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Prepared by Dr. Dominic Cosgrove from recent Walsh files and past reports submitted by Dr. Edward Walsh.

**14. ABSTRACT**
The primary purpose of the project was to test a novel pharmaceutical treatment strategy involving a drug that has been shown to protect neural tissues from injury by blocking the degenerative outcomes of inflammation. The compound in question is glatiramer acetate (GA), a chemical that modulates the immune response to inflammation and diminishes associated pathology. The rationale underlying this project is that exposure to intense sound causes inner ear inflammation, and synaptopathy. Treatment of mice with GA alone, or in combination with anti-inflammatory drugs protected against noise-induced haring loss and synaptopathy.

**15. SUBJECT TERMS**
Copaxone, noise induced hearing loss, synaptopathy

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**FINAL REPORT**

## I. Heading

- **A. PI Name:** Edward J. Walsh
- **B. Organization:** Boy's Town National Research Hospital
- **C. ONR Award Number:** N000141410562
- **D. Award Title:** Glatiramer Acetate (Copaxone) Treatment of Noise-Induced Hearing Loss

## II. Scientific and Technical Objectives

**Summarize the current project objectives noting if they deviate from those listed in the original proposal.**

The primary purpose of the project was to test a novel pharmaceutical treatment strategy involving a drug that has been shown to protect neural tissues from injury by blocking the degenerative outcomes of inflammation. The compound in question is glatiramer acetate (GA), a chemical that modulates the immune response to inflammation and diminishes associated pathology.

The rationale underlying this project is that exposure to intense sound causes inner ear inflammation, presumably, and partially, as a direct consequence of trauma-enhanced expression of pro-inflammatory proteins and reduced expression of anti-inflammatory proteins in the inner ear, and that agents exhibiting anti-inflammatory properties, like GA, may protect and/or rescue individuals from noise-induced hearing loss (NIHL). To that end three specific hypotheses that were to be tested in this project:

(1) That treatment with GA leads to improved auditory function following traumatizing noise exposure.

(2) That the protective power of GA and antioxidant compounds, which reduce the noise-induced buildup of certain molecules that can also damage and/or kill cells, together have additive or synergistic properties leading to more complete protection of the inner ear from acoustic trauma than that observed with GA or antioxidants alone.

(3) That GA reduces inner ear inflammation via the up-regulation of anti-inflammatory proteins and the down-regulation of pro-inflammatory proteins following noise exposure; the proteins in question are cytokines.

In previous work, we reported that the efficacy of GA treatment was linked to the expression level of an anti-inflammatory cytokine; that there appeared to be a threshold effect above which recovery from NIHL was significantly enhanced. In this project we extended that work by analyzing the same relationship in outbred mice treated with combined GA/NAC.

One significant deviation from the original proposal was the transfer of proposed work from an outbred guinea pig (GP) to an outbred mouse model. The transfer was necessitated in the wake of the discovery that GPs reacted pathologically from the cumulative exposure to the immuno-modulatory compound under evaluation.

While not a significant deviation from the original plan, in light of recent morphological findings that have revealed heretofore unrecognized noise-induced neuropathology, commonly known as auditory synaptopathy, cochlear morphological studies proposed originally will be expanded to include the quantitative analysis of ribbon synapse distributions in the cochleae of control and treated animals. In addition, the physiological phenotyping plan was expanded to include studies designed to assess noise exposure influence on temporal processing of acoustic signals in an effort to develop a functional assay of auditory synaptopathy.

## III. Approach

The approach was to use a small battery of auditory physiology tools, the auditory brainstem response (ABR) and the distortion product otoacoustic emission (DPOAE), to evaluate auditory performance in outbred mice, principally concentrating on measures of sensitivity, but including evaluation of input/output properties of the system in a frequency dependent context. The use of these tools permits assessment of the physiological integrity of both sensory and neural aspects of auditory function and both methodologies are used to track recovery from NIHL in GA treated, GA+antioxidant treated and saline treated control animals following noise exposure. Two protocols, a prevention protocol and a rescue protocol, were used to determine the capacity of GA, or GA combined with an antioxidant, to prevent and/or treat NIHL. In addition, cytokine expression profiles were assayed using the qRT-PCR approach to test the hypothesis that GA promotes the up-regulation of anti-inflammatory cytokines and down-regulation of pro-inflammatory cytokines.

