Advances in medicine seem to have a more punctuated history than slow evolution. They can be driven by the occasional individual genius, serendipitous discoveries (i.e., penicillin), technological breakthroughs (i.e., gene sequencing), or basic science discoveries with more immediate translational impact. In the recent history of otology, the introduction of the operating microscope and the development of the cochlear implant are examples of technological innovations that suddenly propelled the specialty in new directions.

Minimally invasive surgery and robotic surgery promise similar advances in our field. Certainly, they have proven their merit and have significantly altered many of the surgical paradigms in other disciplines, such as general and urologic surgery.

At MUSC, we have increasingly used minimally invasive endoscopic endocrine, salivary gland, and skull base surgery during the last five years. Approximately 50% of our thyroid procedures are now done endoscopically by Drs. Eric Lentsch and Joshua Hornig, using the video-assisted technique as popularized by Paolo Miccoli. Our experiences parallel that from other centers, namely ease of performance, safety, decreased post-operative pain, and improved cosmesis. More recently, Drs. Terry Day and Joshua Hornig of our Head and Neck Division have been treating selected thyroid and parathyroid tumors with the DaVinci system. The high definition, magnified 3D visualization and precision movements afforded by this system will certainly impact our discipline over the next 5-10 years.

We were one of the first centers in the US to offer minimally invasive endoscopic surgery for patients with obstructive salivary gland disease, and Dr. Boyd Gillespie is currently performing over 50 cases per year. Karl Storz has designated MUSC as the “U.S. Reference Center for Sialendoscopy.” A similar number of endoscopic skull base approaches are...
Nationally, he was very active in the American Academy of Otolaryngology – Head and Neck Surgery. He served on the Board of Directors, as the Coordinator for Education, and as the Chair of multiple committees. He was also active in the American Academy of Otolaryngic Allergy, serving on its Executive Committee for many years and then leading the group as its President. He was a Senior Examiner for the American Board of Otolaryngology, Chair of the Board of Governors and President of the South Carolina Society of Otolaryngology – Head and Neck Surgery. Several years ago, Dr. Osguthorpe conceived and brought to fruition the highly popular Academic Bowl for residents at the annual Academy Meeting.

Institutionally, Dr. Osguthorpe served on the Admissions Committee for the Medical School, the Faculty Senate, and most recently as Operating Room Surgical Director. It was in this latter role that Dr. Osguthorpe may have had his most significant impact on MUSC. He was instrumental in codifying standards of practice for surgeons, nurses, administrators and other OR staff; he developed metrics of efficiency based on national data; and he insisted on accountability and transparency. Simply stated, his 5-years of leadership in this role were transformative for operating room function.

Although Dr. Osguthorpe, or Dr. “O” as he is known to his colleagues and residents, has retired from fulltime practice, he will have a part time position in the VA hospital, interacting with residents in the clinic and OR. We are all pleased that the wisdom, skills, and leadership he has provided over the years will still be available. He, in turn, is pleased that this part time position will allow him more time to don his real working clothes and mount his tractor to redistribute earth, trees, shrubs, and other inanimate objects around his waterfront property just north of Charleston. With this transition, we wish Dave and Nancy many fulfilling and happy years.

Paul R. Lambert, M.D.
Professor and Chair, Otolaryngology Head & Neck Surgery

Robotic and Minimally Invasive Surgery, continued from page 1

performed for sinus tumors, meningiomas, encephaloceles, etc. by our Minimally Invasive Skull Base Surgical Team directed by Dr. Rod Schlosser.

We are pleased to be at the forefront of these technological innovations and to participate in the education of physicians about them. Please visit our web site muscENT.org to learn about our CME courses.

