CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

Hearing Restoration Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. Programs managed by the CDMRP have formalized strategic plans that identify program-specific research priorities; how to best address these urgencies; short- and long-term goals; investment strategies; and ways to identify and evaluate program successes with respect to the priorities.

The Hearing Restoration Research Program (HRRP) Strategic Plan identifies the high-impact research goals that are most important to the program and its stakeholders while providing a framework that is adaptable to changes in the medical research and clinical care environments to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time. Congress appropriates funding for the HRRP on an annual basis; therefore, there is no guarantee of future funding. The HRRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

HRRP BACKGROUND AND OVERVIEW

Congress established the HRRP in 2017 to pursue *"regenerative strategies and other options that reduce the burden (of hearing loss) among Servicemembers."*

THE BURDEN OF HEARING LOSS

Hearing loss is a silent epidemic. A survey conducted by the Centers for Disease Control and Prevention found 15% of adults aged 18 and over had some degree of hearing loss, making it the third most common chronic physical condition in the United States and more prevalent than diabetes (9%) or cancer (8%).[1] Hearing loss is especially common among older adults, affecting nearly 25% of those aged 65-74 and 50% of those 75 or older. Globally, approximately half a billion people had disabling hearing loss in 2015, and the prevalence is rising.[2]

Hearing loss is one of the most common disabilities among Veterans. The Veterans Benefits Administration's report for fiscal year 2022 (FY22) shows that more than 1.4 million Veterans are affected by service-connected disability due to hearing loss.[3]

Although invisible, hearing loss has a significant impact on quality of life and is a major risk factor for social isolation, cognition decline, anxiety, and depression.

SENSORINEURAL HEARING LOSS

There are three types of hearing loss: conductive, sensorineural, and mixed. Sensorineural hearing loss (SNHL), the more common type that accounts for the majority of all hearing loss, is due to damage to the inner ear, auditory nerve, or central nervous system. SNHL can be caused by noise exposure, head trauma, exposure to jet fuel, ototoxic drugs, infections, genetics, and age.

SNHL is a permanent condition without a cure. Patients may benefit from hearing aids and cochlear implants. However, neither hearing aids nor cochlear implants cure or restore normal hearing. In contrast, conductive hearing loss, which is caused by damage to the outer ear or middle ear, can usually be cured by medicine or surgery.

SNHL AND THE MILITARY

Service Members are exposed to high levels of noise such as gunshots, helicopters, ship engines, and explosions. A study of a random sample of 77,047 U.S. military members from all service branches and components who were on active rosters as of October 2000 showed that combat experience was associated with a 63% increased risk for hearing loss.[4] SNHL and other auditory injury-related dysfunction adversely impact force readiness, survivability, and lethality.

Hearing Protection Devices (HPDs; e.g., ear plugs) provide important but incomplete protection against hearing loss induced by combat noise, which is unpredictable and can exceed the capacity of protective gear. HPDs may also interfere with the Warfighters' ability to communicate and listen/respond to sounds in the battlefield, impeding situation awareness.

To reduce the burden of hearing loss on Service Members and Veterans, the HRRP focuses on hearing restoration after noise-induced SNHL.

VISION: Reduce the burden of hearing loss on Service Members, Veterans, and the American public.

MISSION: Deliver groundbreaking research and solutions for hearing restoration by advancing the understanding, diagnosis, repair, and regeneration of the auditory system.

FUNDING HISTORY

Between FY17 and FY22, the HRRP received $60 million (M) in congressional appropriations. Award data and abstracts of funded research proposals can be viewed on the CDMRP website (http://cdmrp.health.mil). The FY23 HRRP appropriation is $5M.

FUNDING LANDSCAPE

FEDERAL INVESTMENTS IN SNHL RESEARCH IN FY21

The HRRP is the only federal office whose investment is solely focused on SNHL. In FY21, the HRRP invested $9.2M in funding nine awards.

Overall, investment in hearing loss trails significantly behind other prevalent diseases and conditions.[5] The National Institutes of Health invests ~$160M annually on hearing loss.[5] The National Institute on Deafness and Communication Disorder (NIDCD) oversees the execution of the majority of this investment, which supports research in a broad range of areas, including hearing restoration after SNHL. In FY21, the NIDCD invested ~$26.5M on cochlear implants, ~$12.6M on noise-induced hearing impairment research, ~$9.6M on hearing aids, and ~$3.1M on hair cell regeneration research, respectively.

