

2010 HEARING & BALANCE RESEARCH GRANT RECIPIENTS

Since its inception in 1958, we have awarded over \$26 million through more than 2,000 scientific research grants to researchers who are dedicated to exploring new avenues of hearing and balance science. This research, which most likely would not have happened without DRF funding, has led to dramatic innovations that increase options for those living with hearing and balance loss as well as protect those at risk. A complete list of the 2010 grant recipients is provided below, including recipients whose research is funded in whole or part by the DRF Centurion Clinical Research Award, the C.H.E.A.R. Endowment Award, The Burch-Safford Foundation, Inc., and The Todd M. Bader Research Grant of The Barbara Epstein Foundation, Inc.

DRF continues to live up to its well-established reputation as the leading source of private funding for research in hearing and balance science in the United States.

DRF FIRST YEAR HEARING & BALANCE RESEARCH GRANT RECIPIENTS

Ranjan Batra, Ph.D., University of Mississippi Medical Center

Organization of frequency encoding in the inferior colliculus

Frequency is key to most aspects of hearing. The inferior colliculus is a center in the midbrain that is important in analyzing frequency. Multiple pathways converge here, and the separate representations of frequency carried by each are unified. The unification appears to be based on the architecture of the inferior colliculus, which is layered like a stack of pancakes. The currently accepted theory is that each layer encodes a single frequency or, perhaps, a band of frequencies along its length. The adjacent layers encode a neighboring frequency or band. In this way, the audible spectrum is segmented. An alternative theory proposes that the layers overlap, and frequency is encoded continuously perpendicular to the stack. Previous studies advanced an electrode perpendicular to the stack and observed steps in the encoded frequency that were presumed to correspond to the layers. Such steps could have been due to irregular penetration of the tissue. In the proposed experiment, novel double-barreled microelectrodes with tips separated by less than the thickness of a layer will be advanced parallel to the layers. The encoded frequencies at the tips should be near equal if the discrete band theory is correct, but show consistent differences if frequencies shift gradually.

Fangyi Chen, Ph.D., Oregon Health & Science University

In vivo study of backward propagation of the basilar membrane vibration

Understanding the mechanism of the backward propagation of otoacoustic emission (OAE) is essential not only for the use of the OAE, but also for verifying the basic physical assumption of bidirectional wave propagation in the cochlear mechanics. Recent experimental results (Ren 2004) on OAE propagation have shaken the fundamental believe of bidirectional wave propagation in the cochlea. Ren proposed the alternative 'compression wave theory' to interpret his experimental results. However, Ren's results were criticized in two ways: a) the longitudinal range of his basilar membrane measurements is too small and b) the generation site of the OAE is too wide (Shera et. al., 2005). In this study, we will address the critiques of Ren's experiment by developing: 1) An in vivo preparation with wide opened basilar membrane area; 2) A new stimulation method to deliver localized BM vibration. These two developments will clarify the ambiguity concerning backward wave propagation. Our preliminary experiments on an artificial cochlea, a mechanical device mimicking the hydromechanical structure of the cochlea, have demonstrated results supporting the backward traveling wave. This result has to be verified in the cochlea in vivo, which is the aim of this study.

Soyoun Cho, Ph.D., Oregon Health & Science University

Dynamics of exo- and endocytosis at hair cells

Hair cell synapses are the first synapse in the auditory pathway. Sound waves are converted into electrical signals via this synapse and these signals are delivered throughout the auditory nerve system. Hair cell synapses accomplish this task continuously and very accurately. The mechanisms underlying this unique synaptic transmission are not well understood. In this proposed study, we plan to investigate basic characteristics of mature hair cell synapses to understand how these synapses satisfy the remarkable demands of auditory signaling. First, we will determine the size of multiple vesicle pools. This information is very critical for a better understanding of how hair cells accommodate both fast and sustained release very accurately and without being tired. Secondly, we will investigate short-term plasticity of this synapse. It is possible that short-term plasticity helps the high acuity and versatility of auditory coding at this synapse. Thirdly, we will study the endocytosis of released vesicles. Especially with prolonged stimulus or with repetitive stimulation, endocytosis is critical to refill the vesicle pool.

