

AWARD NUMBER: W81XWH-17-1-0172

TITLE: Mechanism-Based Prevention of Noise-Induced Tinnitus: Protection and Repair of Peripheral Auditory Neuropathy

PRINCIPAL INVESTIGATOR : Dr. Avril Genee Holt

CONTRACTING ORGANIZATION: Wayne State University

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14. ABSTRACT Studies test a potential treatment for noise-induced tinnitus in the rat model. We hypothesize that noise-induced loss of synaptic connection between Inner Hair Cells (IHC) and the auditory nerve (AN) contributes to the induction of tinnitus and rapidly repairing this loss will therefore decrease the incidence of tinnitus. Treatment with the neurotrophic factor NT-3 was previously shown by our consultant Dr. Corfas to induce significant IHC-AN synapse reconnection after a different type of noise in his mouse model (Suzuki et al., 2016). During the first year of studies we have found that we can duplicate these results using a more military relevant small arms fire (SAF)-like noise in the rat model, showing a large and significant re-connection (described later in Section 3 of the Results Section). NT-3 in poloxamer was applied to the round window with the trans-tympanic approach that has been successfully applied in people for other treatments. These results show that it is possible to reverse noise induced synaptic loss from a military relevant noise exposure with a treatment paradigm that can be applied to those in the service. Such noise-induced synapse loss can cause a "Hidden Hearing Loss" that can impair speech understanding (Lieberman et al., 2016, 2017). Therefore the ability to repair and reverse Hidden Hearing Loss has immediate impact. The major goal, however, is to test if such reconnection will decrease or prevent the later development of tinnitus and that is the focus of the next stage of our ongoing studies. Studies are now underway to determine if this rapid reconnection from NT-3 treatment will decrease the incidence of noise induced tinnitus compared to noise exposed rats without treatment. If successful, this would provide a military relevant treatment to prevent and treat noise-induced tinnitus.					
15. SUBJECT TERMS Tinnitus, Deafness, Neurotrophins, NT-3, Synaptopathy, Noise, Small Arms Fire, Cochlea, Auditory, Hidden Hearing Loss					
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1. INTRODUCTION:

Studies test an underlying mechanism and potential mechanism-based treatment for noise-induced tinnitus in the rat model. We hypothesize that noise-induced loss of synaptic connection between Inner Hair Cells (IHC) and the auditory nerve (AN) contributes to the induction of tinnitus and repairing this loss will decrease the incidence of tinnitus. Treatment with the neurotrophic factor NT-3 was previously shown by our consultant Dr. Corfas to induce significant IHC-AN synapse reconnection after a different type of noise in his mouse model (Suzuki et al., 2016). In our first phase of studies Site 1 reported that they can duplicate these results using a more military relevant small arms fire (SAF)-like noise in the rat model, showing a large and significant reconnection when this treatment is applied 1 day after the noise. During Year Two Site 1 has tested NT-3 treatment beginning after a delay of 1-2 weeks to determine if it remains effective in inducing re-connection of IHC-AN synapses. In Year One, Site 2 reported that we could generate military relevant blast-noise with different spectral characteristics. During Year Two, Site 2 has tested these different blast-noise in animal models, showing differences in cochlear injury and hearing function. Both of these results have relevance to those in the field that might not be able to get immediate treatment (Site 1) and those that are exposed to blast-noise (Site 2) which can vary in spectral content. Our initial results for Site 2 suggest that blast-noise with lower frequency spectral content have significantly different effects on cochlear damage and hearing when compared to exposure to blast-noise containing slightly higher frequencies. Year Two studies are also testing if the NT-3 poloxamer treatment given one day after blast-noise will also promote IHC-AN reconnection as it does after SAF-like noise exposure. These studies began in Year One and are still underway (and we remain blind as to the results). These assessments will continue into Year Three when we will “unblind” and report results. We will also begin testing efficacy of treatment 1 day after and 1-2 weeks after noise in reducing tinnitus in Year Three, continuing into a fourth year (we requested a no-cost extension). Reconnection could reduce the incidence of tinnitus but could also be effective in treating “Hidden Hearing Loss” that can impair speech understanding (Liberman et al., 2016, 2017). Either or both would provide benefit to Veterans and those in general population exposed to noise. **Nothing new to report due to pandemic related restrictions, equipment failure and lack of necessary funds to complete and/or publish studies. The current goal is to continue and complete data analysis.**

2. KEYWORDS:

Tinnitus, Deafness, Neurotrophins, NT-3, Synaptopathy, Noise, Small Arms Fire, Blast-noise, Cochlea, Auditory, Hidden Hearing Loss

3. MAJOR GOALS AND ACCOMPLISHMENTS

MAJOR GOALS - from Statement of Work (SOW):

YEARS THREE & FOUR:

Timeline & Milestones: Aim 1 studies continued (staggered start from Year One) into Year Two.