The Department of Veterans Affairs (VA) Rehabilitation Research and Development Service's investment in hearing, tinnitus, and vestibular research encompasses a broad range of topics such as diagnosis and automated assessments to predict and monitor changes to hearing, restoration, and prevention of hearing loss (including cochlear implants and hearing aids); tinnitus/hearing/vestibular rehabilitation; and understanding genetic and environmental influences on chronic hearing, tinnitus, and vestibular disorders. In FY21, the VA's expenditure on hearing, tinnitus, and vestibular research was $3.819M (representing direct costs only; the VA program does not include indirect costs because it is an intramural program). The total approved costs for the full award period for projects active in FY21 was $21.975M (direct costs only).

The Department of Defense (DOD) Military Operational Medicine Research Program's (MOMRP) Neurosensory Portfolio supports research on devices and therapeutics for vision, hearing, and balance restoration and rehabilitation following traumatic injury. The MOMRP invested $6M in the Neurosensory Portfolio in FY21.

NON-FEDERAL FUNDERS OF HEARING RESEARCH

Non-federal funders play important roles in supporting hearing research.

Many non-federal funders provide seed funding for investigators to develop research ideas and collect preliminary data. The American Hearing Research Foundation, the American Tinnitus Association, the American Speech-Language-Hearing Foundation, and many others also offer award opportunities specifically to early-career investigators.

Some non-federal funders offer innovative funding mechanisms. For example, the Hearing Health Foundation's Hearing Restoration Project is an international consortium that features open and almost immediate data sharing among members. Cure Within Reach partners with philanthropists to provide donor-directed clinical trials.

Finally, non-federal funders work closely with patients and their families, providing education, advocacy, and resources. For example, The Royal National Institute for Deaf People provides technology and assistive devices support to patients. The American Academy of Audiology Foundation conducts educational humanitarian and public awareness work.

COLLABORATIONS AMONG FUNDERS

Both non-federal and federal funders share common goals and complement each other in the overall hearing research funding landscape.

The HRRP has closely collaborated with the NIDCD, VA, and MOMRP to synergize efforts, leverage capabilities, and avoid funding duplications. Representatives from all three agencies participate in the HRRP's Programmatic Panel, providing input and recommendations on the HRRP's funding decisions and investment strategy. Likewise, a representative from the HRRP participated in the NIDCD's 2023-2027 Strategic Planning, and in 2021, the HRRP and NIDCD held a joint workshop entitled, "Improving Ex Vivo Models to Accelerate Therapies to Treat Hearing Loss."

To expand our partnership with other funders and foster communication and collaboration among all stakeholders, the HRRP founded the Hearing Research Funders Network (HRF-Net), which currently consists of 24 federal and non-federal organizations that fund hearing research/education or are stakeholders of hearing research. The HRRP hosted the first HRF-Net meeting in 2023.

RESEARCH LANDSCAPE

Several areas have experienced rapid development with a significant impact and a promising horizon; however, significant hurdles need to be overcome in each area.

DRUGS AND THERAPEUTICS

Research in the past two decades has yielded unprecedented insights into the cellular and molecular mechanisms of auditory system development and hearing loss. Capitalizing on mechanistic discoveries, various ideas for regenerative therapies are being tested in animal models, and a small number have entered early clinical testing.[6] Several molecular pathways with key roles in hair cell production during development, notably Notch, Wnt/beta-catenin, and histone deacetylase (HDAC), are being targeted either alone or in combination by multiple research teams. However, none has shown sufficient evidence of efficacy to advance to a phase 3 clinical trial.

DEFINE AND DIAGNOSE HEARING DYSFUNCTION

The inner ear is encased in the hardest bone of the human body, the petrous portion of the temporal bone. The cochlea, the hearing component of the inner ear, is the size of a pea and spiral-shaped. Approximately 15,000 sensory hair cells line up along the fluid-filled spiral canal. Because hair cells at different positions along the canal transmit sounds at different frequencies, normal hearing requires the integrity of the entire canal.

These unique anatomical features of the inner ear severely hinder the advancement of diagnostic capabilities beyond behavioral functional tests. Current diagnostic tools and methods are not capable of identifying the underlying pathology, i.e., they do not identify sensory, neural, synaptic, or central auditory dysfunction.

