Additionally, ablation of IL-6 signaling by genetic knock-out or systemic treatment with anti-IL-6 receptor antibody significantly reduces angiogenesis and administered either as stand alone drugs or in combination with VEGF blockade.

Background Biology: Diabetic macular edema (DME) is a serious, vision-threatening condition affecting nearly 8% of diabetic patients (You J-WY et al., 2012). DME results in peripapillary retinal ischemia, capillary leak, and neovascularization leading to swelling in the macula while several treatment options exist, including photocoagulation, local or systemic steroids, and anti-VEGF therapies, these are each limited by toxicity or inadequate efficacy. Therefore, there remains a significant unmet need for safe and effective therapies to be administered either as stand alone drugs or in combination with VEGF blockade.

IL-6 is a pleiotropic cytokine with established roles in inflammation and angiogenesis. Excessive IL-6 signaling is implicated in several neurodegenerative diseases with the IL-6 receptor-antagonist Tocilizumab approved for treating muscular dystrophy. In the eye, vitreal IL-6 levels are significantly elevated in patients with DME and positively correlate with disease severity. Monoclonal injection of IL-6 reduces retinal thickness (Rojas et al.). Additionally, ablation of IL-6 signaling by genetic knock-out or systemic treatment with anti-IL-6 receptor antibody significantly reduces angiogenesis and macrophage infiltration in a mouse laser-induced choroidal neovascularization (CNV) model (Jones et al.).

IL-6 is a cytokine with a high affinity for the type 2 cytokine receptor (IL-6Rα) and is regulated by either the membrane-bound (cis-) or soluble (trans-) form, both of which are capable of signaling and either can drive pathologic signaling. The IL-6Rα, capable of signaling against both the angiogenic and inflammatory components of disease. Local blockade of IL-6 signaling is efficacious in a rat model of laser-induced choroidal neovascularization.

Existing IL-6 antagonists are designed for systemic administration and may have suboptimal pharmacokinetic properties for local delivery, leading to frequent administrations or risk of systemic toxicity.

EPI-029 is a humanized, affinity matured antibody that binds Site 2 of IL-6 and potently blocks the cis- and trans- signaling pathways that drive pathologic signaling.

EPI-029 has excellent stability and solubility sufficient for high concentration IVT delivery.

An engineered version of EPI-029 with ablated FcRn binding has been developed to reduce transcytotic clearance from the eye and prevent systemic accumulation.

Additional studies are underway to assess the role of IL-6 in DME and characterize EPI-029 activity and PK.

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