(Years 1-2)

Aim 1A: Determine if NT-3 treatment 1 day after a blast-noise will induce reconnection of lost IHC-AN synapses and prevent Tinnitus from appearing.

- **Subtask 1:** Influence of NT-3 elevation 1 day after blast-noise to prevent appearance of tinnitus based on Gap Detection & and behavioral (operant conditioning) metrics
- **Subtask 2:** Influence of Treatments on Blast-Induced changes to Inner Hair Cell –Auditory Nerve synaptic connections.

(Milestones: Break Code and determine treatment effects in Months 20-26)

(Years 2-3)

Aim 2: Determine the influence of NT-3 treatment given at later times after a blast-noise on inducing re-connection of IHC-AN synaptic connections and preventing Tinnitus

- **Subtask 1:** NT-3 treatment two weeks after noise
- **Subtask 2:** NT-3 treatment six week after noise

Task 6 Milestones: *Break Code and determine treatment effects in Months 33-36*

1. Determine efficacy in re-connection (Year 2 and 3)
2. Determine treatment effects on tinnitus (Years 3 and 4)
3. *Complete analysis of re-connection data (Years 4 and 5)*

ACCOMPLISHMENTS:

Major Activities Task 4:

- Aim 1 Group 1 – Blast Noise – no NT-3
- Aim 1 Group 2 – Sham Noise – no NT-3
- Aim 1 Group 3 – Blast Noise – NT-3 post-treatment 1 day after noise
- Aim 1 Group 4 – Sham Noise – NT-3 post-treatment 1 day after noise

Major Activities Task 6:

- Aim 2 Group 1 – Blast-Noise – no NT-3
- Aim 2 Group 2 – Sham Noise – no NT-3
- Aim 2 Group 15 – Sham Noise – NT-3 post-treatment 1-2 weeks after noise
- Aim 2 Group 16 – Blast-Noise – NT-3 post-treatment 1-2 weeks after noise

Rats received base-line measures of auditory brain stem response (ABR) and Gap Detection (GD). Rats then received either operant conditioning or Gap Detection as metrics for later tinnitus testing. Animals were then randomly divided into groups receiving either Sham noise or blast-noise (one ear protected-plugged). Animals in each group were then again randomly divided and received either Poloxamer containing NT-3 or Poloxamer only (no NT-3), delivered with a trans-tympanic approach into the left middle ear by the round window, done one day after the noise or sham (Groups 3 & 4) or one to two weeks after the noise or sham (Groups 15 & 16). All animals then receive testing with either the GD and Operant Conditioning as metrics for the presence of tinnitus. After two months of assessments all rats are tested for ABR and then euthanized. Cochleae are processed to determine hair cell loss and loss of IHC-AN synaptic connections.

Unanticipated Problems: As previously mentioned in the Year One Progress Report, there was more delay than anticipated in building the new operant conditioning testing stations and generating the software necessary for testing rats for tinnitus in these stations. There was also delay in receiving the new Gap Detection testing stations from Kinder Scientific and making these stations (with new design) operational to test for tinnitus. New problems arose during Years One and Two in the testing. Test stations were not able to accommodate the increasing sizes of male rats during the course of their testing and required additional changes to allow their use for larger animals. The studies testing for tinnitus in Groups 1-4 are now fully underway, but the delayed and subsequent needs for changes in test stations have reduced the number of animals that could be tested to date. This has delayed completion and “unblinding”. It was, however, possible to finish Subtask 2 (that did not require testing for tinnitus) for Groups 1-4 and we will now analyze the effectiveness of NT-3 for reconnection of lost IHC-AN synapses after blast-noise. However, the influence of the immediate reconnection on incidence of tinnitus (Subtask 1) is still underway due to reduced staffing as noted below.

