HEARING RESTORATION RESEARCH PROGRAM

Scanning electron micrograph of a stereoclia bundle on the apical surface of a human pluripotent stem cell-derived hair cell.* Magnification: x10,000

**Image Courtesy of Dr. Eri Hashino, Indiana University*

Scan me to access even more information about the program.

VISION

Improve the operational performance/effectiveness, medical readiness, and quality of life of Service Members and Veterans with auditory system injuries

MISSION

Advance the science of hearing restoration by delivering groundbreaking research and solutions that remove barriers to the successful treatment of auditory system injury

PROGRAM HISTORY

Congress established the Peer Reviewed Hearing Restoration Research Program (HRRP) in 2017 to pursue regenerative strategies and other options that reduce the burden of hearing loss among Service Members.

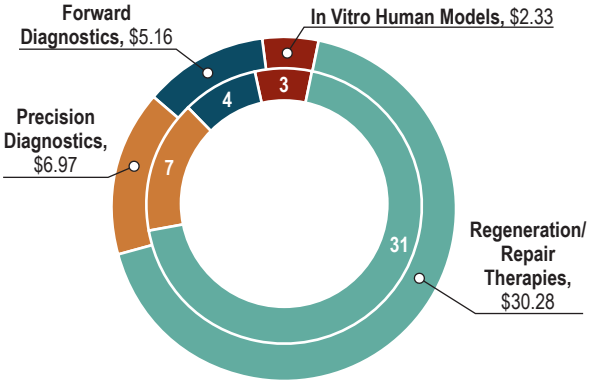
Disabling hearing loss affects more than 30 million Americans, including over 1.3 million Veterans. While hearing loss has profound impact on quality of life, there is no drug approved by the FDA for hearing restoration. The development of hearing restoration therapeutics has been hindered by difficulties in the validation/translation of preclinical findings and limitations in precision diagnostic capability. The HRRP aims to advance the science of hearing restoration by funding groundbreaking research that removes barriers to translation and diagnosis.

RELEVANCE TO MILITARY HEALTH

Service Members face high risks of auditory system injury from extended exposure to combat and operational noise such as gunshots, explosions, helicopters, etc. Protection against combat noise is complicated by its unpredictable nature and by the need for Warfighters to communicate and to listen/respond to sounds. Furthermore, Service Members often operate in austere/remote environments where diagnostic and treatment resources and medical personnel are unavailable or limited for extended periods of time. To improve military auditory health, the HRRP addresses both diagnosis and mitigation of auditory system injury.

FOCUS AREAS

- Regeneration/Repair Therapies
- Precision Diagnostics
- In Vitro Human Models
- Forward Diagnostics



HRRP Funding (Millions) and Awards by Focus Area FY17-FY21

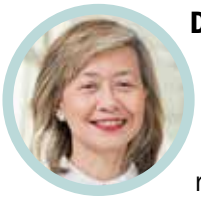
2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$10M	Focused Research Award – Funding Level 1 ..... $1,140,361 Focused Research Award – Funding Level 2 ..... $8,078,036 Modification to ongoing awards $3,500	USAMRDC ..... $193,340 SBIR/STTR ..... $333,000 Mgt Costs (2.66%) $251,763
Total: $10M	**Total:** $9,225,397	**Total:** $778,103

CDMRP and NIDCD Host Joint Workshop on Ex Vivo Models

The CDMRP and the National Institute on Deafness and Other Communication Disorders (NIDCD) co-hosted a virtual workshop in November 2021 to encourage the enhancement of ex vivo models and techniques to expedite translation of hearing loss therapies. The workshop consisted of focused sessions on ear organoids, organoids of other organs, and enabling technologies, all aimed at accelerating the development, validation, and clinical throughput of hearing loss therapies. Dr. Debara Tucci, director of NIDCD, and Col. Sarah Goldman, director of CDMRP, noted the importance of the research and collaboration between the two organizations. Following the presentations, speakers and attendees participated in discussions on the opportunities and challenges associated with ex vivo models and possible steps needed to fulfill the promise of these approaches.

