Rapid Delivery of Protein Therapeutics into Retinal and Corneal Cells Following Intravitreal Injection

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Background: In the combat theater, members of the Armed Forces are exposed to a very large variety of traumas that can ultimately lead to blindness. These traumas include blast pressure waves or chemical burns. Immediately following a blast pressure wave, a very specific biological pathway is triggered in the eye known as apoptosis. This pathway is ultimately responsible for causing the death of light-sensitive cells that are responsible for vision. Unfortunately, unlike the liver or skin, the light-sensitive cells in the eye cannot regenerate. Thus, once these cells are lost, the individual suffers from blindness that is irreversible. During the previous few decades, a significant amount of knowledge has been gained about the process of apoptosis. Specifically, we now know of several hundred different drugs (proteins) that can arrest the progression of apoptosis. The barrier to doing so in the context of the combat theater is that there is no method currently available to deliver these proteins to the inside of the cells of the eye. Using ongoing funding from the Department of Defense, we have developed the first such efficient system to deliver proteins to the inside of the light-sensitive eye cells -- specifically those cells that are lost following blast trauma. Subsequent to injury, a part of the healing process involves the pathway of inflammation. If inflammation is uncontrolled, it can result in the formation of scar tissue that exacerbates loss of vision. The process of light-sensitive cell loss due to apoptosis and the process of scarring following chemical burn can be modeled in mice exposed to near ultraviolet light and chemical alkali burn respectively. When approached in a humane manner, these animal models can be used as a reliable system in which to validate our technology prior to testing in humans. Importantly, our drug delivery system is practical and not merely theoretical for the following reasons: (1) It utilizes a technology that is already found to be safe in humans. (2) It utilizes an injection procedure (directly into the eye) that is currently used by millions of American civilians on a monthly basis and thus has been well tested and found to be safe. (3) The major component of the technology is stable at room temperature and thus can be envisaged to be included in the medical kit.

Our study is thus relevant to the Fiscal Year 2015/2016 Vision Research Program Technology/Therapeutic Development Award Capability Gap of: Inadequate mitigation and treatment of damage to ocular structures and the visual system consequent to military-relevant injuries and diseases incident to military service; and a Focus Area of: Preclinical animal studies to evaluate safety and/or efficacy of treatments or technologies returning form and function after traumatic injury. However, our technology is a platform for the delivery of many types of molecules into the cells of the eye and thus we believe the potential long-term impact is even greater than the scope of the current study.

Upon completion of this study, we will have demonstrated the practical feasibility and biologically validated our protein delivery system in animal models in which we have triggered the same biological pathways that are triggered in members of the Armed Forces in the combat theater following blast trauma or pathogenic healing following exposure to chemicals in the combat theater. Because the major component of this system is already found to be safe in humans, we envisage that the Food and Drug Administration would only require some bridging studies in the eyes of monkeys prior to testing in humans.

While we envisage that the major benefit will be to members of the Armed Forces as a consequence of blast trauma or chemical injury in the combat theater, certain diseases in humans such as retinitis pigmentosa also involve light-sensitive cell loss due to apoptosis. Thus, it is likely that beyond its use in the combat theater, our technology will potentially also help reduce loss of vision in the civilian population.
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