

2009-2010 HEARING & BALANCE RESEARCH GRANT RECIPIENTS

Each year since its inception, the Deafness Research Foundation (DRF) has funded promising research in the field 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. Below is a list of the 15 awarded recipients along with their project abstracts who are funded from July 1, 2009 to June 30, 2010. In addition are the names of recipients whose research is funded in whole or part by the Centurion Clinical Research Award, C.H.E.A.R. Endowment Award and The Burch-Safford 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

Edward L. Bartlett, Ph.D., Purdue University

Cellular mechanisms contributing to in vivo neuronal responses in auditory thalamic neurons

Auditory thalamic neurons provide sensory input to auditory cortex, and aberrations in the auditory thalamus are correlated with dyslexia, schizophrenia, and Alzheimer's disease in humans. Despite its importance in normal and abnormal hearing, the mechanisms by which auditory thalamic neurons process sound are poorly understood. Neuronal recordings in live animals typically only provide the final output of the neuron, while the complex integration of excitatory and inhibitory inputs that led to the output is unknown. Though dissociated from a full neural network, recording intracellularly from neurons in brain slices allows excellent control of the cellular environment and detailed observations of the cellular and synaptic mechanisms by which neural responses are generated. From these observations, it becomes possible to formulate and test mechanistic hypotheses about the input patterns that produced a given neural response, as well as isolating the roles of different cellular mechanisms in normal and pathological responses. This research will study individually, by intracellular recordings, the properties of the main inputs to auditory thalamic neurons. Then the inputs will be combined in an attempt to recreate responses to repetitive sounds observed in live animals, since representations of repetition rates are important for encoding speech and other relevant sounds.

Martin L. Basch, Ph.D., Baylor College of Medicine

Live imaging of the developing cochlea

During development the cochlear duct grows from the ventral side of the inner ear and a prosensory domain is established that contains common progenitors for hair cells and supporting cells. As these cells differentiate they form a highly organized pattern that in mammals consists of one row of inner hair cells (IHC) and three rows of outer hair cells (OHC), each surrounded by supporting cells. The organization of this intricate pattern is concomitant with the elongation of the cochlea from the base to the apex. Because there is little or no cell proliferation at this time, these processes rely heavily on cell movements. We propose that an active process of cell movement is responsible for achieving the complex architecture of the cochlear epithelium. In recent years we began to understand the molecular mechanisms underlying hair cell and supporting cell differentiation. However, the cellular mechanisms involved in this process have been difficult to study. To address this question, we have developed an organ culture method that allows us to study the individual movements of genetically labeled cells through 3 dimensional time-lapse confocal microscopy.

Adrian Rodriguez-Contreras, Ph.D., The City College of New York

Defining the role of olivo-cochlear feedback in the development of the auditory brainstem

During early brain development auditory neurons spontaneously generate highly patterned electrical activity in the absence of sound. In this project Rodriguez-Contreras will explore the role of cholinergic brainstem neurons in modulating the patterns of spontaneous activity. His work could provide clues to develop treatments that ameliorate hearing impairments such as tinnitus and deafness.

Alain Dabdoub, Ph.D., University of California, San Diego

Canonical wnt signaling in the developing organ of corti

Within the organ of Corti, a single row of inner hair cells and three rows of outer hair cells extend along the basal- to-apical axis of the cochlea. Every sensory hair cell is separated from the next by an intervening non-sensory supporting cell, resulting in an invariant and alternating mosaic. The importance of the formation of this structure is illustrated by the significant auditory deficits in animals with patterning defects in the cochlear duct. Since the perception of sound is based on the integrity and function of this strict cellular organization, it is important to elucidate the developmental processes responsible for generating and regulating this pattern. The development of the cochlea and the organ of Corti requires several events including growth, specification of cell fates, proliferation and differentiation. In many systems the Wnt/-catenin pathway plays a crucial role in determining cell fate, growth and proliferation. We have data indicating that several Wnt signaling genes are expressed in the cochlea. Furthermore, our preliminary results demonstrate that activating the Wnt/-catenin pathway in whole organ cochlear explant cultures results in a robust increase in the size of the prosensory domain that gives rise to the organ of Corti and increases in auditory hair cells.