Zhengqing Hu, M.D., Ph.D., Wayne State University School of Medicine

Innervation of in vitro-produced hair cell by neural progenitor-derived glutamatergic neurons

Two types of cells are critical for hearing: sensory hair cells and spiral ganglion neurons (SGNs). To regenerate hearing, we have recently identified the stem cells from the mouse inner ear and induced these stem cells to differentiate into hair cells and SGN like nerve cells - glutamatergic nerve cells, entirely in the culture dishes. The next fundamental and critical question is if the regenerated nerve cells could innervate the hair cells that are produced in the culture dishes? In this project, we will culture inner ear stem cell derived glutamatergic nerve cells and hair cells entirely in the culture dishes and observe if there is any neural connections between these two types of cells. The advantage of this approach is that we can fully control the culture conditions since we can generate the SGN like cells and hair cells entirely in the culture conditions, thus avoiding the tedious and difficult inner ear tissue harvesting and variances between the batches of dissections. This approach will provide a good model to study the innervation of hair cells and help us understand the regeneration of hearing.

Judith S. Kempfle, M.D., Massachusetts Eye and Ear Infirmary

Influence of bone morphogenetic protein 4 and retinoic acid on differentiation of inner ear stem cells

The cells that are responsible for hearing in the inner ear are hair cells and neurons. These cells don't usually regenerate after damage. Stem cells offer a powerful tool for future replacement strategies of these cells. Thereby, stem cells have to follow different developmental steps to ultimately differentiate into hair cells or neurons. Guiding factors such as BMP4 and RA are patterning the inner ear during development along a concentration gradient. We use BMP4 and RA to influence inner ear stem cells in order to form hair cells and neurons in vitro. Our preliminary data suggest that BMP4 and RA can reciprocally influence the stem cells of each cell type: high amounts of BMP4 lead to neurons, high amounts of RA seem to favor formation of hair cells. We propose an in vitro system that allows us to specifically increase the yield of hair cells and neurons from inner ear stem cells.

Hongzhe Li, Ph.D., Oregon Health & Science University

Mechanisms of ototoxic synergy due to sound and aminoglycosides

Exposure to loud sounds causes temporary or permanent threshold shifts in auditory perception, with reversible or irreversible cellular damage in the cochlea. Aminoglycoside antibiotics used for treating or preventing life threatening bacterial infections also induce cytotoxicity in the cochlea. Combined sound and aminoglycoside exposure, such as blast injuries with subsequent treatment with aminoglycosides; or chronic sound exposure and aminoglycoside treatment in neonatal intensive care incubators, can degrade auditory functions greater than simple summation of the two insults. The proposed research will determine if sound stimulation synergistically enhances sensory cell uptake of aminoglycosides.

Sho Ohta, M.D., Ph.D., University of Utah School of Medicine

The role of bmp signaling in regulating e-cadherin endocytosis during vestibular organ formation

The vertebrate inner ear derives from the otic placode, a platelike region of thickened epithelial cells adjacent to the hindbrain. During subsequent development, the otic placode invaginates and pinches off from the overlying ectoderm to form the hollow otocyst. This simple saclike structure in turn gives rise through region-specific morphogenesis to the two major components of the membranous labyrinth, the vestibular and auditory organs. In preliminary studies, we identified a regional change in the shape of the otocyst that heralds the establishment of the vestibular organ: namely, the dorsolateral wall of the early otocyst undergoes a rapid expansion. This expansion is driven by change in otocyst cell shape from columnar to squamous and is induced by BMP signaling through the SMAD pathway. According to a model derived from changes that occur in cell shape preceding epithelial cell transformation, 4 key steps involving E-cadherin drive cell shape changes in epithelia: E-cadherin phosphorylation, ubiquitination, endocytosis, and proteolysis. These four steps result in E-cadherin fragmentation, which changes adhesive properties among adjacent columnar cells, allowing cell shape change to occur. We investigate the roles in the developing chick dorsolateral otocyst of activation of the endocytotic pathway as a result of BMP/SMAD signaling, resulting in E-cadherin fragmentation and change in epithelial cell shape, thereby driving the regional morphogenesis of the otocyst that results in epithelial expansion and initiation of development of the vestibular organ.

