AMERICAN OTOLOGICAL SOCIETY

WE ARE RECOGNIZING OUR AOS RESEARCH AND FELLOWSHIP GRANT RECIPIENTS FROM 2015 & 2020!

WHERE ARE THEY NOW? 5 & 10 YEARS LATER

DON'T MISS THE SCIENTIFIC POSTER DISPLAY IN "CELESTIN BALLROOM E"
DURING THE AOS SCIENTIFIC PROGRAM!

Renee Banakis-Hartl, MD, AuD
Assistant Professor, Otology and Neurotology - University of Michigan
FELLOWSHIP GRANT 2020

Yew Song Cheng, MD
Assistant Professor Otology, Neurotology, and Skull Base Surgery
University of California San Francisco
FELLOWSHIP GRANT 2015

Sumana Ghosh, PhD
Instructor, Department of Otolaryngology, Head and Neck Surgery
University of Mississippi Medical Center
FELLOWSHIP GRANT 2020

Christopher Nielson, MD
Medical Student Research Fellow; University of Utah
FELLOWSHIP GRANT 2020

Aaron Remenschneider, MD, MPH
Associate Professor, Harvard Medical School, Boston Children's Hospital
RESEARCH GRANT 2015

Gabriel Sobczak, MD
PGY3, Indiana University School of Medicine
FELLOWSHIP GRANT 2020

Zachary D. Urdang, MD, PhD
Postdoctoral scholar, University of Iowa Otolaryngology
Incoming resident, University of New Mexico Pediatrics
FELLOWSHIP GRANT 2015

Douglas E. Vetter, PhD
Associate Professor, University of Mississippi Medical Center
Dept. Otolaryngology Head and Neck Surgery
RESEARCH GRANT 2020

AMERICAN OTOLOGICAL SOCIETY

Renee M. Banakis Hartl, MD, AuD

Assistant Professor, Otology and Neurotology

University of Michigan

"Cochlear Implant Insertion Trauma: Intracochlear Pressure Measurements and Anatomic Changes on Cadaveric Specimen"

FELLOWSHIP GRANT 2020

AMOUNT AWARDED BY AOS: $44,000

ONGOING FUNDING (Agency, Amount, Year):
$55,000 (American Otological Society Research Grant, 2024-current), $ 50,000 (Hearing Health Foundation, 2024-current), $ 138,580 (NIH NIDCD F32, 2024-current)

PUBLICATIONS (*Supported by AOS Grant*):

Banakis Hartl RM, Greene NT. *Measurement and Mitigation of Intracochlear Pressure Transients During Cochlear Implant Electrode Insertion*. *Otol Neurotol*. 2022 Feb 1;43(2):174-182. doi: 10.1097/MAO.0000000000003401. PMID: 34753876.

Boscoe EF, **Banakis Hartl RM**, Gubbels SP, Greene NT. *Effects of Varying Laser Parameters During Laser Stapedotomy on Intracochlear Pressures*. *Otolaryngol Head Neck Surg*. 2023 Mar;168(3):462-468. doi: 10.1177/01945998221104658. Epub 2023 Jan 19. PMID: 35671134; PMCID: PMC10097413.

Chabuz CA, **Banakis Hartl RM**, Rodriguez K, Gonzalez J, Cass SP, Greene NT. *Characterization of Tip Fold-Over Using Fluoroscopy and Intracochlear Pressure in Cadaver Specimens*. *Laryngoscope*. 2024 Dec 24. doi: 10.1002/lary.31977. Epub ahead of print. PMID: 39719824.

RESEARCH SUMMARY:

With increasing focus on hearing preservation during cochlear implant surgery, atraumatic electrode insertion is of the utmost importance. It has been established previously that large pressure spikes can be generated in the cochlea during the electrode insertion. Estimates of equivalent ear canal pressure suggest these peak pressures may be of sufficient intensity to cause trauma similar to that of an acoustic blast injury and may be one source for postoperative loss of residual hearing. Here, we investigated insertion trauma as a mechanism for postoperative loss of residual hearing. The overall objective of this research was to characterize changes in the intracochlear environment resulting from implant insertion in order to better understand the mechanism of loss of residual hearing. To accomplish this objective, we characterized changes in intracochlear pressures during cochlear implant insertions in a human cadaveric model, investigating the influence of multiple factors, including electrode geometry, the presence of a sheath or stylet, insertion speed, and post-insertional electrode manipulations. Simultaneous fluoroscopy measurements were made to correlate the location of the electrode with measured pressure changes.

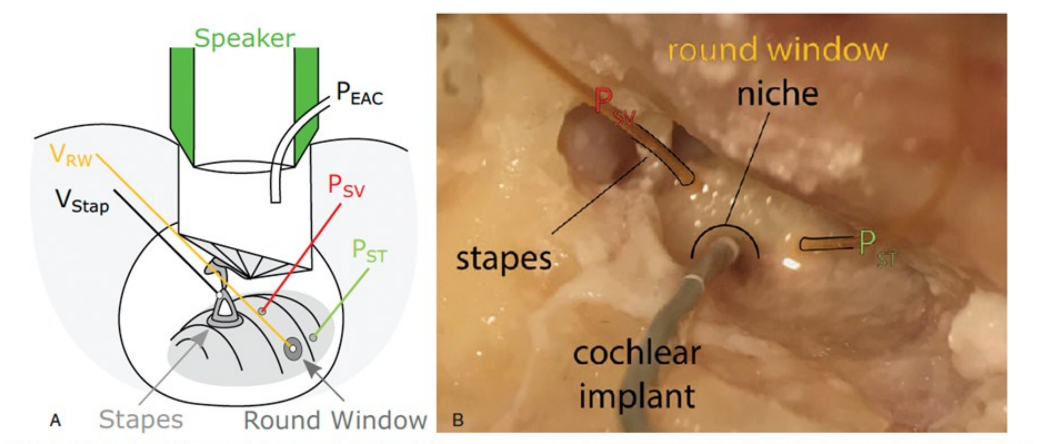


FIG. 1. Illustration of the surgical approach to the middle ear, pressure probe placement, acoustical stimulation, and cochlear implant insertion approach. Pressure probes were inserted into the scala vestibuli (P_{SV}) and scala tympani (P_{ST}) through small cochleostomies adjacent to the stapes footplate and round window, respectively. Cochleostomies were sealed with alginate dental impression material. Cochlear implants were inserted, under water, through the round window membrane.

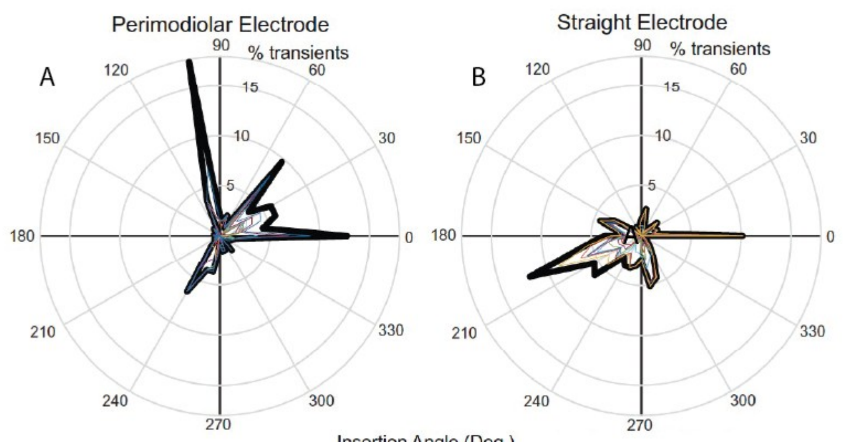


FIG. 5. The patterns of transient generation were quantified by calculating the percentage of transients occurring at each insertion angle (in 10 degrees increments), for both the perimodiolar (*A*) and straight (*B*) electrodes. The overall percentage of transients occurring at each angle is illustrated with a heavy black line, the percentage of transients occurring in each insertion, at each angle, are shown with colored lines, for both electrodes. Note, the percentages are cumulative, thus the difference between adjacent colored lines indicates the % within each insertion.

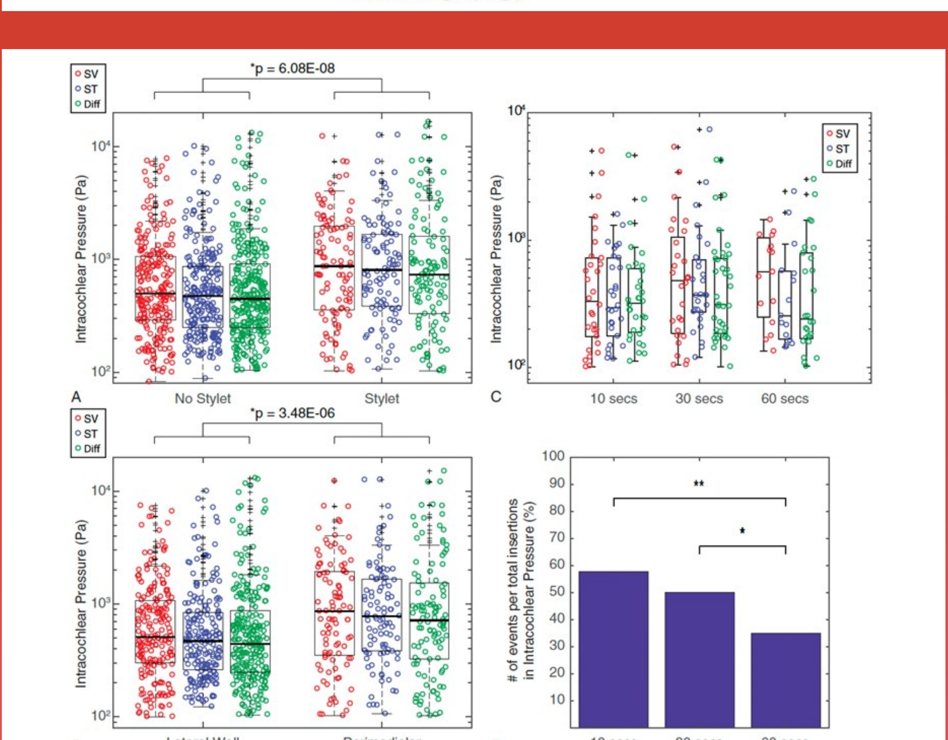


FIG. 3. Summary of peak pressure levels observed in all specimens during all electrode insertions by electrode characteristics and analyses of insertion duration. Unfiltered peak intracochlear pressure measurements are shown by electrode characteristics (straight or precurved in Panel A, styleted or non-styleted in Panel B). Panel C shows a summary of peak pressure levels observed in all specimens during all electrode insertions by insertion duration. Box plots represent the median ±25% of the range of pressures observed, whiskers show the full range of the estimated distribution, and +'s mark outliers. Panel D shows the percent of insertions with a significant pressure event by insertion duration. Chi-squared analysis with Bonferroni correction revealed a significant pattern of fewer exposures with longer insertions. Significant differences between groups are indicated with asterisks (* $p<0.05$, ** $p<0.01$).

