The MUSC Department of Otolaryngology–Head & Neck Surgery has a history of research excellence that spans more than two decades. The first R01 grant from the NIH was received by Jack Mills, Ph.D. in 1975. Under his leadership, the Auditory Neuroscience Laboratory developed a hearing research program consisting of a strong basic science core supplemented by ongoing translational research in human patients.

Auditory Neuroscience Laboratory

1975 • First R01 (PI, Jack Mills, PhD)

1981 • 3 RO1s, 1 NSF, 1 NIH Contract
Hearing and deafness funding

1987 • Program Project Grant in Age-Related

2002 • $2.2 million institution and NIH matching
grant for laboratory renovation and expansion

Present Investigators:

John H. Mills, Ph.D.           Ning-Ji He, Ph.D.
Judy R. Dubno, Ph.D.         Amy R. Horwitz, Ph.D.
Jayne B. Ahlstrom, M.S.    Fu-Shing Lee, Ph.D.
Mark A. Eckert, Ph.D.       Lois J. Matthews, M.S.
Kelly C. Harris, Ph.D.     Richard A. Schmiedt, Ph.D.

Extramural Funding

The Department’s research growth parallels our institution’s success in expanding basic and translational research. In the last 5 years, the Medical University of South Carolina has increased research funding almost 50% (9th fastest growth in NIH dollars among academic medical centers).

Balance characterizes the Department’s research activities – balance in the areas of investigation (auditory, cancer, swallowing, sinus/immunology); balance in the compliment of investigators (junior, senior, emeritus); and balance in the funding sources (NIDCD, NCI, VA, CDC, and various foundations, societies and industry/pharmaceutical companies). In addition to the Auditory Neuroscience Laboratory, there are robust research programs in Tumor Biology, Oral Cancer and Functional Outcomes, Rhinosinusitis and Allergy, Swallowing Physiology and Cochlear Implantation.

This edition of the Scope celebrates our faculty’s research success. Our mission of discovering new knowledge and translating it into novel strategies for disease prevention and improved health and quality of life is made possible by their work. This research environment also facilitates our mission of training the next generation of clinician–scientists.
Allergic fungal rhinosinusitis (AFRS) appears to be a unique subset of chronic rhinosinusitis (CRS) with nasal polyposis that has an increased incidence in the southeastern US. Our division has been active in studying both the clinical and immunologic characteristics of this disease.

**Clinical characteristics:** A retrospective review of 54 AFRS patients, 58 CRS patients with nasal polyps (CRSwNP) who did not meet classic AFRS diagnostic criteria, and 57 non-polyp CRS patients (CRSsNP) was performed. AFRS patients present at an earlier age (p < 0.001), are more commonly African-Americans (p < 0.001) and more often uninsured or have Medicaid (p < 0.001) than other CRS groups. AFRS patients resided in counties with higher percentages of residents below poverty level (p < 0.01), lower mean income (p < 0.05), and higher percentage of AA residents (p < 0.05) than CRSsNP. No significant differences were found between diagnostic groups for gender; physicians per 1,000 county residents, or geographic region of patient residence within the state of SC.1 AFRS patients are also more likely to present with bony erosion of the orbit or skull base when compared to other types of CRS;2 (figure) and within the AFRS group, bony erosion appears to be more common in males while race and socioeconomic factors do not appear to play a role.3 In patients with significant proptosis due to orbital erosion/expansion, comprehensive surgical and medical management has been shown to be adequate treatment and proptosis typically resolves within months without any significant diplopia.4