Paul R. Lambert, M.D.
Professor and Chair,
Otolaryngology Head & Neck Surgery
The Carolinas Pediatric Airway Course
October 15 - 16, 2009
This two-day course co-hosted by the University of North Carolina focused on endoscopic and open airway surgical techniques. Directors: David R. White, MD & Carlton J. Zdanski, MD, Surgical Director, North Carolina Children’s Airway Center

Temporal Bone Dissection Course
Intensive two-day otology courses for the practicing otolaryngologists in our state-of-the-art temporal bone lab focused on procedures for chronic ear disease. Course Director: Ted A. Meyer, MD, PhD.
Fall - November 6 - 7, 2009
Guest Lecturer: Anil K. Lalwani, MD
Mendik Foundation Professor of Otolaryngology
New York University Langone Medical Center

Spring - May 14 - 15, 2010
Guest Lecturer C. Gary Jackson, M.D.
Professor, Division of Otology-Neurotology

24th Annual Putney Lectureship & 2nd Annual Salivary Gland Endoscopy & Ultrasonography Course
November 13 - 14, 2009
This course provided a thorough and insightful review of the current management of salivary cancer, introduced techniques of salivary ultrasound and endoscopy in the management of obstructive salivary diseases, and included a hands-on salivary ultrasound and endoscopy lab. Course Director: M.Boyd Gillespie, MD
Guest Lecturers: David W. Eisele, MD, Professor & Chair, UCSF Department of Otolaryngology - Head and Neck Surgery; Johannes Zenk, MD and Michael Koch, MD of the University of Erlangen, Germany

Pediatric Audiology Conference
March 12, 2010
This one-day course focused on diagnostic, rehabilitative and educational considerations for managing children with hearing loss. Directors: Meredith Edgerton, AuD & Andrea Hannan Dawkes, AuD
Guest Lecturers: Angela LaRosa, MD, MUSC Genetics and Developmental Pediatrics; Lisa Borden, MEd, SCSDB Hearing Outreach Program

Emerging Controversies in the Management of Thyroid & Parathyroid Disease
April 23 - 24, 2010
This course provided two half days of lectures and hands on demonstrations, focusing on emerging technologies and treatments for thyroid and parathyroid disease. Course Directors: Joshua D. Hornig, MD, FRCSC
Jyotika Fernandes, MD
Guest Speaker: Ralph Tufano, MD, FACS
Associate Professor, Director
Johns Hopkins School of Medicine
Facial nerve dysfunction is a frequent clinical presentation that challenges many specialties, and carries with it both diagnostic and treatment dilemmas. Patients suffering from facial paresis or paralysis often experience multiple functional, aesthetic and psychosocial consequences. Etiology and course of progression typically guide the management of these devastating effects.

Identifying the unique timeline, etiology and associated prognosis of facial nerve dysfunction is imperative in determining appropriate treatment. Etiologies are vast and may include neoplasm, infection and trauma, as well as autoimmune, congenital and neuromuscular disorders. Unfortunately, however, the patient presenting with facial paresis or paralysis is sometimes merely given the default label of “Bell’s palsy” without investigation, potentially resulting in suboptimal outcomes. Thus, pivotal in the management of facial nerve disorders is the early identification of underlying etiology, along with analysis of nerve function and facial musculature. Multidisciplinary expertise from specialists in Head & Neck Cancer, Neurotology/Skull Base Surgery, Neurosurgery, Neuroradiology, Ophthalmology, Neurophysiologic Analysis, Genetics, Physiotherapy and Facial Plastic & Reconstructive Surgery, including Microvascular Surgery allow a comprehensive evaluation of the patient.

Patients with facial paralysis may suffer an array of adverse manifestations including lagophthalmos, ectropion, corneal exposure, nasal valve collapse, oral incompetence, articulation difficulties and significant psychological effects of the disfigurement. Accordingly, surgical interventions are focused on each of the unique zones of the face and their corresponding goals: forehead and brow symmetry; eyelid closure; nasal valve competence; smile symmetry; and oral commissure competence. Goals for facial rehabilitation include a ‘normal’ appearance at rest, symmetry with movement and restoration of muscle control. However, ideal rehabilitation of the paralyzed face remains a significant challenge for the reconstructive surgeon. This is, in part, due to the great variability within the disorder itself, and the fact that no single procedure completely restores normal facial function. Thus, guided by etiology, degree and duration of dysfunction, as well as individualized patient factors, the MUSC Department of Otolaryngology Facial Plastic & Reconstructive Surgery Division offers the full spectrum of surgical procedures to manage facial paralysis, and continues to strive towards improved reanimation outcomes.