There was a “ramping down” of research activities at Wayne State University because of the COVID-19 pandemic starting in February 2020. We were unable to continue testing animals already in study due to the “stay at home order”. Now, we are able to “ramp up” at Wayne State University, but at a reduced level due to staffing constraints. We will be able to continue our testing procedures and analyses, dissemination, but we still have constraints on the number of staff that can be present in the laboratory at a given time so we cannot operate at full capacity. Therefore, full results will not be known until Year Four and possibly into Year Five when unblinding will be possible. Assessment of synapses in Groups 15 and 16 is underway and assessment for

influence on tinnitus will continue into Year Five. We may need to ask for a continuation of the “no-cost extension” in order to be able to complete studies.

Major Activities 2: Because of the delay (mentioned above) in being able to use the needed metrics to test rats for tinnitus, the studies first focused on the effect of blast-noise with distinct spectral content on cochlear damage, hearing, and synaptic connections, since these measures do not require tinnitus testing stations to be utilized to generate initial results. Studies first correlated spectral characteristics of the blast-noise with hearing thresholds, ABR wave 1 amplitude, distortion product of otoacoustic emissions (DPOAEs), hair cell loss, and synaptopathy. The effects of modulating spectral content of blast-noise on cochlear trauma and hearing are currently in the process of being written and submitted for publication. The studies next examined NT-3 treatment given one day after the blast-noise for repair of lost IHC-AN synapses (synaptopathy; Groups 1 – 4). The analysis examining anti-excitotoxicity treatment given after the blast-like noise are now being completed.

RESULTS:

Studies examining pre-treatment with anti-excitotoxicity agents using SAF-like noise were published by Site 1 (Altschuler et al., 201). Studies comparing effects of delivering NT3-poloxamer to the inner ear to combat blast-noise induced cochlear trauma and hearing were completed and assessments were begun in Year Three and are summarized below.

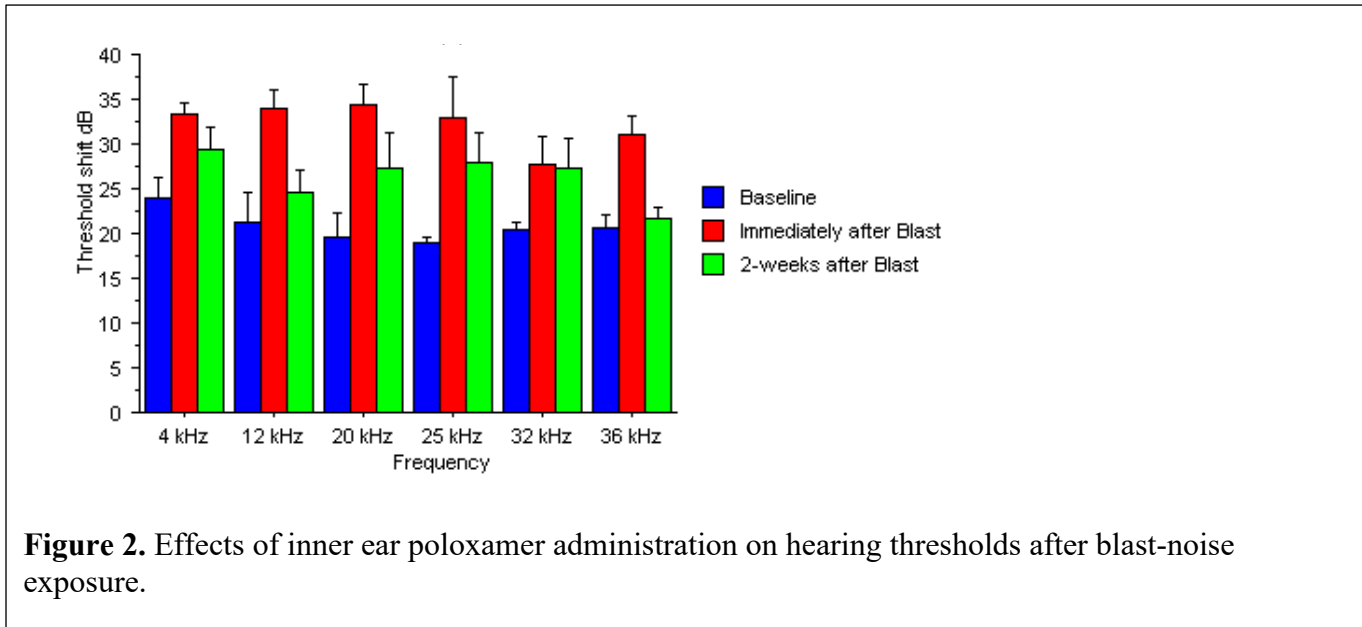
Sprague Dawley rats were tested for ABR threshold, wave 1 amplitude, and latency. Only rats with normal responses were placed into the study. The blast-noise groups were exposed to 22 psi blast overpressure generated and delivered either by a 20’ or an 8’ configuration of the WSU shocktube, described in studies performed in Year One. They received a second ABR within one hour following the blast-noise. The left cochlea was infused with either poloxamer alone or poloxamer with an anti-excitotoxicity agent. Then a third ABR assessment was performed two weeks later and animals were then euthanized. Cochleae received intrascalar fixation with 4% paraformaldehyde fixative and were then processed for assessment of hair cell loss and loss of IHC-AN synaptic connections, using CTBP2 ribbon immunolabeling as a marker for IHC synapses. Blast exposure using the 20’ configuration of the WSU shocktube (sound pressure levels – up to 180 dB SPL at 50-500 Hz with a precipitous decline in sound intensity from 2.5 – 3.5 kHz from 80-less than 40 dB SPL) resulted in a significant temporary threshold shift (**Year Two report**).