**Immunologic characteristics:** Our previous research into the pathophysiology of AFRS has demonstrated that systemic IgE to inhaled fungal antigens leads to a Th2 eosinophilic inflammatory response, in contrast to the mixed Th1/Th2 response with elevated innate mediators, such as surfactant proteins, seen in cystic fibrosis.5,6 Prior to this immune response, antigen must be taken up and processed in order to trigger subsequent innate and adaptive responses. Dendritic cells (DC) are potent antigen presenting cells, and their role in influencing the immune response in AFRS has not been described. We stained immunohistochemically for CD207, a marker of Langerhans cells, and CD208, a mature DC marker and found a greater subepithelial infiltrate of CD208 positive cells in AFRS (p<0.001).7 This study suggests that mature dendritic cells, which have already presented antigen and are located in the subepithelium, may play an active role in the pathogenesis of AFRS and polyp formation. Additionally, our group is in the process of examining the role of localized IgE in AFRS. We have found that AFRS polyps and turbinates have increased IgE compared to control sinus and turbinates tissue and that AFRS polyps have increased IgE compared to turbinates tissue in the same patient. This variability in localized IgE may contribute to anatomic differences in polyp formation within the sinonasal cavity despite and increased exposure to inhaled antigen at the inferior turbinate. Further work is being conducted to determine the exact site of this localized IgE expression and if it is specific for fungal antigen or a broader spectrum of antigens.

**Conclusion:** AFRS appears to be a subset of CRS with unique clinical and immunological characteristics. Further investigations are needed to determine if these characteristics impact clinical treatment and prognosis.

**REFERENCES**

The central focus of the Hearing Research Program is age-related hearing loss (presbycusis). The National Institutes of Health reports that 30% of Americans age 65-74 and 50% of those 75 and older have impaired hearing. Hearing loss is among the most common chronic conditions of aging, ranking first among males and fourth among females, after arthritis, cardiovascular disease, and cataracts (National Center for Health Statistics). In the next 30 years, the number of persons over age 65 will nearly double, substantially increasing the number of Americans with hearing loss. To meet these challenges, basic and clinical research focused on mechanisms of age-related hearing loss, new diagnostic procedures, improved options for treatment and rehabilitation, and methods to prevent or delay the onset of presbycusis, will be of great importance.

Our preliminary neuroimaging findings indicate that declining central nervous system function could contribute to the hearing problems of older adults, particularly in challenging listening conditions, and explain why some adults are unsatisfied with their hearing aids.

The deterioration of hearing that occurs with age can vary in severity from mild to severe. As shown in Figure 1, it begins with a loss of the ability to hear high-frequency sounds and progresses to mid-frequency sounds, which are critical for the understanding of speech. Indeed, the most common complaint associated with age-related hearing loss is not the inability to hear, but the inability to understand what is being said, especially in noisy environments. With increasing age, word recognition declines faster than expected based on declines in hearing, more so for females than males (Dubno et al., 2007b). Older persons also derive less benefit from binaural listening (Dubno et al., 2002, 2007a). Hearing aids should restore important speech information and improve speech understanding, but only a small fraction of older adults who could benefit from amplification are satisfied hearing-aid users. Our preliminary neuroimaging findings indicate that declining neural resources limit the ability of older adults to focus on speech, causing communication to be tiring and likely to fail in challenging listening conditions.

The most dominant pathology associated with “pure age-related hearing loss” is an age-related systematic degeneration of the lateral wall of the cochlea (“metabolic presbycusis”) including the capillary beds of the stria vascularis, which is responsible for generating electrochemical gradients and helping to regulate cochlear homeostasis. These changes in the stria vascularis and spiral ligament significantly alter the basic physiology of the cochlea, particularly potassium recycling and the production and maintenance of the endocochlear potential (EP), the 80-100 mV dc resting potential in scala media. A second source of pathology in the aging gerbil cochlea is primary degeneration of about 10-15% of the spiral ganglion neurons, which occurs in the presence of an intact population of inner hair cells (Mills et al., 2006). Among the most prominent changes in the physiological properties of the aging inner ear are increased thresholds of the compound action potential and dramatic decreases in the slope of the input-output function observed in the auditory brainstem response of aging humans (Mills et al., 2007). This is most likely indicative of poorly synchronized activity of the auditory nerve. The 80-100 mV EP declines with age, reducing gain of the cochlear amplifier in the cochlear apex by as much as 20 dB and in the base by as much as 60 dB (Schmiedt et al., 2002). These age-related declines can be temporarily reversed by current injections into scala media. Moreover, age-related declines in the EP can be reproduced in normal young animals by the chronic application of the loop diuretic, furosemide, which produces a systematic and reversible threshold shift that is correlated with the EP shift (Schmiedt et al., 2002).

