Development of a Small Molecule Drug Targeting Galectin-3 to Prevent Neovascularization and Fibrosis of Ocular Tissues

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Objectives and Rationale: Eye injuries can occur in the front and the back of the eye, i.e., cornea and retina. Proper healing is essential to regain vision. Unfortunately, unlike scars on the skin, which are mostly a cosmetic problem, scars on the cornea and retina impair the affected individual's vision and can even cause blindness. Maintaining a "scar-free" cornea or retina after healing is extremely challenging with the available treatments for eye injuries. Currently, injuries caused due to chemical exposure, fragmentary munitions explosions, penetrating wounds to the eye, or blunt force trauma often result in scarring and fibrosis of the affected tissue, leading to severe vision impairment. Our pilot studies in animal models of scarring, fibrosis, and growth of blood vessels in the cornea suggest galectin-3, a carbohydrate-binding protein, as an attractive drug target for the prevention and treatment of eye fibrosis. We hypothesize that inhibiting galectin-3 early after injury can reduce vision loss due to pathological healing. We propose animal studies in mice and rabbits to identify the most potent galectin-3 inhibitor out of four existing molecules and to develop it for optimal reduction of fibrosis in the healing process of eye injuries, thus providing a novel strategy for controlling scarring.

Ultimate Applicability and Potential Impact: Target population: The proposed treatment could benefit anyone at risk of scar formation in the intricate eye tissues as a result of eye injury, such as: (1) Corneal scarring: a third leading cause of global blindness, which is often caused due to injury, trauma, and/or infection to the eye. Although corneal transplantation is effective at restoring vision, some patients are at high risk of graft rejection due to the presence of blood vessels in the injured cornea. (2) Subretinal scarring, which occurs subsequent to blunt force trauma, irreversibly damages photoreceptors and leads to substantial vision loss. (3) Pre-retinal scarring, which occurs subsequent to penetrating wounds to the eye and, in almost 50% of cases, leads to proliferative vitreoretinopathy (PVR), a potentially blinding disease. Current PVR management is restricted to surgical repair of the detached retina, and no effective drug treatment has been found.

Clinical Applications, Benefits, and Risks: The proposed drug target has broad clinical applications to prevent scar formation and loss of vision after various kinds of eye injuries. All the drugs to be tested are nontoxic in vitro. Therefore, we expect that the benefits will far outweigh the risks.

Projected Timeline: During the proposed 3-year project, preclinical animal studies will be completed. Subsequently, Good Manufacturing Practices (GMP) manufacturing of the selected drug substance and drug product will be conducted, along with safety and toxicological testing in two species. At this point, about 3 years after project initiation, the drug is expected to be ready for clinical trials and thus benefiting patients.

Advancing the Field of Vision Dysfunction: Scarring of ocular tissues is the leading cause of blindness, and yet current treatment options are limited and their outcomes are typically poor. There currently are no Food and Drug Administration-approved drugs that selectively reduce scar formation. If successful, the study will represent a significant advance in controlling scar formation after ocular injuries, thereby preventing vision loss.

Benefit to Military and Other Individuals Living with Visual Dysfunction: With the small, fragmentary nature of modern weaponry, injury patterns sustained by combatants have significantly changed. Notably, the incidence of ocular injuries has increased from 0.5% of all injuries during the American Civil War to 13% during Operations Iraqi and Enduring Freedom (OIF/OEF). During OIF/OEF alone, 24% of the Soldiers suffered ocular trauma despite wearing eye protection, and the number is likely higher, as 41% of cases have undocumented status of eye protection. Approximately 5% of Soldiers in OIF/OEF were enucleated (had complete removal of the eye) after failed recovery from eye injury, at a cost of at least $38 million. This estimation is based on 198 (5%) Soldiers with ocular trauma in OIF/OEF alone, and on at least $189,000 in Veteran Disability Compensation over the expected lifetime of a 20-year-old E4 (Specialist) who loses an eye in the line of duty. If an O5 (Lieutenant Colonel) with 18 years of service loses an eye in the line of duty, he will receive at least $477,000 in compensation. Scarring and pathological healing response in traumatized ocular tissues can lead to vision loss, which could be particularly devastating for Soldiers by
destroying their ability to see and accomplish their mission on the battlefield, thus leading to an immediate loss of career, in addition to the obvious major lifestyle changes encountered by any individual losing his/her sight. It is our hope that the proposed galectin-3 inhibitor administered as eye drops and/or injectable gel can be used to properly control ocular scarring, and thereby prevent vision loss and even enucleation in Soldiers and Veterans with ocular trauma.