Project Title: Treatment of Cornea Using Transcytotic Delivery in the Tear Film
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Background: With the increased prevalence of asymmetric warfare, improvised explosive devices (IEDs) have raised the incidence of blast injuries. The visual system is easily impacted by these polytraumatic injuries; furthermore, during a recent study, half of all eye injuries sustained in the battlefield resulted from IEDs. The exterior of the eye (cornea) sustains the direct damage. Blasts leave microscopic debris/cuts that are challenging to extract/repair in field hospitals. Debris may not be effectively removed until the warfighters are moved to hospitals thousands of miles away. Better ocular drug delivery strategies need to be applied immediately after onset of trauma to speed healing and preserve remaining tissue. Unfortunately, ocular drug delivery remains a challenge due to the rapid drainage of the tear film.

Objective: Utilize novel polypeptide-based nanoparticles to target the LG for ocular delivery of an emerging biopharmaceutical protein called lacritin.

Hypothesis: Therapeutic nanoparticles assembled from protein polymers that target the coxsackievirus and adenovirus receptor (CAR) can target sustained delivery of the biopharmaceutical, lacritin, in the tears. Enhanced ocular bioavailability will reduce dosing frequency and improve efficacy for this and other ocular biopharmaceuticals.

Specific Aims: 1) Characterize the transcytotic behavior of knob elastin like polypeptide (ELP) NPs in the lacrimal gland; 2) synthesize and evaluate lacritin-ELP; and 3) test lacrimal gland transcytosis of lacritin/knob NPs.

Study Design: Briefly, the aims of this study are: AIM1) Characterization of the transcytotic behavior of LG-targeted ELP nanoparticles. They will follow-up on the observation that the adenoviral knob protein mediates transcytosis from the blood to tear side of the LG. Transcytosis will be characterized ex vivo and in vivo utilizing intravital fluorescence microscopy and biochemistry. The deliverable will be an LG-targeted nanoparticle capable of carrying cargo across the lacrimal gland and to the surface of the eye. AIM2) Synthesis and evaluation of lacritin-ELP. The purpose is to characterize the biological activity of lacritin-ELP fusion proteins. AIM3) Lacrimal transcytosis of lacritin/knob nanoparticles. The therapeutic effect of ELP-targeted lacritin will be optimized in a murine model of corneal epithelial wound healing.

Relevance: To maintain or recover sight after a war-related injury, there is a strong need to improve the healing and recovery of the ocular surface following injury. Some of the most powerful emerging drugs are protein biopharmaceuticals; however, there remain few effective methods for retaining therapeutic concentrations of protein drugs at the eye surface. This project will explore a new approach to treat corneal injury with targeted biopharmaceuticals.