Molecular Solutions to Low Vision Resulting from Battlefield Injuries

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TECHNICAL ABSTRACT

Background: An increasing percentage of battlefield injuries occur to the eye in modern warfare. Even treatable battlefield injuries to the eye can lead to blindness because of collateral damage to adjacent tissues. This blindness results from injury-induced inflammation, cell death, failure to regenerate or repair, and development of scar tissue. This proposal is a multidisciplinary project that addresses corneal blindness resulting from abrasions, burns, and penetrating wounds acting on normal corneas or exaggerated in corneas that have undergone refractive surgery, as well as retinal blindness resulting from physical trauma, infection, or laser-induced injuries that destroy retinal nerve cells.

Objective/Hypothesis: The effect of battlefield trauma on corneal, retinal, and optic nerve function and on dry eye after refractive surgery will be investigated, and molecular solutions to prevent or reverse the damage will be developed. We hypothesize that targeted molecular interventions can preserve vision threatened by trauma-induced corneal and retinal inflammation, corneal and retina/optic nerve apoptosis, ocular surface dry eye after refractive surgery, and retinal degeneration.

Specific Aims: (1) Prevent the consequences of trauma-induced inflammation in the cornea and retina using molecular strategies utilized by ocular immune privilege. (2) Prevent cell death in the cornea and retina/optic nerve after trauma using molecular strategies directed at regulating apoptosis. (3) Prevent the consequences of trauma after refractive surgery by developing molecular strategies to diagnose dry eye syndromes. (4) Repair injured retina after trauma by tissue engineering a composite retina using the molecular strategy of integration of retinal stem cells into explant cultures.

Study Design: To prevent consequences of trauma-induced inflammation in the cornea, a gene therapy approach of providing soluble Fas ligand to the cornea will be used to determine if this ligand can suppress the inflammation of bacterial infection and corneal burns in a murine model. To prevent consequences of trauma-induced inflammation in the retina, we will examine the extent to which an exogenous source of transforming growth factor-beta, thrombospondin, and somatostatin, delivered into the subretinal space, can suppress inflammation within the retina secondary to autoimmune uveoretinitis and light-induced damage in a murine model. To prevent cell death by apoptosis and promote regeneration in the cornea after trauma, we will use molecular strategies to identify the anti-apoptotic gene with the greatest capacity to suppress corneal cell apoptosis, using murine models. To prevent cell death and promote regeneration in retina after trauma, we will use murine models to determine the extent to which systemic treatment with lithium chloride, which increases the level of a specific anti-apoptotic protein in nerves, can prevent or reduce collateral damage to retinal neurons and promote optic nerve regeneration following injury. To prevent the consequences of trauma after refractive surgery, we will determine how to minimize dry eye and related consequences of trauma after LASIK and LASEK refractive surgery by determining the effects of interoperative variables on the prevalence of dry eye and developing new tests to predict predisposition to refractive surgery-induced dry eye. To repair the injured retina after trauma, we propose to generate, in vitro, stem cell polymer composites for transplantation to the injured retina by applying the new technologies of tissue engineering, biodegradable polymers, and stem cells.

Relevance: Low vision caused by battlefield injury to the cornea, retina, and optic nerve is an ever-increasing problem caused by modern...
warfare. The consequences of this trauma, including inflammation, scarring, and degeneration, can be prevented if the appropriate molecular strategies can be developed. The research described in the present proposal is aimed at developing molecular solutions to prevent the collateral damage that occurs as a result of trauma to critical components of the eye, the cornea, its associated tear film, the retina, and the optic nerve. In addition, this research will aid the civilian population by using the same strategies designed for military use to prevent the inflammation and scarring associated with corneal infection, corneal burns, failed corneal transplantation grafts, and refractive surgery-induced corneal flap irregularities and dry eye, as well as the neuronal cell death that accompanies glaucoma and retinal degenerative diseases.