2006-2007 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.

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
Funded July 1, 2006 through June 30, 2007

Rajeshwar Awatramani, PhD, Northwestern University
Conditional Genetic Manipulations at Molecular Intersection Points to Identify the Embryonic Origin of Brainstem Auditory Neurons
Essential to normal sound recognition is the proper development of the auditory processing centers in the brainstem. Auditory information from the inner ear coalesces in a tonotopic distribution upon the brainstem cochlear nuclei. Utilizing a newly developed intersectional genetic fate mapping approach, the aim of this research project is to decipher genetic programs underlying the formation of these auditory nuclei.

Gregory J. Basura, MD, PhD, University of North Carolina at Chapel Hill
Synaptic Organization and Plasticity in the Auditory Cortex Following Cochlear Ablation: Role of Serotonin Neurotransmission
The long-term objective of this proposal is to investigate mechanisms of plasticity in auditory cortex neurons following bilateral cochlear ablation. The evaluation of auditory cortex neuronal functioning in an animal model of deafness and the progressive identification of neurotransmitter receptor systems that may modulate their activity after hearing loss, may lead to the development of pharmacologic tools to facilitate restorative hearing.

Elizabeth Bryda, PhD, University of Missouri-Columbia
Role of Otocadherin and CAML in the Inner Ear
By exploring the underlying biological pathways involved in normal as well as abnormal hearing and balance, a more targeted approach to treatment is possible. By exploring the relationship between otocadherin and CAML, increased knowledge of the role of otocadherin, including which proteins it interacts with, will enable researchers to determine if it will be possible to correct defects in patients with Usher syndrome.

Irina Calin-Jageman, PhD, Emory University
Harmonin Interactions with Voltage-gated Ca3+ Channels in a Mouse Model of Usher Syndrome
Usher syndrome is the leading cause of hereditary deafness and combined deafness and blindness in humans. This research will illuminate a novel mechanism of Ca3+ channel regulation that may be important for auditory function. By carefully characterizing the defects in Ca3+ channel properties in the mouse Usher syndrome model, the researcher will be able to follow-up with strategies to restore function to these mice, which may be ultimately useful in limiting deafness and balance problems in human patients of Usher syndrome.

Donald E. Coling, PhD, University at Buffalo, SUNY
Proteomic Investigation of Cisplatin-Induced Ototoxicity
Cisplatin is one of the most frequently used chemotherapeutic agents. However, side effects of hearing loss and kidney failure limits its clinical use. More than 50% of patients treated with cisplatin suffer cochlear hair cell death. Identification of proteins whose degradation or synthesis is induced by cisplatin is expected to lead to new methods of clinical intervention to reduce negative side effects.

James M. Coticchia, MD, Wayne State University School of Medicine
Nasopharyngeal Biofilms in the Pathogenesis of Recurrent Acute Otitis Media
Ear infections are a significant problem in infants and children. Research has shown bacteria that cause ear infections are resistant to antibiotics. By understanding which bacteria form these chronic infections and by evaluating new treatments we hope to reduce the number of children that require ear tubes. This will allow researchers to understand which bacteria form biofilms; when biofilms develop and help to better understand the role of biofilms in recurrent ear infections; and new treatment options for children with frequent ear infections.

Michael R. Deans, PhD
Harvard Medical School, Department of Neurobiology
Genetic Dissection of Planar Cell Polarity Within the Inner Ear
It is broadly accepted that hearing and balance requires the correct orientation of hair cells and their stereocilia bundles within the inner ear. This patterning is called planar cell polarity and involves the coordinated organization of adjacent hair cells. This project aims to understand the developmental mechanisms generating planar polarization and to determine the effects of hair cell disorganization upon auditory and vestibular function.

Gregory I. Frolenkov, PhD, University of Kentucky
Mechanoelectrical Transduction Without Myosin XVa
The long-term goal is to define the molecular and biophysical mechanisms shaping mechanosensitivity in cochlear hair cells. A common structural feature of hair cells in all vertebrates is the staircase arrangement of stereocilia, which is thought to be critical for mechanotransduction. This study will determine the distinguishing features of mechanotransduction in auditory hair cells of deaf shaker 2 mice that have abnormally short stereocilia due to a mutation in the motor domain of Myosin XVa.

Todd A. Hillman, MD, Pittsburgh Ear Research Foundation, Allegheny Singer Research Institute
Otologic Implant Polymers for Biofilm Control in Chronic Otitis Media
Chronic otitis media, including chronic serous otitis media and chronic otorrhea, is a leading cause of hearing loss in the world. This proposal will investigate the role of bacterial biofilms in chronic otitis and explore novel biofilm resistant materials for use in patients with this disease process.

Mingqian Huang, PhD, Massachusetts General Hospital
Expression and Function of Mlf1, a Candidate Gene Involved in Both Pou4f3 and pRb Pathways, in Zebrafish Model
The proposed research is to understand the potential role of Mlf1 gene in hair cell development. Mlf1 has been implicated in the pathways controlled by two hair cell genes, Pou4f3 and pRb, both of which could give rise to deafness if mutated. Therefore dysfunction of Mlf1 may play a role in deafness.

Yayoi S. Kikkawa, MD, PhD, University of Texas, Southwestern Medical Center at Dallas
Molecular and Morphological Analysis of Protocadherin 15 in Vestibular Stereocilia Development
Stereocilia of the inner ear hair cells are micro-scale mechanosensors which converts mechanical forces into electrochemical signals and its precise integrity is critical for hearing and balance. However, the molecular mechanism that regulates stereocilia integrity is not well understood. This proposal focuses on a cadherin-like protein, protocadherin 15 (Pcdh15). Mutations in human Pcdh15 cause Usher syndrome (USH type 1F), the leading cause of combined hearing and vision loss. The molecular characterization of Pcdh15 will lay the foundation for therapeutic strategies not only for Usher syndrome but also for other inner ear disorders associated with abnormalities of hair cell transduction.