## IV. Concise Accomplishments

**Briefly summarize accomplishments from the current reporting period and briefly note the significance of data/results.**

The work completed during first reporting period was stunted by the discovery that guinea pigs react adversely to the immunomodulatory compound selected for use in this project. In light of this highly unanticipated outcome, we migrated to an outbred mouse platform. This move delayed experimental progress in the first year.

In the second reporting period we found that animals treated with GA suggest that recovery from hearing loss is greater than that observed in saline-treated controls, and that recovery in animals treated with GA and N-acetylcysteine (NAC) in combination is enhanced beyond the degree observed with GA treatment alone. In addition, preliminary efforts to evaluate the presence of IHC-auditory nerve fiber ribbon synapses were successful and early findings suggest that ribbon synapse numbers are reduced following exposure to traumatizing noise and treatment with combined GA and NAC restores, or nearly restores, normal synapse counts.

Recovery from NIHL was characterized comprehensively in NMRI mice and outcomes indicated that, as anticipated, recovery dynamics are similar to those observed in inbred mice based on ABR and DPOAE findings.

We also tentatively conclude that outbred NMRI mice are more vulnerable to noise exposure than inbred CBA/J mice, and preliminary analyses suggest that, as anticipated, overall outcome variability is greater than that observed in CBA/J mice, suggesting further that concerns related to the need for large sample sizes to achieve equivalent statistical power may be necessary.

## V. Expanded Accomplishments

**a. Describe in greater detail the progress achieved during the current reporting period and include the significance of data/results. b. You are encouraged to include graphs, charts, and photos.**

While the centerpiece of accomplishments achieved during the previous funding period was the successful launch of the experimental phase of the project, the bulk of time and effort was devoted to the comprehensive characterization of functional recovery from noise-induced hearing loss in a group of NMRI outbred mice that were exposed to an octave wide band of white noise centered on 11.3 kHz. Noise level was varied to determine the degree of temporary

hearing loss, as well as extent of permanent damage resulting from different exposure energies. That work is summarized below.

***General Findings***

We first set out to determine if sex was a variable requiring extended consideration as the study moved forward and to determine if significant audiometric differences might be observed in inbred vs. outbred mice. Because acoustic sensitivity (threshold estimates) was one, if not the primary metric to be used as an assessment tool in the larger investigation, sensitivity measurements representing male and female, young adult outbred NMRI mice and CBA/J mice were compared. Only minor differences in sensitivity curves representing males and females of both inbred and outbred strains were statistically insignificant, ruling sex out as an independent variable. However, although greatest sensitivity was observed in the 10 to 20 kHz range in both inbred and outbred strains, NMRI mice exhibited lower sensitivity to high frequency stimuli and higher sensitivity to low frequency stimuli relative to CBA/J mice; i.e., the threshold vs. frequency curve is tilted along the sensitivity axis towards lower frequencies by approximately 15 dB relative to CBA/J mice, with the fulcrum in the region of greatest sensitivity. This finding underlines the need to comprehensively assess the physiological phenotype of each mouse strain included in an investigation as a key component of a balanced experimental design. In addition, to confirm the anticipated lack of influence of noise-exposure on ABR waveforms, responses elicited by 11.3 kHz tone pips at different stimulus levels were unremarkable (i.e., normal) regardless of experimental circumstances.

Recovery of response thresholds is a key dependent variable when evaluating the efficacy of treatment protocols during the experimental phase of the investigation, necessitating the accurate assessment of active recovery from NIHL among control animals generally. Considerable time and effort was initially devoted to the selection of a suitable noise exposure protocol to accomplish this goal, to identify the exposure conditions that will produce the desired hearing loss profile. Using the same noise condition and exposure duration, recovery dynamics were tracked when stimulus levels were 94, 97, 100, 103 or 106 dB SPL. At the two highest noise exposure levels considered (103 and 106 dB SPL), threshold values immediately following noise exposure were as high as 100 dB SPL and loss of sensitivity was as high as 80 dB at frequencies within the exposure band. The severity of trauma, revealed by loss of sensitivity, diminished at frequencies above and below the exposure band. As expected based on previous work in our lab and the labs of others, recovery from temporary hearing loss occurred rapidly during the first post-exposure week producing a degree of residual (permanent) loss of sensitivity within the exposure band of between 20 and 30 dB on the low frequency margin and 40 dB on the high end margin. The greatest loss of sensitivity was observed approximately one octave above the exposure band center frequency. Permanent loss of sensitivity at relatively low- and high-frequency regions were in the vicinity of 10 and 20-30 dB respectively.