Albert Park, M.D., University of Utah School of Medicine

Translational studies for antiviral treatment of cytomegalovirus induced sensorineural hearing loss

Cytomegalovirus (CMV) infection affects approximately 40,000 infants annually in the United States and is a leading cause of newborn hearing loss (SNHL). Delay in its identification and a lack of definitive treatment contribute to the billions of dollars required for hearing testing and special services. Active research has concentrated on vaccination or other therapies for the neurologic effects of this condition. Less work has been done to develop treatment for CMV mediated SNHL. We have successfully shown hearing loss in newborn guinea pig pups infected with CMV[1]. Pregnant females inoculated with guinea pig CMV during the second trimester transmitted the virus transplacentally to the pups. Hearing loss was detected based on auditory brainstem response (ABR) click and 8 kHz thresholds. The type of loss was progressive and asymmetric, a characteristic reported in human clinical reports of this infection. We also detected gpCMV in the temporal bones of the inoculated pups via polymerase chain reaction testing. We propose to use this guinea pig model to evaluate the potential efficacy of an antiviral agent ganciclovir against hearing loss.

Neeliyath A. Ramakrishnan, Ph.D., Wayne State University School of Medicine

Molecular interactions of the hair-cell afferent synapse

Hair cells process complex sound stimuli and convert them into modulated neuro-secretion from hair cells. Identification of molecular correlates of the hair cell exocytosis should indicate spatial-temporal and tonotopical modulation of neuro-transmission. In the present investigation we target otoferlin and voltage dependent calcium channel Cav1.3, two proteins that are important for hair-cell exocytosis and cause deafness when defective. In neuronal cells, vesicle fusion is achieved by synaptotagmin1 C2 domain-phospholipid interaction. Phospholipid interactions of otoferlin are currently unknown. We hypothesize that otoferlin bind specifically to phospholipids at the pre-synaptic membrane leading to calcium-dependent vesicle fusion and neurosecretion. We will explore the secondary structural changes in otoferlin C2 domains and their possible role in Ca²⁺ and phospho-lipid binding. C2 domains are versatile interaction modules capable of binding a variety of molecules such as lipids and proteins. We will use select regions of otoferlin as bait to screen for binding partners in a rat organ-of-Corti cDNA preparation. Hair-cell calcium nano-domains are essential for fast synchronous exocytosis. In hair cells discrete calcium nano-domains are formed by clustering of calcium channel molecules around the ribbon synapse. Our investigation will explore protein molecules involved in the transport and targeting of Cav1.3 channels in the hair cells.

Soledad Miranda-Rottmann, Ph.D., Howard Hughes Medical Institute, The Rockefeller University

Regulation of the efferent innervation to the mouse cochlea

The inner ear sends information to the brain like all other sensory organs, but it has the unique feature of a feedback mechanism consisting of neurons that send information from the brain to the cochlea, called the efferent innervation pathway. The role of this pathway is still controversial and the molecular cues that determine the differentiation and pathfinding of these neurons are still unknown. We generated mutant mice that lack regulatory proteins important for neuronal function, called Nova1 and Nova2 (Nova1/2). In the mouse lacking Nova2 the efferents are largely missing, while the mice lacking both Nova1/2 have no afferents at all. These mouse models allow to address the question of the unknown efferent molecular cues for the first time. In our advanced work using a new biochemical approach, four novel genes and one previously described one, were selected as candidate genes. These genes are still expressed in the mutant mouse, but in a modified form, because Nova1/2 are necessary for the expression of the normal form. Finally, we propose to unequivocally test the role of these candidate genes by re-introducing the expression of the normal proteins in the mutant mice and look for the restoration of the innervation defect.

Armin H. Seidl, Ph.D., Virginia Merrill Bloedel Hearing Research Center, University of Washington

Morphometrics of the mammalian low frequency sound localization circuit

The goal of this proposed project is to measure axon length and to assess biophysical properties responsible for conduction velocity in the mammalian low frequency sound localization circuit. We will measure the fiber length of axons extending from the bilateral anteroventral cochlear nucleus (AVCN) to the medial superior olive (MSO) in the gerbil. Additionally we will determine axon diameter and distances between Nodes of Ranvier at strategic position along different segment of the AVCN axon. Our recent study on the avian sound localization circuit showed that conduction velocity parameters might compensate for axon length differences. This led us to hypothesize about a physiological delay line system in the mammalian low frequency sound localization circuit. Instead of axon length, conduction velocity parameters such as axon diameter and internode distances may be responsible for creating systemic variations of conduction times. The mammalian low frequency sound localization circuit is a matter of much interest. We believe we can contribute to this important topic by the experiments we propose. Understanding the low frequency sound localization mechanism in the mammal will help us develop tools to overcome hearing related health issues, such as loss of sound discrimination with age.

