DEPARTMENT OF DEFENSE - CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

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Retina-Targeted Estrogen Prodrug: A New Concept for Retinal Protection

Principal Investigator: WU, HONGLI
Institution Receiving Award: NORTH TEXAS, UNIVERSITY OF, HEALTH SCIENCE CENTER, FORT WORTH
Program: VRP
Proposal Number: VR190074
Award Number: W81XWH-20-1-0896
Funding Mechanism: Investigator-Initiated Research Award - Funding Level 1
Partnering Awards:
Award Amount: $376,863.00

View Technical Abstract

PUBLIC ABSTRACT

The retina is a thin layer of light-sensing tissue that is located in the back of the eye. The healthy retina gives us the sense of vision, allowing us to see the surrounding world and people we love. Retinal injury due to strong light exposure, such as laser, nuclear explosion, and fire, during military duties often results in serious vision damage to Soldiers. In spite of intense research, there is currently no effective therapy to prevent vision loss once retinal damage has begun in the back of the eye. Therefore, for those Veterans identified with war-related eye conditions, up to 75% experience short-term visual damage or permanent vison loss. The objective of this project is to help these visually impaired Veterans by identifying an effective and safe site-specific delivery agent that can stop vision loss.

Other than the well-known function of estrogen as a sex hormone, estrogen exhibits strong neuroprotective effects, including within the retina. Both animal and clinical studies have shown that estrogen can strongly protect the retina from bright light-induced retinal damage. However, the side effects of estrogen, including increased risks of cancers and blood clot, greatly limit its clinical use. Another serious issue for estrogen is the feminizing effect of estrogen in male Veterans. Therefore, developing the retina-targeted estrogen therapy is crucial for its use as a preventative and/or curative agent for treating retinal damage.

To overcome these limitations, we have developed a smart estrogen called DHED. This molecule can only be converted as active estrogen by the enzyme presented only in the brain and the retina. We have worked for more than a decade and tested it as a brain and retina-specific "prodrug." Compared with estrogen, DHED has several advantages: 1. DHED does not have cancer-promoting effects. 2. DHED does not affect male function and can be safely used in male Veterans. 3. DHED is more effective in protecting the brain and retina. Our objective of the present study is twofold. We will test the effects of DHED in protecting light-induced retinal damage. Additionally, we will confirm that DHED protects the retina without affecting the rest of the body such as the heart, liver, and kidney.

In the short term, we anticipate that successful completion of the proposed project will identify the unprecedented potential of the small-molecule and non-steroidal DHED, as an efficacious and safe site-specific delivery agent to produce robust E2-mediated retinal neuroprotection at the preclinical level. Thereby, the proposed experiments will likely lay the groundwork for the further development of this novel neuroprotective intervention to finally combat structural and functional damage of the retina and stop or slow vision loss owing to bright light-induced retinal damage to military and civil populations.

In the long term, potential embodiments and deliverables resulting from the proposed project after adequate regulatory follow-up studies are acute preventative treatment of high-risk groups prior to engaging in high-risk work and acute treatment of damage of the retina relevant to military personnel, Veterans, and civilians. As such, our patented approach has the potential not only to advance the field of vision research but also to change how neurodegenerative diseases can be treated.

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