As exposure level decreased, the contours of average sensitivity curves reflected increasingly focal regions of trauma; i.e., sensitivity in the lowest frequency range was essentially restored when exposure level was 100 dB SPL and an increasingly narrow band of permanent sensitivity loss was observed as level was decreased from 100 dB SPL to 97 dB SPL. Recovery from trauma produced by exposure to 94 dB SPL noise was complete in the low frequency domain, however, a residual, permanent loss of sensitivity in the range of 20 to 30 dB was observed at frequencies within the exposure band; sensitivity loss diminished gradually at frequencies above the exposure band and remained in the vicinity of 10 dB permanently.

Our original aim was to identify a noise level and duration that produced a sensitivity curve profile exhibiting of approximately 40 dB of permanent hearing loss (generally within the exposure band) with gradually decreasing threshold shifts above and below the noise exposure

band, a measure of gradually diminishing trauma as a function of cochlear distance from the primary site of lesion. To that end, an octave wide band of white noise centered on 11.3 kHz, delivered at 97 dB SPL for one hour was selected as the exposure condition of choice for the remainder of the study.

### *Noise Exposure Vulnerability*

One question of general interest addressed during the second year had to do with the relative vulnerability of inbred versus outbred mice to noise overexposure. The most relevant observation in relation to the present investigation is that data acquired from NMRI mice exhibited a shallower PTS curve as a function of exposure energy and the loss occurs at lower exposure energies. This led us to conclude that outbred NMRI mice appear to be more sensitive to noise-exposure than are inbred CBA/J mice.

### *ABR Waves I and IV Amplitudes Reduced in the Vicinity of the Noise Exposure Band*

In addition to tracking threshold recovery from NIHL in terms of stimulus frequency, comparison of response input-output (IO) features will serve as a key measure of two important outcome variables; treatment efficacy and noise-exposure consequences. IO characteristics associated with stimulus frequencies within the noise exposure band are of particular interest and findings made during the first reporting period that are related to changes in ABR input-

