Bispecific antibodies targeting the ENG-ALK1-BMPRII axis as a novel approach for the treatment of HHT

JC Hus, M. Geddie, E. Duhaime, A. Sullivan, H. Yue, T. de Rham, E. Murphy, A. Alrfooh, X. Wang, S. Guo, A. Vishwanathan, P. Marambaud†, P. André & A. Lugovskoy

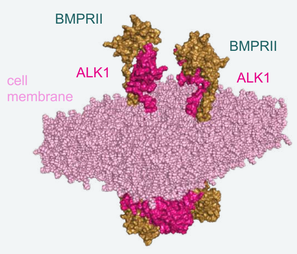
Diagonal Therapeutics, 200 Arsenal Blvd, Suite 220, Watertown, Massachusetts 02472

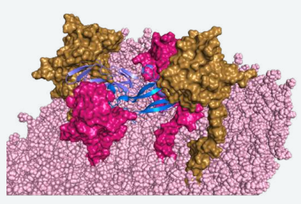
†The Feinstein Institutes for Medical Research, 350 Community Dr, Manhasset, New York 11030

Summary

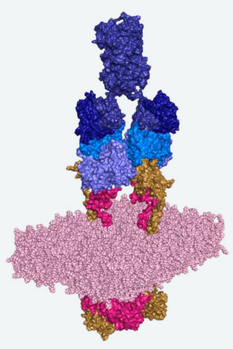
- Hereditary Hemorrhagic Telangiectasia is marked by impaired signaling pathways mediated by the Bone Morphogenetic Protein (BMP) receptor family: ENG-ALK1-BMPRII axis. The creation of therapeutic bispecific antibodies that target and directly activate these critical receptors offers a novel approach for the treatment of HHT. Diagonal Therapeutics has developed a cutting-edge platform that utilizes high-throughput screening of immune repertoires and harnesses sophisticated computational algorithms and bioinformatics to identify antibodies that exhibit high specificity and affinity. Because ALK1 is preferentially expressed in the vasculature, our bispecific antibodies are designed to enhance selectivity to the target tissues impacted by HHT. Significant antibody engineering efforts were undertaken to maximize therapeutic efficacy and minimize potential side effects. Various antibody formats were evaluated to identify the most suitable structure that provides stability, effective targeting, and reduced immunogenicity. Additionally, linker optimization was crucial, involving adjustments to the linker's length and flexibility to facilitate the appropriate orientation and function of the bispecific antibodies.
- These engineered antibodies are characterized by their dual engagement with ALK1 and BMPRII, positively modulating the signaling pathways implicated in HHT.
- *In vitro* and *in vivo* characterization of the Diagonal antibodies has demonstrated that their use can prevent and reverse vascular malformations in two preclinical models of HHT and that they restore deficient signaling in HHT patient-derived endothelial cells.

Mechanism of action





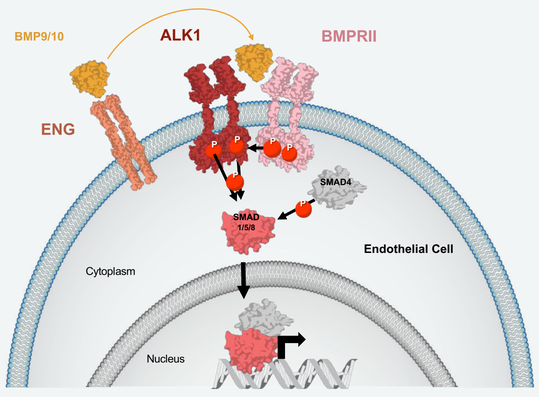
BMP9 is a natural ligand binding ALK1 and BMPRII in a tetrameric format as a dimer



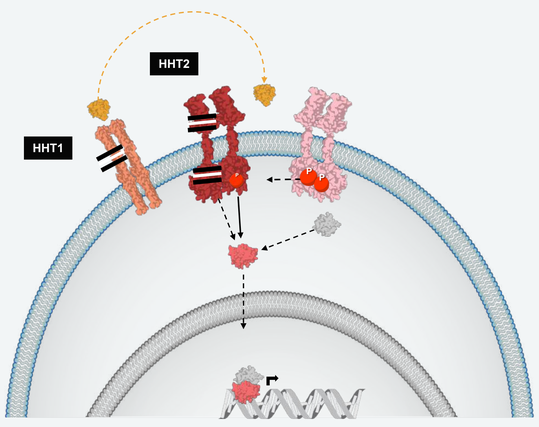
DGL bispecific antibody in DVD-Ig format

