini-pig Tissue Distribution Study	196	0.170
Rabbit Vascular Leakage Study	202	0.143

K106 Tissue Distribution in Mini-pigs

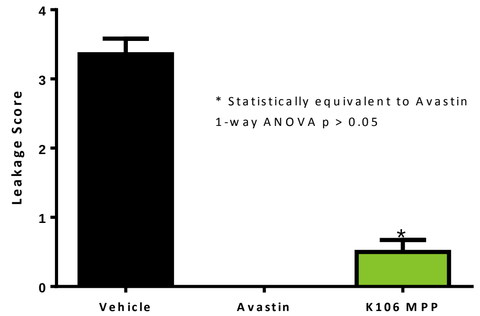
Tissue distribution studies in the mini-pig revealed retinal and choroid levels well above the cellular IC50 and higher compared to systemic compartments (*i.e.*, plasma, heart, kidney and brain).

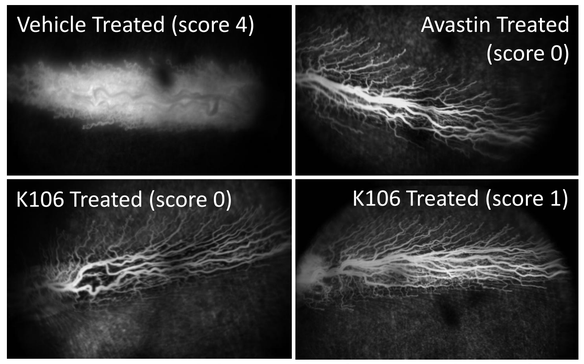


	K106 [nM]
Choroid	429
Retina	43
Plasma	0.7
Heart	1.3
Kidney	30
Brain	18

K106 in a Rabbit Vascular Leakage Model

In a rabbit model of vascular leakage, topically applied K106 MPP reduced neovascularization and leakage statistically equivalent to an IVT injection of Avastin®. Rabbit retinal drug levels were 861 nM, with 25-fold higher in the choroid, approximately 5 hours following the last dose.





Representative images including examples of a score 0 and score 1 for K106

Conclusions

K106 is a potent and selective VEGF receptor inhibitor which, when formulated as MPP and applied topically in animals, reached the back of the eye where it was pharmacologically active. In a rabbit model of vascular leakage, topically applied K106 was statistically equivalent to treatment with Avastin®. These data support further studies as a noninvasive therapy for VEGF pathway blockade would be a breakthrough in the treatment of neovascular ophthalmic diseases.

References

[1]Khan M, Agarwal K, Loutfi M, Kamal A, Present and Possible Therapies for Age-Related Macular Degeneration, *ISRN Ophthalmol.* 2014, 2014:1–7.

[2] Schopf L, Enlow E, Popov A, Bourassa J, Chen H, Ocular Pharmacokinetics of a Novel Loteprednol Etabonate 0.4% Ophthalmic Formulation, *Ophthalmol. Ther.*, 2014, 3:63-72.