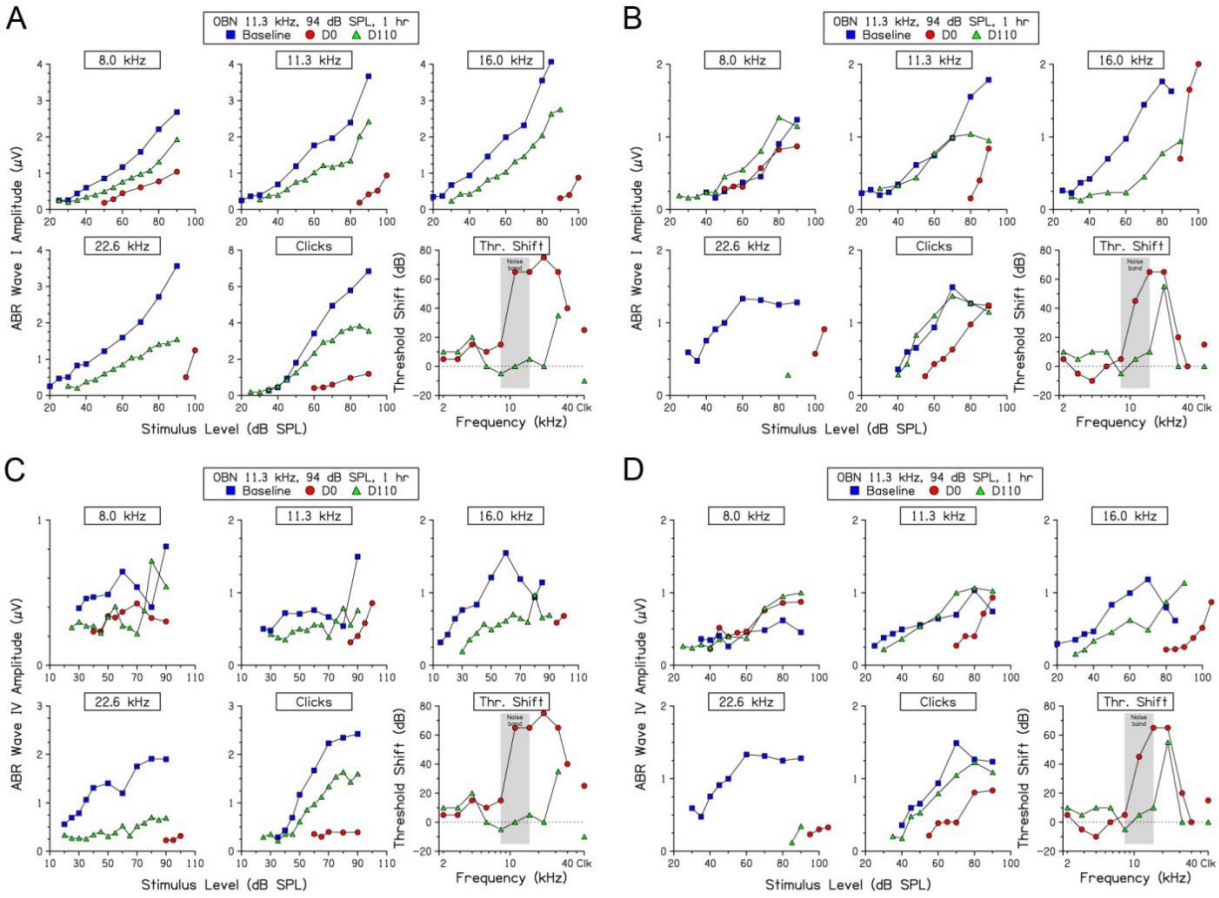


**Figure 1:** Amplitudes of ABR wave I (A-B) and wave IV (C-D) as a function of stimulus level are shown for different stimulus frequencies and at various times relative to noise exposure (blue symbols, before exposure; red symbols, immediately following exposure and green symbols after recovery from exposure). The lower right panel of each 6-panel group represents threshold shift following noise exposure and recovery.

output features following noise-exposure are summarized in **Fig. 1.** Wave I IO curves representing individual animals are shown in panels A and B, and wave IV IO curves in panels C and D; the parameter is post-exposure day. Under all frequency conditions reported here, conditions representing amplitudes at stimulus frequencies in or near the exposure band, amplitudes of both waves I and IV were reduced dramatically immediately following noise-exposure (red symbols) and partial recovery was evident 3.5 months following exposure (green symbols). If one considers the lower right panel in each block, threshold shift vs. frequency plots indicate that, although ABR amplitudes remain elevated, response thresholds returned to pre-exposure values, a finding reminiscent of those reported by Kujawa and Liberman (2009) in which inner hair cell-primary afferent synaptopathy was observed. In addition, animals with residual high-frequency threshold elevation exhibited a reduction in response amplitudes to broadband stimulation (click stimulation), whereas in animals with focal lesions, click-evoked response amplitudes returned to baseline values. Response latency findings were essentially consistent with amplitude findings; response latencies were prolonged when amplitudes were reduced, again suggesting loss of input from basal regions of the cochlea as expected under conditions of auditory synaptopathy.

This aspect of the study is important for developing meaningful synaptopathy metrics with translational value. These electrophysiological outcomes will be compared directly with IHC-auditory nerve fiber (ANF) synapse expression in control and treated animals to determine the effects of treatment on synaptic recovery following noise.

