

COMP-ANG1: VASCULAR NORMALIZATION AND NEUROPROTECTION FOR DIABETIC RETINOPATHY

The goal of this project is to effectively prevent progression of diabetic retinopathy (DR). Diabetic hyperglycemia is toxic to the retinal microvasculature, causing pericyte apoptosis, which in turn disrupts microvascular intracellular trafficking of the adherent cadherin:catenin (e.g., VE-cadherin) components of retinal vascular endothelial cell-cell junctions. While the pathogenesis of DR is complex with a variety of interlacing signals, systems and mechanisms, blood-retinal barrier dysfunction is a key element, as multiple growth factors and cytokines promote dissolution of cell-junctions, disrupting cell-cell contact and junctional integrity, leading to leakage, migration, and proliferation of microvascular endothelial cells. DR derives in large part from this vascular-destabilization process, resulting in an inflammatory milieu, angiogenesis, edema, neuronal loss, and gliosis. Our central hypothesis is that long-term gene delivery of COMP-Ang1 (angiopoietin-1 combined with the short coiled-coil domain of cartilage oligomeric matrix protein) has efficacy in promoting vascular normalization and neuroprotection in the presence of retinal ischemia. These experiments will elucidate the mechanisms underlying the vascular normalizing and neuroprotective capabilities of COMP-Ang1, define methods for optimizing the formulation of AAV.COMP-Ang1 gene delivery to the retina, particularly within the context of DR, and establish whether COMP-Ang1 promotes vascular regeneration by enhancing endothelial progenitor cell integration and vascular repair. Further, this project will enhance our understanding of the underlying mechanisms of DR. The Specific Aims are to determine whether: 1. Broadening tropism of AAV.COMP-Ang1 improves its retinal delivery 2. COMP-Ang1 has an ameliorative impact on intracellular mechanisms of diabetic retinal inflammation, endothelial flow responsiveness, and neuronal retinal dysfunction 3. COMP-Ang1 improves neurovascular structure and function in diabetic retinopathy 4. Constitutive expression of COMP-Ang1 enhances endothelial progenitor cell (EPC) integration in diabetic retinal vasculature This proposal is being submitted under the US-Ireland R&D Partnership Programme, and brings together investigators from the Moran Eye Center (University of Utah, US), the School of Biotechnology (Dublin City University, Republic of Ireland) and the Centre for Experimental Medicine (Queen's University of Belfast, Northern Ireland). The project fulfills the requirements of the US-Ireland R&D Partnership Programme by increasing the level of collaborative R&D amongst researchers across the three nations in an area focused on the development of new therapeutic approaches for enhancing disease prevention and healthcare. Funding for the proposed work in Dublin and Belfast will come from the Republic of Ireland (Science Foundation Ireland) and Northern Ireland (R&D Office), respectively. NIH funding is requested for the US component.

The goal of this project is development of a novel therapeutic, called COMP-Ang1, to promote vascular normalization and neuroprotection to treat diabetic retinal ischemia.