The question of what constitutes the initial injury in age-related hearing loss remains unclear. The age-related loss in EP likely reflects the degeneration of marginal and/or intermediate cells. It is tempting to speculate that atrophy of these cells occurs secondarily to vascular insufficiency resulting from capillary necrosis; however, the reverse could also be true. Is neural degeneration primary or secondary to a chronically-reduced EP? The EP is basic to cochlear homeostasis but does it also have a trophic influence on spiral ganglion cells? These and other questions will need to be addressed in future studies using animal models and validated in studies of older humans. Strikingly absent in gerbil data and some human data are age-related losses of outer and inner hair cells, except in the most basal and apical regions of the cochlea. Thus, in the absence of confounding factors such as noise and drug exposures, aging effects in the ear are largely the result of the deterioration of the cochlear battery, not necessarily the loss of hair cells. These results and others suggest that age-related hearing loss should be viewed as a vascular, metabolic, neural hearing loss rather than a sensory hearing loss.

REFERENCES
Achieving Better Outcomes Faster with Rapid Prototyping

Betsy K. Davis, D.M.D., M.S.

In 2003 Clemson University (CU) and the Medical University of South Carolina (MUSC) began a joint bioengineering program that pooled resources, knowledge and talents of both institutions to better serve the citizens of South Carolina. The Center for Functional Outcomes and Reconstructive Biotechnology was among the first MUSC clinics to engage Clemson University bioengineers in a project to use advanced medical imaging for rapid prototyping in the fabrication of extra-oral prostheses. As a result of this collaboration, all extra-oral prostheses (e.g. nasal, auricular, orbital, and facial) are made with this technology. A patient’s CT scan is sent to Clemson University where the Mimics imaging program is used to design the prostheses followed by the creation of a wax pattern by rapid prototyping. The primary advantage of this technique is that it saves both the patient and the clinician time in waxing the prosthesis. For example, the average time spent in waxing an auricular prosthesis was 20 hours per wax pattern using the conventional method. In contrast, the average time spent with the medical imaging and rapid prototyping technique was nine hours. Furthermore, the morphology of the wax pattern with this technique is excellent (Figure). This effort is supported by NIH grant# P20RR16461, and South Carolina INBRE Program.

Dr. Davis and colleagues have also joined forces with Drs. Bonnie Martin-Harris and Martin Brodsky from the MUSC Evelyn Trammell Voice and Swallowing Institute to perform a pilot study comparing the functional outcomes of patients whose palate defects are reconstructed with palatal prostheses compared to surgical flaps. Functional outcomes being measured include masticatory efficiency, facial appearance, swallowing-related quality of life, overall quality of life, and speech intelligibility. This important work will provide patients with information about the functional trade-offs of choosing one reconstructive technique over another. This research is funded by the NIH T32 Grant, NIH/NCRR Project # P20RR17699, U24 Grant, and MUSC College of Graduate Studies and Dental Medicine.

MUSC Evelyn Trammell Institute for Voice and Swallowing

Experts Collaborate on a Respiratory-Swallowing Measurement Model

Bonnie Martin-Harris, Ph.D.