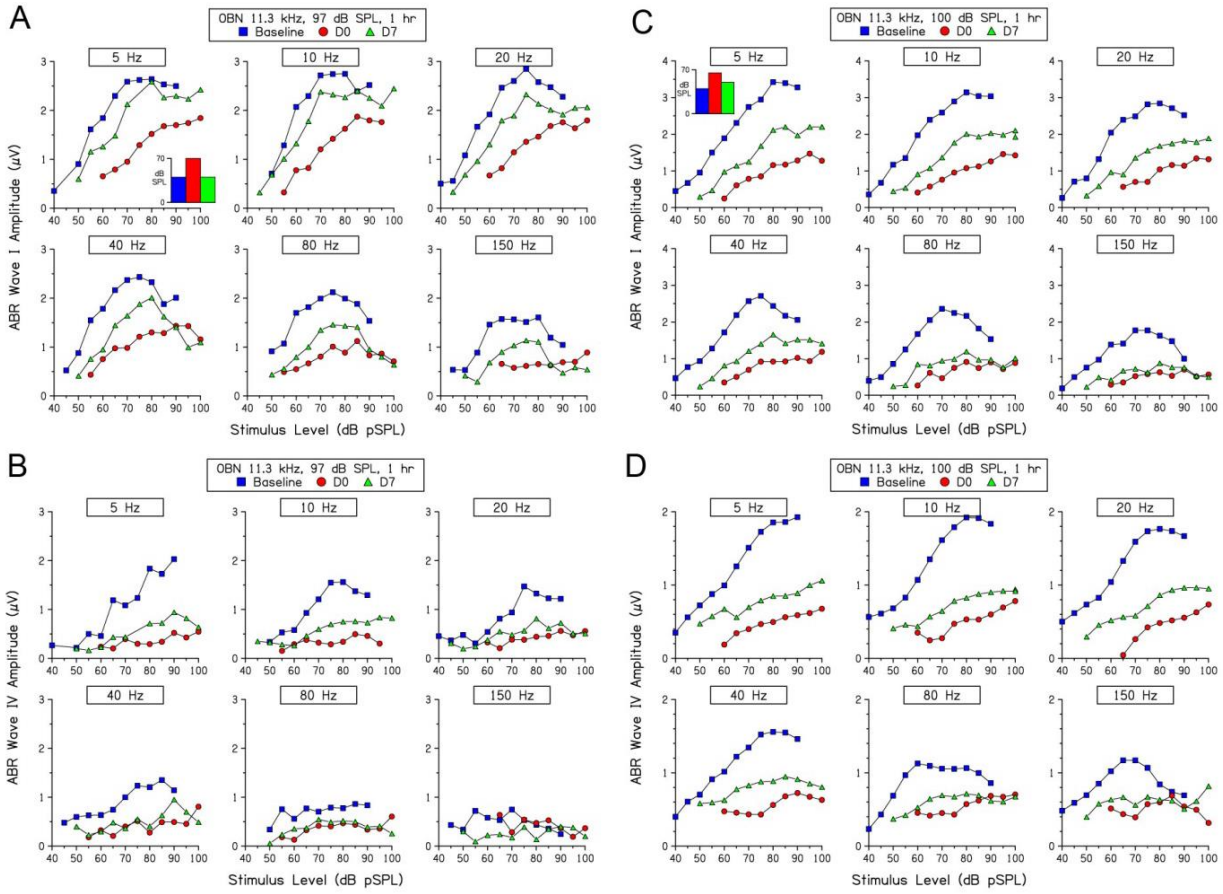


**Figure 2:** Amplitudes of ABR wave I (A,C) and wave IV (B,D) as a function of stimulus level are shown for responses to clicks presented at various rates from 5 to 150 Hz, and at various times relative to noise exposure (blue symbols, before exposure; red symbols, immediately following exposure and green

symbols after recovery from exposure). In panels A-B, noise was presented at 97 dB SPL and in panels C-D exposure level was 100 dB SPL. Histogram insets in the top left panels of A and C represent thresholds to clicks at 5 Hz at various times relative to noise exposure (blue, before, red, immediately after, and green, following recovery from exposure).

***Stimulus Rate Challenge Further Enhances Evidence Supporting Peripheral Auditory Synaptopathy following NIHL***

In addition to the direct comparison of ABR amplitudes in control and treated animals, as well as in experimental animals receiving GA and GA + NAC, as a measure of auditory synaptopathy, the loss of highly efficient neural drive associated with reduced IHC-ANF synapse numbers under conditions of synaptopathy suggests that diminished temporal processing may one primary outcome of the pathology. In that regard, examples of the changes in click-evoked ABR wave I amplitudes for two exposure levels (97 dB SPL in **Fig. 2**, panels A and B and 100 dB SPL in panels C and D) under varying stimulus levels and presentation rates (shown for 5 Hz to 150 Hz in different panels) suggest that response amplitudes are greatly reduced immediately following noise-exposure (red symbols) and remain reduced one week later (green symbols), a time point generally consistent with recovery from temporary threshold elevation. The reduction in wave I amplitude is more prominent for higher stimulation rates, a condition consistent with animals exhibiting IHC-ANF synaptopathy. Large reductions in amplitude are also observed for wave IV as stimulus rate is increased, in some cases exceeding those observed for wave I.