Efforts to accurately define and diagnose hearing dysfunction take several different approaches, including imaging, biomarker analysis, and electrophysiological-behavioral test batteries. The HRRP has funded a number of these efforts, with promising results. For example, a miniature intracochlear micro-optical coherence tomography (µOCT) catheter was tested on human cadaveric cochlea.[7] Combining a 1-µm resolution µOCT system with a sub-millimeter-diameter, flexible optic probe inserted through the round window, the catheter successfully collected intracochlear µOCT images of the organ of Corti inside the inner ear's bone casing. Another HRRP-funded study dissected the contribution of two cortical subsystems in speech-in-noise (SiN) processing and demonstrated the clinical potential of a short SiN-electroencephalographical paradigm in evaluating cortical function during SiN.[8]

EX VIVO MODELS

Encased in the petrous bone, the cochlea is difficult to access and not amenable for biopsy. Even in rare circumstances when it can be accessed, retrieving tissue samples from the tiny and intricately structured cochlea poses high risks of permanently damaging the patient's hearing. Consequently, it has been difficult, if not impossible, to confirm to which degree the pathological processes, developmental/regenerative mechanisms, molecular pathways, or potential therapeutics that have been discovered in animal models are applicable to humans.

In vitro models are a promising approach to enable/accelerate research on human tissue. For example, an HRRP-funded study developed a method to generate three-dimensional (3D) inner ear organoids from human pluripotent stem cells.[9] Sensory epithelia within the organoids contain inner ear hair cells, supporting cells, as well as neurons forming synapses with the hair cells. Additional research is needed to improve the scalability, reproducibility, and robustness of the process, as well as to control the spatial organization, so that the in vitro model both mimics the natural inner ear sensory epithelium and is conductive to experimental manipulation. The next generation of in vitro inner ear model may combine organoid technology with organ-on-chip microfluidic platforms and 3D scaffolds, similar to what has been achieved for other organs/tissues such as the gut.[10]

TIMELY MITIGATION OF AUDITORY DAMAGE

The past 8-10 years have witnessed innovations in diagnostic practices that are changing the mindset regarding the who, how, and where of diagnostics service delivery and data collection. For example, VA Audiology has promoted tele-audiology and audiology services that do not require a sound-proof booth (termed "boothless") to provide care to Veterans living in remote areas and to meet access-to-care standards. Additionally, during the COVID-19 pandemic, the Hearing Center of Excellence, Walter Reed National Military Medical Center, and Army Public Health successfully incorporated boothless audiometry into annual screening. In FY22, the DOD and VA began a resource-sharing collaboration via the DOD/VA Joint Incentive Fund to demonstrate boothless audiology and tele-audiology services in a variety of DOD and VA settings. Adoption of boothless audiometry not only helps maintain or improve readiness during pandemic restrictions, but also demonstrates how the technology can be used in a more mobile application. Finally, boothless delivery of audiology service by non-government providers increased during the COVID-19 pandemic.

Concurrent with the developments in tele-audiometry and boothless audiometry, there has been an increased focus on timely mitigation of auditory damage. Research exploring the mechanisms causing cell/synaptic damage after noise exposure have provided insight into how various molecular pathways affect auditory injury and cellular repair. Several potential therapeutics targeting these pathways (e.g., glutamate excitotoxicity, nitrative stress, oxidative stress, proteostasis, and neuroinflammation) are being tested for their ability to prevent secondary injury leading to permanent hearing loss. Some have shown significant promise in animal studies. However, a common feature of these mitigating therapeutics is that they need to be administrated within hours after auditory injury or even before injury. Use of more portable, ambulatory, tele-audiometry and/or boothless audiology technology could facilitate meaningful auditory assessment closer to the time of injury, which may better support future developed therapeutics.

