Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

https://cdmrp.army.mil

Hearing Restoration Research Program

VISION

Improve the operational performance, 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

https://cdmrp.army.mil/hrrp

PROGRAM HISTORY

Hearing loss is highly prevalent in the military population. Soldiers, Sailors, Airmen, and Marines are exposed to various high-intensity noises that are unique to the combat environment, for example weapon systems, explosions, helicopters, ship engines. As a result, military personnel are at higher risks of noise-induced hearing loss and auditory system injury in comparison to the general public. The most recent data from the Department of Veterans Affairs (VA) indicate that service-connected hearing loss affects more than 1.1 million Veterans and is the second most prevalent of all service-related disabilities.

The Department of Defense Hearing Restoration Research Program (HRRP) was established in 2017 to fund innovative research for the treatment of auditory system injuries and the restoration of hearing. The HRRP received a $10 million (M) Congressional appropriation in fiscal year 2017 (FY17), its inaugural year, and selected seven grant applications for funding. The FY18 HRRP appropriation is $10M.

PROGRAM PRIORITIES

The following program priorities were identified at the FY18 HRRP Vision Setting meeting. These program priorities are expected to be stable for the next 5 years. They will be reviewed during the HRRP's annual Vision Setting meetings and revised/updated as needed.

ACCELERATE DRUG DISCOVERY AND THERAPEUTIC DEVELOPMENT FOR HEARING RESTORATION

Currently, there is no Food and Drug Administration-approved drug to treat hearing loss. There has been significant progress in the molecular and cellular understanding of hearing loss and regeneration mechanisms in the inner ear. However, the majority of research is preclinical, and the findings need to be verified in more clinically relevant research and translated to clinical applications. Translation of preclinical findings into drugs and therapeutics is an area with great potential for growth and breakthroughs within the next 5 years.

ACCELERATE ADVANCES IN THE ASSESSMENT AND TREATMENT OF AUDITORY DYSFUNCTION

Noise exposure may induce auditory dysfunction such that an individual's hearing sensitivity is within normal limits, but their capacity to listen and understand speech is substantially impaired. This type of auditory dysfunction is often referred to as "hidden hearing loss." The military has a great need to reliably assess and mitigate auditory dysfunction, including hidden hearing loss, in the battlefield/deployed environment.

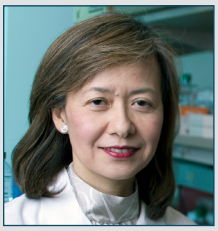
INVESTMENT STRATEGY

To address the program priorities identified above, the HRRP will focus its investments on translational and applied research over the next 5 years. The HRRP will solicit and support research that accelerates drug discovery and therapeutic development; for instance, research that translates promising laboratory findings into clinical applications and research that removes barriers and/or builds paths to drug discovery. Additionally, the HRRP will solicit and support research that accelerates advances in the assessment and treatment of auditory dysfunction, including technology and methods to assess auditory dysfunction in the battlefield/deployed environment, diagnosis of auditory system injuries, and technology and methods to prevent and/or mitigate auditory system injuries and treat auditory dysfunction.

For each fiscal year, the specifics of the HRRP's investment strategy, including award mechanisms, focus areas, and funding levels, will be determined at the annual Vision Setting meetings, taking into account the most current state of the science and available Congressional appropriations.

In FY18, the HRRP is offering two award mechanisms. The Translational Research Award (TRA) mechanism is intended to support translational research that will accelerate the movement of promising laboratory research relevant to hearing restoration into clinical applications. The Focused Applied Research Award mechanism is intended to support applied research that will advance the diagnosis and treatment of auditory dysfunction where hearing sensitivity may be within normal limits, but the individual's capacity to listen and understand speech is substantially impaired.

HRRP RESEARCH HIGHLIGHTS



HUMAN INNER EAR ORGANOIDS AS AN IN VITRO MODEL FOR HEARING THERAPY DEVELOPMENT

Eri Hashino, Ph.D., Indiana University School of Medicine

The inner ear is one of only a few organs for which biopsy is not applicable, which severely limits the availability of human tissues for testing of potential therapeutics. Dr. Hashino, a recipient of an FY17 HRRP TRA, is leading the research effort to overcome this critical problem. Dr. Hashino's team recently established a novel means to generate inner ear sensory epithelia from human pluripotent stem cells in a three-dimensional culture. These stem cell-derived tissues, designated as "human inner ear organoids," harbor a layer of tightly packed hair cells whose structural, biochemical, and functional properties are indistinguishable from native sensory hair cells in the human inner ear. With funding from the HRRP TRA, Dr. Hashino will develop the human inner ear organoids technology to the next level. Her team will establish and validate the organoids as a novel in vitro model to recapitulate human cochlear development and degeneration, elucidating the signals and genetic pathways underlying cochlear hair cell induction and differentiation. Additionally, the organoids will be used as a human in vitro model to test the ability of a small molecule inhibitor to promote hair cell differentiation and regeneration. If successful, the human inner ear organoids technology will offer unprecedented opportunities to discover therapeutic targets and test therapeutic agents to restore hearing.

HAIR CELL REGENERATION IN MATURE MAMMALIAN INNER EAR

Zheng-Yi Chen, Ph.D., Massachusetts Eye and Ear Infirmary

The mature mammalian inner ear is not responsive to regenerative signals that have proven successful in young inner ears that are still undergoing development. This suggests that most of the developmental pathways that render the inner ear responsive to hair cell induction are no longer available in the mature inner ear. With support from an FY17 HRRP TRA, Dr. Chen aims to tackle this problem. Dr. Chen will utilize a strategy known as "reprogramming" to reset the biological clock of the mature inner ear and restore it into a stage reminiscent of the young inner ear, so that the mature inner ear cells regain the capacity to respond to regenerative signals. Previous work by Dr. Chen's team indicate that it is feasible to reprogram adult cochlear cells, as evidenced by cell cycle re-entry, activation of optic genes, and the ability to transdifferentiate supporting cells to hair cells. Capitalizing on this knowledge and on the team's expertise in adult whole cochlea explant culture, in vivo injection, and transgenic mouse models, Dr. Chen will test a strategy to reprogram mature and aged mammalian cochlea by the transient and reversible co-activation of two critical genes. The reprogrammed inner ear will be evaluated for hair cell regeneration and hearing recovery in response to hair cell induction signals in a mouse model of noise-induced hearing loss. The approach can also be applied to regenerate other inner ear cell types critical for hearing in adult cochlea. If successful, the study will provide a significant conceptual and practical advance toward the goal of hearing restoration in human patients.