***Effects of Treatment on NIHL* (Year 3)**

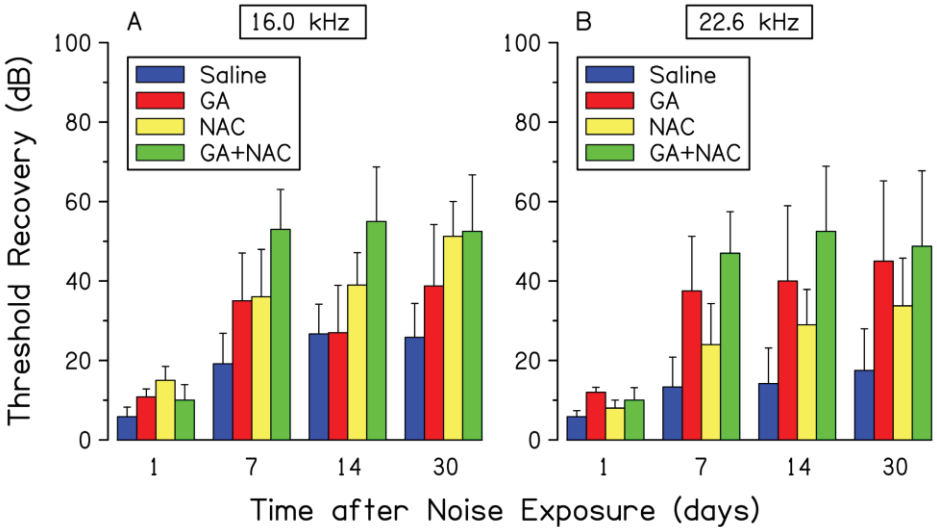


**Figure 3:** GA alone enhances post-noise exposure recovery of function in outbred mice and the power of the outcome was similar to that observed in inbred mice. NAC alone also enhances post-noise exposure recovery of function in outbred mice. Early findings indicate that the power of NAC to promote recovery from NIHL is roughly the same as that observed in GA treated animals. In combination GA and NAC treatment produce outcomes that are additive.

Early efforts to assess the influence of GA treatment in outbred mice, and combined GA and NAC treatment on recovery from existing NIHL have been highly encouraging. In the third year of this work we have performed replicates of this study which uphold the original observations. A summary of findings indicate with confidence that GA alone enhances post-exposure recovery in outbred mice, and that treatment with the GA/NAC combination further enhances the degree of recovery under some stimulus frequency conditions. Concentrating on frequencies that fall within approximately one-half octave to one octave above the center frequency of the exposure band (i.e., 16 and 22.6 kHz), bar graphs shown in **Fig. 3** illustrate this

outcome. It is clear by the 7th post-exposure day the enhancement hypothesized earlier was observed. **Fig. 4,** which plots wave 1 amplitudes against stimulus levels shows that the combination treatment with both GA and NAC results in post-noise recoveries across the dynamic range of stimulus levels compared to saline-treated outbred mice.

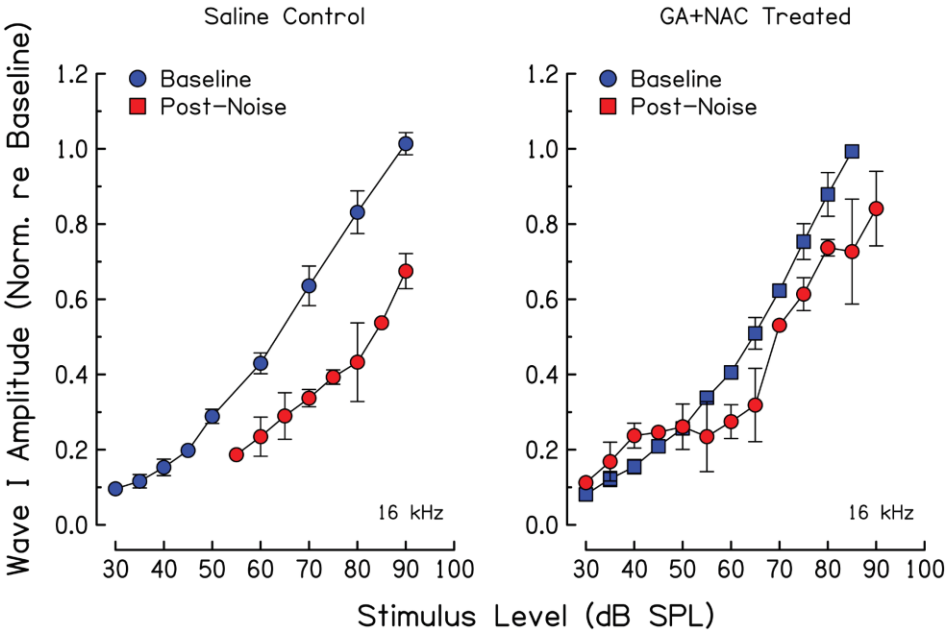


**Figure 4:** Further evidence that treatment with GA and NAC combine to restore substantial function following noise exposure can be seen in a plot of ABR Wave I amplitude vs. stimulus level. Findings shown in the right hand panel clearly indicate that recovery occurs throughout the dynamic stimulus level range.

### *IHC-ANF Synapses are Restored Following Noise-Exposure and Treatment with Combined GA and NAC* (Year 3)

Early findings associated with efforts to quantitatively assess the number of IHCANF ribbon synapses in control, noise-exposed and noise-exposed animals treated with combined GA and NAC are also highly encouraging and consistent with the tentative conclusion that synapse pathology resulting from traumatic noise-exposure can be restored by treating noise-exposed animals with the drug combination. In the left panel of **Fig. 5**, confocal images of IHC-ANF ribbon synapses in a whole mount section of the cochlear sensory epithelium from a normal NMRI mouse are shown. Both inner and outer hair cells are labeled with antibodies to myosin VIIa (blue stain), the inner hair cell nuclei are lightly stained with antibodies to CtBP2 (diagonal row of nuclei) and adjacent to the IHC nuclei, presynaptic elements of ribbon synapses are labeled with CtBP2 (red) and post-synaptic receptors on the afferent dendrite are labeled with antibodies to GluA2. Presynaptic ribbons of outer hair cells can also be seen. In **Fig. 5B**, the number of IHC-ANF synapses observed in the mid-frequency region of the cochlea of control animals was approximately 13 synapses per inner hair cell (blue bar). Following exposure to OBN centered at 11.3 kHz (along with a single treatment of GA and NAC), the number of synapses in the same general region of the cochlea was reduced to approximately 5 synapses per IHC immediately following noise exposure and to approximately 11 synapses per IHC in a region slightly apical (red bars). The number of synapses per hair cell was restored to the normal number, or nearly so (12-13 synapses per hair cell), in the same cochlear location, as well as more basal regions following NAC treatment combined with 7 days of GA treatment (green bars), suggesting that drug therapy may be efficacious in synapse restoration.