Configuration	# of 10 mil mylar	# of 3 mil mylar	# of Tests	peak pressure (psi)	peak avg pressure (psi)	BOP duration (ms)
Long Tube (all rats)						
694	1	1	1	25.362	23.1900	16.79
695	1	1	1	25.706	23.2220	15.15
741	1	1	1	20.526	19.99	13.8
742	1	1	1	20.526	19.96	13.84
average				23.03	21.5905	14.8950
STD				2.8947	1.8655	1.41045
Short Tube (all rats)						
696	1	1	1	24.00437	22.2638	2.92
697	1	1	1	23.16916	21.62134	3.2400
743	1	1	1	29.82158	22.85	5.36
744	1	1	1	26.633711	22.08894	3.98
745	1	1	1	26.6234	22.5567	3.92
746	1	1	1	26.07691	21.52773	2.1500
average				26.05485517	22.1514	3.5950
STD				2.340031867	0.517452	1.0989768

Figure 1. Rats in long tube blast tube tests were exposed to prolonged BOP durations. Long tube configuration on the left and short tube configuration on the right.

Male SD rats were divided in to two groups and exposed to blast exposure using either the long or short tube configuration. In animals exposed to long tube BOP, the peak blast pressure was 23.03(± 2.9) compared to a

much higher peak BOP of 26.05 (\pm 2.3) in the short tube exposed animals. However, the peak average pressures in both the set-ups were very similar with 21.59 (\pm 1.87) and 22.15 (\pm 0.5) respectively. Furthermore, BOP in the long tube tests persisted for a prolonged duration of 14.9 ms (\pm 1.4) compared to a very short duration BOP in short tube tests of 3.6 ms (\pm 1.1). The prolonged BOP duration may be related to the differences in the pathology observed in the cochlea and the small, but permanent ABR threshold shift (Year Two report). We used the short tube configuration to determine whether an anti- excitotoxicity agent would be an effective treatment for blast-noise induced hearing loss. Administering the poloxamer without the anti-excitotoxicity agent did not alter the normal progression of hearing loss after the blast-noise exposure



Our current analyses will assess effects of administering the poloxamer **with** the anti-excitotoxicity agent on the normal progression of hearing loss after the blast-noise exposure. Our previous results demonstrated that animals exposed to blast-noise generated by the short shocktube configuration had fewer CtBP2 labeled puncta near the base of the cochlea. Therefore, in addition to thresholds we will also assess ABR wave I amplitude and latency as well as ABR wave V/I amplitude ratio to determine both inner hair cell-auditory nerve reconnection and central auditory system effects.

Our ongoing SubTasks will be continue to be directed at studying the role of therapeutic agents in mitigating some of the observed pathological changes due to loss of synaptic connections.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

- One Poster Presentation, * - presenter

Braun RD, Kuhl A, Hali M, Kallakuri S, ***Holt AG**, Noise impacts neuronal activity in vestibular pathways, Annual meeting of the Society for Neuroscience, Chicago, IL. October 19-23, 2019

- Two Invited Platform Presentations, * - presenter

***Holt AG**, Kuhl A, Hali M, Braun RD Impact of Noise on Manganese Uptake Following Otolith Stimulation 47th Annual Scientific and Technology Meeting of the American Auditory Society, Scottsdale, AZ. March 5-7, 2020.