Yan Li, PhD, New York University, School of Medicine
Mouse Models of Human Syndromic Hearing Loss Linked to Mutant MYH9 Alleles
Mutations within the nonmuscle myosin heavy chain type IIA (MYH9) have been linked to human hearing loss. The study will examine the biological role of MYH9 in hearing and the role of its mutant alleles MYH9R702C in hearing loss with the goal of developing and characterizing transgenic mouse models that express the mutant alleles MYH9R702C which is linked to syndromic hereditary hearing loss in humans. Characterizing these mice models will lead to elucidation of the role of MYH9 in hearing and help to development of therapeutic stategies for circumventing hearing loss due to MYH9 mutation.

Iain M. Miller, PhD, Ohio University
The Distribution of Glutamate Receptors in the Turtle Utricle: A Confocal and Electron Microscope Study
When stimulated by acceleration and head tilt (gravity), sensory hair cells in the turtle utricle, an organ in the inner ear, transmit information about these stimuli to the brain. The long term goal of this research is to understand what role synaptic structure and composition play in the observed spatially heterogeneous and diverse discharge properties of afferents supplying the vestibular end organs, and in particular, the utricle. This knowledge is central for accurate diagnosis and rational treatment strategies for vestibular dysfunction.

Lavanya Rajagopalan, PhD, Baylor College of Medicine

The Structural and Functional Basis of Electromotility in Prestin, the Outer Ear Amplifier Protein

Prestin, a membrane protein in outer hair cells in the cochlea, is involved in cochlear amplification leading to frequency sensitivity. The long-term objectives of this study are to understand the molecular basis of prestin function, to advance the field closer to designing therapeutics in certain types of hearing loss. This will provide insight into the molecular basis of prestin-related hearing loss, and can lead to rational design of therapeutics to treat such conditions.

Sonia M. S. Rocha-Sanchez, PhD, Creighton University

Role of Central Auditory Neurons in Pathogenic Mechanism of Progressive High Frequency Hearing Loss (PHFHL)

The long-term objective of this study is to assess the relative contribution of Central Auditory Neurons (CANs) to high frequency hearing loss. The peripheral auditory system suggests that progressive hearing loss is resultant of SGNs and/or IHCs dysfunction. This study proposes to determine the effects of the mutations using genetically engineered mice with DN-KCNQ4 expression specific to CANs. Achieving these objectives will open doors to the formulation of therapeutic modalities and possible interventions to PHFHL treatment.

Takunori Satoh, PhD, Purdue University

Gene Discovery Related to Congenital Deafness

Congenital deafness in humans occurs in approximately 1 in 1,000 live births, yet few of the responsible genes are known. This study aims to discover new genes important to the development of the auditory system using zebrafish to determine if they correspond to genes underlying congenital deafness in humans. Utlizing a new process, this study hopes to facilitate gene discovery then determine the involvement of the genes in the development of the auditory system.

Jung-Bum Shin, PhD, Laboratory of Peter Gillespie, PhD, Oregon Hearing Research Center & Vollum Institute

Proteomic Analysis of Stress-Response Proteins in the Sensory Hair Bundle

This study will examine the molecular mechanisms that underlie auditory mechanotransduction. A principal understanding of this process is essential for studying the pathophysiology of hearing loss. We will address the question whether the hair bundle possesses special mechanisms that protect it from harmful environmental influences such as mechanical stress and free radicals.

Wenxue Tang M.D, Emory University School of Medicine

The molecular diversity of gap junction channel systems in the cochlea

The long-term objective of this study is to understand how molecular mechanisms of different subtypes of connexins (Cxs) contribute to cochlear functions. Connexins (Cxs) are a family of proteins constituting the gap junctions (GJs). GJs allow direct intercellular exchanges of nutrients, inorganic ions, signaling molecules. The importance of Cxs in hearing functions has been revealed by large amount of genetic linkage studies showing that mutations in Cx genes are associated with about half of patients with childhood nonsyndromic hearing losses. Mutations in Cx26 are responsible for most of the cases. However, mutations in a myelinating Cx (Cx32) have also been linked to Charcot-Marie-Tooth syndrome that includes hearing defects in many cases. Despite their importance in hearing, we know very little about molecular mechanisms that GJs play in the cochlea.

Kathleen T. Yee, PhD, Tufts University School of Medicine

The Role of Neuregulin1 Signaling in the Developing Cochlear Nucleus

The long-term objective of this study is to understand the genetics of cochlear nucleus neuronal differentiation and specification to examine how information-transmitting cells in the brain (neurons) obtain their identity and acquire specific characteristics that endow them to perform very specific functions.

DRF SECOND YEAR HEARING & BALANCE RESEARCH GRANT RECIPIENT
Funded July 1, 2006 through June 30, 2007

Micheal L. Dent, PhD, University at Buffalo, SUNY

Complex Sound Perception in Birds

This study examines the abilities of birds to hear complex sounds in natural listening environments before, during, and following acoustic trauma. Birds are an excellent model for studies on hearing loss because, like humans, they learn and modify their vocalizations throughout their lives, and because, unlike humans, they are able to regenerate auditory sensory hair cells. This allows for experiments not only on hearing loss, but also on how hearing recovery occurs after a trauma and on how birds perceive the world when hearing is restored.