Variants of IGT-427 are long-acting, bispecific antibodies for the treatment of degenerative retinal diseases

Eric Furfine[1], Stacy Capehart[1], Josh Slocum[1], Tobin Brown[1], Marion Weir[1], Alex Jackson[1], Minkyung Choo[2], Kwangsoo Kim[2], Philip Durost[2], Sangyeul Han[2]
[1]Mosaic Biosciences, Boulder, CO and [2]Ingenia Therapeutics Cambridge, MA

Results

- IGT-427 is a bi-specific protein therapeutic that simultaneously binds VEGF and Tie-2
- The drug candidate non-competitively overrides Ang2 suppression of Tie-2 and is a more durable and stronger activator of Tie-2 than the endogenous activator Ang1
- IGT-427 blocks Tie-2 proteolytic down-regulation, sustaining beneficial signaling under disease-like inflammatory conditions
- PEGylation of IGT-427 doubles its intravitreal half-life, with potential to reduce the frequency of administration

Conclusions

- PEGylated IGT-427 has the potential to be a best-in-class treatment of AMD and DME because of comparable VEGF blockade, stronger Tie-2-mediated vasculature stabilization, and a longer vitreal half-life than standard of care therapies
- These characteristics improve the probability of greater efficacy and reduced frequency of administration compared to the standard of care

Introduction

Despite the great benefit of anti-vascular endothelial growth factor (VEGF) therapy in degenerative retinal diseases, many patients incompletely respond to therapy and the frequency of administration is relatively high. Faricimab, the recently approved bi-specific antibody that blocks Ang2, the negative regulator to Tie2, and VEGF signaling, was non-inferior in vision improvement with lesser frequent administration compared to aflibercept.

Importantly, persistent disease activity, assessed by interstitial retinal fluid (IRF), was significantly improved with faricimab, compared to standard aflibercept treatment (43%~48% vs 23%~27%) (https://www.vabysmo-hcp.com). In addition, faricimab was more effective in reducing retinal thickness, a biomarker of disease used to define dosing intervals in DME. These improved reductions in IRF and retinal thickness indicate the clinical benefit of Ang2 antagonism and its resulting indirect Tie2 activation. Despite the advantages of faricimab, approximately 52% of DME patients after 56 weeks treatment were incomplete responders. We propose that further clinical benefit might be gained by an increased Tie2 activation beyond that induced by faricimab.

Herein, a bispecific pegylated antibody, IGT-427, that has dual function of VEGF inhibition and direct Tie2 activation, also has long-lasting half-life in the vitreous. The improved activity of IGT-427, includes direct activation of Tie2 that exceeds Ang2 blockade in vitro and protection against Tie2 downregulation from proteases, which together may provide for a higher and longer-acting pharmacodynamic response after intravitreal administration.

Methods

Binding affinities to its targets were assessed by SPR analysis (Biacore). Potency and soluble Tie2 assays were carried out in either human umbilical vein endothelial cell (HUVEC) with native Tie2 expression or CHO cell overexpressing human Tie2. For measuring endothelial barrier integrity, TEER (trans-endothelial electrical resistance) assay was performed using CellZscope® (Nanoanalytics).

PEGylated IGT-427 was produced by engineering cysteines near the C-terminus of IGT-427 heavy chain. The two free cysteines in this variant of IGT-427 were reacted with 20 kDa linear or 40 kDa branched PEG-maleimide.

To assess the ocular PK of IGT-427 and PEGylated variants, total drug levels were measured by ELISA in the vitreous of rabbits after intravitreal injection with 500 µg of aflibercept, faricimab, IGT-427, 20 kDa linear PEGylated IGT-427, or 40 kDa branched PEGylated IGT-427.

Results

Figure 1. IGT-427 has dual function of Tie2 activation and VEGF inhibition by IGT-427