***Holt AG**, “Novel QUEST MRI In Vivo Measurement of Noise-induced Oxidative Stress in the Cochlea” at the Department of Otolaryngology, Wayne State University, December, 2019.

Plans for next reporting period

Year Four will continue the Aim 1 (Task 4) and Aim 2 (Task 6) with rats in all the groups entering and completing an “in-life phase” of blast-noise exposure (or sham) and NT-3 treatment 1 day (Task 4) or 1-2 weeks (Task 6) after the blast-noise exposure (or no treatment) followed by testing for indication of tinnitus:

Aim 1

1. NT-3 treatment (or poloxamer only without NT-3) one day after the noise
2. Testing for tinnitus (using GD and Operant Conditioning) for two months
3. Final ABR and DPOAE

Aim 2

1. Base-line Auditory Brain Stem Response (ABR), Gap Detection (GD and Pre-Pulse Inhibition (PPI) of the Acoustic Startle Reflex (ASR) and Distortion Production OtoAcoustic Emission (DPOAE) and training in operant conditioning.
2. Noise exposure (or sham noise)
3. NT-3 treatment (or poloxamer only without NT-3) one to two weeks after the noise
4. Testing for tinnitus (using GD and Operant Conditioning) for two months
5. Final ABR and DPOAE

After the in-life phase animals are then euthanized and assessed for hair cell loss and loss of Inner Hair Cell – Auditory Nerve synaptic connections.

We will request a continuation of our no-cost extension to continue assessments into Year Five in order to complete Tasks.

4. IMPACT:

There were three important results that impact hearing research and rehabilitation:

- Our studies show that spectral content of a military relevant blast-noise is highly relevant to the type of cochlear injury and hearing dysfunction that results. Focus only on the intensity of the blast overpressure risks missing important information about the cause of injury and potential treatment.
- We are in the process of preparing our studies for publication. The first study shows that modifying the shocktube (length) results in modification of the characteristics of the blast-noise. The second study demonstrates the effects of shifting these spectral characteristics on cochlear damage, hearing function, and synaptopathy.
- Our more recent studies with NT-3 even one day following the blast-noise is promising. We will continue our experiments and analyze data in Years four and five to determine the efficacy of NT-3 to induce re-connection and repair of the lost connections and will also assess treatment at a later time (1-2 weeks) following blast-noise. Treatment following noise will be more applicable and the trans-tympanic middle ear approach to applying NT-3 is feasible for clinical application.

There is also more general impact as study results:

- Demonstrated frequency content of blast-noise is crucial for predicting hearing dysfunction

- Blast overpressure and spectral content impact cochlear damage

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

REFERENCES

Altschuler RA, Halsey K, Kanicki A, Martin C, Prieskorn D, DeRemer S, Dolan DF (2019) Small arms fire-like noise: Effects on hearing loss, gap detection and the influence of preventive treatment, *Neuroscience* 2019 May 21;407:32-40. PMID: 30053484

Lieberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. (2016) Toward a Differential Diagnosis of Hidden Hearing Loss in Humans. *PLoS One*. 11(9):e0162726. PMID:27618300

Lieberman MC, Kujawa SG. (2017) Cochlear synaptopathy in acquired sensorineural hearing loss: Manifestations and mechanisms. *Hear Res.*;349:138-147. PMID:28087419

Suzuki J, Corfas G, Liberman MC. (2016) Round-window delivery of neurotrophin 3 regenerates cochlear synapses after acoustic overexposure. *Sci Rep*. 6:24907. PMID:2710859

5. CHANGES / PROBLEMS:

There was a delay in being able to apply metrics for the presence of tinnitus significantly delaying tinnitus assessments (outlined above) so that completion of Tasks will be delayed and a continuation of our no-cost extension into a Year Five will be required for their completion. Because of these delays we will need another 9-12 months to complete our studies as proposed. We were unable to continue testing animals already in study due to the “stay at home order”. Now, we are able to “ramp up” at Wayne State University, but at a reduced level due to staffing constraints. The primary use of time will be for analysis of collected data and writing associated manuscripts. Therefore, we will not need to request funds from DOD to fund these studies for the additional 12 months necessary for successful completion. Dr. Holt has taken a reduction in effort from 10% to 5% which will be cost shared by Wayne State University. If any behavioral studies need to be performed the blast noise animals will be transported to the University of Michigan for testing, tissue collection, and analysis.