DGL molecules are bispecific antibodies comprising of two arms, each arm binding to ALK1 and BMPRII receptors in a tetrameric format

Vascular homeostasis

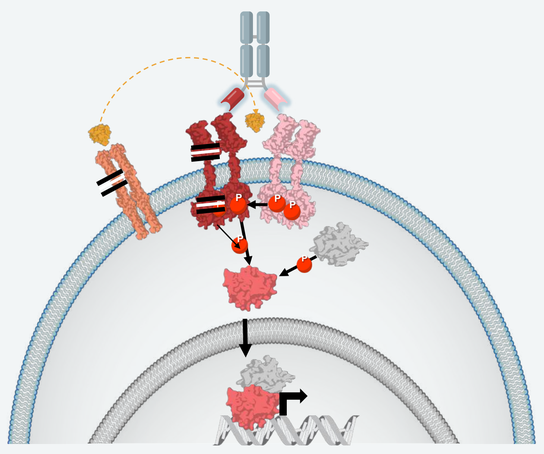


Loss of function mutations in endoglin or ALK1



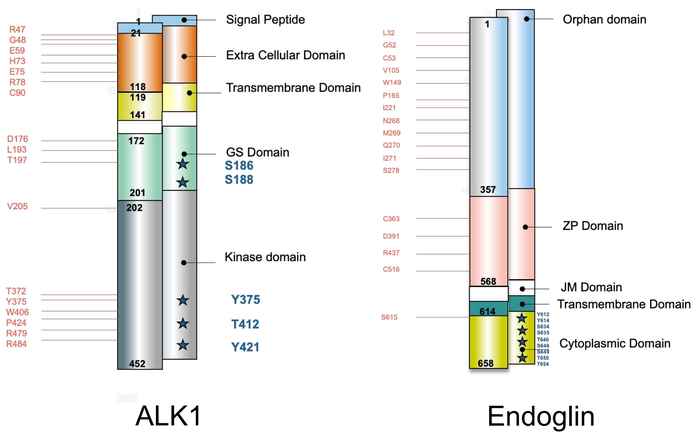
Aberrant blood vessel development

Diagonal approach ALK1:BMPRII agonist antibody



Directly restores ALK1 signaling addressing the root cause of the disease

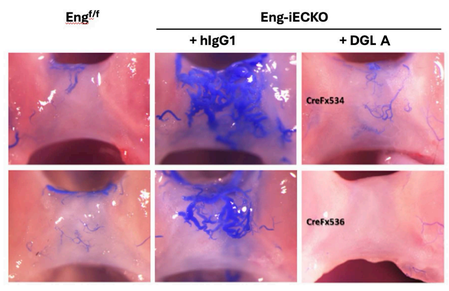
Mutations in ALK1 and ENG

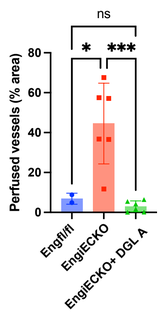


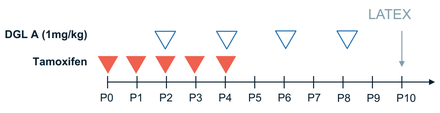
DGL molecules can restore signaling for a majority of ALK1 and ENG mutations