Drs. Martin-Harris and Sapienza conferred with 24 leading researchers and clinicians from around the United States and Canada at the Medical University of South Carolina in the areas of voice, respiration, swallowing, speech science, otolaryngology, pulmonology, gastroenterology, engineering, physiology, and statistics for a 2-day, closed meeting held in mid-July (Figure). Experts from these areas have long recognized the potential contribution of swallowing problems and aspiration to poor pulmonary and nutritional outcomes in patients with upper and lower airway disorders. Aspiration related to swallowing disorders often leads to pulmonary contamination, infection, and death. Unfortunately, there has been no controlled study that has either defined the nature of the respiratory-swallowing impairment in these patients or the relationship of the impairment(s) to patient outcome. Clinical evidence suggests that coordination difficulties between breathing and swallowing may worsen these serious pulmonary conditions. Despite the clinical awareness of the presence of swallowing problems in these patients, clinicians have differed in their overall therapeutic approaches to treatment.

During this interdisciplinary meeting, each expert presented a 30-minute review of the literature surrounding the coordination of respiration and breathing. Topics ranged from infants through adults and upper and lower obstructive airway disorders. Areas of interest for study at the conclusion of the meeting were disturbances in oropharyngeal swallowing physiology, respiratory phase-swallow coupling, protective reflexes, and esophageal function. An expert facilitator led the group to formulation of a set of research hypotheses and specific aims.

Following the R24 meeting, Drs. Martin-Harris and Sapienza will be developing a multi-site, clinical grant application using the information gathered from this collaborative team that will study respiratory, swallowing, and respiratory-swallowing function in the patient subgroups identified, and determine the capability of obtaining meaningful clinical information using a multi-metric, respiratory-swallowing evaluation protocol in patients with obstructive airway disorders. Finally, the group will set out to determine the influence of these measures on the overall health outcome of the patients. Dr. Martin-Harris will also host another large research collaborative initiative in her role as President of the Dysphagia Research Society at its March 2008 meeting at the Wild Dunes Resort on the Isle of Palms, SC.

Co-principal investigators, Bonnie Martin-Harris, Ph.D. (Medical University of South Carolina) and Christine Sapienza, Ph.D. (University of Florida) were awarded $72,959 for a developmental grant titled Measurement model for respiratory-swallowing impairment in obstructive airway disorders. Receipt of the award also resulted in an additional gift of $120,000 by the Mark and Evelyn Trammell Trust to supplement the needs required to accomplish the goals of the project.
MUSC Head and Neck Tumor Program:
Understanding Immune Response in Head and Neck Cancer

M. Rita I. Young, Ph.D.

The MUSC Head and Neck Tumor Program immunology research focuses on improving head and neck cancer patients’ anti-tumor immune responses. One area focuses on means to overcome tumor-induced suppressor cell activity in head and neck cancers. A second area is studying whether immunization with premalignant lesions in a dendritic cell vaccine will stimulate immunity against premalignant lesions as well as oral squamous cell carcinoma.

Tumor-induced immune suppression in head and neck cancer patients significantly impedes their anti-tumor immunity. Head and neck squamous cell carcinoma (HNSCC) patients are known to have a population of tumor-mobilized suppressor cells, called CD34+ cells. These cells are mobilized into the periphery from the bone marrow in about two-thirds of HNSCC patients by a tumor-produced growth factor, granulocyte-macrophage colony-stimulating factor. Several studies have demonstrated that the CD34+ suppressor cells accumulate within tumors of the HNSCC patients and reduce lymphocyte activities. Several basic science research studies demonstrated that these cells are progenitor cells and have the capacity to differentiate into several types of cells, including dendritic cells, monocytes, endothelial cells, and lymphocytes. The laboratory group led by M. Rita Young, Ph.D. determined that Vitamin D3 and its analogues push the progenitor cells to differentiate into dendritic cells. Dendritic cells are the most potent antigen-presenting cells known and are a key component in many anti-tumor cellular vaccines. A Phase I clinical trial treating HNSCC patients with escalating doses of 25-hydroxyvitamin D3 demonstrated a reduction in the suppressive immune cells accompanied by an increase in several other immune indicators. Dr. Young has now initiated a Phase II clinical trial aimed at analyzing intratumoral responses during a 3 week treatment regimen with 1α,25-dihydroxyvitamin D3 (Calcitriol). Patients are randomized to one of 2 arms, treatment with 1α,25-dihydroxyvitamin D3 or no treatment. Dr. Young hypothesizes that the treatment will reduce the intratumoral suppressor cell levels and increase intratumoral immune activity, leading to reduced HNSCC recurrence and metastasis. Almost 20 patients have been enrolled in this study to date. The Phase II study at both MUSC and the Ralph H. Johnson VAMC hopes to enroll 100 patients over the next several years.