Yuan Wang, Ph.D., Virginia Merrill Bloedel Hearing Research Center, University of Washington

The role of subcellular regulation of *trkb* in dendritic geometry of auditory brainstem neurons

During development, neuronal structure and function of the auditory centers in the brain is regulated by level and pattern of auditory inputs from the ears. Of particular interest is rapid breakdown of symmetric dendritic configuration of neurons in nucleus laminaris (NL) following activity deprivation. This breakdown could lead to impairment of the computation of binaural cues that are essential for speech recognition and sound localization. We hypothesize that TrkB, a high-affinity neurotrophin receptor, regulates dendritic geometry of NL neurons by selectively controlling dendritic branch length of a subset of dendrites. We will study effects of activation or inhibition of TrkB signaling on dendritic length and configuration in active or activity-deprived NL neurons in slice preparations. These effects will be evaluated on individual cell level with single cell filling with fluorescent dyes, confocal microscopy, and 3D reconstruction software. Symmetric configuration of NL neuron dendrites is critical for the specialized function of the NL in binaural hearing. Understanding the role of neurotrophin signaling in the maintenance of dendritic geometry could provide a therapeutic target for rescuing NL neurons from degeneration and thus improve impaired binaural hearing function.

Jeong-Im Woo, Ph.D., House Ear Institute

Role of vasopressin-aqp2 system in endolymph regulation of es epithelial cells

To date, no known cures for Meniere's disease have been identified and the current treatments are merely palliative, aimed at reducing the severity of attacks of vertigo. Dysfunction of endolymph water regulation is thought to be the cause of Meniere's disease. It is not well known how inner ear water/ion homeostasis is maintained. The finding that obliteration of the endolymphatic sac (ES) causes hydrops, suggests a role of ES as a regulator in fluid absorption, but further studies are needed to understand the precise role of ES in fluid homeostasis. The evidence to support an important role for the regulation of fluid homeostasis by the vasopressin-AQP2 system in the inner ear comes from both clinical and experimental studies. Recently, we have successfully developed an epithelial cell line (HEIHESEC- I) derived from the normal human ES. We propose to further characterize HEI-HESEC-I cell line and to determine the mechanism of vasopressin-induced AQP2 regulations in regard to water/ion homeostasis. This study will provide detailed cell/molecular insight into the fundamental physiology and pathophysiology of the water/ion balance and its disorders of the inner ear.

DRF SECOND YEAR HEARING & BALANCE RESEARCH GRANT RECIPIENTS

Ronna Hertzano, M.D., Ph.D., University of Maryland School of Medicine

A new protocol for selective and efficient sorting of the auditory sensory epithelium

The goal of this project is to develop methods for separating and characterizing the unique cell types of the auditory sensory epithelium using methods commonly used by immunologists. This could also result in the identification of new cell type-specific proteins and possibly new deafness genes.

Olga Stakhovskaya, M.D., Ph.D., University of California, San Francisco School of Medicine

Estimating optimum insertion depth for the hifocus electrode array in individual human cochleae based on high resolution ct images

Optimizing the insertion depth of the electrode array in individual human cochlear implant recipients may significantly reduce the extent of trauma to the cochlea during surgical implantation, improve speech recognition and pitch perception ability, and help to preserve residual hearing in patients with combined acoustic and electrical stimulation. This study will determine whether the size of an individual cochlea estimated from high resolution CT images (and verified in histological sections) can be used to define the optimum insertion depth and help to guide electrode insertion to the desired frequency range and prevent trauma.