OUTCOMES:

- Implant insertion and post-insertion manipulations produced high-intensity pressure transients with all electrodes tested, with some exceeding 170 dB peak SPL.

- Average peak pressures were significantly lower for lateral wall, non-stylet electrodes ($p<<0.001$). There was no correlation between electrode length, diameter, or volume and transient intracochlear pressure amplitudes.

- The likelihood of generating transients was lowest with the slowest insertions ($p<<0.001$) of at least 60 seconds.

- Post-insertional manipulations, including removal, can generate significantly higher peak pressure than insertions ($p<0.0003$).

- Pressure transients appear to be generated when the leading electrode directly contacts intracochlear structures (particularly the medial or lateral walls).

- There appear to be 3 morphologically distinct patterns of electrode tip fold-over: anterior-posterior, medial-lateral, and s-shaped. Elevated pressure transients were noted before and during the tip fold-over event related to electrode twisting.

FURTHER FUNDING HAS ENABLED US TO:

- The collaborative team (led by Dr. Nathaniel Greene at the University of Colorado) has submitted for NIH funding to continue investigation into the mechanisms underlying and implications of observed intracochlear pressure changes, including development of an animal model and an outcomes-based clinical protocol.

- The primary investigator has expanded research to focus on psychoacoustical outcomes for cochlear implant recipients, particularly with regards to single-sided deafness and binaural hearing tasks. A recently renovated anechoic chamber at the University of Michigan has facilitated the development of a novel combined speech-in-noise and localization task during which subjects head movement is tracked with the goal of evaluating the effects of cochlear implant use on ecologically valid speech localization performance and examine the resulting behavioral adaptations . This effort is also funded by the American Otological Society.

LAY SUMMARY:

While there does not appear to be a particular cochlear implant electrode geometry or size that correlates with higher peak intracochlear pressures, the insertion conditions that are associated with fewer pressure transients include the adoption of non-styleted electrodes and slow insertion speeds. Data presented here also demonstrate that higher changes in peak intracochlear pressures can be generated by post-insertional manipulations, including manipulation and withdrawal of electrodes. Avoiding such manipulations may further mitigate cochlear trauma generated during surgery.

Yew Song Cheng, BM BCh

Assistant Professor

Otology, Neurotology, and Skull Base Surgery

University of California San Francisco

“A Study of the "Third Window" Phenomenon using Inner-ear Pressure Measurements”

FELLOWSHIP GRANT 2015

Amount Awarded by AOS: $40,000

Ongoing Funding: Hearing Research Inc. UCSF

PUBLICATIONS:

Guan XY, Cheng YS, Galaiya D, Rosowski JR, Lee DJ, Nakajima HH. *Bone conduction hyperacusis induced by superior canal dehiscence in human – the underlying mechanism*. Submitted May 2020 to Scientific Reports. Sci Rep. 2020 Oct 6;10(1):16564. doi: 10.1038/s41598-020-73565-4. PMID: 33024221.

Cheng YS, Raufer S, Guan XY, Lee DJ, Halpin CH, Nakajima HH. *Superior canal dehiscence similarly affects cochlear pressure in temporal bones and audiograms in patients*. Ear Hear. 2019 2020 Jul/Aug;41(4):804-810.

Guan XY, Cheng YS, Galaiya D, Nakajima HH. *The Effect of Round Window Reinforcement on Human Hearing*. AIP Conference Proceedings. 2018 May; 1965(1):150004.

Cheng YS, Kozin ED, Remenschneider AK, Nakajima HH, Lee DJ. *Characteristics of wax occlusion in the surgical repair of superior canal dehiscence in human temporal bone specimens*. Otol Neurotol. 2016 Jan;37(1):83-8.

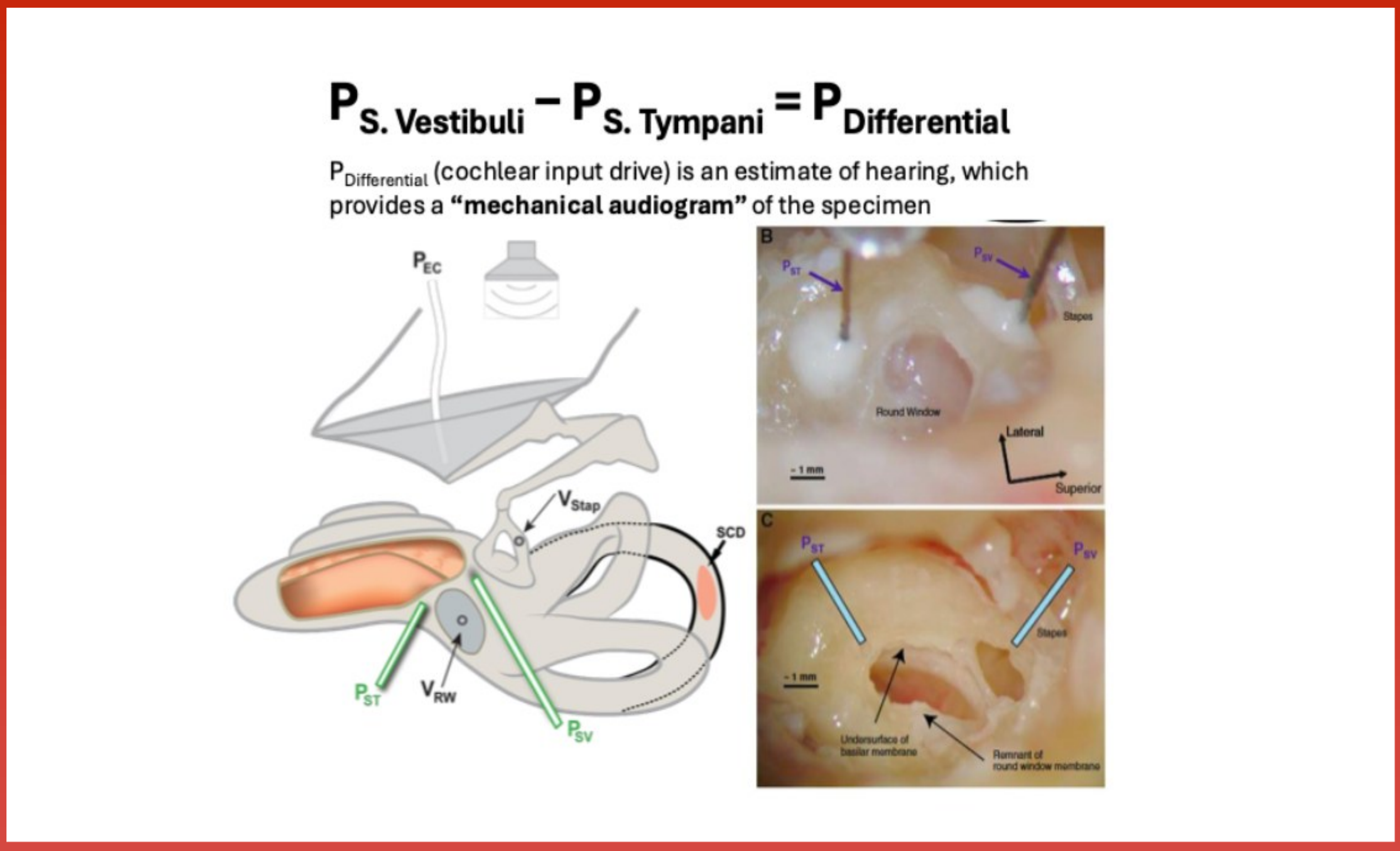
Noij KS, Duarte MJ, Wong K, Cheng YS, Masud S, Herrmann BS, Curtin HD, Kanumuri VV, Guinan JJ Jr, Kozin ED, Tarabichi O, Jung DH, Lee DJ, Rauch SD. *Toward Optimizing Cervical Vestibular Evoked Myogenic Potentials (cVEMP): Combining Air-Bone Gap and cVEMP Thresholds to Improve Diagnosis of Superior Canal Dehiscence*. Otol Neurotol. 2018 Feb;39(2):212-220.

Jan TA, Cheng YS, Landegger LD, Lin BM, Srikanth P, Niesten ME, Lee DJ. *Relationship between surgically treated superior canal dehiscence syndrome and body mass index*. Otolaryngol Head Neck Surg. 2017 Apr;156(4):722-727.

Barber SR*, Cheng YS*, Owoc M, Lin BM, Remenschneider AK, Kozin ED, Lee DJ. *Benign paroxysmal positional vertigo commonly occurs following repair of superior canal dehiscence*. Laryngoscope. 2016 Sep;126(9):2092-7.

RESEARCH SUMMARY:

Symptoms in superior semicircular canal dehiscence (SCD) syndrome can be explained by the SCD behaving as a “third window” of the inner ear, which results in leak of volume velocity or sound flow towards the defect. We measured intracochlear sound pressures the scala vestibular, and tympani of fresh human temporal bones and quantified the change in inner ear mechanics when an SCD is present. We used this model to test the influence of SCD size and position, as well as various repair surgical techniques including round window reinforcement.



OUTCOMES:

The human temporal bone model provides an excellent model for studying SCD syndrome

Surgical repair of the SCD restores normal inner ear mechanics.

Round window reinforcement does not restore normal inner ear mechanics, but results in small, frequency-specific changes in cochlear drive.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

The experimental measurements we obtained have helped us refine and create an accurate computational model of the middle and inner ear. This has been valuable in understanding both pathology affecting the mechanics of the ear, but also in advancing knowledge on physiology of hearing.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Patients can suffer debilitating symptoms from SCD syndrome. We have demonstrated that surgical repair can restore normal mechanics in the human ear. Other technique may affect symptoms in unexpected ways, but with the human temporal bone model, we can study and quantify these effects.

AMERICAN OTOLOGICAL SOCIETY

Sumana Ghosh, PhD

Instructor, Department of Otolaryngology - Head and Neck Surgery

University of Mississippi Medical Center

“Novel Role of Transcription Factor Six2 in Vestibular Planar Cell Polarity (PCP)”

FELLOWSHIP GRANT 2020

Amount Awarded by AOS: $44,000

PUBLICATIONS: Ghosh S, Baker B, Thapa P, Vanga V, Zettler K, Walters BJ. *The novel of transcription factor Six2 in inner ear morphogenesis.* (Manuscript in preparation).

RESEARCH SUMMARY:

The transcription factor Six2 is known to function in the embryonic development and patterning of many tissues including kidney and heart. Previous studies suggest the highly related Six1 protein plays an important role in the development of the inner ear. However, little is known about the role of Six2 in this context. Here, we investigated the expression pattern and function of Six2 during inner ear development.

Our data suggests that Six2 is expressed in both the pro-sensory and non-sensory cells throughout the development of the otic vesicle. Six2 is expressed broadly, but more ventrally, in the otic vesicle at E10.5. From E12.5 to E14.5, Six2 can be seen in both the otic floor (sensory) and the otic roof (non-sensory). By E17.5 and at postnatal day 0 (P0) Six2 expression in the cochlear floor becomes enriched in cochlear outer hair cells and some modest expression persists in supporting cells. In the vestibular epithelia, Six2 persists in both the type I and type II hair cells and at lower levels in supporting cells. Germline deletion of Six2 led to changes in the morphogenesis of the inner ear organs, with some disruption of the polarity of cells and other regional changes to the organs. For example, the area occupied by the striola was larger in Six2-/- utricles compared to controls, while the number of OCM+ve cells was actually decreased. Reduced numbers of OCM+ cells were also noted in the central region of the lateral cristae. Misorientation of hair cells in Six2-/- animals may not represent disruption of the canonical planar cell polarity pathway as intracellular orientations of VANGL2 and Gαi3 were largely preserved, rather hair cell maturation appears delayed by Six2 deletion leading to disorganization being most prominent in still developing areas of the utricle at E17.5. Consistent with the hypothesis that Six2 may promote hair cell maturation, greater numbers of developing hair cells lack phalloidin and/or espin in the Six2-/- mice vs. controls. However, with overexpression of Six2, the markers of mature type I and type II hair cells, SPP1 and MAPT, were decreased at P3-P4 which would either suggest either dose and/or timing of Six2 may be critical for proper timing of various aspects of vestibular hair cell development and maturation.

OUTCOMES:

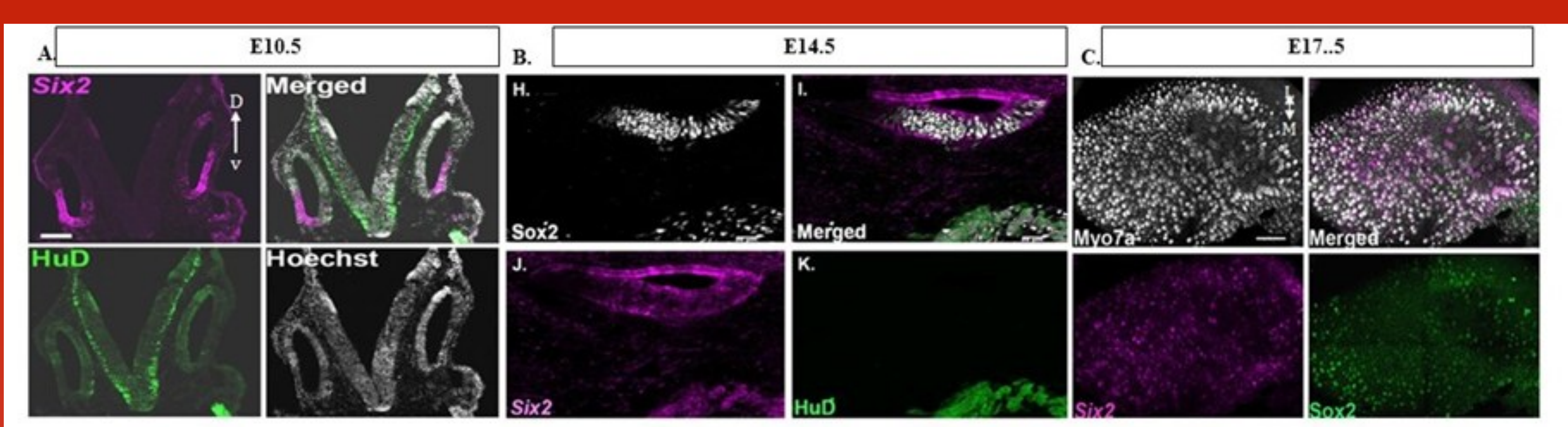


Figure 1: ***Six2*** **is expressed during embryonic development of the inner ear.** RNA Expression of *Six2* (magenta) was examined at E10.5, E14.5 and E17.5 followed by immunostaining. **A)** As early as E 10.5 *Six2* is expressed in both sensory and non sensory cells of the otic vesicles. HuD (green) was used to visualize neurons and Hoechst (white) was used to label cell nuclei. **B)** At E 14.5 *Six2* is still present in Sox2 +ve (white) prosensory and non-sensory epithelia and in the ganglion. **C)** *Six2* is expressed at E17.5 in Myo7a (white) positive hair cells and Sox2+ve (green) supporting cells.

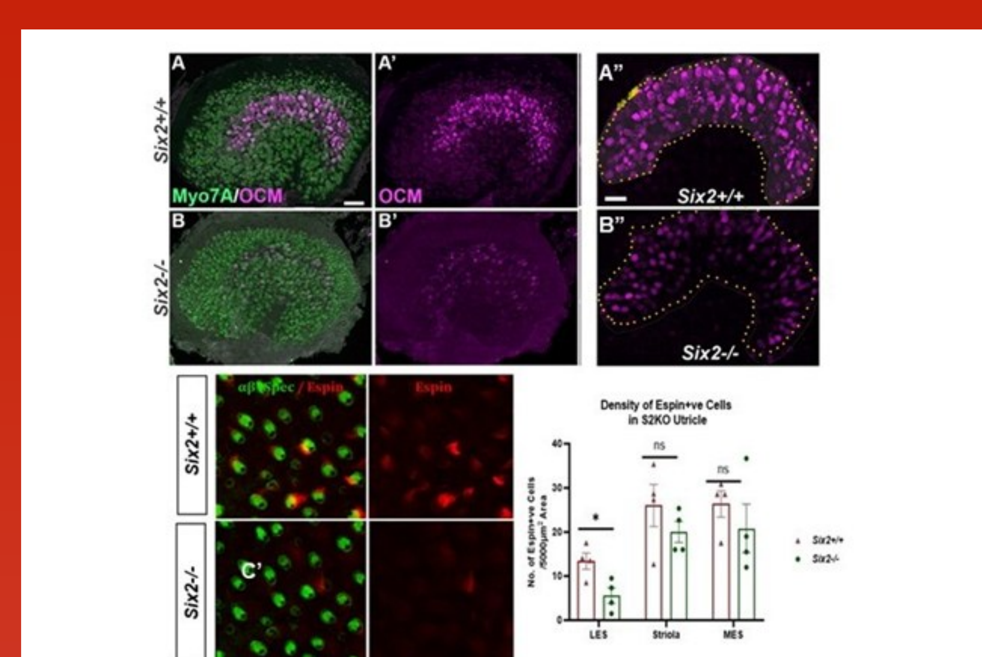


Figure 2: Reduced oncomodulin and Espin expression in response to ***Six2*** **deletion suggests impaired hair cell maturation at E17.5** At embryonic day 17.5 (E17.5) utricles were collected and immunolabelled with OCM and Myo7a (A-B”). Our data suggests that deletion of *Six2* results in reduction of the area and total number of OCM+ve cells. C-E) The utricular hair cells were labelled with αβ-Spectrin II (all hair cells) and espin (mature hair cells). Quantification (E)of our data shows that there is decreased density of the espin+ve cells in the *Six2-/-* mice, suggesting that deletion of *Six2* results in increase of the immature hair cells.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

This grant award has enabled us to investigate the role of transcription factor Six2 in the development of the vestibular organ. This work led to unexpected finding that Six2 may play a role in maturation of the sensory hair cells in the utricle. We will further explore the molecular mechanisms how Six2 regulates maturation processing. Our preliminary data suggested that germline deletion of Six2 results in misorientation of hair cells. Therefore, we will further investigate the effect of Six2 deletion in the function of the vestibular system in the conditional Six2 knockout model by performing vestibulo-ocular reflex (VOR), vestibular evoked myogenic potential (VeMP).

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Vestibular organ located in our inner ear regulates our balance and proprioception. Ototoxic damage such as blast, noise and chemotherapeutic agents and age can result in dysfunctions of the system. This increase fall risk which could be fatal. Despite the importance of the physiological functions of the vestibular system, there is paucity of understanding about the development of this organ. In this current study we investigated the role of a protein (transcription factor) Six2 in the development of the vestibular organs including utricle and cristae. We found that Six2 regulates the development of the sensory cells in the utricle.

During ototoxic damage and natural aging process, the sensory hair cells of the vestibular organ dies. Although some of the hair cells spontaneously regenerate, it fails to fully recapitulate the properties and the function of normal cell population. Therefore, to restore normal vestibular function we need to regenerate the hair cells. Data gleaned from this study will facilitate to understand how the sensory cells develop and this knowledge can be exploite to regenerate sensory cells restoring normal vestibular function.

AMERICAN OTOLOGICAL SOCIETY

Christopher Nielson, MD

Medical Student Research Fellow

University of Utah

"Determining the Role of Macrophages in the Pathogenesis of Cytomegalovirus Induced Sensorineural Hearing Loss"

FELLOWSHIP GRANT 2020

Amount Awarded by AOS: $40,000

PUBLICATIONS: Otsuka KS, Nielson C, Firpo MA, Park AH, Beaudin AE. *Early Life Inflammation and the Developing Hematopoietic and Immune Systems: The Cochlea as a Sensitive Indicator of Disruption*. Cells. 2021 Dec 20;10(12):3596. doi: 10.3390/cells10123596. PMID: 34944105; PMCID: PMC8700005.

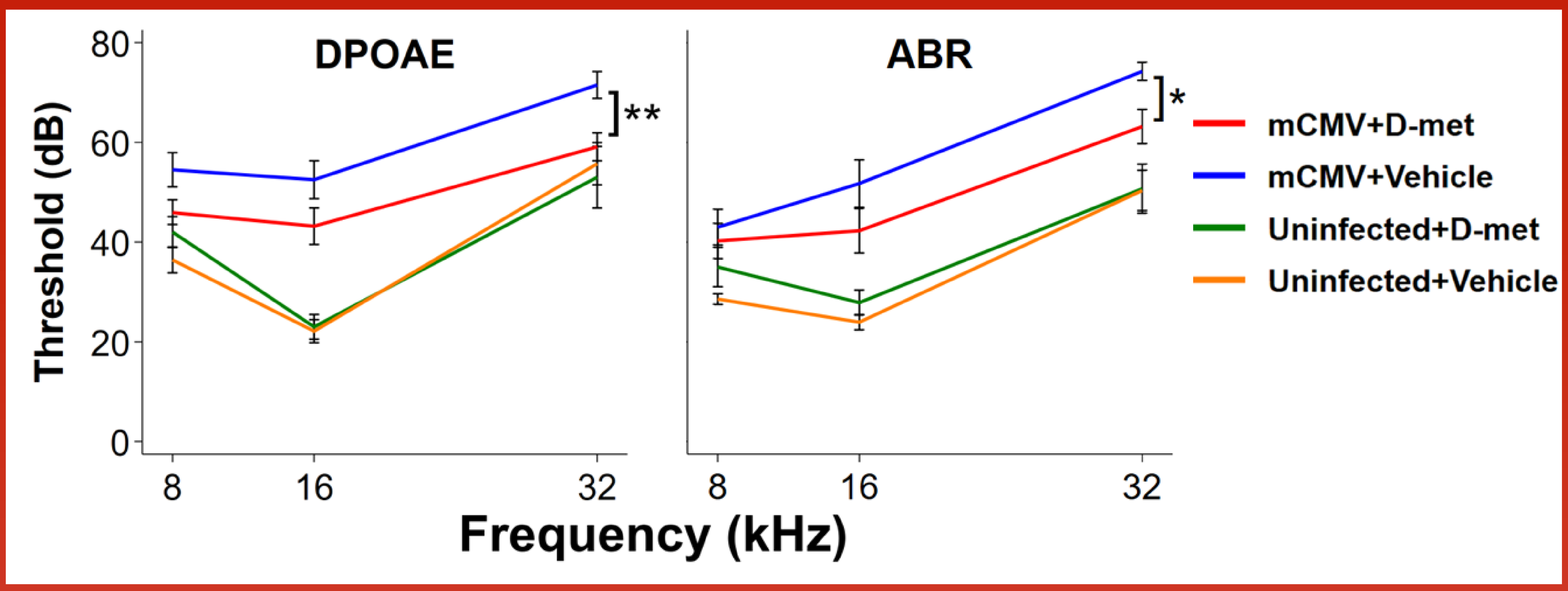
Otsuka KS, Nielson C, Suarez D, Park AH, Beaudin AE, *The contribution of fetal-derived tissue resident macrophages to cytomegalovirus-associated sensorineural hearing loss*, The Journal of Immunology, Volume 208, Issue Supplement_1, May 2022, Page 50.40, https://doi.org/10.4049/jimmunol.208.Supp.50.40

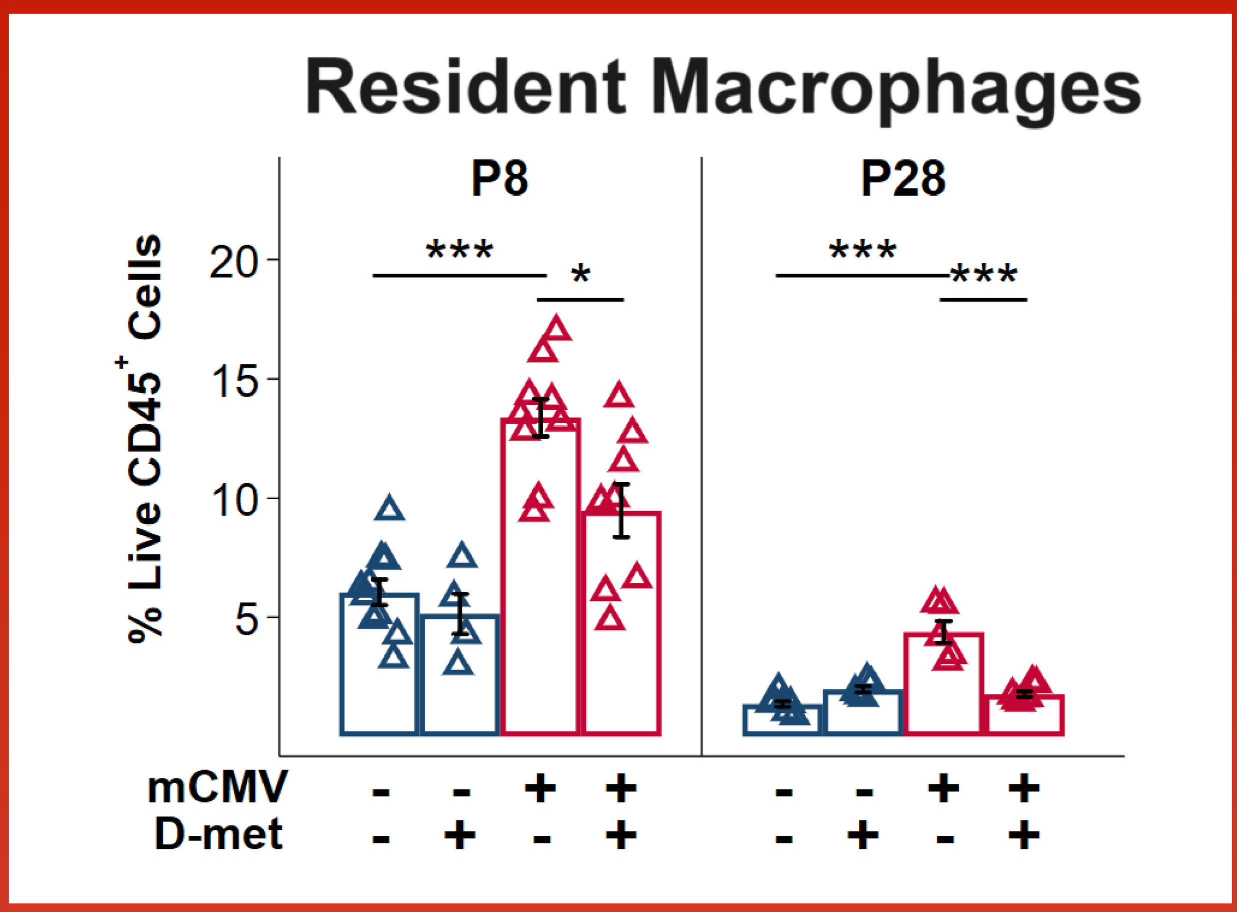
Hillam K, Suarez D, Nielson C, Traxler A, Sommer E, Winslow A, Holley A, Huang E, Hughes M, Firpo MA, Rower J, Park AH. *Hearing Following Prolonged and Delayed Ganciclovir Treatment in a Murine Cytomegalovirus Model.* Laryngoscope. 2024 Jan;134(1):433-438. doi: 10.1002/lary.30860. Epub 2023 Jul 8. PMID: 37421238.

Suarez D, Kjar A, Scott B, Hillam K, Vargis E, Nielson C, Sommer E, Zhang E, Holley A, Traxler A, Hughes M, Wang Y, Firpo MA, Britt D, Park AH. *Can Ganciclovir and Quercetin-P188 Ameliorate Cytomegalovirus Induced Hearing Loss?* Laryngoscope. 2024 Mar;134(3):1457-1463. doi: 10.1002/lary.30975. Epub 2023 Aug 17. PMID: 37589298.

RESEARCH SUMMARY:

Congenital cytomegalovirus (CMV) is the most common non-genetic cause of hearing loss in newborn infants, yet the mechanism is poorly understood and treatment options are limited. We hypothesized that an exaggerated immune response may contribute to the progressive nature of patients with congenital CMV infection. To test this hypothesis, we evaluated immune cell frequencies in the cochleae of a mouse model of congenital CMV hearing loss.





OUTCOME:

We demonstrated a persistent expansion of cochlear macrophages in response to congenital infection compared to the ears of uninfected mice. When treated with the reactive-oxygen species scavenger, D-methionine, hearing improved and cochlear macrophage frequencies were reduced.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

Collaborate with fetal stem cell researchers at our institution to successfully obtain R01 funding.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Our research demonstrates that an inflammatory response may play a key role in hearing loss for infants infected with congenital CMV. We have demonstrated that a specific type of immune cell may be central to this process, and may represent a specific target for treatment.

AMERICAN OTOLOGICAL SOCIETY

Aaron K. Remenschneider, MD, MPH

Otology, Neurotology and Skull Base Surgery

Boston Children's Hospital and Mass Eye and Ear

Associate Professor, Harvard Medical School

"Optimized 3-Dimensional Printed Tympanic Membrane Prosthesis"

Research Grant 2015

Amount Awarded by AOS: $55,000

Ongoing Funding: NIH, NIDCD K08 (2020-25), $950,400 (Mechanisms of Conductive Presbycusis)

DoD SBIR (2019-23), $488,278 (Innovative Solution to Tympanic Membrane Repair)

Foundation Grants (2016-23), $767,188 (Biomimetic Grafts for Tympanic Membrane Reconstruction)

PUBLICATIONS:

Remenschneider AK, Lookabaugh S, Aliphas A, Brodsky JR, Devaiah AK, Dagher W, Grundfast KM, Heman-Ackah SE, Rubin S, Sillman J, Tsai AC, Vecchiotti M, Kujawa SG, Lee DJ, Quesnel AM. *Otologic outcomes after blast injury: the Boston marathon experience.* Otol Neurotol. 2014 Dec; 35 (10):1825-34. PMID: 25393974

Kozin ED, Black NL, Cheng JT, Cotler MJ, McKenna MJ, Lee DJ, Lewis JA, Rosowski JJ, Remenschneider AK. *Design, Fabrication and In Vitro Testing of Novel Three-Dimensionally Printed Tympanic Membrane Grafts.* Hear Res. 2016 Oct; 340:191-203. PMID: 26994661

Trakimas D, Ishai R, Ghanad, I, Black N, Kozin ED, Cheng T, Remenschneider AK. *Otopathologic Evaluation of Temporalis Fascia Grafts Following Successful Tympanoplasty in Humans.* Laryngoscope 2018 Oct;128(10);E351-E358. PMID 29756238

Polanik MD, Trakimas DR, Black NL, Cheng JT, Kozin ED, Remenschneider AK. *High-Frequency Conductive Hearing following Total Drum Replacement Tympanoplasty.* Otolaryngol Head Neck Surg. 2020 Jun;162(6):914-921. PMID: 32097057

Ghanad I, Polanik MD, Trakimas DR, Knoll RM, Castillo-Bustamante M, Black NL, Kozin ED, Remenschneider AK. *A Systematic Review of Nonautologous Graft Materials Used in Human Tympanoplasty*. Laryngoscope 2021 Feb;131(2): 392-400 PMID: 33176008

Roychowdhury P, Polanik MD, Kozin ED, Remenschneider AK. *In Office Repair of Tympanic Membrane Perforation.* Otol Neurotol. 2021 Dec 1;42 (10):e1636. PMID: 34420025

Eberhard KE, Masud SF, Knudson IM, Kirubalimgam K, Khalid H, Remenschneider AK, Nakajima HH. *Mechanics of Total Drum Replacement Tympanoplasty Studied with Wideband Acoustic Immittance*. Otolaryngol Head Neck Surg. 2022 Apr;166(4):738-745. PMID: 34281437

Remenschneider AK, Cheng JT, Herrmann BS, Rosowski JJ. *Characterization and Clinical Use of Bone Conduction Transducers at Extended High Frequencies*. Hear Res. 2023 Mar 1;429:108688. PMID: 36628803

Patel H, Pavlichenko I, Grinthal A, Zhang CT, Alvarenga J, Kreder MK, Weaver JC, Li Q, Ling CWF, Choy J, Li Z, Black NL, Bispo PJM, Lewis JA, Kozin ED, Aizenberg J, Remenschneider AK. *Design of Medical Conduits with Selective Fluid Transport Properties*. Sci Transl Med. 2023 Apr 5;15(690):edadd9779 PMID: 37018418

Schmeltz M, Ivanovic A, Schleputz DM, Wimmer W, Remenschneider AK, Caversaccio M, Stampanoni M, Anschuetz L, Bonnin A. *The human middle ear in motion: 3D visualization and quantification using dynamic synchrotron-based X-ray imaging.* Commun Biol. 2024 Feb 7;7(1):157. PMID: 38326549

RESEARCH SUMMARY:

Our multidisciplinary team of otologists, acoustical engineers and materials scientists developed at-scale biomimetic scaffolds with fibrous structure similar to the tympanic membrane. A novel biocompatible degradable polymer was developed for use in ultra-high resolution 3D printing to fabricate grafts of varied fibrous architecture. Sound induced velocities of grafts were evaluated to optimize a wide range of frequency responses. In-vivo animal testing was performed to confirm biocompatibility, tympanic membrane perforation closure and hearing threshold improvement.

OUTCOMES:

We developed a novel biodegradable, printable polymer and to demonstrated tunable acoustic and mechanical properties for optimized biomimetic membranes that behave similar to the native tympanic membrane in vitro. Subsequent in vivo animal and histological studies demonstrated the safety and feasibility of the grafts as biodegradable scaffolding for the regrowth of normal TM structure.

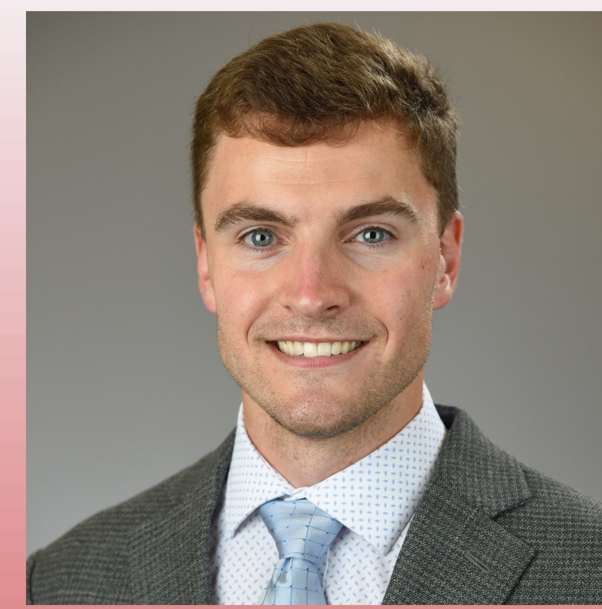
FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

In 2021 a start-up company built around the technology was acquired by Desktop Health where pre-clinical testing, clinical trials and FDA submission have been initiated.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

Biomimetic grafts made with 3D printing improve our understanding of how eardrum structure affects function, and they represent a viable path to obtain consistent hearing outcomes after tympanic membrane repair.

AMERICAN OTOLOGICAL SOCIETY



Gabriel Sobczak, MD

Resident - Indiana University

"fNIRS Evidence for Underlying Neural Mechanisms of Spatial Release from Masking in Single-Sided Deaf Cochlear Implant Listeners"

FELLOWSHIP GRANT 2020

Amount Awarded by AOS: $44,000

Ongoing Funding: NIH – National Institute on Deafness and Other Communication Disorders, $535,459 Year: FY 2025

PUBLICATIONS:

Cortical mechanisms of across-ear speech integration investigated using functional near-infrared spectroscopy (fNIRS). Sobczak GG, Zhou X, Moore LE, Bolt DM, Litovsky RY (2024). PLOS ONE 19(9): e0307158. https://doi.org/10.1371/journal.pone.0307158

RESEARCH SUMMARY:

This study aimed to identify potential neural signatures of across-ear speech integration. We presented sentence segments alternating between ears to participants, while measuring cortical activity using functional near-infrared spectroscopy (fNIRS). Cortical activation in each region of interest (Figure 1) was recorded using fNIRS while typical-hearing listeners were presented with 12 conditions (Figure 2). In a separate session, speech intelligibility scores were calculated for each of the 12 conditions. The study was motivated by evidence that people with hearing loss who are fitted with CIs show deficits in being able to integrate information across the two ears.

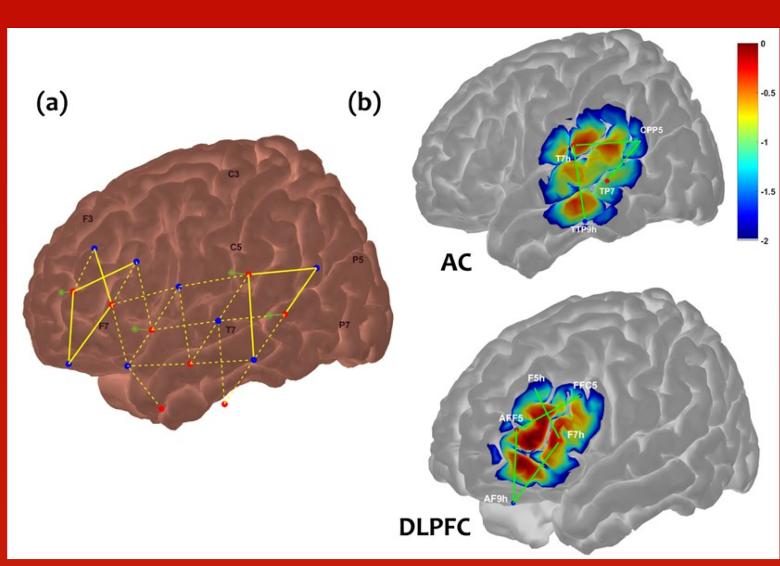


Figure 1. Illustration of fNIRS montage and cortical regions of interest. (a) fNIRS montage, showing sources (red dots), detectors (blue dots) and short-channel detectors (green asterisks). Yellow lines connecting a source and detector represent measurement channels. fNIRS montage was symmetric between the left and right hemisphere. (b) Selected channels comprising a priori ROIs, the auditory cortex (AC) and dorsolateral prefrontal cortex (DLPFC); ROIs are only shown on the left hemisphere for demonstration purposes. Colormap corresponds to sensitivity profiles for each ROI channel grouping, in units of log -10 mm-1.

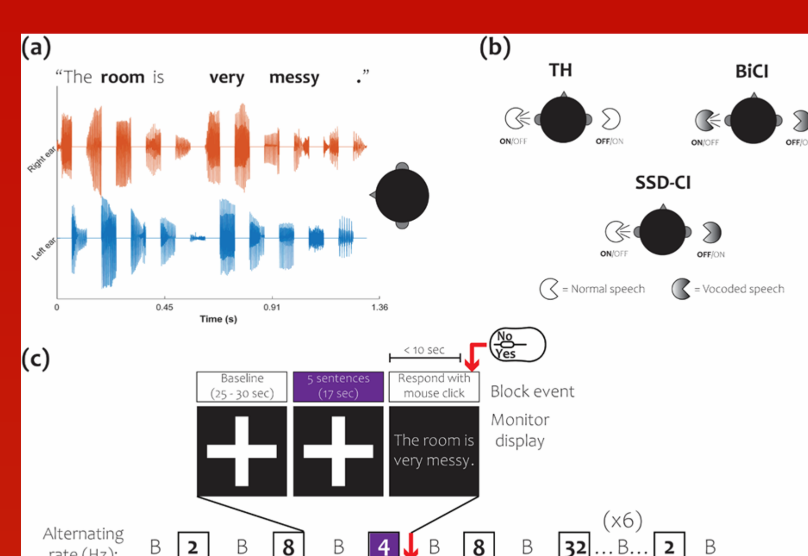


Figure 2: Alternating speech stimulus, speech conditions, and fNIRS data collection. (a) Spectrogram demonstrating an example non-degraded AuSTIN sentence, "The room is very messy ", segmented and alternating between ears at 8 Hz. Additional alternation rates included 2, 4, and 32 Hz. (b) Organization of speech conditions: TH = non-degraded speech in both ears; SSD-CI = vocoded speech in right ear, non-degraded speech in left ear; BiCI = vocoded speech bilaterally. (c) Pseudorandom block design, with stimuli in 4 listening conditions (boxes); 4 alternating rates presented at one speech condition in random order during each data collection session.

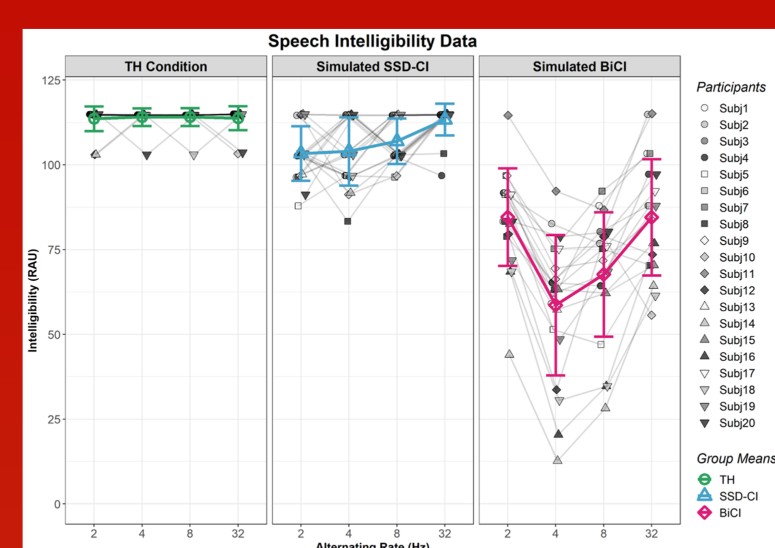


Figure 3: Participant-level speech intelligibility data in rationalized arcsine units (RAU), at all four alternating rates. Figure panels are separated by speech condition. Connecting lines between each participant's datapoints are added to illustrate participant-level patterns across alternating rates. Group-mean speech intelligibility ± 1 standard deviation (SD) is superimposed on participant -level data. Speech intelligibility data were collected in a separate behavioral experiment without fNIRS recording.

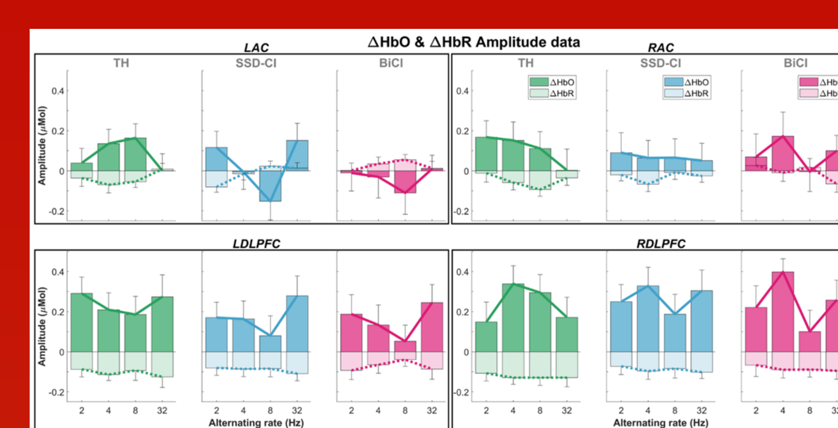


Figure 4: Group-averaged DHbO and DHbR amplitude data, in the cortical regions of interest (ROIs). Amplitudes are plotted across alternating rates, and error bars correspond to ± 1 standard error of the mean (SEM). Connecting lines between amplitude bars (solid = DHbO, dotted = DHbR) demonstrate overall patterns in amplitude changes across alternating rates. Columns contain data from one speech condition, and black boxes contain data from one cortical ROI.

OUTCOMES:

Figure 3 shows that speech intelligibility scores were at ceiling levels across all rates for the nondegraded condition. For the bilateral CI condition, there is reduced performance with a minimum at 4 Hz. The SSD-CI condition does not show a similar "V" shape, but comparisons of typical-hearing and SSD-CI scores between 2 – 32 and 4 – 32 Hz suggest that switching attention between normal and degraded speech at low alternating rates reduces speech understanding.

Figure 4 demonstrates cortical activity (fNIRS response) in the four cortical regions of interest, expressed in terms of changes in relative concentration of oxygenated and deoxygenated hemoglobin (ΔHbO and ΔHbR, respectively). The AC and DLPFC exhibited significantly different activity across alternating rates in the non-degraded condition, with altered activity patterns in both regions in the SSD-CI and bilateral CI conditions.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

Evaluate the relationship between binaural hearing (spatial release from masking) and listening effort in listeners with SSD-CI, using pupillometry as an objective measure of attention and effortful cognitive processing.

Suveg L, Thakkar T, Burg E, Godar SP, Lee D, Litovsky RY. The Relationship Between Spatial Release From Masking and Listening Effort Among Cochlear Implant Users With Single-Sided Deafness. Ear Hear. Published online February 19, 2025. doi:10.1097/AUD.0000000000001611

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

In the present study, we demonstrate that cortical activity in the four regions of interest suggests employment of different listening strategies across the four alternating rates. Addition of degraded speech in one or two ears alters patterns of auditory cortex and dorsolateral prefrontal cortex activity across alternating rates compared to the non-degraded speech condition. These findings suggest that degraded speech inputs in one or two ears impacts cortical integration of binaural speech stimuli in ways not necessarily revealed by behavioral data alone. In the future, objective neuroimaging data in clinical settings may better inform auditory rehabilitation techniques to improve cochlear implant outcomes.

Zachary D. Urdang, MD, PhD

Postdoctoral scholar, University of Iowa Otolaryngology
Incoming Resident, University of New Mexico Pediatrics

"Neutrophil and Toll-Like Receptor Four Contributions to Endotoxemia-Enhanced Aminoglycoside Ototoxicity"

FELLOWSHIP GRANT 2014-2015

Amount Awarded by AOS: $54,500 (2)

Ongoing Funding:

2024: **Iowa Institute for Artificial Intelligence** – Internal Pilot Grant ($15,000)

2022: **PhRMA Foundation** – Health Equity Challenge Award Winner ($10,000)

2022: **76'ers Philadelphia NBA** team philanthropic donation to Jefferson Screening Van ($75,000)

2022: **American Head and Neck Society** Cancer Prevention Community Service Award ($1,000)

2022: **Goldman Humanism Honors Society Grant**. DEAFMed: A Jefferson MD-student led initiative for Deaf education in MD school ($1,500)

2015-2018: **NIH NIDCD F30** – Combined MD/PhD Specific Fellowship Grant – ($186,090)

PUBLICATIONS:

Urdang ZD, Bills JL, Cahana DY, Muldoon LM, Neuwelt EA. *Toll-like Receptor 4 Signaling and Downstream Neutrophilic Inflammation Mediate Endotoxemia-Enhanced Blood Labyrinth Barrier Trafficking*. Otology & Neurotology, 2020. 41(1), Pg. 123-132. PMID: 31568132.

Urdang ZD, Kargbo IM, Noss EE, McNair C, Jin H, Cottrill EE, Winer-Jones JP. *Federated EHR Database via A Public-Private Partnership to Enhance Healthcare Equity By Disparity Discovery and Equitable Clinical Trial Recruitment*. Invited manuscript to Journal of Healthcare for the Poor and Underserved, 2022. 33(5), Pg. 124.

Urdang ZD, Jain A, Li M, Haupt TL, Wilcox TO, Chiffer RC, Gurgel RK. *Conductive Hearing Loss Associates with Dementia and Middle Ear Reconstruction Mitigates This Association: A Multinational Database Study.* Otology & Neurotology, 2024. 45 (9), 1078-1086. PMID: 39167564.

Urdang ZD, George-Jones N, Musa M, Al-Qurayshi Z, Pagedar NA, Cottrill EE, Cognetti DM, Mady LJ, Curry JM. *Head and Neck Cancer Screening Value Enhancement Via Machine Learning to Predict Diagnoses*. Presented at AAO-HNSF September 2024 as a late breaking abstract. In-submission.

Urdang ZD, George-Jones N, Shamin H, Eckard P, Gantz B, Hansen M, Bennion D, Claussen A. *Aspirin, Losartan, and Unbiased Discovery of Medications Associated with Improved Vestibular Schwannoma Outcomes – A Multi-National Database Study*. Presented at AAO-HNSF ANS Skull Base Tumor Study Group 2024.

RESEARCH SUMMARY:

Enhanced blood-labyrinth barrier trafficking during sepsis requires down-stream neutrophil activity. Using neutropenic mice this work demonstrates that both up-stream cyto/chemokine signaling, and down-stream neutrophil activity are required to enhance trafficking at the blood-labyrinth barrier.

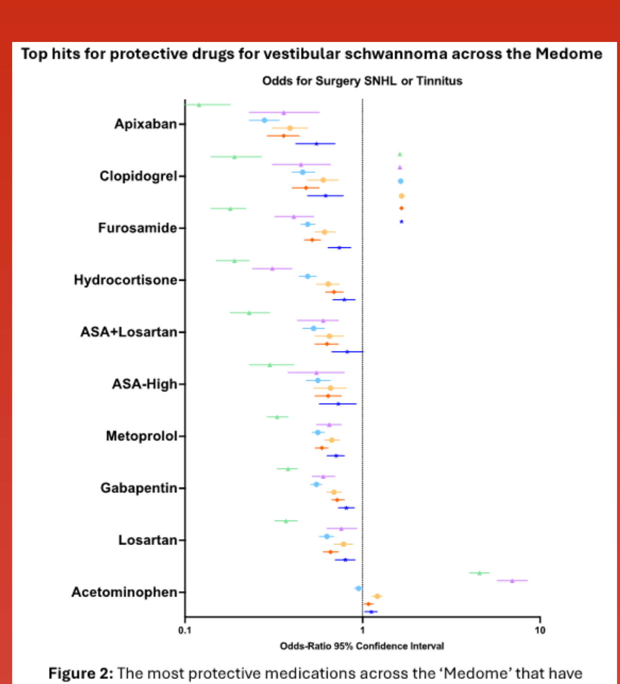
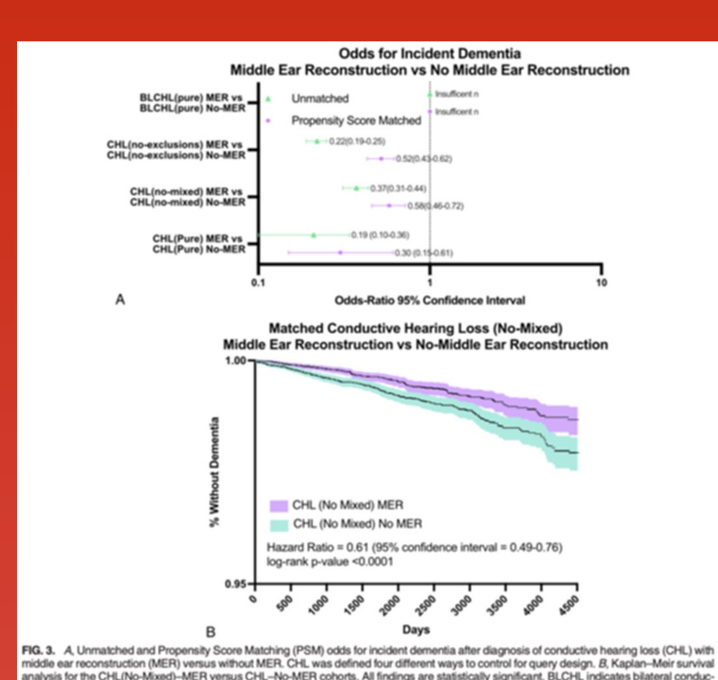


Figure 2: The most protective medications across the 'Medome' that have protective associations against the progression of tumor.



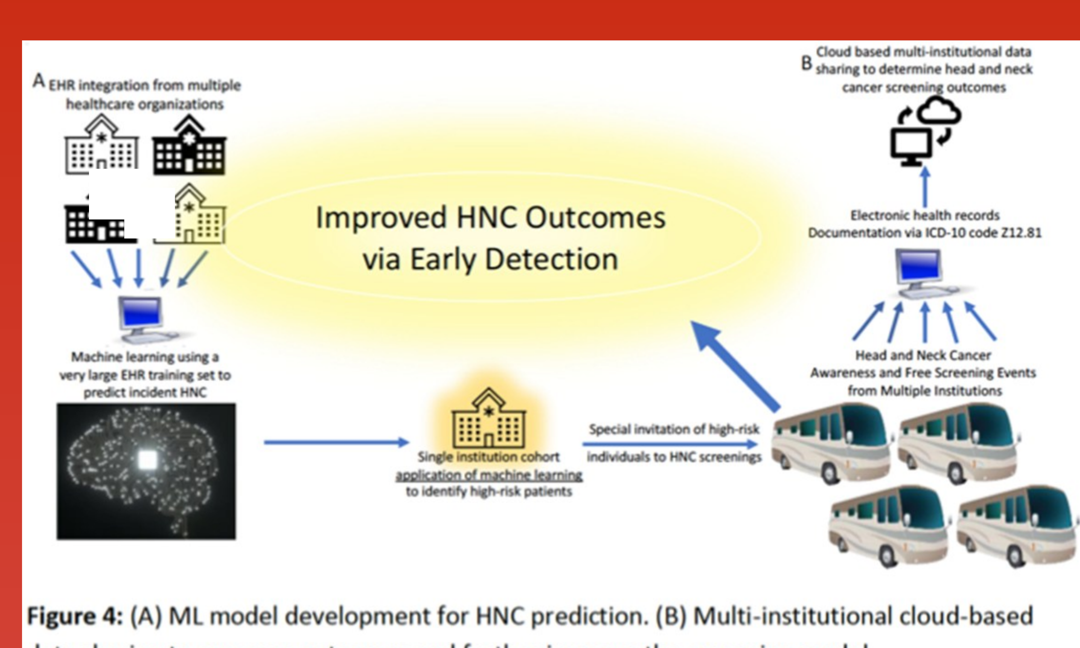
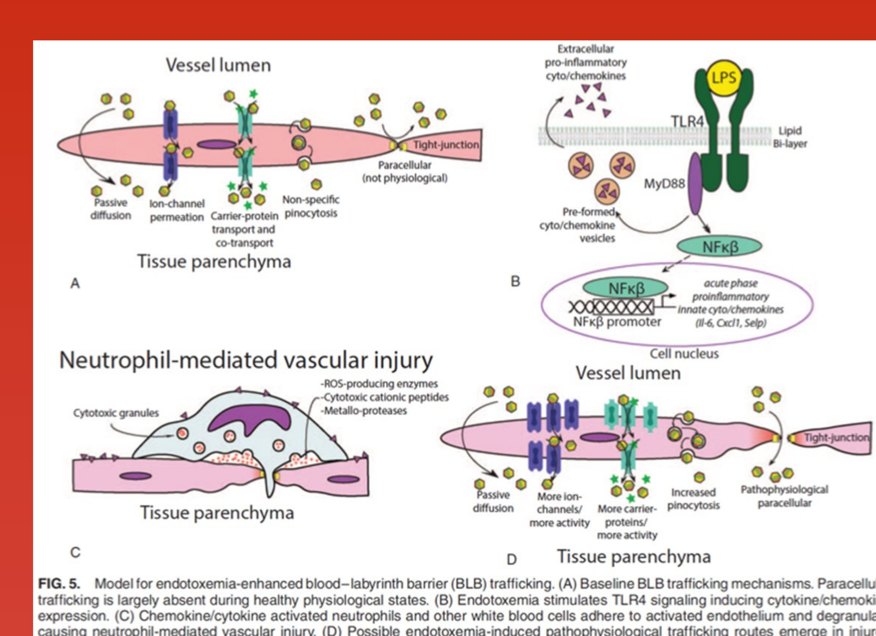


Figure 4: (A) ML model development for HNC prediction. (B) Multi-institutional cloud-based data sharing to measure outcomes and further improve the screening model.



OUTCOMES:

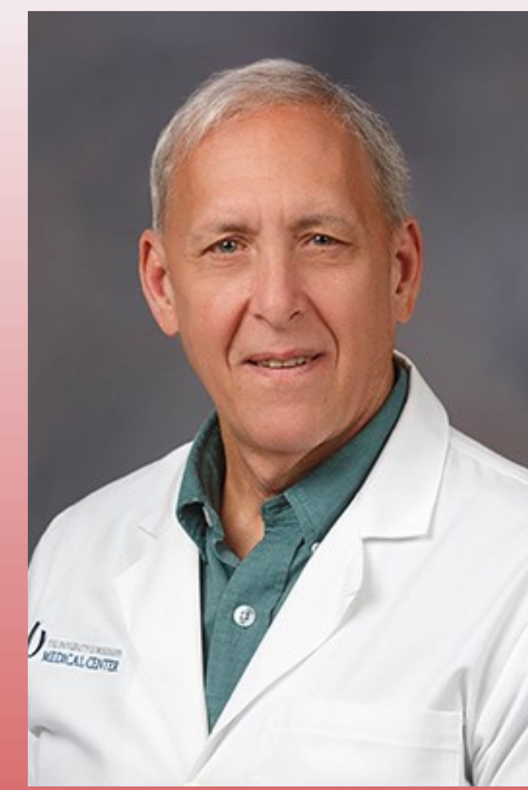
Cytokine signaling alone is insufficient for fully enhanced blood-labyrinth barrier trafficking during sepsis.
Neutrophils are key factors required for enhanced blood-labyrinth barrier trafficking during sepsis and subsequent ototoxicity.
Dr. Urdang has published and mentored numerous data science papers in otolaryngology across the sub-specialties with a personal focus/interest in otology/ neurotology.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

Since completion of his MD/PhD with OHSU Dr. Urdang has completed two postdocs with Jefferson U. and U. Iowa focusing on data science and machine learning. Dr. Urdang also completed a professional certificate from MIT in data science and machine learning. His work spans otolaryngology subspecialties with a focus on otology. His future research will focus on pediatric otolaryngology with a focus on otology/neurotology.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

This work describes the key role that an immune cell called the neutrophil plays to enhance inner-ear drug transport in critically ill patients. We demonstrate that molecular signaling is insufficient on its own to enhance inner-ear drug trafficking in critically ill patients and that downstream neutrophils are required to enhance the risk of hearing loss. If you are interested in working with Dr. Urdang clinically or for data science research, please reach out at zachary.urdang@gmail.com



Douglas E. Vetter, PhD

Associate Professor

Department of Otolaryngology - Head and Neck Surgery

University of Mississippi Medical Center

"Novel Peptidergic Signaling Systems Protective Against Noise-Induced Hearing Loss- A Role for Orexin Signaling in the Mammalian Cochlea"

RESEARCH GRANT 2020

Amount Awarded by AOS: $55,000

Ongoing Funding: $175,000 R21 funding, NIH (NIDCD) 2022-2025

PUBLICATIONS:

Peptidergic and related steroid signaling in the cochlea:Barnes, CC, Yee, KT, and Vetter, DE (2023) *Conditional ablation of glucocorticoid and mineralocorticoid receptors from cochlear supporting cells reveals their differential roles for hearing sensitivity and dynamics of recovery from noise-induced hearing loss*. Int. J. Mol. Sci. 24(4):3320. doi: 10.3390/ijms24043320. PMID: 36834731

Vetter, D.E. and Yee, K.T. (2018) *Corticotropin Releasing Factor in the Mammalian Cochlea: An Integrative Niche for Cochlear Homeostatic Balance Against Noise.* in: Inflammatory Mechanisms in Mediating Hearing Loss, V. Ramkumar and LP Rybak, eds., Springer Press.

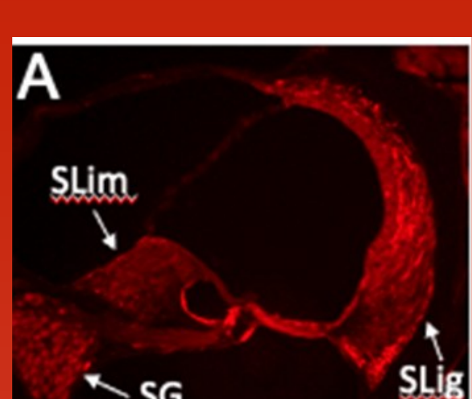
Orexin signaling in the cochlea: Yee, K.T., Ghadiyaram, A., and Vetter, D.E. (in prep) *The role of Orexin A and Orexin B peptides and the Orexin receptor 1 in the mammalian cochlea.*

RESEARCH SUMMARY:

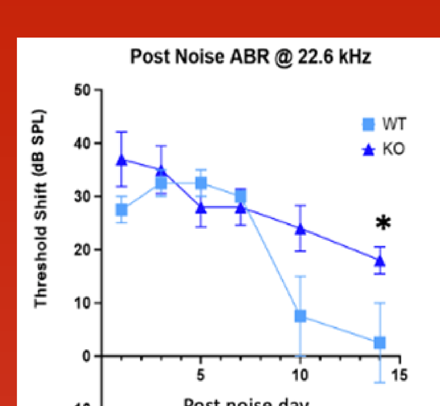
We have used genetic modifications to investigate the role of Orexin signaling in the mouse cochlea. Here, we demonstrate that loss of Orexin receptor 1 (OxR1) gene expression results in greater susceptibility to noise-induced damage at both the physiological and structural levels. Noise exposures that produce mild and temporary elevation of hearing thresholds in normal mice produce a longer lasting and apparently permanent hearing loss in mice lacking the OxR1 gene. Similar research is proceeding to investigate the role of the Orexin R2 gene in noise-induced hearing damage.

OUTCOME:

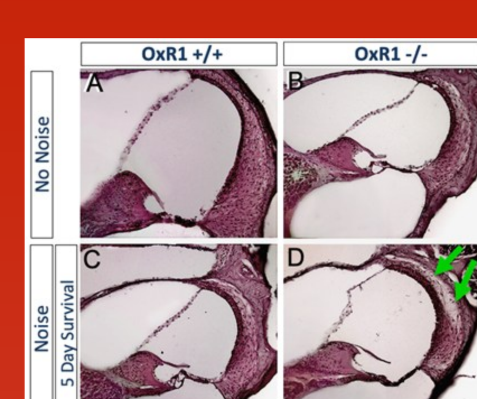
Orexins are hypothalamic peptides typically associated with control over feeding and sleep wake cycles. Orexin receptor (OxR1 and OxR2) antagonists such as Suvorexant (Belsomra®) are marketed to treat insomnia. Orexin receptor antagonist drugs are often taken for much longer periods than prescribed (months to years) for sleep dysfunction, especially by those suffering from anxiety, PTSD, and the general effects of aging. We previously demonstrated peptides normally associated with the hypothalamic function are expressed in the cochlea (Graham et al., 2010, 2011). We asked whether Orexin peptide signaling is present in the cochlea, and if so, whether long-term use of Orexin receptor antagonists might pose an increased risk for hearing loss.



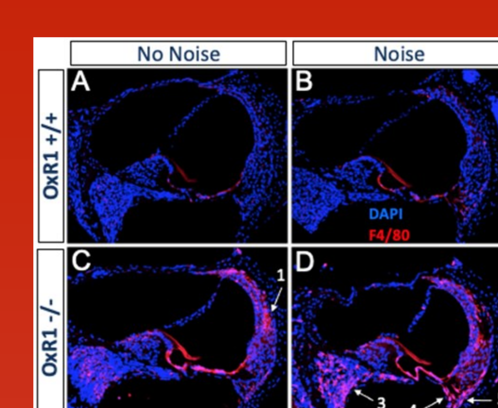
We localized both Orexin peptides (Orexin A and B) to the support cells along the basilar membrane and within the lateral wall of the mouse cochlea (red fluorescence) and both Orexin receptors (OxR1 and OxR2) to the same regions of the mouse cochlea (not shown). (SLim- spiral limbus; SG- spiral ganglion; SLig- spiral ligament)



Using mice with a mutation interrupting OxR1 gene expresson, we demonstrated that exposure to noise intensity normally producing a temporary ABR (wave 1) threshold shift (light blue) in normal mice produces a longer lasting, perhaps permanent, threshold shift (dark blue) in the OxR1 null mice.



Noise also induces a greater degree of damage to the lateral wall in the OxR1 null mice (green arrows) compared to that occurring in wild type mice.



In the absence of noise exposure, F4/80, a marker for macrophages, is higher without noise in the OxR1 null mouse than in controls (cf. C to A). While moderate intensity noise exposure results in F4/80 upregulation in both WT and KO conditions, following noise exposure, marked upregulation of F4/80 occurs in the spiral ganglion (#3 in D), within the spiral ligament in putative type IV fibrocytes (#4 in D) and type III fibrocytes (#5 in D) in OxR1 null mice compared to controls, indicating a greater immune response to noise.

FURTHER FUNDING HAS ENABLED US TO EXPAND OUR RESEARCH TO:

We are developing a full gene expression profile of the major cell types (snRNAseq from baseline and 14 days following noise exposure) of the OxR1 null versus wild type mice. This will advance our understanding not only of the baseline normal response to noise, but also how the Orexin signaling system shapes the cochlea's response to moderate level noise.

LAY SUMMARY OF FINDINGS AND IMPLICATIONS OF THIS RESEARCH:

How the cochlea is protected from the moderate levels of noise intensities typically encountered every day is still incompletely understood. Because the sensory cells (hair cells) of the mammalian cochlea do not regenerate once significantly damaged, there must be a means by which they are protected across our lifetimes, and such protection might stem from metabolic and immunologic support of the inner ear. Our research into the roles of the support (non-sensory) cells of the cochlea has shown that many peptides and their receptors involved with cellular stress responses and metabolic support are critical for protection of normal hearing following exposure to moderate intensity noise. Importantly, the Orexin genes are involved in hearing protection, but this signaling system is also the target of drugs for insomnia. Our research suggests a potential that use of these drugs heightens the potential for hearing loss when exposed to moderately high intensity noise.