A second highlighted area of study introduces a novel twist to the concept of using dendritic cell-based vaccines against HNSCC. The study will investigate whether premalignant lesions in a dendritic cell-based vaccine will stimulate immunity against not only premalignant lesions but also oral squamous cell carcinoma. This concept is based on the observation that patients with select types of premalignant lesions have a high rate of lesion recurrence and progression of their lesions to oral squamous cell carcinoma (OSCC). In addition, in vitro analyses of lesions in a mouse model demonstrated that the lesions express tumor antigen (Figure). The study will use lesion tissue and peripheral blood from patients undergoing excision of their premalignant lesions to demonstrate that immune reactivity against both premalignant lesions and OSCC is generated. To study more mechanistic questions, Dr. Young’s group is using a mouse carcinogenesis model where 4-NQO is placed in the drinking water of mice to induce lesion formation. 4-NQO has previously been shown by other research groups to cause DNA abducts similar to tobacco. Thus far, the studies have not only demonstrated the development of premalignant lesions that progress into OSCC in the mice but have also shown promise in stimulating immunity when the mice are vaccinated with dendritic cells pulsed with premalignant lesions. The immunology group will be continuing these and other studies in hopes of improving anti-tumor immunity in the head and neck cancer patients as well as the patients with recurring oral lesions.

Dr. Young hypothesizes that the treatment will reduce the intratumoral suppressor cell levels and increase intratumoral immune activity, leading to reduced HNSCC recurrence and metastasis.
Meet the Residents

Three PGY2 residents join the Department following an internship in general surgery at MUSC.

Geoffrey Pitzer, M.D., grew up in Springfield, Virginia, a suburb of Washington, DC. He attended the University of Virginia for both his undergraduate and medical education. At UVA, Geoff earned a BA in biology with distinction and was an AOA medical honor society member and recipient of the Merck Manual, James R. Cash, and McGraw-Hill Lange academic awards. Geoff enjoys playing and writing music, and surfing.

Jake Smith, M.D., was born and raised in Arkansas, the son of a truck driver and a teacher. He attended the University of Arkansas where he received a B.S. in biology, followed by medical school at the University of Arkansas. He was honored for professionalism and leadership by his classmates. He was elected to AOA and spent 2 weeks doing surgical mission work in China repairing cleft lips and palates. He is a grateful husband to Melissa and father to Corban (3), Finley (2), and his baby girl Piper (2 months). Hobbies used to be golfing and guitar but have since changed to reading, spending time with family, and more reading.

Natalka Stachiw, M.D., grew up in Greenville, SC, before attending Presbyterian College where she graduated magna cum laude and received a B.A. in music. She enjoyed her time balancing her burgeoning career with organic chemistry research and piano performances, especially accompanying vocalists and instrumentalists. Prior to medical school at MUSC, she was an environmental scientist with Georgia Power Company working to clean-up polychlorinated biphenyls. In her spare time, Natalka enjoys playing piano, soccer, running, and gardening.

Magnolia Conference ~ 2007

The 2007 Magnolia Conference was held May 31 – June 2, 2007. Attendees from 17 states enjoyed a superb educational event. Highlights included ethics and facial plastic presentations by G. Richard Holt, M.D.; a cochlear implant update by Richard T. Miyamoto, M.D.; a discussion of American Board of Otolaryngology activities, including Maintenance of Certification by Robert H. Miller, M.D.; and a review of transoral laser microsurgery for upper aerodigestive tract cancer by Wolfgang Steiner, M.D. The MUSC faculty presented clinical updates and participated in various panel discussions with electronic audience participation (figure).

