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The Effects of Combined Inhibition of Platelet-derived Growth Factor (PDGF-B) and VEGF-A Signaling in Murine Models of Ocular Neovascularization

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PURPOSE
While the inhibition of VEGF-A signaling can prevent new blood vessel growth in cancer and ocular pathologies, more mature vessels appear to be less susceptible. Since PDGF-B signaling is essential for pericyte recruitment to the developing vasculature, we examined the effect of concurrent inhibition of VEGF-A and PDGF-B signaling on the growth of both immature and mature blood vessels.

METHODS
Choroidal and corneal neovascularization in adult mice were induced by laser wounding and epithelial debridement, respectively and retinal vascular development was studied in neonates. The effects of PDGF-B were inhibited by intraperitoneal (IP) injection of antibody APB5 or gavage administration of imatinib, both inhibitors of PDGF receptor (PDGFR)-B. VEGF was inhibited by IP pegaptanib. Mice were treated with either an anti-PDGFR-B agent, pegaptanib or both at varying times following injury/birth. Eyes were enucleated and ocular vascularization was assessed microscopically.

RESULTS
Pegaptanib alone did not impede growth of retinal vasculature or recruitment of pericytes in developing neonates. Both processes were inhibited by blocking PDGF-B signaling, and inhibition of vessel growth was significantly greater when both VEGF-A and PDGF-B were blocked. In the corneal model, blocking PDGF-B prevented pericyte recruitment and led to loss of pericytes in established blood vessels, while minimally affecting new vessel growth. Blocking VEGF-A inhibited corneal blood vessel growth but not pericyte recruitment. Inhibition of both signaling pathways had an additive benefit in inhibiting new growth and in regression of established vessels. Inhibition of neovascularization by pegaptanib declined at late time points, but combined VEGF-A/PDGF-B inhibition remained effective. In the choriodal revascularization model, pegaptanib significantly blocked neovascularization, while PDGF blockade had no effect; combined therapy showed additive effects.

CONCLUSION
These data show that new blood vessels become refractory to VEGF-A deprivation over time, and that concurrent inhibition of both VEGF-A and PDGF signaling is more effective at causing vessel regression than inhibition of only the VEGF-A pathway. Combined PDGF-VEGF inhibition may be more effective in treating ocular neovascular disease than blocking VEGF-A alone.

* Financial interest disclosed