Arminda Suli, Ph.D., University of Washington School of Medicine

Assessing functional recovery after mechanosensory hair cell regeneration in the zebrafish lateral line

Sensory hair cells located in the inner ear are responsible for converting sound into understandable signals for the brain. Damage of these cells from age-related factors, noise, and therapeutic drugs leads to hair cells loss, a process that is irreversible in humans and other mammals. In contrast, non-mammalians, such as zebrafish, are very effective in regenerating sensory hair cells; therefore, we use this organism to find mechanisms that lead to sensory hair cell regeneration. Since restoration of function depends on restoring the correct connections between hair cells and the brain, I am using a behavioral assay and molecular markers to determine how this process is accomplished during regeneration.

Ruili Xie, Ph.D., University of North Carolina at Chapel Hill School of Medicine

Synaptic transmission in the principal cells of the anteroventral cochlear nucleus during age-related hearing loss

Age-related hearing loss (AHL) is a common disorder that affects most individuals as they age and causes conditions from deteriorated hearing sensitivity to complete deafness. Anatomical and physiological changes in the auditory system during AHL underlie the perceptual loss of hearing. Changes in cochlear nucleus, which is the first processing center of the central auditory system, are of special interest in studying AHL. However, little is known about the changes of synaptic transmission in principal cells of the cochlear nucleus during AHL except a pioneering study from this lab. This project will utilize DBA/2j mice as the animal model for AHL to study the changes of synaptic transmission in principal cells of anteroventral cochlear nucleus (AVCN) during AHL. Specifically, the study will use whole-cell recording techniques to evaluate the glycinergic transmission in bushy cells as well as both glycinergic and glutamatergic transmission in stellate cells of the AVCN in brain slices prepared from DBA/2j mice at three age groups, which represent three different developmental stages of AHL (normal hearing, intermediate hearing loss, and complete hearing loss). The study seeks to identify physiological changes in synaptic transmission in the principal cells of AVCN during AHL that may underlie the perceptual loss of hearing.

Eunyoung Yi, Ph.D., The Johns Hopkins University School of Medicine

Dopaminergic modulation of inner hair cell afferent synaptic transmission

In the inner ear, the inner hair cells convert sound information into electrical signals. Auditory nerve fibers pick up information from the hair cells via the hair cell afferent synapse and transmit the sound signal to the brain. Interestingly, auditory nerve fiber activity can be modulated by feedback mechanisms from the brain. Lateral efferent fibers originating in the auditory brainstem innervate auditory nerve fibers at their endings, directly where they contact the inner hair cells. Dopamine is one of the neurotransmitters found in lateral efferent endings and dopamine release is thought to provide a protective role against noise-trauma. However, the cellular mechanisms underlying this process are not well understood. In this project, we will use histological techniques to identify the cellular locations and subtypes of dopamine receptors at the inner hair cell afferent synapse. We will also use electrophysiological techniques to measure electrical impulses in auditory nerve fiber endings at the hair cell afferent synapse in an excised cochlear preparation. We will apply drugs that specifically imitate or inhibit the actions of dopamine, and investigate the mechanisms and intracellular targets by which dopamine receptors modulate the signals at the inner hair cell afferent synapse.

DRF CENTURION CLINICAL RESEARCH AWARD RECIPIENT

Craig A Buchman, M.D., University of North Carolina at Chapel Hill School of Medicine

Auditory neuropathy spectrum disorder in children

Auditory Neuropathy Spectrum Disorder (ANSD) is an important clinical syndrome affecting about 10% of children with newly identified hearing loss. Currently available testing modalities are unable to predict auditory thresholds or speech perception abilities in children with ANSD, necessitating dependence on behavioral testing, thereby delaying intervention significantly. The overarching goal of this project is to facilitate appropriate intervention among ANSD children by identifying functional biomarkers that can predict successful use of a particular intervention strategy (hearing aids or cochlear implants). To this end, a systematic investigation of the ANSD population is proposed to measure both early (electrocochleography) and late (cortical) auditory potentials elicited either acoustically or electrically (cochlear implant). Robust speech perception data that are available for these children will be used to gauge relevance of these measures for predicting performance. The results gleaned from these studies will provide the necessary tools to reconstruct the diagnostic framework for these children according to validated electrophysiologic biomarkers, thereby eliminating prolonged behavioral observation and optimizing intervention.

This research award is funded by the Centurions of the Deafness Research Foundation. DRF has partnered with CORE Grants Program of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) to offer a one-year Centurion Clinical Research Award (CCRA) for clinical research in hearing and balance science.