DGL molecule shows *in vivo* activity in ENG KO adult mice

DGL A prevents pelvic AVMs in Eng-iECKO adult mice



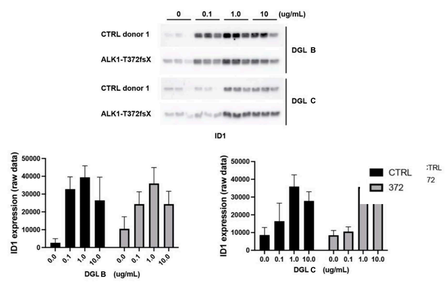




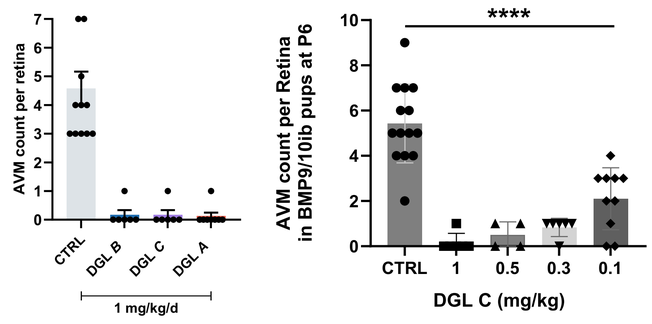
Experiments conducted by the group of Dr. Philippe Marambaud
Model described in Tual-Chalot, et al., Circ Res 2020

DGL molecule promotes signaling in HHT endothelial cells and prevent AVM formation *in vivo*

PoC in BOEC ACVRL1 mutant

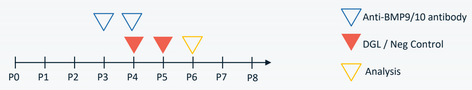


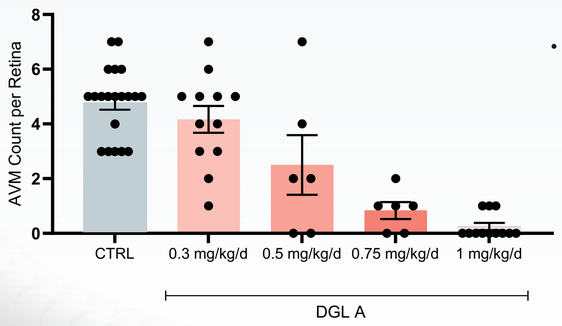
In vivo PoC in BMP9/10 imAb



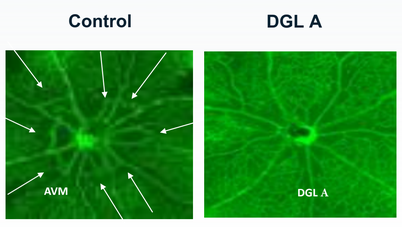
DGL molecule prevents formation of AVMs in a dose-dependent manner

Treatment protocol: mice are dosed with anti-BMP9/10 antibody the same days as DGL A or control antibody



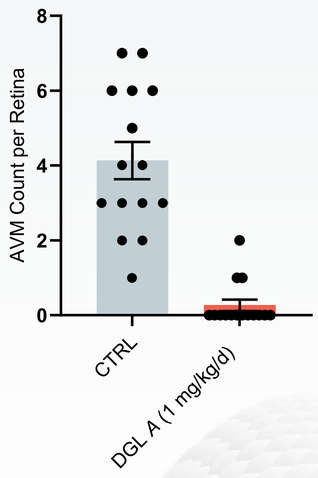


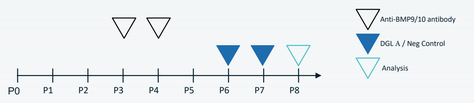
- DGL A has demonstrated potent **dose-dependent AVM resolution effect**
- Minimal efficacious dose of 0.5mg/kg enables formulation for **convenient subcutaneous dosing** in patients

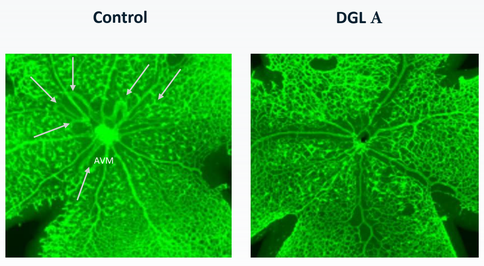


DGL molecule potently reverses AVM formation

Rescue protocol: mice are dosed with anti-BMP9/10 antibody three days prior to the first dose of DGL A or control antibody







Conclusions

- Agonistic antibodies offer a compelling therapeutic approach as they can overcome the liabilities of natural ligands and their modified variants.
- DIAGONAL platform combines computational and experimental techniques to rapidly deliver agonist antibodies to any multimeric receptor complex in a single, deterministic campaign.
- By merging innovative biotechnological techniques with detailed molecular engineering, this study underscores the emerging role of bispecific antibodies as a transformative therapeutic option for managing HHT.

Acknowledgements

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