
# Novel targeted therapeutic regimen to modulate inflammatory molecular pathways for high-level and blast-associated noise

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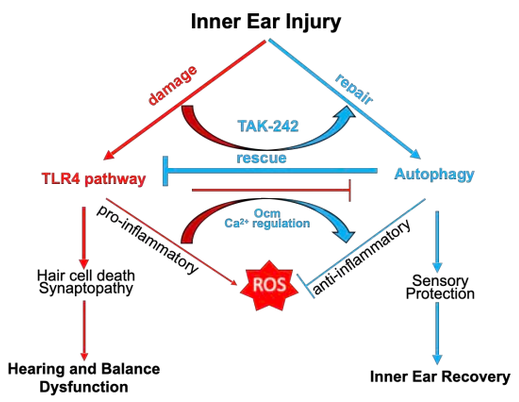
## BACKGROUND PROBLEM

The signature injury of the Iraq/Afghanistan wars is traumatic brain injury (TBI) caused by blast exposure on the battlefield (Carrick, 2015). In addition to cognitive function decrement, blast results in over 50% of patients suffering from vestibular and auditory dysfunction (Aravind 2020). Noise-induced hearing loss (NIHL), from blast or continuous noise exposure, makes hearing loss the most prevalent Department of Defense (DoD) disability (Le 2017). Permanent hearing loss develops in about 2% of the force population and 14% develop temporary hearing loss (Esquivel 2018). In the past, temporary hearing loss was thought to have minimal consequences on the hearing mechanism. However, results from animal models reveal significant cochlear synaptopathy following extended exposure to noise though only a temporary threshold shift (TTS) was recorded (Kujawa 2009). More recently, TTS has been suggested to be a potential predictor in the development of tinnitus and hearing difficulties even when hearing thresholds are consistent with pre-exposure thresholds (Brungart, 2019). Taken together, service-related hearing loss costs the DoD 1 billion dollars annually (Pfannenstiel 2014, Remenschneider 2014), but these costs likely underestimate the true impact of auditory damage. Hearing loss impairs the soldier's ability to communicate, as well as detect life threatening sounds (Yong 2015). Current regimens for NIHL following blast or intense noise include oral administration of steroids, with or without hyperbaric oxygen therapy, with variable improvements (Bayoumy 2019, Remenschneider 2014, Van Haesendonck 2018). High-dose steroids are not benign and can have serious side effects. Moreover, hyperbaric oxygen therapy is resource intensive and not widely available especially in the deployed setting.

**Loud noise and blast exposure can lead to inner ear injury through activation of inflammatory pathways such as TLR4-associated mechanisms, ROS production, and inhibition of autophagy. TLR4 inflammatory pathways can be induced by lipopolysaccharide (LPS). We propose a novel therapeutic regimen using an inhibitor of inflammatory pathways, to restore/rescue function (Figure 1).**

## FIGURE 1: Sensory Protection Model

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## APPROACH AND RESULTS

### TAK-242 attenuates LPS-induced hearing loss.

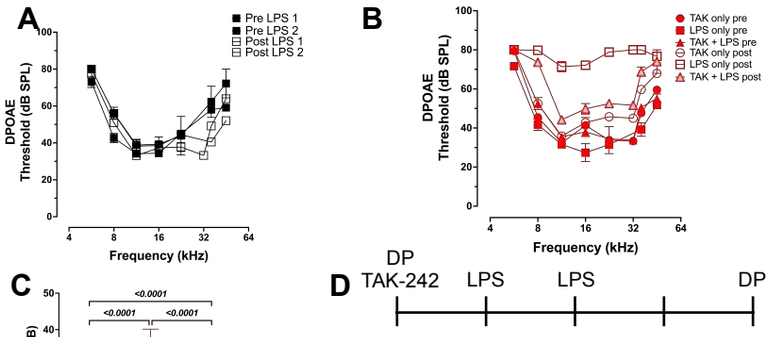


**Figure 2.** TAK-242 attenuates LPS-induced hearing loss. DPOAE thresholds of mice pretreated with TAK-242 before 2 days of consecutive 5mg/kg LPS i.p. injections. A) 48hr post LPS, WT. B) 48hr post LPS, KO. C) Threshold shifts in WT and KO mice. D) Injection timeline.

