The University of Miami Miller School of Medicine Center for Hereditary Deafness

Mission:

The goal of the Center for Hereditary Deafness is to promote and support basic and clinical research in genetic deafness and to translate these discoveries into clinical practice. The creation of a formal center will allow us to continue playing a leadership role in the arena of hereditary deafness and remain at the forefront of research and clinical care for this common sensory disorder. The Center will bring together several well-funded investigators (five NIH R01 grants with over 10 million dollars over the next five years) interested in basic and clinic aspects of genetic deafness. The Center will provide a multi-disciplinary platform through its research labs and special clinics while building on the existing strengths and interests of the faculty in the Departments of Human Genomics and Otolaryngology. Furthermore, the Center would provide more visibility for promotion, marketing, and philanthropy to which provide additional financial support for related clinical and academic programs.

Background:

Having secured over $10 million in grant funding over the next five years with five NIH R01 grants to conduct basic and translational research on hereditary deafness, the investigators propose to formally establish a Center for Hereditary Deafness. The Center builds upon the research acumen and clinical care of the programs in genetic hearing loss in the Departments of Otolaryngology and Human Genetics. Currently, UM has a highly interactive group of investigators who individually represent unique strengths in many areas of hereditary deafness ranging from basic sciences to patient care. The five R01 grants awarded speak to the reputation of our research and put UM’s otogenetics program at the top in the country in terms of NIH funding.

The great challenge for studies of human genetic deafness is not only to provide new scientific discoveries, but to develop applications of these discoveries for medical diagnosis and treatment in an ethical fashion. Given the success of gene mapping/identification in Mendelian forms of hearing loss, it is a natural progression to begin to investigate more complex forms of hearing loss. Such studies will affect a greater proportion of the population, as they include noise-induced and age-related hearing losses. While the genes identified for the Mendelian forms comprise an excellent starting set of candidate genes, it will require the investigation of large datasets combined with state-of-the-art statistical and laboratory methods to make substantial inroads into our understanding of these disease processes. In addition to our current strengths, a solid multi-institutional basic to clinical collaborative effort through a strong team of investigators with expertise in various aspects of genetic deafness will assure the success of our strategies.

What is learned from one aspect of a study clearly feeds into the other pieces of the group’s research results, making a whole center greater than the sum of the individual research programs. With growth and recruitment resulting from the success in NIH funding, this group of researchers will cover all aspects of hereditary hearing loss, from the clinical assessment, to initial gene identification and correlation of mutations with phenotype and risk, and then ultimately to understanding the biology behind the hearing loss. This will lead to better predictive models for risk, especially for complex forms, and ultimately to better treatment and/or prevention. The clinical component will take the information learned from the genotype/phenotype studies, the risk prediction models, and the functional studies and translate these results into clinical care.

The Department of Otolaryngology is one the busiest departments of its kind in the United States due, in part, to the Ear Institute and Otology program. The Department has been one of the nation’s leading hubs for the treatment of diseases of the ears, nose, throat and neck for over 45 years. Consistently ranked as a top specialty program by US. News & World Report, its national reputation continues to grow significantly.
**Programs and Services:**

Hearing loss is an economically and socially important cause of human morbidity. Genetic factors are one of the main etiologies underlying hearing loss. The Center for Hereditary Deafness would be uniquely positioned to improve patient care through the research programs and clinical services described below. The clinical component would be responsible for identifying/categorizing patients and for systematically collecting phenotypic data for use in phenotype/genotype studies. The gene mapping/identification would involve both genetic epidemiologists and molecular geneticists. They would work closely with the clinician on study design, as well as on developing phenotype/genotype correlations and developing models for predicting risk. The functional group will work with the gene mapping group to prioritize genes for evaluation in appropriate models. In turn, the functional group will provide feedback for likely candidate genes and mutations.

**Research Programs**

The Center will develop research programs that use state of art genomic and genetic techniques to identify the genes underlying Mendelian and complex forms of hereditary deafness, study their underlying functionality and phenotypic correlations as well as investigate the social and population genetic sequelae of hereditary deafness.

**Gene identification research led by Drs. Liu, Tekin, and Blanton:** During the past years, our Miami Otogenetic Program has made significant contributions to the identification of genes for hereditary hearing loss and has amassed an extensive and expanding collection of DNA samples and clinical data from the several unique population-based cohorts. We have been involved in mapping 10% of all known non-syndromic hearing loss loci and cloned 15% of all genes implicated in deafness, providing an extraordinary resource for the Center. We will use state-of-the art technologies – such as whole exome sequencing and exome chips with next generation sequencing - to identify the genes underlying Mendelian and complex forms of hereditary deafness.

