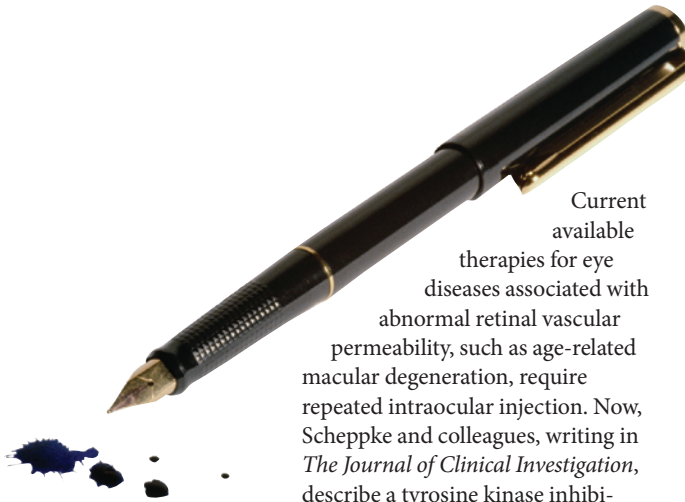


 EYE DISEASES

Convenient leakage reduction



Current available therapies for eye diseases associated with abnormal retinal vascular permeability, such as age-related macular degeneration, require repeated intraocular injection. Now, Schepcke and colleagues, writing in *The Journal of Clinical Investigation*, describe a tyrosine kinase inhibitor that can be topically applied to reduce vascular leakage in the eye, potentially addressing the delivery-related limitations of existing drugs.

Vascular endothelial growth factor (VEGF) activates common pathways of vascular leakage associated with various pathological processes, and injectable VEGF antagonists, including pegaptanib (Macugen, Pfizer) and bevacizumab (Avastin, Genentech), are used clinically to treat neovascular eye diseases.

As VEGF-induced vascular leakage is mediated by members of the SRC family of tyrosine kinases, the authors first investigated the function of SRC and YES kinases in retinal VEGF-mediated vascular permeability.

In *Src*^{-/-} and *Yes*^{-/-} mice, intraocular VEGF injection did not alter vascular permeability of the eye.

Also, in a mouse model of VEGF-induced retinal vascular permeability, systemic pretreatment with SRC kinase inhibitors prevented 90% of VEGF-induced leakage, demonstrating the involvement of the SRC family of tyrosine kinases.

Previous structure-based drug design studies identified TG100572, a VEGF receptor 2 (VEGFR2)/SRC kinase inhibitor, and its prodrug form TG100801. After confirming that the *in vivo* target of TG100572 is the SRC phosphorylation site of focal adhesion kinase, bioavailability and tissue distribution of the prodrug and active compound were evaluated. In the rabbit eye, topical instillation of TG100801 resulted in well-defined posterior ocular tissue concentration–time profiles for the prodrug and the active compound. Conversion of the prodrug to the active compound was observed in all ocular tissues, and plasma concentrations of both compounds were not detectable.

Next, the authors investigated the effect of TG100572 and TG100801 on VEGF-mediated retinal vascular permeability. TG100572, topically applied to the mouse cornea three times a day resulted in 80% inhibition

of VEGF-induced leakage. When the prodrug form was topically administered once a day, this resulted in an almost complete inhibition of VEGF-induced retinal leakage.

The authors then assessed the effects of pegaptanib and bevacizumab on blood–retinal barrier breakdown in mice. The results suggested that TG100801 appeared to be as effective as clinically used VEGF antagonists.

An antivascular permeability compound that is also anti-angiogenic would have added therapeutic benefit. Indeed, in a mouse model of angiogenesis, intraperitoneal administration of TG100572 resulted in inhibition of both VEGF-induced and fibroblast growth factor-induced angiogenesis by 88% and 100%, respectively.

Overall, this study indicates that a topically applied SRC/VEGFR inhibitor — such as TG100801, which is currently in clinical trials — might represent an improved option for the treatment of vascular eye diseases, including diabetic macular oedema and macular degeneration.

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ORIGINAL RESEARCH PAPER Schepcke, L. et al. Retinal vascular permeability suppression by topical application of a novel VEGFR2/Src kinase inhibitor in mice and rabbits. *J. Clin. Invest.* **118**, 2337–2346 (2008)