INTRACEPTOR INTERFERENCE OF VEGF PATHWAYS IN CORNEAL ANGIOGENESIS

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Public Abstract

The growth of blood vessels (i.e., angiogenesis) is a key element in loss of vision after injury to the cornea, front of the eye, as the cornea's transparency requires it to be free of blood vessels. Current drugs attacking growth of blood vessels work primarily by targeting molecules involved in blood vessel growth outside cells. However, blood vessel cells make their own factors and receptors that render them resistant to such extracellular therapies. Developing ways to fight angiogenesis by attacking processes inside the cell would contribute to preserving or restoring vision after injury to the cornea and may also help other diseases involving angiogenesis, such as cancer, diabetes, and macular degeneration.

In this proposal, we present a novel approach that attacks a key factor (VEGF) in blood vessel formation by sequestering it within cells using "intraceptors," which are subunits of a VEGF receptor coupled with an amino acid sequence that enables sequestration. We feel that by disrupting the VEGF pathway intracellularly, we can disrupt the self-stimulating feedback loops that power blood vessel formation in many cancers. Further, we present an approach to deliver intraceptors using nanoparticles to enable long-term expression with systemic administration. We first plan to demonstrate the effectiveness of intraceptors in the cornea. Then we will further characterize the mechanisms of intraceptor activity. Finally, we will determine the effectiveness of nanoparticles for delivery of these intraceptors in a long-term fashion. Tasks to be undertaken during this research will include assessment of these intraceptors on human blood vessel cells in culture, human corneal cells in culture, and effectiveness in suppressing vessel formation in a mouse model of corneal injury.

The proposed research will, hopefully, advance our understanding of the mechanisms needed to disrupt angiogenesis, as well as provide a basis for a novel treatment to suppress angiogenesis with long-term therapeutic ability. We anticipate that intraceptors will successfully inhibit VEGF expression and angiogenesis induced by injury. Furthermore, we predict that intraceptors will be able to regress pre-existing angiogenic blood vessels. Lastly, we anticipate that nanoparticles will be able to successfully deliver intraceptors for long-term biological use.

The ultimate applications of this research may be useful in treating eye injuries after trauma such as with shrapnel or Improvised Explosive Devices to prevent development of or induce regression of abnormal blood vessels in the cornea in an effort to help restore or preserve vision. Furthermore, this therapeutic approach may be of potential utility in cancer, diabetic retinopathy, or macular degeneration. It may take 5 years or more to achieve such military health-related outcomes.