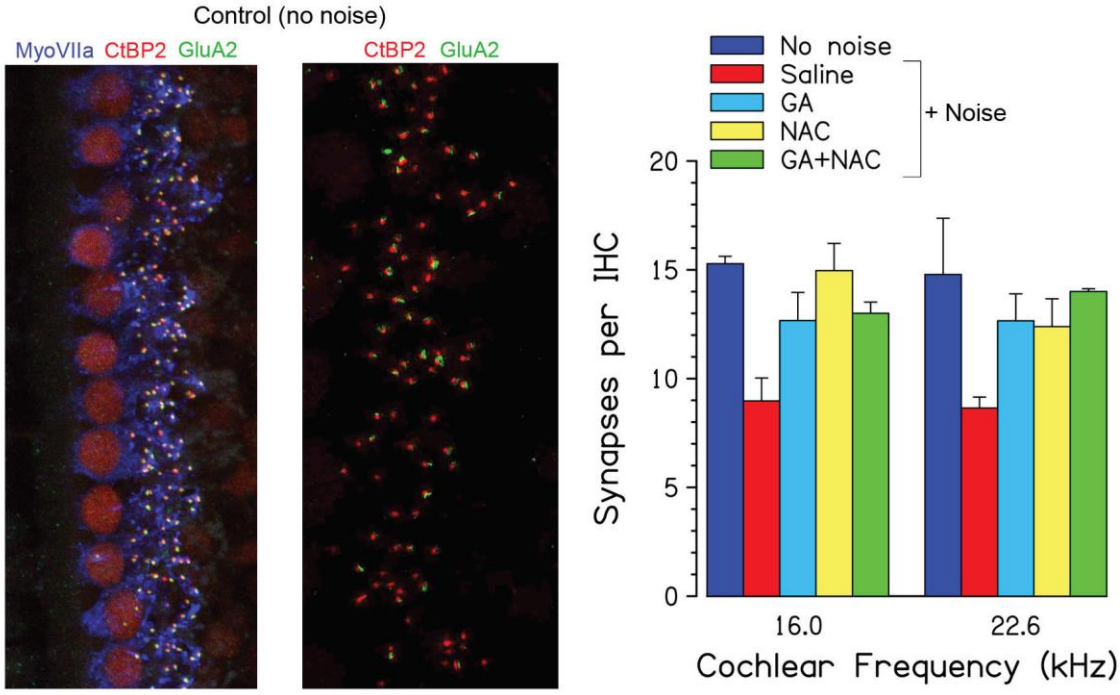


**Figure 5:** Efforts to quantitatively assess the number of IHC-ANF ribbon synapses in control and noise-exposed animals treated with combined GA and NAC were also highly encouraging and consistent with the view that synapse pathology resulting from traumatic noise-exposure would be largely restored by treating noise-exposed animals with the drug combination.

### *Overall Conclusions*

The most relevant preliminary finding reported here is that the combined actions of GA and NAC serve to enhance the degree of NIHL recovery observed with GA alone in the NMRI outbred mouse line. Future studies might consider the influence of treatment dose. Work completed for this project was carried out at doses that produced positive outcomes in other systems and in the treatment of other pathologies. Understanding the treatment power in a dose-dependent context is a potentially critical clinical issue to address. As for our efforts to relate treatment outcomes to IHC-primary afferent synapse pathology resulting from traumatic noise exposure, we are highly encouraged by findings shown in **Fig. 5.** This figure now represents a larger group of samples suggesting that the restoration of ribbon synapses is in fact real.

Based on these results, we conclude that manipulation of the immune system to promote the synthesis and release of anti-inflammatory proteins by as yet unknown inner ear immune cells, along with a subset of well recognized growth factors, is a novel and promising strategy in the struggle to identify effective NIHL treatment protocols. We also conclude that outbred NMRI mice are more vulnerable to noise exposure than inbred mice, and preliminary analyses suggest that, as anticipated, overall outcome variability is greater than that observed in CBA/J mice, suggesting further that concerns related to the need for larger sample sizes to achieve appropriate statistical power may be necessary.

The third aim, “That GA reduces inner ear inflammation via the up-regulation of anti-inflammatory proteins and the down-regulation of pro-inflammatory proteins following noise exposure”, was not addressed.

**Publications:** None

**Patents:** US patent # 9,763,992 : Treatment of noise induced hearing loss.

**Presentations:**

Walsh, E.J., Sveeggen, T.M., Dawson, L., Bohn, A.C. & McGee, J. (2017). Combined actions of immune system modulation and antioxidant therapy enhance recovery from noise-induced hearing loss. *Assoc. Res. Otolaryngol.* 40.

Walsh, E.J., Dawson, L., Sveeggen, T. & McGee, J. (2016). Glatiramer acetate (copaxone) treatment for noise-induced hearing loss. *Office of Naval Research Noise-Induced Hearing Loss Program Review*, pg. 15-16.

Walsh, E.J., Cohn, E.S., Drescher, K. & McGee, J. (2014). Glatiramer acetate (copaxone) treatment of noise-induced hearing loss. Office of Naval Research Noise Induced Hearing Loss Program Review.

McGee, J., Cohn, E., Drescher, K., Roark, K., Brunette, K., Anton, A. & Walsh, E. (2014). Recovery from noise-induced hearing loss is enhanced by the immunomodulator glatiramer acetate. *Assoc. Res. Otolaryngol.* **37**, p. 363, Abstract PS 573.