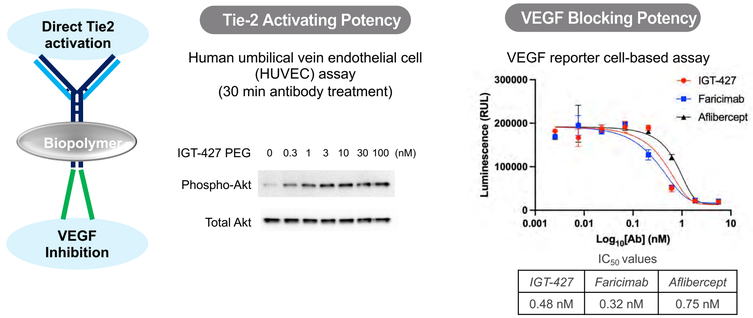

Figure 2. IGT-427 binds Tie2 and VEGF simultaneously

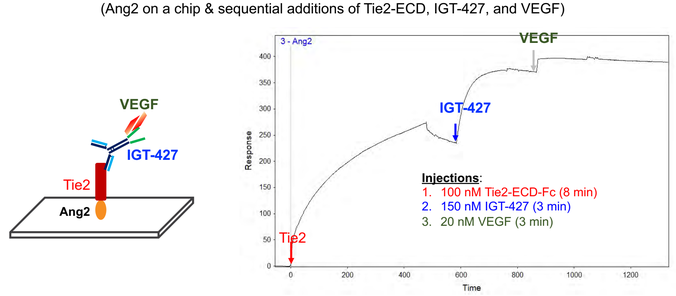

Figure 3. IGT-427 bypasses Ang2 inhibition and induces stronger and durable activation of Tie2 than endogenous activator, Ang1

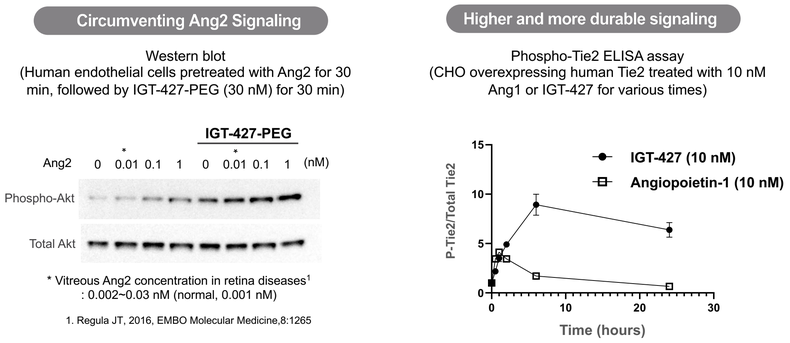

Figure 4. IGT-427 protects Tie2 cleavage, blocking down-regulation and maintaining beneficial signaling under inflammatory conditions

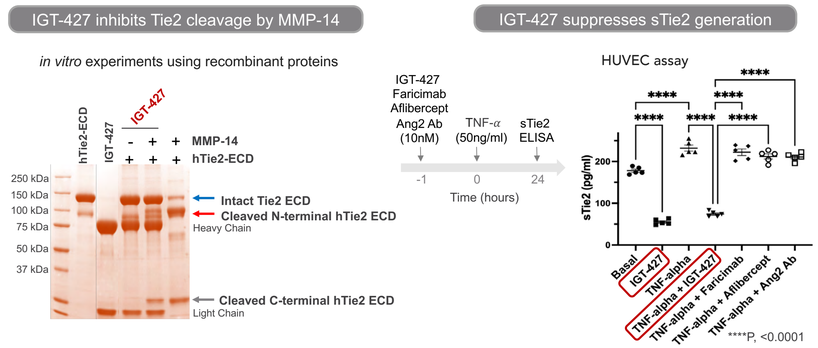

Figure 5. IGT-427 reverses endothelial barrier leakage induced by VEGF

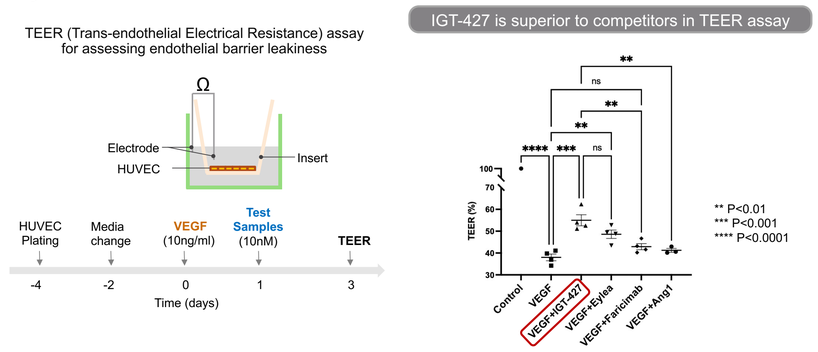

Figure 6. PEGylation of IGT-427 doubles the ocular half-life in rabbits