**Gene functional research led by Drs. Liu and Lu:** With his new NIH R01 funding, Dr. Liu has recently established a new Gene Function Lab which would add a new dimension to the deafness research not found at most institutions. We are now able to conduct in vitro structural and functional studies of deafness genes using instrumentation such as the BioRad Helios GeneGun system. We also set up access to generate animal models of human deafness. A state-of-the art zebrafish facility located in the Department of Biology led by Dr. Lu is available for the assessment of auditory function of target human genes that are conserved in zebrafish. Dr. Lu has collaborated with Drs. Liu and Tekin on defining auditory function of the zebrafish models for new deafness genes identified in their labs.

**Translational Research led by Drs. Liu, Angeli, Tekin, and Blanton:** The Center will provide a unique platform for us to translate laboratory research into clinically deliverable genetic services including next generation sequencing (NGS) information. We have established guidelines for diagnosis and counseling of patients with genetic deafness at UM. The Center will create a novel Genomic Deafness Database (GDD) and Personalized Sequence Profile (PSP) for the clinical care of deaf patients where data is ranked based on clinical validity and utility. This is an innovative way to provide a unique opportunity to make genetic testing the most important diagnostic test after a history, physical examination and audiological assessment. The databases and DNA repository are a unique resource because of our diverse patient population, since little is known about the emergence of deafness in African Americans and recent immigrants from Latin America. With Hispanics as the fastest growing minority, this resource will be crucial for the study and treatment of deafness in this ethnic group. The Center will also search for clinically relevant genotype-phenotype correlations to better understand individual genetic variation in patients suffering from hearing loss and how the variation affects the reaction to specific treatments, such as defining the performance of cochlear implants (CI) as a function of genotype.
Clinical Services:

**Clinical diagnosis and management efforts - Hearing Loss Clinics:** We have extensive experience in diagnosis and management of individuals with hearing loss. Drs. Liu and Angeli have Hearing Loss Clinics weekly at the 5th floor of CRB to provide services to patients with genetic deafness. The Center also benefits from resources within the Department of Otolaryngology – with four physician neurotologists - and the University of Miami Ear Institute, which includes one of the largest academic audiology divisions in the country. The Ear Institute houses a unique cross disciplinary clinical and research facility involved in the diagnosis and management of hearing loss and related disorders. The available state-of-the-art equipment and processes allow for the characterization of hearing phenotypes, including human auditory measurements, surgical imaging, physiology, auditory processing, vestibular testing, and analysis of therapy outcomes. The sister divisions and personnel that group together for the management of patients with hearing disorders also include a) staff in the division of Audiology, The Hearing Aid Center, and the tinnitus Clinic; b) diagnostic services including vestibular and balance evaluations; c) the Cochlear and Auditory Implant centers and the Barton G Kids Hear Now Cochlear Implant Family Resource Center; d) surgeons skilled not only in surgery for hearing loss, but also in procedures for various diseases of the temporal bone and skull base.

**Molecular diagnosis and genetic counseling – Multi-Specialty Hereditary Deafness Clinics:** Drs. Tekin and Liu along with genetic counselors, audiologists, and nurse specialists have established the Hereditary Hearing Loss Clinic which is held on the first floor of the Mailman Center. The genetic counselor will provide information on the risks (e.g. may affect ability to obtain life insurance or have psychological effects), benefits (e.g. improved preventive care or clinical management), and limits (e.g. not all disease causing variants will be found).

**Organization Leadership**

The Center for Hereditary Deafness will be led by a Director who will report to the Dean of the Miller School and represent the Center in the Miller School and the University. He/she will articulate the Center vision and enhance the synergism and cross-fertilization of its programs by promoting common research, clinical collaborations, education, and community outreach activities. The Director will work to integrate the Center within the structure and mission of the Miller School and UHealth system by nurturing interactions among academic departments, Centers, and Institutes. There will be two Associate Directors who will report to the Director – one managing the Center’s research activities and the other focused on clinical services.

The proposed Director is Xue Zhong Liu, MD., Ph.D., FACS, Director of Research, Department of Otolaryngology, Associate Professor of Otolaryngology, Human Genetics, and Pediatrics. Dr. Liu is an American Board Certified Otolaryngologist and Fellow of the American College of Surgeons who has been fully trained in Human Genetics (Ph.D.) and Molecular Genetics (Postdoctoral training). He has had a career-long interest in genetic deafness and has directed the Laboratory of Molecular Genetics for Deafness since creating the lab in 2001. He and his collaborators established The Hereditary Hearing Loss Clinical Program. Dr. Liu published or co-authored more than 100 peer reviewed manuscripts in high impact journals – covering a wide range of topics in genetics, molecular biology, clinical diagnosis, and treatments in otolaryngology. His laboratories on hearing loss have received numerous grants from the National Institutes of Health over the past decade. The proposed Associated Director for research services is Dr. Mustafa Tekin, MD, an Associate Professor in the Dr. John T. Macdonald Foundation Department of Human Genetics (DHG), a member of the John P. Hussman Institute of Human Genomics and a Board Certified Clinical Geneticist. Dr. Tekin’s main research interest is in the identification of new genes for inherited deafness and he has extensive laboratory, clinical and genetic counseling experience with hearing loss. The proposed Associated Director for clinical services is Simon Angeli, M.D., a Professor of Clinical Otolaryngology, Co-Director of the University of Miami Ear Institute, and Director of the ACGME-accredited Neurotology Fellowship Program at UM. He is a board-certified otolaryngologist and board-certified neurotologist with more than 15 years of experience in the
diagnosis and treatment of hearing disorders. He has focused on translational research covering all aspects of diagnosis, treatments, outcome-studies, and genotype-phenotype correlations of hereditary hearing loss.
The Center will be organized as follows:

**Organizational Chart** (see below)

**Steering Committee:**
A Steering Committee will meet at least annually to advise the Director on the management, operations, and governance of the Center, including project prioritization and allocation of resources. The Committee will be chaired by the Center Director and will include the Associate Directors and University of Miami faculty who are demonstrated experts in hearing loss and genetics. The faculty members will be determined by a majority vote of the Committee and will serve for three-year terms, which will be renewable at the discretion of the Committee.

The Committee will reflect the interdisciplinary nature of the Center and include representatives with expertise in deafness and genetics, animal models, and genomics, the Chair of the Department of Otolaryngology, the Chair of Department of Human Genetics. The Committee may allow other members of the University community to attend the meetings.

**Professional Staff:**
The Center is staffed by clinical and research faculty (otolaryngologists, medical geneticists, population geneticist, biologists, and audiologists), research scientists/fellows, a genetic counselor, a registered nurse, and a secretary. The staff will emphasize a team approach, be it in the research, clinical, education, and/or community outreach activities of the Center.

**Membership:**
The Center openly seeks and supports research and activities related to its mission and does not have a formal membership policy. Per University of Miami policy, all faculty and physicians are required to have an appointment through a Miller School of Medicine Department. University faculty interested in affiliating with the Center can contact Dr. Liu.

**Space:**
No additional space is required for Center activities.

**Research Programs:** The Molecular Genetic laboratories of the Center are located at the 6th floor of the Mailman Center (Dr. Liu) and the 6th floor of the Hussman Institute of Human Genomics (Dr. Tekin); The Gene Function laboratories are located on the 3rd floor of the Rosenstiel Medical Sciences Building (Dr. Liu) with the University of Miami Ear Institute and at The Auditory Neurobiology Laboratory in the Department of Biology in Cox Science Building (Dr. Lu).
**Clinical Services:** The clinical services are housed on the fifth floor of the Clinical Research Building (Drs. Angeli and Liu) and the first floor of Mailman Center (Drs Tekin and Liu) on the Miller School campus. They include high-tech offices for diagnostic evaluations, genetic counseling, and treatment visits.

**Funding Resources and Budget Projections:**
The creation of the Center is not associated with any additional expenses for space, staff, or faculty - therefore the Center does not require any new dollars from the Miller School of Medicine or from other University sources. The Center will be funded through five NIH R01 grants ($12 million) for hereditary deafness. As the Center’s activities are an expansion of research programs and services currently provided, it is anticipated that the cost of Center operations will change in parallel with research funds and philanthropy.

Below are the projections for (1) sponsored activity: we are planning to submit a Core Facilities P30 or Clinical Center P50 proposals to the National Institute on Deafness and Other Communication Disorders (NIDCD) within three years; (2) philanthropy over the next five years.

**Current funding resources for genetic hearing loss research:**

**Identification of new deafness gene**
1. PI - Liu, NIH /NIDCD R01 DC05575 (since 2001), 3/1/12- 2/30/017. $ 584,596 / year “Molecular basis of non-syndromic hearing loss (NSHL)”.
3. PI - Tekin, CoIs - Liu, Blanton, and Lu NIH/NIDCD R01 10/01/12 – 09/31/17, $600.000/year “Genetic Studies of Inner Ear Anomalies”

**Gene function/therapeutic studies**
1. PI - Liu, NIH/NIDCD 1R01DC012546-01 (8/1/2012-7/30/2017), $325,120/year.“Molecular Genetics of autosomal dominant non-syndromic hearing loss”.

**Translational studies**
1. PI - Liu, CoIs -Tekin and Blanton, NIDCD/NIH R01 3/1/2013-2/28/2018 “Implementing genomic medicine in clinical care of deaf patients”. The grant is for NIDCD Translational PAR11-003. The grant will focus on implication of molecular advances in deafness patient care., $650,000/ cost per year,

**Grants in preparation**
1. PI - Liu, Cols -Blanton, and Angeli “Genetic studies of age-related hearing loss (presbycusis)”
2. PI - Lu, CoIs - Tekin and Lu”Zebrafish in human genetic deafness”
3. PI - Liu, CoI - Lu “Molecular mechanisms of PRPS1 deafness” The studies will dissect in vitro and in vivo pathophysiology of the PRPS1 related hearing impairment.