**Project Title:** Characterization of Molecular Mechanism of Ocular Blast Trauma  
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**Background:** Ocular damage amongst war fighters has skyrocketed in recent wars due to massive use of explosive munitions that target people and vehicles. One of the most vulnerable body parts in primary blast injury are the air-fluid interfaces of the eye. When the head is exposed to blast explosion, cellular tissues in anterior and posterior chambers of the eye are rapidly distorted and ruptured due to the envelopment of the body in the over-pressurized wave. Injuries caused by compressive and tensile mechanical forces generated by the high-pressure blast wave often involve retinal detachment, loss of retinal neurons, and degeneration of the optic nerve and loss of vision. Just as detrimental is secondary post-blast injury associated with inflammation, immune system activation and hypertrophy of retinal glial cells.

**Objective:** Characterize, at the molecular level, the signaling mechanisms that transduce the effects of pressure/mechanical trauma caused by the blast into pathophysiological responses of retinal cells.

**Hypothesis:** High-pressure blast activates mechanosensitive calcium channels (through both pressure and tensile forces), causing calcium influx and retinal cell apoptosis with a fairly rapid glaucoma like outcome.

**Specific Aims:** 1) Simulate the primary effect of the blast by quantifying the relationship between tensile and compressive components of high pressure, cell swelling and activation of pressure-sensitive channels in cells isolated from the mouse retina. 2) Focus on the relationship between pressure stimulation, mechanosensitive channel activation and its role in excitatory signaling. 3) Characterize the role of mechanosensitive channels in secondary post-blast injury by focusing on their modulation of inflammatory signaling in reactive glial cells. 4) Characterize the effect of the blast on neuronal survival, glial reactivity under *in vitro* and *in vivo* conditions, and assess the neuroprotective role of pharmacological manipulation and genetic elimination of mechanosensitive channels in mice that had been exposed to mechanical impact in an ocular trauma model.

**Study Design:** The project focuses on TRPV4, a mechanosensitive calcium channel. TRPV4 is pressure activated, and the PI proposes to study its role in retinal damage inflicted by blast (which creates a high-pressure airwave and can severely damage retinal cells, including RGCs and Müller cells). The PI has recently published that stimulation of TRPV4 with excessive calcium influx can cause apoptosis of RGCs. The strongest observation of the PI is that knockout mice have no RGC loss after TRPV4 stimulation, contrary to wild-type mice, thus creating a good animal model for studies of this channel in blast injury. Although a number of mechanosensitive retinal proteins exist, the rationale behind focusing on TRPV4 is its localization to RGCs and Müller cells, and that stimulation can cause cell apoptosis.

**Relevance:** This project addresses the urgent need to define mechano-biological coupling in the eye in molecular terms. An understanding of mechanisms involved in primary and secondary injury is essential for diagnosis and treatment of blast-induced ocular injuries. First, the proposed research will shed light on the fundamental mechanisms of blast-induced retinal injury. This could translate into therapeutic rescue on the battlefield where a single systemic injection can provide rapid treatment. Second, by elucidating how primary injury drives secondary glial activation and inflammation it may be possible to prevent long-term functional losses which will help the reintegration of soldiers in civilian life and thus impact society as a whole.