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Fluorenone Drug for Treatment of Combat-Related Traumatic Optic Neuropathy

Principal Investigator: PETRUKHIN, KONSTANTIN

Institution Receiving Award: COLUMBIA UNIVERSITY MEDICAL CENTER

Program: VRP

Proposal Number: VR180114

Award Number: W81XWH-19-1-0851

Funding Mechanism: Investigator-Initiated Research Award

Partnering Awards:

Award Amount: \$809,722.00

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PUBLIC ABSTRACT

Traumatic optic neuropathy (TON) is a frequent cause of significant visual loss after the combat-related frontal head trauma. In TON, the injury of the optic nerve originates from concussive forces to the head. There is no clinically proven therapy for improving visual outcomes in TON patients. Our goal is to conduct studies needed to advance the proposed drug candidate, B-3(+), to clinical development for the TON indication. The injury-induced swelling of the optic nerve leads to its compression, triggering significant damage to optic nerve axons, which transmit visual information from the eye to the brain. Reduction of optic nerve swelling is a sound strategy for the prevention of TON-related loss of vision. B-3(+) is an abandoned drug that has demonstrated significant efficacy in preventing mortality in animal models of concussive brain injury. B-3(+) acts as a polypharmacological agent capable of significantly reducing insult-induced nerve cell swelling in a number of experimental systems. Given the efficacy of B-3(+) in animal models of traumatic brain injury and assuming that mechanisms of neuronal damage in the optic nerve are likely to be analogues to those of the rest of the central nervous system, we suggest that intraocularly administered B-3(+) may be used as a treatment for traumatic optic neuropathy associated with combat-related traumatic brain injury. Our preliminary data indicates that intravitreally administered B-3(+) confers optic nerve protection in the guinea pig optic nerve crush model which is consistent with desired preclinical efficacy of the drug candidate.

The overall objective of the proposed project is to conduct studies needed to support regulatory filings required for B-3(+) to enter clinical development for the TON indication. B-3(+) had been systemically administered to humans in Phase I clinical trials for trauma-induced brain edema indicating that it successfully passed some hurdles of preclinical development. However, B-3(+) has never been approved by the US Food and Drug Administration due to kidney toxicity associated with the systemically administered drug. We suggest that intraocular delivery of relatively small B-3(+) doses would lead to the negligible systemic exposure, alleviating the concern for drug nephrotoxicity. Additional studies are required for advancing B-3(+) as a treatment for TON. We will conduct B-3(+) evaluation in a standard set of in-vitro ADMET assays and develop a data package required to support preclinical and clinical development of the drug candidate. In addition, we will perform characterization of ocular and systemic pharmacokinetic properties of B-3(+) in beagle dogs, and define the range of efficacious ocular drug concentrations in the guinea pig optic nerve crush model. The results of our study will facilitate clinical development of B-3(+) as a treatment for TON.

Literature indicates that 59% of all blast-exposed patients admitted to Walter Reed Army Medical Center in 2003-2005 received a diagnosis of traumatic brain injury. Traumatic optic neuropathy represents a devastating ophthalmic complication in Soldiers with closed or penetrating head trauma. There is no clinically proven therapy for improving visual outcomes in TON patients. Identification of a new treatment option for TON will have a significant impact on medical management of this condition thus providing an important military benefit.

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