Michelle L. Hastings, Ph.D., Rosalind Franklin University of Medicine and Science

Therapeutic correction of ush1c splicing in a mouse model of usher syndrome

Usher syndrome is the leading genetic cause of combined hearing and vision loss. The long-term objective of this project is to develop therapeutics for the disease. Antisense oligonucleotides (ASOs) will be used in a mouse model of Usher syndrome to correct a specific genetic defect that causes the disease. This work will demonstrate the efficacy of ASOs as a therapeutic for Usher syndrome and will also provide insights about curing the disease.

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

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.

Christina L. Kaiser, Ph.D., Boston University School of Medicine

An active role for the supporting cell cytoskeleton in controlling hair cell death and regeneration

Cochlear hair cells are the primary targets of most damaging agents. When these cells are lost in humans and other mammals, the resultant hearing loss is permanent. However, chickens and other avian species have the ability to replace lost cochlear hair cells. Cochlear hair cell regeneration occurs through two different mechanisms: Direct Transdifferentiation (DT) and mitotic proliferation. In DT, supporting cells directly alter their gene expression to become new hair cells. Alternatively, in mitotic proliferation, normally quiescent supporting cells are induced to proliferate and differentiate into new hair cells and new supporting cells following the death and ejection of the original sensory cells. The experiments in this research are designed to examine how supporting cells regulate hair cell death and how this subsequently regulates supporting cell proliferation. Additionally, we are trying to prevent both the death and ejection of cochlear hair cells. If cochlear hair cells can be “trapped” and “rescued” by treatment with various inhibitors, these compounds may be useful therapeutic tools in hearing loss prevention.

Khaleel A. Razak, Ph.D., University of California, Riverside

Impact of age-related hearing loss on cortical processing of frequency modulated sweeps

Ageing-related plasticity of the central nervous system causes impairments in auditory processing, including speech processing difficulties. This is exacerbated by peripheral hearing loss. Speech-processing difficulties may arise due to the inability to discriminate frequency modulated (FM) sweeps. However, the mechanisms underlying deterioration of FM sweep processing remain unknown. Understanding plasticity of FM processing will provide fundamental insights on how spectrotemporal integration by auditory neurons is altered in the aging population. Neural selectivity for FM sweeps depends on the balance between excitatory and inhibitory inputs to auditory neurons. It is known that inhibitory neurotransmission is down-regulated during aging. The aim of the studies proposed here is to initiate research on age-related changes in inhibition in the auditory cortex of mice and the consequences of such changes to neural processing of FM sweeps. The proposed studies will characterize the spectral bandwidth and timing of sideband inhibition in the young (1-3 mo), middle aged (5-8 mo) and old (>12 mo) mouse cortex and test the hypothesis that weakening inhibition with age is a mechanism of altered FM processing. These studies will serve as a baseline for research into cortical processing in various genetic strains of mice with varying degrees of age-related hearing loss.

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

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

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-mammals, 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.

Patricia A. White, Ph.D., House Ear Institute

Forkhead box o transcription factors and mammalian cochlear regeneration

To restore hearing to the deaf will require an understanding of the genes that regulate proliferation of adult supporting cells. While tumor suppressors, such as Cdkn1b, have well described functions in the cochlea, upstream regulators of such genes are not understood. White's research will characterize the expression and function of Foxo3, a candidate regulator of Cdkn1b, in supporting cells.