RECENT ACHIEVEMENTS FROM HRRP-FUNDED RESEARCH



Directed Differentiation of Human Pluripotent Stem Cells into Inner Ear Organoids[1]

Dr. Eri Hashino, Indiana University-Indianapolis

Evaluating pharmaceutical treatments for inner ear hair cell regeneration is limited by the lack of in vitro cell culture systems that mimic the inner ear. Funded by an FY17 TRA, Dr. Eri Hashino and team are growing human inner ear organoids in a three-dimensional format that represents the structure and function of human inner ear tissues. Published in *Methods in Molecular Biology*, the team has successfully developed a protocol to use human pluripotent stem cells to generate these organoids containing sensory epithelia with hair cells. This protocol provides a platform for further research in the human inner ear, including a model system to discover therapeutic targets for hearing restoration.

Miniature Imaging Probe to Visualize Cellular Pathology in the Inner Ear[2]

Dr. Konstantina Stankovic, Stanford University

Damage to cells or cellular structures in the inner ear is a leading cause of hearing loss. Coiled into a few millimeters in diameter and encased in hard bones, the inner ear is difficult to access and examine, creating a tremendous hurdle for matching potential therapeutics to the correct patients and evaluating therapeutic effects. With funding from an FY19 Focused Research Award, a team led by Dr. Konstantina Stankovic and Dr. Guillermo Tearney developed a sub-millimeter-diameter, flexible endomicroscopic probe to image cellular structures in the inner ear at micron-scale resolution. The probe holds great promise for in vivo examination of inner ear pathology, a missing yet crucial piece in the puzzle of sensorineural hearing loss therapeutic development and clinical trials. Its potential clinical applications also include real-time guidance of cochlear implantation, thus improving the positioning of implant electrode arrays and hearing outcomes in implant patients.

Hair Cell Regeneration in Cultured Adult Cochlea[3]

Dr. Zheng-Yi Chen, Massachusetts Eye and Ear Infirmary

Dr. Zheng-Yi Chen received an FY17 Translational Research Award to study molecular mechanisms of hair cell regeneration to promote hearing restoration after noise-induced hearing loss. As recently published in *Frontiers in Molecular Neuroscience*, the research team established a new system to culture adult mouse cochlea with the surrounding bone to maintain the overall structure. Using the explant system, they showed that the cochlear supporting cells can be reprogrammed by Atoh1 to become hair cell-like cells, which are able to make contact with neurons. These advancements will allow researchers to study the inner ear in vitro to understand how to promote functional regeneration of cochlear tissue.

Christina Becude, Vestibular Disorders Association, Consumer Peer Reviewer FY21-FY22

"The intricacies of hearing loss are so complex and oftentimes frustrating. Being a consumer reviewer for the Hearing Restoration Research Program was an honor and eye-opening experience, serving alongside the brilliant scientists in reviewing the multi-faceted research programs that seek to discover therapies, enhancement of listening devices, as well as discovering a cure for hearing loss. Having lost my hearing at a very young age, I was honored the scientists listened to and appreciated my input as a consumer. Being a part of the process gives me hope that this crucial research will provide different avenues of relief one day to those who suffer from hearing loss!"

Jack King, Vestibular Disorders Association, Consumer Peer Reviewer FY19-FY21

"I would just say that I'm delighted to have had the opportunity to serve with HRRP these past few years. It is rewarding to know that I am playing a role in guiding the future of hearing research that can help others with hearing loss, especially Soldiers who have given up much for our country. I look forward to each year's committee because I enjoy meeting and interacting with other wonderful people who are like-minded!"

References: [1] doi: 10.1007/7651_2021_448. | [2] doi: 10.1038/s41598-021-95991-8. | [3] doi: 10.3389/fnmol.2021.757831.