DRF C.H.E.A.R. ENDOWMENT GRANT RECIPIENT

Frances Hannan, PhD, New York Medical College

1st Year DRF Grant Recipient

The role of diaphanous in the auditory cytoskeleton

Dominant mutations in two separate human genes that produce closely related Diaphanous proteins (DIAPH1 and DIAPH3), lead to hereditary hearing loss and auditory neuropathy respectively. We also observe hearing loss in fruit flies with mutations affecting the Drosophila Diaphanous gene. This is not surprising given the many similarities between the auditory organs of humans and flies, including the use of stretch-sensitive neurons to detect sound waves. Diaphanous proteins belong to the formin family of proteins, which bind to both actin and microtubules. These proteins are important for the architectural structure of the hearing apparatus, and for the movement of other proteins within the auditory neurons. Our preliminary data shows dramatic disruption of microtubules in the auditory neurons of Diaphanous mutant flies. We will use the powerful genetic tools available in Drosophila, combined with live imaging techniques, to understand the role of Diaphanous proteins in fruit fly hearing. This will enhance our knowledge of Diaphanous dysfunction in human hereditary hearing loss and auditory neuropathy, and may lead to novel strategies for treatment and diagnosis of these disorders.

The C.H.E.A.R. endowment was created to support an annual Sensory-Neural Deafness Research Grant. C.H.E.A.R. (Children Hearing Education and Research) was absorbed into DRF in 1991, and we are very proud to continue their legacy of funding research in sensory-neural deafness.



THE BURCH-SAFFORD FOUNDATION, INC. RECIPIENT

Saima Riazuddin, PhD, Cincinnati Children's Hospital Medical Center

1st Year DRF Grant Recipient

Defining the role of tricellular tight junction protein in the inner ear

Hearing impairment is a highly heterogeneous disorder. We previously reported DFNB49, a locus for recessive deafness on chromosome 5, among eight large families. Subsequently, I found four different mutations among our DFNB49 families, in a gene named as TRIC. The protein encoded by Tric is a tight junction protein and is named as tricellulin. The identification of DFNB49 raises an important question and that is despite the wide spread expression of tricellulin in most epithelial cells the phenotype in patients is restricted to ear. It's likely the inner ear compared to other tissues is very sensitive and has a unique requirement for tricellulin. Another possibility is that DFNB49 mutations are clustered in a fairly small genomic segment. It is possible the mutations in other parts of this gene especially exon 3 that encodes the transmembrane domain, will give rise to phenotype in other tissues. Here, we will evaluate the inner ears of a knockin mouse that we have engineered to contain a nonsense mutation that we previously reported for a DFNB49 family. In addition a complete null mouse of Tric will be generated and evaluated. These mouse models will help us understand the function of Tric.

This research award is funded by The Burch-Safford Foundation, Inc.

THE TODD M. BADER RESEARCH GRANT OF THE BARBARA EPSTEIN FOUNDATION, INC., RECIPIENT

Marcello Peppi, Ph.D., Massachusetts Eye and Ear Infirmary

1st Year DRF Grant Recipient

Molecular mechanisms of dexamethasone-mediated protection from acoustic trauma

The cochlea can be "conditioned" to resist an acoustic trauma via a corticosteroid-dependent process. Our recent discovery of a transcription factor (PLZF) that is essential for corticosteroid-mediated protection (i.e. PLZF-deficient mutant mice can not generate protection) provides a tool with which these molecular mechanisms can be identified. An understanding of these mechanisms will provide discrete and concise targets for drug therapy. While corticosteroids are widely used and highly beneficial drugs for the treatment of inner ear and other disorders, the broad spectrum of action and widespread side effects limit their ultimate advantage. The possible presence of a protective sub-pathway among the broad variety of pathways initiated by corticosteroids may provide significantly improved therapies for degenerative hearing loss. Corticosteroids have also proven useful in other nervous system traumatic disorders, such as stroke and spinal cord injury, though those mechanisms of protection have not been identified. PLZF is present throughout the nervous system. If, as in the cochlea, PLZF is the transcriptional trigger for protection in those cases, findings on its role in cochlear protection could have obvious broader implications.

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