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

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. Interesting, 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 SECOND YEAR HEARING & BALANCE RESEARCH GRANT RECIPIENTS

Christian N. Paxton, Ph.D., University of Utah

The role of fgf4 in otic placode induction

Development and patterning of the inner ear is a complex process that is mediated by several signaling molecules, including members of the Fibroblast growth factor (FGF) family. We recently found that Fgf4 is expressed in the earforming region just prior to the induction of ear development. Fgf4 has not previously been described in the induction or formation of the inner ear. Based on its temporal and spatial pattern of expression we hypothesize that Fgf4 is involved in the early processes of ear development and propose to investigate its role(s) in these processes by determining whether it is sufficient and/or required to induce the early stages of inner ear development. We also will examine the signals responsible for localizing Fgf4 expression to the otic forming domain.

Kathleen T. Yee, Ph.D., Tufts University School of Medicine

A role for pax6 in cochlear nucleus development

We are interested in how information-transmitting cells in the brain (neurons) obtain their identity and develop characteristics that allow them to perform specific functions. To address these questions, we study a region of the brain that forms the cochlear nucleus, the first and only direct brain region that receives auditory input. A large body of knowledge exists on the features of mature cochlear nucleus neurons, but studies are only beginning to examine the role of genes during development. Our preliminary data shows that the molecule, Pax6, a transcription factor (a molecule that binds to DNA and controls the activity of other genes), is expressed in the developing cochlear nucleus. Our data demonstrating Pax6 gene expression in the cochlear nucleus suggests that hearing problems may emerge at an earlier stage of the auditory pathway in AN2 (human) patients. Our research project will examine the extent of organizational changes in the cochlear nucleus and how these changes potentially affect hearing.

DRF FIRST YEAR CENTURION CLINICAL RESEARCH AWARD RECIPIENT

Mark Eckert, M.D., Medical University of South Carolina

Neural changes underlying speech-perception training in the aging brain

Many older adults with hearing loss have difficulty understanding speech in noisy environments and some feel socially isolated. Although hearing aids can improve speech understanding, hearing aid benefit may be limited if the perception of certain speech sounds has changed. Speech training programs have been shown to improve the recognition of amplified speech by older adults by focusing on re-learning cues important for perception of specific sounds. The goal of our study is to examine how the brain changes during speech training programs designed to improve speech understanding in noise. To achieve this goal, we are using MRI to examine brain activation before and after speech training and relate this activation to improvements in speech recognition. Our long term goal is to enhance the effectiveness of speech training programs by understanding the brain systems that are important for learning to hear amplified speech.

This research award is funded by the Centurions of the Deafness Research Foundation. DRF 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 sciences.

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

Chin-Tuan Tan, Ph.D., New York University, School of Medicine

2nd Year DRF Grant Recipient

Nonlinearly distorted music and speech as perceived by hearing-impaired people

Hearing aids and other communication devices, such as telephones, introduce significant nonlinear distortion which reduces sound quality and may interfere with speech perception. The goals of the proposed research are to characterize and model the perception of distorted speech and music by hearing-impaired listeners. The first objective of the proposed research is to conduct listening tests to determine how hearing-impaired listeners evaluate the perceived quality of distorted speech and music. The second objective of the proposed research is to develop a computational model for predicting perceived quality judgments made by hearing-impaired listener; in other words, to predict the data obtained in the first part of the project. The third objective of the proposed research is to test, and if necessary to refine, the developed models using recordings of speech and music replayed via existing assistive hearing devices.

A portion of this research award is funded by the C.H.E.A.R. Endowment Grant. This endowment was created in 1991 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

Adam Markaryan, Ph.D., The University of Chicago

Mitochondrial DNA deletions and cochlear element degeneration in presbycusis

The long term goal of the Bloom Temporal Bone Laboratory is to understand the molecular mechanisms involved in age-related hearing loss and develop a rationale for therapy based on this information. This project will quantify the mitochondrial DNA common deletion level and total deletion load in the cochlear elements obtained from individuals with presbycusis and normal hearing controls. The relationship between deletion levels, the extent of cochlear element degeneration, and the severity of hearing loss will be explored in human archival tissues to clarify the role of deletions in presbycusis.

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