Procedures to address facial rehabilitation are typically categorized as dynamic or static, and each conveys unique benefits and limitations. Static interventions include facial slings, upper eyelid weights, medial and/or lateral canthoplasty, upper blepharoplasty, browlifting, asymmetric rhytidectomy, functional rhinoplasty for nasal valve reconstruction and assorted other soft tissue procedures aimed at refining facial symmetry, but without imparting inherent motion. In contrast, dynamic interventions impart some means of movement, and include primary neurorrhaphy, interpositional nerve grafts, crossover techniques, muscle transposition techniques and neurotized microvascular free flaps. We offer all of these procedures at the Medical University of South Carolina.
Muscle transposition techniques historically have had significant drawbacks, however, recent modifications of the temporalis tendon transfer described by Drs. Byrne and Boahene et al, at Johns Hopkins University, offer great promise for a less invasive and safer approach for dynamic reanimation of the paralyzed face. This innovative technique transfers the insertion attachments of the temporalis tendon from the mandible condyle to the oral commissure via an intraoral or nasolabial incision. Employing activity-based therapy both before and after this surgery, the patient is ‘retrained’ to smile using a teeth-clenching motion that subsequently generates an upward movement of the lateral lip on the affected side. Facial Plastic & Reconstructive Surgeons, Drs. Krishna Patel and Judith Skoner are now performing this latest advance in facial rehabilitation at the MUSC Facial Nerve Center.

For questions or referrals, please contact:

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Research Realm

A Novel Mechanism-Based Therapy Targeting mTOR for Head and Neck Cancer

Terry A. Day, MD, J. Silvio Gutkind, PhD, M. Boyd Gillespie, MD, Keisuke Shirai, MD

Head and neck squamous cell carcinomas (HNSCC) represent 6% of all cancers diagnosed each year in the United States, affecting approximately 43,000 new patients and resulting in approximately 12,000 deaths. In spite of recent advances in surgical procedures and other treatment modalities, the 5-year survival rate for HNSCC patients, approximately 50%, has improved only marginally in the past three decades. As in other cancers, specific molecular targets have been identified in certain subpopulations of patients who may be susceptible to emerging targeted therapies such as cetuximab.

Although stage 1 or 2 cancers may be effectively treated with surgery or radiation therapy, combination therapy

Figure 1. The K-ras and p53 two-hit oral carcinogenesis model is dependent on mTOR.

A, left, representative papillomas developed by K14-CreERTam/LSL-K-rasG12D/+ mice treated with rapamycin or vehicle for 3 consecutive days. The H&E histologic sections depict the typical features of the papillomas. Note the elevated level of pS6 in these tumors treated with vehicle in contrast with the remarkable reduction on rapamycin treatment. Original magnification, 5. Right, Western blot analysis of pS6 in tumors treated with rapamycin. pS6 levels were examined in total cell lysates from papillomas developed in K14-CreERTam/LSL-K-rasG12D/+ mice treated with rapamycin or vehicle during 3 d. The high pS6 levels in control K14-CreERTam/LSL-K-rasG12D/+ mice are in contrast with the absence of pS6 in tumors treated with rapamycin. Tubulin was used as loading control.

B, representative examples of K14-CreERTam/LSL-K-rasG12D/+ mice treated with rapamycin or vehicle as indicated. Left, papilloma development in a control mouse at the indicated age; right, K14-CreERTam/LSL-K-rasG12D/+ animal treated with rapamycin did not develop papillomas at the same age. Kaplan-Meier survival curve of the indicated mice lines treated or not with rapamycin. No animal death was observed in any of the control animals treated with rapamycin or vehicle. The treatment of K14-CreERTam/LSL-K-rasG12D/+ mice with rapamycin prevented the development of oral papillomas and increased their life span when compared with vehicle control (P < 0.0001). Arrowhead, tamoxifen treatment. Horizontal arrow, beginning of the rapamycin or vehicle treatment that was started 1 wk after tamoxifen induction.

