Novel Strategy to Combat Corneal Injury at Early and Late Stages and to Promote Transplant Survival

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PUBLIC ABSTRACT

Among the five senses, vision is the most vulnerable in military defense. Its damages constitute a disproportionally high percentage of battlefield injuries. After traumatic, chemical, toxic, inflammatory or infectious damage, the normal alymphatic cornea is rapidly invaded by newly formed lymphatic vessels, which accelerate immune responses and transplant rejection. The graft rejection rate in lymphatic-rich cornea can be as high as 90%. However, to date, there is still no effective treatment for this high rejection condition. It is therefore an area of pressing military need.

This project aims to develop novel therapeutic strategies to modulate corneal lymphatic formation at various stages after acute or chronic injury and to promote transplant survival in the modified host cornea. It is based on a large amount of scientific evidence we have collected over past few years on corneal lymphatic research using a repertoire of in vivo, in vitro, and in real-time model systems and methods. For a brief summary, the most pertinent data to this project include that corneal lymphangiogenesis (LG; formation of lymphatic vessels) is a primary mediator of transplant rejection and that corneal LG experiences different stages after a pathologic insult. As LG proceeds from early to late stage, luminal valves are formed inside lymphatic vessels, which functions to direct lymph flow for transplant rejection; and corneal LG can be interfered with molecular blockade of lymphatic specific factors, such as VEGFR-2, VEGFR-3, and integrin alpha-9. While combined blockade of VEGFR-2 and VEGFR-3 markedly suppresses corneal LG at both early and middle stage, integrin alpha-9 is critically involved in valve formation.

We propose to achieve the following objectives with this project: (1) assess the therapeutic effect of combined blockade of VEGFR-2 and VEGFR-3 on modification of corneal graft beds with early- or middle-stage LG and transplant survival on modified cornea; and (2) assess the therapeutic effect of combined blockade of integrin alpha-9 and VEGFR-3 on modification of corneal graft beds with late-stage LG complicated with valve formation and corresponding transplant survival on modified corneas. Preclinical models of corneal LG and transplantation will be used to evaluate the therapeutic effects of neutralizing antibodies against VEGFR-2, VEGFR-3, or Itga-9. Since anti-human VEGFR-2 and VEGFR-3 antibodies are already in clinical trials for cancer treatment, it is hopeful that this study will result in clinical trials for eye diseases in the near future.

This study directly addresses the Vision Research Program Translational Research Award Focus Area of "mitigation and treatment of traumatic injuries, war-related injuries, and diseases to ocular structures and visual system." It is aimed to provide novel treatments for corneal injuries at both acute and chronic phases. This study is important because (1) it is estimated that corneal blindness affects 39 million people worldwide and accompanies many corneal diseases after a variety of pathologic insults and (2) the burdens associated with transplant rejection is tremendous due to the high rejection rate and poor prognosis, irrespective of current treatment modalities. This
study promises to provide novel and radical strategies to promote transplant survival for ultimate vision restoration. Moreover, as a major circulatory system in the body, the lymphatic network penetrates most tissues. Its dysfunction has been found in a wide array of disorders from cancer metastasis to major organ transplant rejection, which affect hundreds of millions of people worldwide. Results from this study using the cornea, one of favorite tissues for lymphatic investigation in general, may shed some light on the development of new therapeutic protocols for other lymphatic diseases outside the eye as well.