STRATEGIC DIRECTION

TARGETING MAJOR OBSTACLES TO HEARING RESTORATION

To maximize impact and return, the HRRP will continue to target major scientific obstacles to hearing restoration by advancing research along three lines of effort:

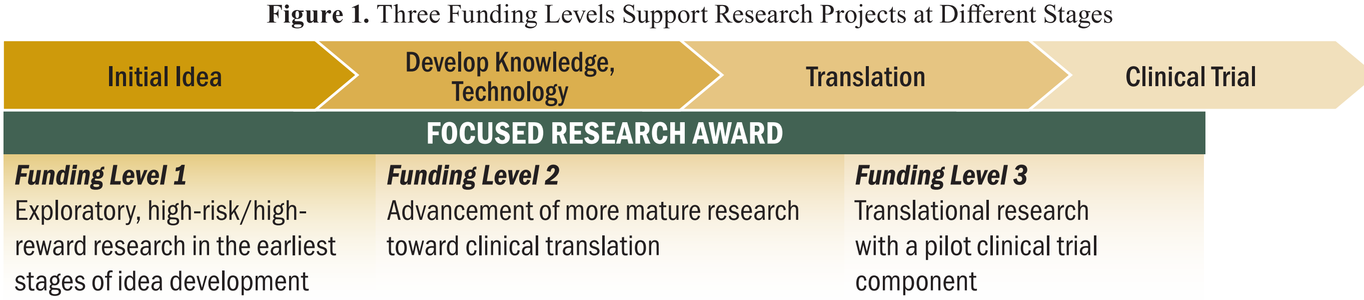
- Validate and translate biological regeneration/repair mechanisms into clinical applications
- Advance diagnostic capability to support clinical testing of potential therapeutics
- Accelerate the development of reliable in vitro human models to facilitate therapeutic development

Within these lines of effort, the HRRP will determine its Focus Areas each year at annual Vision Setting meetings.

INVESTMENT STRATEGY

The HRRP will invest in innovative research that has the potential to significantly advance one or more of our lines of effort. To support research projects at different stages and the exploration/development of ideas of different maturity levels, the HRRP has offered the Focused Research Award at three funding levels (**Figure 1**). Funding Level 1 supports exploratory, high-risk/high-reward research that is in the earliest stages of idea development. Funding Level 2 supports advancement of more mature research

Figure 1. Three Funding Levels Support Research Projects at Different Stages



toward clinical translation. Funding Level 3 supports translational research that includes a pilot clinical trial designed to inform the feasibility, rationale, and design of subsequent clinical trials through limited clinical testing of a novel intervention. The funding levels enable promising projects to enter and exit the HRRP's pipeline at any phase between early preclinical to early clinical. Interventions that successfully complete Funding Level 3 will be sufficiently de-risked to attract funding from other sources for clinical trials.

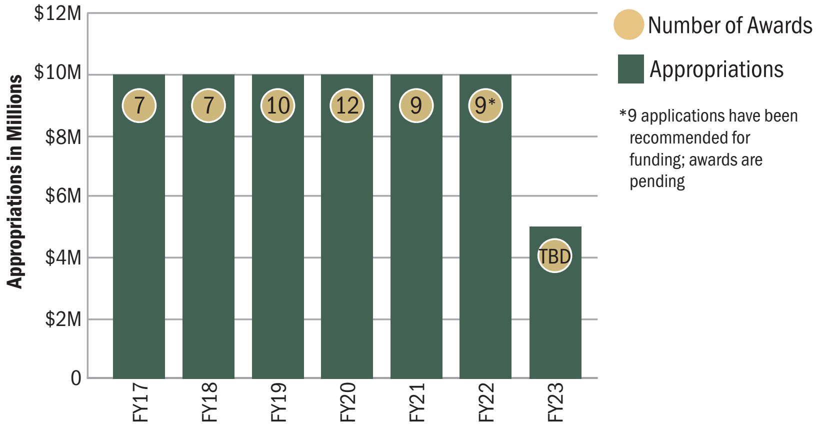
At annual Vision Setting meetings the HRRP will review and determine the award mechanism and funding level(s) to be offered in the next program cycle so that the program's investment strategy can be adapted to the most current research and funding landscapes.

MEASURING PROGRESS

The HRRP has made 45 awards between FY17 and FY21. Program evaluation is conducted annually prior to Vision Setting and ad hoc, as needed. Scientific return is measured by publications, presentations, funding applied for and obtained, and patent applications filed and granted. Through the last quarter of 2022, research funded by the HRRP has resulted in 9 patent applications, 26 peer-reviewed publications, and 90 conference presentations.

The majority of HRRP-funded research is in the preclinical or translational stage. As projects mature and advance to clinical testing, the HRRP will assess the clinical return of its investment. Parameters to be considered will include Investigational New Drug/Investigational Device Exemption applications, clinical trials, and interventions or diagnostics that successfully transition to clinical applications.

Figure 2. HRRP Appropriation Received and Awards Made by Fiscal Year



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