C, left, representative tongues of K14-CreERTam/LSL-K-rasG12D/+ p53flx/flx mice treated with rapamycin or vehicle. Left, a tongue carcinoma (arrow) in a mouse of the control group at 60 d of age; right, K14-CreERTam/LSL-K-rasG12D/+ p53flx/flx animals treated with rapamycin did not develop tongue carcinomas at the same age. Right, Kaplan-Meier survival curve of the indicated mice lines treated or not with rapamycin. Rapamycin treatment of K14-CreERTam/LSL-K-rasG12D/+ p53flx/flx mice prevented the development of tongue carcinomas and increased their life span (P < 0.005). Arrowhead and horizontal arrow treatments. (Gutkind et al., 2009)

with surgery and radiation or chemotherapy with radiation is now the standard of care for the management of many patients with late-stage disease. Neoadjuvant chemotherapy for the treatment of HNSCC patients is regaining support, particularly the combination of cisplatin and 5-fluorouracil or combinations which include the FDA approved, Taxotere™. Although these drugs all have high rates of initial response, toxicity remains a concern. However, randomized trials have failed to demonstrate a significant impact on overall survival.

Pre-clinical studies by several investigators including Dr. Silvio Gutkind, Chief of Oral and Pharyngeal Cancer Branch of the National Institute of Dental and Craniofacial Research indicate that rapamycin analogs have anti-tumor activity in HNSCC, providing a rationale for pilot investigation of rapamycin as a neo-adjuvant treatment with surgery. Early clinical work by Dr. Cherie-Ann Nathan at LSU Medical Center in Shreveport also support this hypothesis. At MUSC, Drs. Terry Day, Keisuke Shirai, M. Boyd Gillespie, and Hollings Cancer Center staff are collaborating with Dr. Gutkind on managing HNSCC by targeting mTOR with rapamycin in stage 3 and 4 oral and pharyngeal cancers (Figure 1).

mTOR is a novel therapeutic target in HNSCC. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription (Figure 2). mTOR functions by integrating the input from upstream pathways, including insulin, growth factors (such as IGF-1 and IGF-2), and mitogens. The mTOR pathway is dysregulated in human diseases, especially certain cancers. Rapamycin (Sirolimus, Rapamune®), is a macrocyclic lactone originally isolated from Streptomyces hygroscopicus that has been approved by FDA in 1999 for the prophylaxis of organ rejection in renal transplant patients, which has also displayed antitumoral effects in a variety of pre-clinical cancer models. One of its analogs, CCI-779 (temserolimus), has been recently approved by the FDA for the treatment of advanced renal carcinoma. Rapamycin can inhibit mTOR by associating with its intracellular receptor FKBP12. The FKBP12-rapamycin complex binds directly to the FKBP12-Rapamycin Binding (FRB) domain of mTOR.

Recent studies showed that rapamycin administered orally once a day in cancer patients is well tolerated, and can lead to a persistent blockade of mTOR in tumoral tissues with limited toxicity. Toxicities described in cancer patients are similar to those previously reported in transplant patients who are treated with daily dosing of up to 5 mg, including reversible mucositis, asthenia (weakness and fatigue) and thrombocytopenia, with no grade 4 or 5 documented. Thus, given the extensive clinical experience with rapamycin, its oral administration, known pharmacodynamic and recent clinical studies showing its effectiveness in blocking mTOR function in tumor tissues, we selected rapamycin to explore the biochemical and biological activity of inhibiting mTOR in HNSCC.

This study is designed to assess the contribution of the mTOR pathway to the growth and survival of HNSCC cancer cells, and thus the potential clinical benefit of inhibiting mTOR HNSCC patients. It will also provide novel information regarding the nature of the mTOR regulated signaling networks in HNSCC tissues, and whether the direct inhibition of mTOR or combined inhibition of EGFR, PI3K and mTOR may represent a future therapeutic strategy for HNSCC.

