**Discovery of FDA-Approved Drugs that Promote Retinal Cell Survival or Regeneration**

**Principal Investigator:** MUMM, JEFFREY S  
**Institution Receiving Award:** JOHNS HOPKINS UNIVERSITY  
**Program:** VRP  
**Proposal Number:** MR130301  
**Award Number:** W81XWH-14-1-0407  
**Funding Mechanism:** Vision Research Program - Translational Research Award  
**Partnering Awards:**  
**Award Amount:** $1,000,000.00

**PUBLIC ABSTRACT**

United States military personnel are subjected to a high incidence of injuries, both in combat and non-combat zones, that result in physical trauma to facial tissue, including the eye (a total of 50,000 non-superficial eye injuries from 2000-2010). Typically, extensive eye damage leads to greatly diminished visual acuity or complete loss of vision. Although ocular combat casualty care has greatly improved, once retinal tissues/cells have been extensively damaged, there is no therapy currently available that is capable of restoring visual function. This is a striking fact as a vast majority of the afflicted are enlisted servicemen in their 20s, signifying that these patients and their families will live with the after-effects of these injuries for decades. Some of the difficulties they will face, aside from the obvious recurring medical expenses, include a diminished capacity to find employment and earn at the same income level as their non-Visually challenged cohorts. This serves to underscore that the true cost of these injuries, both economically as well as on a personal level, must be evaluated over a lifetime. Therefore, to reduce these costs to U.S. military personnel and to improve the quality of life for the affected servicemen and their families, we seek to develop protective regenerative therapies for those patients who have suffered severe traumatic ocular injury.

Here we propose to use a novel drug discovery approach to identify drugs that promote improved survival or repair of eye cells and tissues. Fish and mouse models of ocular trauma will be used to screen a large "library" of Food and Drug Administration-approved drugs, thus to "repurpose" existing drugs for new uses. Importantly, the same "adult" stem cells of the eye responsible for protection and regeneration in these model species appear to have an untapped potential for repair in the human eye. We seek to unlock this potential in order to provide new curative therapies to patients facing loss of their sight. Furthermore, as the drugs being evaluated have already been approved for use in humans, moving drugs through the approval process (e.g., clinical trials in human patients) can proceed more efficiently, thus speeding the process of delivering life-changing therapies to patients in need.

We have brought together a team of experts in vision research for this proposal. All experts and their respective teams are housed in new state-of-the-art research facility of the Wilmer Eye Institute in The Johns Hopkins University School of Medicine: The Robert H. and Clarice Smith Building. This 200,000 square foot building was opened in July 2009 and contains five floors designed for laboratory research. The Smith Building has been a major step forward for Wilmer's research programs because it facilitates active scientific collaboration through its open lab design and because it has allowed the majority all our ophthalmology researchers to be centralized in one building.

We will initiate our studies in zebrafish as this species allows researchers to assess drugs on a large-scale (nearly 50,000 data points per day) directly in a living animal model. We will then optimize drug delivery for mammals and further validate our initial findings by screening lead compounds in mice, a mammalian animal model more closely related to humans. Thus, in the end we will have identified...
factors that promote eye tissue survival and/or regeneration in two vertebrate model species. Validating drug effects across multiple species increases the likelihood that beneficial outcomes will "translate" to humans. Conservatively, identifying factors that promote survival of damaged eye tissues would help to stop progressive loss of visual acuity in ocular trauma patients. Optimally, identifying factors that promote regeneration would have the potential to return visual function to injured military personnel, a vast improvement to current therapies, which only seek to slow vision loss.

Our strategy of identifying and repurposing existing drugs has already been validated in zebrafish; a drug initially discovered to regulate red blood stem cells in zebrafish is now being tested for its ability to improve engraftment of transplanted cord blood to bone marrow in Phase II clinical trials. In these studies, the identified compound went from preclinical drug discovery to Phase II clinical trials in 7 short years; typically, just the drug discovery process alone can take up to 10 years to generate one lead compound. The main caveat of the proposed studies, as with all drug discovery projects, is that there is no guarantee that identified lead compounds will have a true therapeutic benefit in humans. However, we strongly feel that the proposed approach allows the process of discovery to be markedly accelerated, switching the emphasis from when will we find a cure to what will the cure be.