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Prevention of Blindness by Novel Cytoprotective Small Compounds

Principal Investigator: MATSUYAMA, SHIGEMI
Institution Receiving Award: CASE WESTERN RESERVE UNIVERSITY
Program: VRP
Proposal Number: VR190103
Award Number: W81XWH-20-1-0735
Funding Mechanism: Investigator-Initiated Research Award - Funding Level 2
Partnering Awards:
Award Amount: $804,996.00

View Technical Abstract

PUBLIC ABSTRACT

Background: A new chemical that protects cells from death was invented. We succeeded in developing a new chemical that rescues cells from death. The goal of this project is to develop a strategy to use this new chemical to rescue cells in the eyes and brains of patients who experienced traumatic head injury and/or eye exposure to bright light. The new chemical is named Bax Inhibiting Small Compound (BISC). Bax is a protein expressed in our cells. Bax is known to induce cell death in the eyes and brain after traumatic injuries to the head and eyes. Therefore, BISC is expected to prevent blindness by rescuing cells from death in the eyes and brain after the traumatic damage.

A portable medicine that can be taken orally once a day. The preliminary study in rodents suggests that a single oral administration of BISC can maintain effective concentration in the blood, retina, and brain over 24 hrs. Therefore, success of the proposed study will [be the ability to] develop a potable and orally administrable medicine that can prevent blindness in military personnel who have experienced traumatic injury to the head and/or eyes.

BISC can be used to rescue wounded Soldiers and civilians. In addition to preventing blindness, BISC is also expected to be effective in preventing poor recovery of various organs and tissues after traumatic injuries since Bax-induced cell death is known to be a cause of the degeneration of the damaged organs. For example, the ischemic condition due to bleeding triggered Bax-induced cell death when blood was resupplied in the brain, heart, liver, and kidney. Therefore, BISC administration is expected to prolong the survival of injured patients by preventing Bax-induced cell death in various tissues. Since BISC is orally administrable, BISC may become a portable medicine that can extend the survival period of wounded Soldiers and civilians in the battlefield or disaster. A similar ischemic condition occurs during the organ transplant procedure since the extracted organ is kept in an ischemic condition during transportation. Therefore, there is a time limit for organ transportation. Previous studies showed that the inhibition of Bax-induced cell death was effective in prolonging the lifespan of the extracted organ and tissue. Since BISC can protect cells from Bax-induced cell death, it is expected that BISC can be utilized to extend the storage and transportation period of the organs for the transplantation.

Proposed Studies: Our preliminary study showed that BISC maintains effective concentration in the blood, retina, and brain 24 hrs after a single oral administration using the rat model. In the proposed study, we will develop the most effective strategy to prevent blindness using three mouse models of traumatic injury-induced blindness. First, we will analyze the time-dependent changes of BISC concentration after an oral administration of BISC in the blood, retina, and brain between 2 hrs to 48 hrs (rats and mice will be used). To find the minimum dose to achieve the effective concentration in the retina and brain, we will examine four different doses for the time-course analysis.

Based on the analysis above, we will determine the minimum essential dose and administration cycle period (for example, once a day or twice a day) of BISC treatment. Then, BISC will be administered to three mouse models of traumatic injury-induced blindness to determine its effectiveness in protecting cells in the retina and brain. The three models are (1) Acute optic nerve injury-model (direct injury to the nerve) inducing cell death in the retina and brain within 1 week, (2) Chronic optic nerve injury model (glaucoma model) inducing cell death in the vision system at the age of 8-12 months, and (3) Bright light-induced blindness mouse model (the eye exposure to the bright light causes cell death in the eyes within 1 week). The results in the mouse model will be used to optimize the dose and administration cycle period further to achieve the best protocol for using BISC to prevent blindness.

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