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Phenotype-Based Discovery of Novel Drugs for Ocular Disease.

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Our goal is to discover novel drugs with potential to improve the treatment of ocular disease.

Vascular permeability, angiogenesis, inflammation and neurodegeneration are pathological hallmarks of prevalent forms of human blindness. Thus, we apply phenotype-based screens to identify novel drugs that modulate these disease hallmarks.

A randomised library of ~3000 small molecule drugs was screened for anti-angiogenic efficacy using the zebrafish hyaloid and inter-segmental developmental angiogenesis assays. A hit molecule designated Quininib robustly inhibits developmental angiogenesis in zebrafish and was subsequently shown to reduce secretion of angiogenic and inflammatory factors from human colorectal tumour explants. A hit series of Quininib analogs identified approximately 10 novel chemical entities with greater anti-angiogenic efficacy in the zebrafish model than the parent compound. Here, data will be presented on the anti-angiogenic activity of the parent compound and NCE analogs in zebrafish, in tubule formation assays with human endothelial cells and in explant cultures of rodent aortic rings. Target profiling assays indicate that this novel Quininib series acts do not target VEGF receptors.

Overall, phenotype based screens in zebrafish have identified a novel series of NCEs with robust anti-angiogenic activity that is retained in mammalian models. This Quininib series appears not to target the VEGF receptors and thus offers potential to treat patients non-responsive to the current anti-VEGF treatments or to enhance efficacy in combination with anti-VEGF biologicals.