This time of year Charleston is at its best – beautiful weather for golf and the beach, and a myriad of cultural activities associated with Spoleto Festival USA. I hope you can join us May 29–31, 2008 for another few days of outstanding education and recreation.
MUSC Department of Otolaryngology—Head and Neck Surgery

Faculty

Beverly Attaway, D.M.D., M.S.
Instructor
D.M.D. • University of Alabama, Birmingham
M.S. • University of Texas, San Antonio Fellowship • M.D. Anderson
Head and neck prosthetics, sleep and snoring appliances

Bonnie Martin-Harris, Ph.D., CCC-SLP, BRS-S
Associate Professor
Ph.D. • Northwestern University
Special Interests • Evaluation and treatment of voice and swallowing disorders

K. Gien Hoang, Ph.D., M.D.
Associate Professor
Ph.D. • University of Louisville
M.D. • University of Louisville Residency • University of Maryland and Brooke Army Medical Center Fellowship • Medical University of South Carolina
Special Interests • Endoscopic thyroid and parathyroid surgery, facial plastic surgery, microvascular reconstruction, head and neck tumors

M. Boyd Gillespie, M.D., M.S.
Associate Professor
M.D. • University of Louisville
Residency • University of North Carolina, Chapel Hill Fellowship • M.D. Anderson
Special Interests • Pediatric, airway disorders, laryngology, medical and surgical voice care

Judy Dubno, Ph.D.
Professor
Ph.D. • City University of New York
Special Interests • Age-related hearing loss

Jack King, Ph.D., CCC-A
Assistant Professor
M.Ed. • Temple University
Ph.D. • University of Miami Ear Institute
Special Interests • Cochlear implants, vestibular and balance assessment

Paul R. Lambert, M.D.
Professor and Chairman
M.D. • Duke University
Residency • UCLA Medical Center Fellowship • House Ear Institute, Los Angeles
Special Interests • Adult and pediatric hearing loss, dizziness and vestibular disorders, middle ear infections and cholesteatoma, acoustic tumors, cochlear implants, facial paralysis, congenital ear malformations

Lucinda A. Halstead, M.D.
Associate Professor
Ph.D. • George Washington University
Residency • New England Medical Center, Boston
Special Interests • Pediatric, airway disorders, laryngology, medical and surgical voice care

Eric Lentsch, M.D.
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M.D. • University of Louisville Residency • University of Louisville Fellowship • M.D. Anderson
Special Interests • Head and neck tumors, endoscopic thyroid and parathyroid surgery, melanoma and advance skin cancers, general otolaryngology

M. Rita I. Young, Ph.D.
Professor
Ph.D. • University of Pennsylvania
M.D. • University of Pennsylvania Fellowship • University of Pittsburgh
Special Interests • Tumor immunology, vasculogenesis, tumor vaccines.
Charleston Magnolia Conference

8TH ANNUAL ~ MAY 29-31, 2008

GUEST SPEAKERS

Clough Shelton, M.D., FACS
Professor and Chief
C. Charles Hetzel, Jr., M.D. & Alice Barker Hetzel
Chair in Otolaryngology
Department of Otolaryngology–Head & Neck Surgery
University of Utah School of Medicine

Ramon M. Esclamado, M.D.
Richard H. Chaney, Sr. Professor and Chief
Division of Otolaryngology–Head & Neck Surgery
Duke University Medical Center

Peter H. Hwang, M.D.
Associate Professor
Director, Stanford Sinus Center
Department of Otolaryngology–Head & Neck Surgery
Stanford University School of Medicine

TOPICS

Endoscopic Sinus Surgery
Chronic Otitis Media
Cholesteatoma
Pediatric Airway Disease
Endocrine Surgery
Sleep Apnea

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