6. PRODUCTS:

Other publications, conference papers, and presentations.

Nothing additional over what was reported above

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other Products *Nothing to report*

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name:	Avril Genene Holt
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	avrilhol
Nearest person month worked:	.6
Contribution to Project:	Responsibility for the supervision of the histopathology, quantitative assessments of hair cells and the connection between hair cells and auditory nerve, auditory brain stem response (ABR) measures including thresholds and input-output function, DPOAE, and overseeing the assessment of gap detection and pre-pulse inhibition of the acoustic startle reflex as well as the assessment and interpretation of these results. She will interpret results trouble shoot methods and make decisions on directions.
Funding Support:	W81XWH-17-1-0172 (Holt) 09/30/18 – 09/29/21 .6 calendar months (cost share) DOD (NCE) Mechanism Based Prevention of Noise-Induced Tinnitus: Protection and Repair of Peripheral Auditory Neuropathy, PR160290

Name:	John Cavanaugh
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Dr. Cavanaugh is an expert in the physics of blast overpressure. He will advise on shocktube configuration and the design and analysis of blast experiments.
Funding Support:	W81XWH-17-1-0172 (Holt) 09/30/17 – 09/29/20 0.96 calendar months DOD Mechanism Based Prevention of Noise-Induced Tinnitus: Protection and Repair of Peripheral Auditory Neuropathy, PR160290 Our proposed studies will first test if repair /reconnection will prevent tinnitus from occurring. Next we will determine what is the time window for effective treatment, how long after the noise can reconnection be induced that will prevent or treat the progression of tinnitus.

Name:	Rod D. Braun
Project Role:	Collaborator

Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Dr. Braun has substantial knowledge and expertise in analysis and mathematical modeling of biomedical data. He is developing unique methods for analyzing ASR and operant conditioning data for tinnitus.
Funding Support:	W81XWH-17-1-0172 (Holt) 09/30/18 – 09/29/20 1.2 calendar months DOD

Name:	Jinsheng Zhang
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	0
Contribution to Project:	Set-up operant conditioning. Provide advice and assist in interpretation of data
Funding Support:	

Name:	Mirabela Hali
Project Role:	Research Lab Specialist - Research Assistant
Nearest person month worked:	N/A
Contribution to Project:	Ms. Hali is responsible for the Auditory Brain Stem Response (ABR) measures, DPOAE and assisting with the blast-noise exposures at WSU. She also trained with Diane Prieskorn at KHRI to learn the animal surgeries and drug delivery (by poloxamer on the round window niche). She also is responsible for animal terminations and fixation of cochleae.
Funding Support:	N/A

Name:	Andre Kuhl
Project Role:	Research Assistant

Nearest person month worked:	N/A
Contribution to Project:	Mr. Kuhl will be responsible for assisting with the Auditory Brain Stem Response (ABR), DPOAE measures and the blast-noise exposures at WSU. He will also be trained in the animal surgeries and drug delivery (by poloxamer on the round window niche). He will also assist in animal terminations and fixation of cochleae and some of the quantitative assessment of hair cells to generate cytochrome c and the quantitative assessment of IHC-AN synaptic connections at WSU.
Funding Support:	N/A

Name:	Srini Kallakuri
Project Role:	Research Lab Specialist Senior – Research Assistant Professor
Nearest person month worked:	0
Contribution to Project:	Dr. Kallakuri is responsible for the implementation of the blast-noise exposures and re-configuration of the shocktube at WSU. He also assists in ABR measures and assessment.
Funding Support:	N/A

Name:	Dr. Aaron Apawu
Project Role:	Post doctoral fellow
Nearest person month worked:	0
Contribution to Project:	Dr. Apawu is responsible for assisting in the implementation and assessment of Gap detection (ASR) and operant conditioning.
Funding Support:	N/A

What other organizations were involved as partners?

University of Michigan, Ann Arbor Michigan, is the Corresponding Primary Institution to this project. They will be sending in their collaborative Progress Report separately.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

9. APPENDICES: