First and most important, I hope this finds you safe and well. The COVID-19 pandemic is affecting all of us and our families, with challenges that range from minor inconvenience to game-changers for our health and livelihoods.

Despite these challenges, I want you to know the American Hearing Research Foundation remains steadfast in its mission to fund hearing and balance research. Specifically:

· Funding will be available for 2021. The application deadline is August 14, 2020.

· New for 2021, we’re delighted to announce that AHRF will offer one $75,000 Birtman Grant as part of its funding options. The award is named for Georgia Birtman, a Chicago school teacher who generously donated $2.1 million to AHRF in 1991.

· AHRF is funding 12 studies in 2020. Grant recipients will examine diverse topics including potential treatments for noise-induced hearing loss, Meniere’s disease, and Usher syndrome; how the perception of the emotion in speech is affected as we age; the association between hearing loss and cardiovascular disease, and the biochemistry of how we hear. (See p.2 for the complete list). While most of these projects will need extra time to complete, we look forward to sharing results with you.

The hearing and balance research community is a tremendously resourceful and innovative group. Those of us at AHRF send our encouragement, and promise to continue to be your partner as you pursue answers to hearing loss during these difficult times.

Sincerely,

Richard G. Muench, Chairman, Board of Directors

In 2021, AHRF will offer a one-time grant of $40,000 for research related to the causes of sudden hearing loss. To offer this grant, AHRF is matching funds donated by an individual who experienced two instances of sudden hearing loss over 30 years apart.

Sudden (sensorineural) hearing loss—also known as sudden deafness—can be extremely frightening. It comes on quickly—that is, all at once, over a few hours, or over a several days. Often it affects only one ear, but it can involve both.

Anyone experiencing sudden hearing loss should treat it as a medical emergency and seek a doctor’s care right away. Getting treatment quickly increases the odds of recovering at least some of the hearing lost.
In January 2020, the American Hearing Research Foundation awarded over $288,000 in grants to these investigators. Learn more about the researchers and studies at [https://tinyurl.com/AHRF2020grantees](https://tinyurl.com/AHRF2020grantees).

**AHRF Regular Grants ($20,000 to $45,000)**

- **Rachael R. Baiduc, PhD, MPH; Melinda Anderson, PhD, CCC-A**; University of Colorado Boulder; *Sex Differences in the Association between Hearing Loss and Cardiovascular Disease Risk Burden*

- **Monita Chatterjee, PhD**; Boys Town National Research Hospital, Nebraska; *Age-Related Changes in the Perception of Emotional Speech with Cochlear Implants*

- **Allison B. Coffin, PhD**; Washington State University; *AMPA receptor-mediated glutamate excitotoxicity and noise-induced synaptic damage*

- **Benjamin Johnson, MD**; University Hospitals Cleveland Medical Center / Case Western Reserve University; *Antimalarial Artesunate as a Novel Treatment to Mitigate Hearing Loss Associated with Usher Syndrome Type IIIA*

- **Habib G. Rizk, MD**; Medical University of South Carolina; *Assessing the Efficacy of a Serotonin and Norepinephrine Reuptake Inhibitor for Improving Meniere’s Disease Outcomes*

- **Tal Teitz, PhD**; Creighton University, Nebraska; *Repurposing an FDA Approved Drug Dabrafenib for Protection from Noise-induced Hearing Loss*

- **Jing Zheng, PhD**; Northwestern University; *Investigating functions of a cilium protein in vestibular system*

**Meniere’s Disease Grant ($25,000)**

- **Dhasakumar S. Navaratnam, MD, PhD**; Yale University; *Defining the molecular and cellular basis of Meniere’s disease using single cell RNA sequencing*

**Bernard & Lottie Drazin Memorial Grants for Otolaryngology Residents ($1,000)**

- **Stefania Goncalves, MD**; University of Miami Miller School of Medicine; *Laminin-coated Cochlear Implant Electrodes can Promote Schwan Cell Dedifferentiation, Migration and Guide Neural Axon Growth In Vitro*

- **Matthew T. Maksimoski, MD**; Northwestern University; *Long term outcomes from gamma knife treatment for vestibulocochlear nerve schwannomas in a large, tertiary care, academic hospital*

- **Cody Jeu, MD**; University of Illinois at Chicago; *A cochlear implant simulation study to determine the effects of transposing frequencies on binaural benefits*

- **Michael Ghiam, MD**; University of Miami Miller School of Medicine; *Utility of Perilymph microRNA Sampling for Identification of Active Gene Expression Pathways in Sensorineural Hearing Loss*
We are pleased to announce the American Hearing Research Foundation will offer these grants in 2021:

- **New! Georgia Birtman Grant** - $75,000. A one-year grant for topics related to hearing and balance disorders of the inner ear. Applicants have the option of including an alternative budget for $50,000; if the project is not chosen for the Birtman grant, it will be included in the selection for Regular grants.

- **AHRF Regular Grants** - $20,000 to $50,000. For topics related to hearing and balance disorders of the inner ear.

- **Causes of Sudden Hearing Loss Grant** – A one-year, one-time grant of up to $40,000.

- **Meniere’s Disease Research Grant** - $20,000 to $25,000. For studies related to Meniere’s disease causes, diagnosis, or treatment.

- **Bernard and Lottie Drazin Memorial Grants** - $1,000 (up to five awarded). For otolaryngology residents at specific universities.

Applications must be submitted online by August 14, 2020. Visit [www.american-hearing.org](http://www.american-hearing.org) for grant details and application steps.

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**A Note of Thanks to Our Reviewers**

AHRF’s ability to fund outstanding science depends on the generosity of the scientists who give their time and expertise to review grant applications. We’d like to thank these individuals who participated in the 2020 review:

- Donna Whitlon, PhD, Chair
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- Kazuaki Homma, PhD
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- Nina Kraus, PhD
- Anna Lysakowski, PhD
- Alan G. Micco, MD
- Claus-Peter Richter, MD, PhD
- Katherine Shim, PhD
- Alex D. Sweeney, MD

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**Micco Honored for Service**

At the Foundation’s November 2019 board meeting, Board President Alan Micco, MD, (pictured, right, with Chair Richard Muench) was honored for serving 20 years as Research Committee Chair. The Foundation gratefully acknowledges Micco’s visionary leadership in guiding the selection of novel and transformative discoveries. Micco will continue to participate in the annual review process.
Vestibular Migraine
By Lisa Zhang, Medical Student, Johns Hopkins School of Medicine

“Instead of an aura – a visual cloud of light around light – vestibular migraines come with episodes of vertigo.”

John Carey, MD, received AHRF funding in 2016 and 2017 for the examination of vestibular migraine. Lisa Zhang, a member of his lab team, shared this update with AHRF. She explained, “Vestibular migraines are one type of migraine – a headache that lasts five to 72 hours, with changes in vision. Instead of an aura – a visual cloud of light around light – VMs come with episodes of vertigo. The challenge with diagnosing this is that the vertigo may not come at the same time as the headache. We’re asking, are there biomarkers that say you’re having a VM, and not some other vestibular disease? We think the vertigo is a different form of sensory disturbance within the aura family.”

Vestibular migraine, a disorder of migraines presenting with vertigo and dizziness, is most recently estimated to affect over 2% of the population and is the second most common cause of vertigo.

These attacks are thought to be similar to symptoms associated with classic migraine. The release of pro-inflammatory peptides in the brainstem area is responsible for the vertigo symptoms. One such biomarker that has shown a lot of recent success in migraine research is calcitonin gene-related peptide (CGRP), which has recently also been a therapeutic target for migraine prevention. Preliminary results from our group have demonstrated elevated levels of CGRP in saliva in both migraine and vestibular migraine patients compared to health controls, which additionally makes CGRP a promising target for both diagnosis and treatment of vestibular migraine.

Our future studies hope to better capture a larger breadth of migraine biomarkers utilizing proteomics, the characterization and comparison of proteins present between patients with and without vestibular migraine. These mass-spectrometry-driven methods have allowed for an unbiased search for biomarkers and have risen in popularity with the improvements in technologies over the recent years. These studies also have allowed for identification of multiple biomarkers for disease to improve both the sensitivity and specificity compared to single biomarkers.

While plasma proteomics have been conducted in analyzing various clinical diseases, the recent rise of salivary proteomics has been presented as a noninvasive approach to obtaining similar results. In addition, various neuropeptides involved in migraine have already been detected in saliva, including CGRP as well as various additional inflammatory peptides.

The goal of our current research is to determine how CGRP as a biomarker compares to other potential candidates for vestibular migraine. These results can serve to improve the understanding of the causes of vestibular migraines and establish a biological link with migraine headaches. Ultimately, we hope this research will provide important insights on biomarkers that can serve as potential diagnostic testing and treatment targets for this vestibular disorder.

The AHRF Mission:
To fund significant research to better understand and overcome hearing and balance disorders of the inner ear, and to educate the public about these life-altering conditions. AHRF is a 501(c)(3) nonprofit organization.
Sandeep Sheth’s article titled, “Oral Administration of Caffeine Exacerbates Cisplatin-Induced Hearing Loss,” was published in the July 2, 2019 issue of Scientific Reports. This study reflected work funded by a 2015 AHRF grant while he was at Southern Illinois University.

In discussing his results with AHRF, Sheth explained that cisplatin is a chemotherapy medication used to treat a number of cancers. A well-known side-effect of the drug is permanent hearing loss. Sheth wondered if caffeine, present in so many beverages consumed the world over, might play a part in this impairment.

Sheth and his colleagues examined the degree of hearing loss that occurred in rats when caffeine was consumed at the same time as cisplatin was administered. His team looked at where damage in the ear and auditory pathway occurred. Among the findings:

- The study demonstrates exacerbation of cisplatin-induced hearing loss which results from concurrent consumption of caffeine. We demonstrate worsening of hearing loss following a single-dose administration of caffeine and even greater effects following daily applications of the drug for five days.

- Caffeine consumption did not aggravate cisplatin-induced outer hair cell loss in the rat ears. However, the dose increased synaptopathy [dysfunction of synapses in the peripheral nervous system] and inflammation in the cochlea.

- Cisplatin has recently been shown to persist in [parts of] the cochlea and long bones for months and years following the last drug administration... As such, this drug interaction between caffeine and cisplatin could persist long after cisplatin administration has been terminated.

- The findings suggest that caffeine consumption should be cautioned in cancer patients treated with a chemotherapeutic regimen containing cisplatin.

For Sheth, the study results prompt more questions. He notes, “With caffeine consumed by people around the world, I would like to know if it plays a role in age-related hearing loss. Does it worsen noise-induced hearing loss, for instance for young people who listen to loud music and consume energy drinks? Does caffeine consumption play a role in hearing loss caused by antibiotics or other therapies? Then there’s the issue of how much caffeine makes a difference.”

Source: Oral Administration of Caffeine Exacerbates Cisplatin-Induced Hearing Loss.
Sheth S, Sheehan K, Dhukhwa A, Al Aameri RFH, Mamillapalli C, Mukherjea D, Rybak LP, Ramkumar V.

“Our data suggests that moderate levels of caffeine could contribute to hearing loss in humans who are on cisplatin chemotherapy.”
RESEARCH UPDATE
Steven H. Green, PhD
and Ning Hu, MD, PhD
University of Iowa
Mark Rutherford, PhD
Washington University

“What if you could prevent hearing loss by blocking in advance the effects of loud noise?”

Collaborating researchers Steven Green (pictured, left), Ning Hu (pictured, right), and Mark Rutherford co-authored “Protection of cochlear synapses from noise-induced excitotoxic trauma by blockade of Ca2+-permeable AMPA receptors,” which was published February 18, 2020 in Proceedings of the National Academy of Sciences. Here is an excerpt from a University of Iowa press release.

What if you could prevent hearing loss by blocking in advance the effects of loud noises? That’s a route a team of biologists at the University of Iowa and Washington University, St. Louis, says may be possible after the researchers identified a receptor that, when blocked, can prevent a common type of hearing loss.

Receptors are part of a suite of molecules on nerve cells in the ear that bridge the passage of sound and auditory information from inner-ear hair cells—the sound sensors—to the brain. The successful transmission of sound from hair cells to nerve cells, which occurs through a junction called a synapse, is integral to hearing in animals, including humans.

“The researchers identified that some receptors involved in the hair-cell-to-nerve-cell transmission lack a protein called GluA2, and it is these receptors that are responsible for synaptopathy, or hearing loss caused by irreparable damage to the synapses.

The biologists employed a drug in mice that selectively blocked the GluA2-lacking receptors, and prevented the mice from experiencing synaptopathy when exposed to noise.

The approach was like outfitting the mice with chemical earmuffs that prevented them from sustaining hearing damage by blocking the breakdown that occurs in some synapses between inner ear hair cells and nerve cells when loud noises occur.

“It wasn’t just putting earmuffs on—these earmuffs prevent the damage caused by loud sounds but don’t muffle the sound,” says Steven Green, professor in the Dept of Biology and corresponding author on the study.

The experiments in mice indicate there is the potential to inject a drug that would prevent hearing damage in people before they’re exposed to damaging noise. Conceivably, soldiers who are expected to encounter loud sounds in their duties could take a hearing-protection drug before exposure to those sounds, yet still hear commands.

“Permanent hearing damage can be caused by noise levels that have been considered ‘safe,’ and people need to be careful about noise exposure because we can’t yet repair synapses or regenerate hair cells,” Green says. “Our chemical earmuffs are, currently, just an indication of the direction research can go, not yet a proven, safe means of protection in humans.”

Sources: DOI: https://doi.org/10.1073/pnas.1914247117
University of Iowa press release published 2/5/2020, originally written by Richard C. Lewis.
We first discovered my mother was losing her hearing when I came home for winter break as a college freshman. She seemed to exhibit selective listening – tuning out my dad and myself. When we approached her, she was genuinely shocked she had missed what we said. A subsequent hearing test showed moderate hearing loss. This was odd; at 45 she was still relatively young and had no history of exposure that would cause hearing loss. And unlike typical age-related hearing loss, her impairment was isolated to low - not high - frequencies. That could explain why it was harder for her to hear male voices, like mine and my dad’s, compared to my sister’s. The doctor said the problem was isolated to the inner ear or nerve, but there was no way to tell the cause or whether it would get worse. Hearing aids to amplify low frequency sounds helped her initially.

As her hearing loss progressed, I became curious why she could experience most of her life without any hearing issues, but now suddenly required hearing aids. At the time, I had picked the “Biological Basis of Behavior” as my major. I was captivated by a lecture that detailed the intricate anatomy of the cochlea and how each structure participates in the process of transforming sound vibrations into the neuronal signals sent to the brain. I hunted down the professor from that lecture and begged to volunteer as a student researcher in the lab. That experience convinced me to apply for graduate school.

By the time I started grad school, my mom’s hearing loss had forced her to retire early as a nurse. I became even more invested in the problem after learning about a list of ~150 different genes and their proteins that are responsible for all the specific cellular functions required in hearing. It is fascinating that a single mutation could disrupt any point in the system, and that mutation could happen spontaneously for one individual or be passed on between generations. We investigated genetic testing for my mother, but testing revealed no match for any known hearing loss mutations. This highlights the fact that perhaps only 50% of deafness genes have been identified, and many are waiting to be discovered, especially for late onset hearing loss.

For my thesis work I chose to focus on a couple genes with known functions, and to investigate a new treatment strategy called gene therapy. Using a viral vector to deliver a corrective copy of the mouse’s defective gene, I was able to restore hearing to the inner ear of deaf mice with varying degrees of success. This result was revolutionary for my career, as it became the foundation for what I seek to develop as an independent scientist, and has the potential to help patients by restoring the natural hearing inputs in their ear using a precision medicine approach. Such approaches may be helpful to people like my mom when their hearing loss is detected early and the gene can be identified, providing a chance to intervene and correct the problem before the sensory structures in the ear deteriorate completely. Unfortunately for my mom, the loss of the inputs inside her cochlea progressed to the point where hearing aids became useless, as sound could no longer be turned into neuronal signals.

continued on p.8
A few weeks before my PhD thesis defense, my mom received her first cochlear implant. I have videos of my mom on her activation day, which occurs a month after surgery when the audiologist actually turns on the cochlear implant. To see the look of relief on her face when she could perceive sound in that ear again – erasing her fear that either the implant wouldn’t work for her or that her auditory nerve was too far gone to receive the electrical stimulation – it touches something deep in my core. Cochlear implants are not the perfect solution, but for her they are life changing. Her implant is excellent for providing speech perception in quiet environments, but with the current technology things like music perception and understanding speech in noise is out of reach for her and many others. My motivation is to someday see that same look of relief and joy on someone else’s face after restoring the full function of their natural inner ear machinery, and all of the auditory perceptions that come with it. I hope my research in cochlea gene therapy can make that a reality.

About the Research

The goal of my research is to develop gene delivery vectors that robustly target cell populations within the inner ear, and investigate rescue of hearing in mouse models of inherited human deafness using a gene therapy approach. By manipulating the basic biology of adeno-associated virus (AAV), our lab tailors it as a therapeutic delivery platform. We seek to improve the effectiveness of hearing rescue in animal models, which could eventually lead to human treatments.

Inherited hearing loss affects approximately 1 in 1000 children in the United States, including 16,000-20,000 people with combined deafness and blindness known as Usher Syndrome. Unfortunately, there are no biological or targeted drug therapies currently available to treat genetic deafness. However, in 2017 the FDA approved the first gene therapy for direct administration into the retina, Luxturna, which is capable of restoring vision in patients going blind due to Leber Congenital Amaurosis. This treatment is mediated by corrective gene delivery using recombinant adeno-associated virus (AAV), a non-pathogenic and non-integrating viral vector.

Although our group and others have previously rescued hearing in deaf animal models after AAV-based gene delivery, insufficient targeting of all the pathologically affected cells as well as the dose of vectors required are still issues that need to be addressed. These concerns lead to partial disease correction and can increase immunological toxicities due to high viral vector load, as demonstrated in human clinical trials for AAV in the liver and pre-clinical studies in primates. We are developing methods to modify the AAV delivery vehicle that can increase cell targeting and overcome host barriers to the therapy while reducing antigenic load. We will investigate use of these vectors to restore hearing in a deaf mouse model at time points either shortly after birth or in fully developed adult animals. Our hope is that this work can lay the foundation for eventual clinical trials in humans identified with specific forms of genetic hearing loss.

Mentors

I want to recognize some of my mentors. Dr. Jim Saunders and Dr. Michael Anne Gratton gave me the first opportunity to volunteer in the auditory neuroscience lab at Penn. There I met another researcher, Dr. Jean Bennett, who inspired my curiosity in gene therapy. Jean is a pioneer and wonderfully caring person who led a team to create the first FDA approved gene therapy for blindness, which utilizes the type of viral vector (AAV) that I currently study. My PhD advisor Jeff Holt taught me about many of the proteins involved in mechanosensory transduction in the inner ear, and gave me the opportunity to pursue my interest in gene therapy in his lab. He, along with his wife Dr. Gwen Geleoc, positively impacted my path to continue studying gene therapy for hearing loss. My post-doctoral advisor Dr. Jude Samulski cloned the first AAV vector and has elucidated much of its biology; in this lab I learned about vector engineering approaches. My current advisor Dr. Chengwen Li is making key discoveries related to the immune response surrounding gene therapy, and is enabling me to apply vector engineering approaches to the inner ear.
AHRF Connects with Researchers at ARO Conference on Hearing & Balance

Nearly 1,800 investigators attended the 43rd MidWinter Meeting of the Association for Research in Otolaryngology (ARO) this January in San Jose, California. The event included seminars, workshops, and poster talks, with scientists presenting current findings in hearing and balance research. AHRF Executive Director Joan Wincentsen presented AHRF funding opportunities at the “Get Your Research Funded” panel. Chair Richard Muench hosted a dinner for past grant recipients, so that AHRF can continue relationships with researchers as they network and share ideas with others in the field.

In support of ARO’s public outreach efforts at the conference, AHRF co-sponsored an evening of music and science. Musae on the Brain: Women in Voice and Science included a performance by Musae, San Francisco’s premier women’s choral ensemble, interspersed with talks about how the ear and mind process pitch and harmony by Dana Boebinger, neuroscientist from Harvard, and Sarah Schneider, speech-language pathologist from UCSF.

The conference provided a chance to connect with old and new friends. Arefeh Sherafati, Washington University in St. Louis, shared an update on her studies related to cochlear implants. AHRF 2018 grant recipient Xiaodong Tan, Northwestern University, gave a poster talk on the role of honokiol induced elevated SIRT3 expression and protection from cisplatin-induced cochlear damage.

Allison Coffin, PhD, University of Washington in Vancouver, shared updates about her nonprofit organization, Science Talk, with Richard Muench. This organization focuses on improving science communication among scientists and encouraging scientists to “Talk science. Clearly.” with the public.

MAY IS
Better Hearing and Speech Month

The Center for Disease Control tells us that hearing loss is the third most common chronic health condition in the US.

- About 40 million US adults aged 20-69 years have noise-induced hearing loss.
- More than 1 in 2 US adults with hearing damage from noise do not have noisy jobs.
- About 1 in 4 US adults who report excellent to good hearing already have hearing damage.

Whenever possible:
- Lower the volume
- Move away from the noise
- Wear hearing protection

Source: https://www.cdc.gov/vitalsigns/hearingloss/index.html
You Can Have an Impact on a Cure or a Career

“I so appreciate AHRF because they give an opportunity to young (and young-at-heart) researchers to get support for new and interesting research projects. I know the money they gave me back in the 90’s really made a huge difference in my burgeoning work on the regenerating tectorial membrane.”

- Douglas Cotanche, PhD, University of Illinois at Chicago, Department of Anatomy and Cell Biology

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275 N. York Street, Suite 201
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SUPPORT MENIERE’S DISEASE RESEARCH

People tell us how the symptoms of Meniere’s disease - vertigo, tinnitus, and hearing loss - trigger anxiety and loss in their lives. When Katie Mertz learned there are few treatment options for her mother’s Meniere’s symptoms, she began a grassroots initiative to raise funds for research. Through run because, Katie has completed 26 half-marathons (including New Jersey #25, and Delaware #26!) - over half of her goal of 51 (one in every state plus DC), and raised $38,800 for Meniere’s investigation. You can follow Katie’s progress at www.facebook.com/runbecause. Donations for Meniere’s research can be made via the AHRF website.

CHANGE THE FUTURE

Would you like to find hearing and balance answers for the next generation? When you remember AHRF through a gift in your will (a “bequest”), you can ensure cutting-edge research projects continue. You can choose to leave a specific amount, or a percentage of your estate. Or consider other forms of planned giving: securities, life insurance policy, or a retirement plan. A qualified financial planner can guide you with your decisions.

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Show Some Love to hearing and balance research by giving to American Hearing Research Foundation through the Combined Federal Campaign (CFC). Our designation number is 10571.
Thank You to Our Donors

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Xiaodong Tan, PhD, Northwestern University, explains the protective effect of the honokiol molecule for noise-induced hearing loss at the ARO Conference, February 2020. (Study funded in part by AHRF)