### TAK-242 reduces NIHL in WT mice.

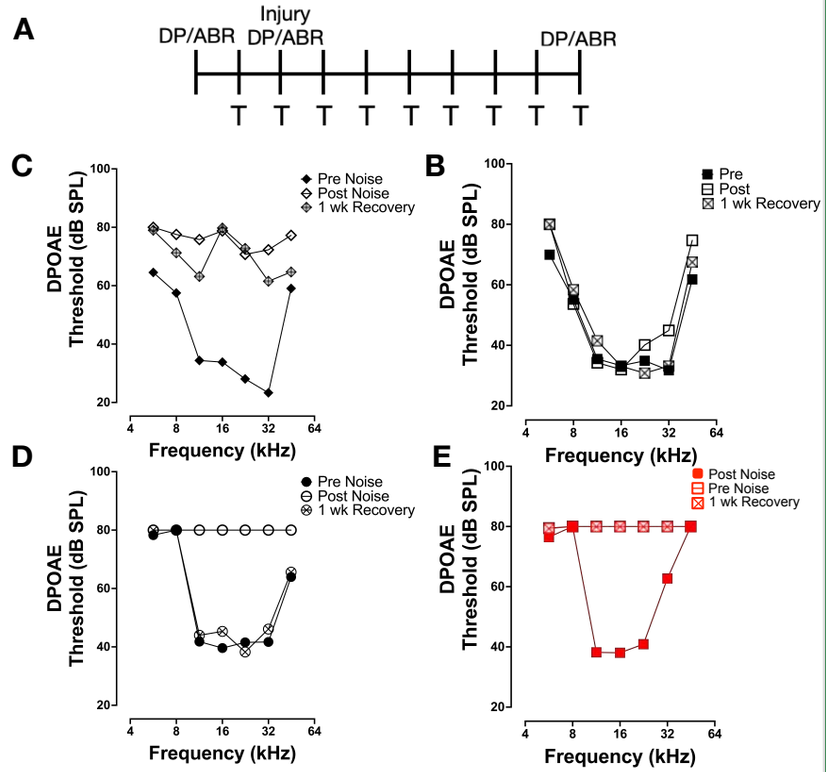


**Figure 3.** DPOAE thresholds of 1 mo mice exposed to 110 dB SPL broadband noise for 2 hours. A) TAK-242 i.p. injection schedule. B) WT, Saline injected, no exposure. C) WT, Saline injected, noise exposed. D) WT, TAK-242 injected, noise exposed. E) KO, TAK-242 injected, noise exposed.

### LPS results in fewer afferent contacts on IHCs and OHCs.

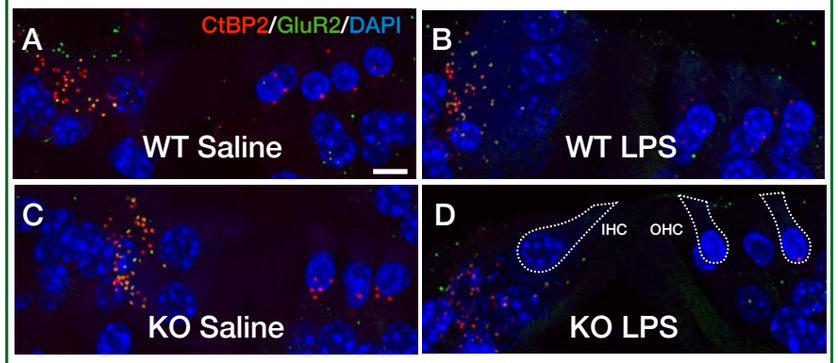


**Figure 4.** 2 month old *Ocm* WT and KO mice treated for 2 days with LPS i.p. Cochlea collected and sectioned 48hrs after 2nd injection. Immunostaining for CtBP2 (red) and GluR2 (green) from basal regions of A) saline injected WT mice, B) LPS injected WT mice, C) saline injected KO mice, or D) LPS injected KO mice. Scale bar = 10 microns.

## MILITARY RELEVANCE

**Currently, no proven treatments or prophylactic therapeutics exist to prevent progression to acoustic-induced cochleovestibular injury. Noise and blast injuries during the Iraq and Afghanistan wars resulted in a substantial increase is acoustic and vestibular trauma leaving thousands of service members severely debilitated without any effective treatments. Persistent hearing loss and vestibular function decline can result in serious reduction in quality-of-life (QOL), operational readiness and potentially be life-threatening in the battlefield. Given the incredible burden that these injured service members live with, we are motivated to develop therapies to address involved molecular pathways.**

Our current approach is to study the ability of the TLR4 inhibitor TAK-242 to attenuate the LPS and noise inflammatory responses in the cochlea. Inflammation from acoustic trauma triggers calcium toxicity that is believed to be a central and early event in the development of hearing and vestibular dysfunction. Our group can probe calcium metabolism with our unique genetic OCM protein knockout mouse model. Administration of TAK-242 should attenuate loss of hearing and vestibular function in mice with intact calcium metabolism, or oncomodulin expression. TAK-242 is an attractive compound to study as it has already passed phase I and II FDA trials for other indications. This known human safety profile makes translation for acoustic trauma protection more likely and feasible. Identification of a safe pharmacologic agent that protects or even recovers hearing and balance function after acoustic trauma will have a tremendous impact on the service member quality-of-life and safety on the battlefield.

## CONCLUSION

- **Lack of OCM enhances sensitivity to LPS.**
- **Greater OHC loss, fewer afferent synaptic junctions.**
- **Lack of OCM results in greater macrophage infiltration into the organ of Corti area after LPS treatment.**
- **TLR4 is a major contributor to LPS and noise-induced hearing loss.**
- **TLR4 inhibitor, TAK-242, reduces LPS and Noise-induced hearing loss.**

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