The study is expected to be open to accrual within the next several months providing an opportunity for patients with Stage 3 and 4 head and neck cancers to enroll in this clinical trial and undergo treatment with rapamycin prior to surgery.

**ELIGIBILITY:**
- Males and females age 18 years and older
- Previously untreated HNSSC of the oral cavity or oropharynx
- Clinical stage III or IVA disease without distant metastasis
- Definitive therapy to include surgical resection for curative purposes
- Life expectancy greater than six months
PUBLICATIONS


Harvey RJ, Sheahan PO, **Schlosser RJ**. Trans-septal approach for extended endoscopic resections of the maxilla and infra-temporal fossa. Am J Rhinol Allergy 2009;23:426-32.


Faculty

Otolaryngology - Head & Neck Surgery

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www.muscENT.org 11
The MUSC Department of Otolaryngology-Head and Neck Surgery takes great pride in the accomplishments of our former residents. Recently, we had the opportunity to catch up with Dr. Bradford A. Woodworth. After finishing his otolaryngology residency at MUSC in 2006, Dr. Woodworth completed an 18-month research and clinical fellowship in rhinology and sinus surgery under the direction of Dr. David W. Eisele at the University of Pennsylvania. For the past 2 years, Dr. Woodworth has served as assistant professor of otolaryngology-head and neck surgery at the University of Alabama-Birmingham where he is the James Johnston Hicks Endowed Chair of Otolaryngology and associate scientist in the Gregory Fleming James Cystic Fibrosis Research Center. Dr. Woodworth currently devotes 3 days a week to his research lab with the remaining 2 days for clinical activity and surgery. His research focuses on the impact of sinonasal disorders on respiratory epithelial cell ion transport and mucociliary clearance. His clinical interests include advanced sinus surgery for refractory inflammatory sinus disease, and endoscopic transnasal surgery for benign and malignant skull base tumors. He was recently awarded the American Rhinological Society new investigator grant, received a $325,000 grant from the Flight Attendant Medical Research Institute, and will be submitting his first NIH RO1 this spring. Dr. Woodworth credits his early success to the strong foundation that he received at MUSC. He especially thanks Dr. Rodney Schlosser for serving as an inspiring clinical and academic mentor. Dr. Woodworth is now a mentor as well. His resident Dr. Frank Virgin won the first place resident research award from the Triological Southern Section for work completed under Dr. Woodworth’s guidance. Dr. Woodworth currently resides in Birmingham with his wife Leslie and three sons.

2009 Putney Lectureship and 2nd Annual Charleston Salivary Course

The 24th Annual F. Johnson Putney Lecture was held November 13-14th, 2009 at MUSC. The lecture is named in honor of the late Dr. F. Johnson Putney, a national leader in head and neck surgery, who brought his busy head and neck cancer practice from Philadelphia to MUSC in the late 1960’s. The seminar, which was attended by clinicians from 11 states and Canada, focused on salivary gland diseases. The Putney lecturer, Dr. David W. Eisele, Professor and Chair of the UCSF Department of Otolaryngology-Head and Neck Surgery, presented a thorough and insightful review of the current management of salivary cancer. Drs. Johannes Zenk and Michael Koch of the University of Erlangen, Germany, and course director M. Boyd Gillespie, M.D., introduced participants to techniques of salivary ultrasound and endoscopy in the management of obstructive salivary diseases. In addition to the lectures, guests enjoyed a hands-on salivary ultrasound and endoscopy lab followed by a reception at the acclaimed restaurant 82 Queen in the Charleston historic district. We invite you to join us for the 25th F. Johnson Putney Lecture and 3rd Annual Charleston Salivary Ultrasound and Endoscopy Course in Charleston in the Fall of 2010.

Fall 2011 Temporal Bone Dissection Course

OCTOBER 15 - 16, 2010

– Guest Lecturer –
LARRY R. LUSTIG, M.D.
Director of Cochlear Implant Center
University of California, San Francisco

An intensive two-day otology course for practicing otolaryngologists in our state-of-the-art 11-station temporal bone lab.

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Go to www.muscENT.org for program brochure, registration form, and other courses the Department offers.