The Department of Otolaryngology - Head and Neck Surgery

has continued to grow both in the realm of patient care and in the arena of biomedical research. In July, our complement of residents increased from two per year to three per year so that our residency program will eventually have fifteen residents in training at the Boston Medical Center. Three new otolaryngologists have joined our team: Dr. Richard Grentzenberg and Dr. Arthur Cohn are with us in the clinic for several days each week and Dr. Michael Platt, who has just completed a Rhinology/Sinus Surgery Fellowship, is with us three days each week so that he can continue to pursue the basic science research that he started last year for two days each week at the Massachusetts Eye and Ear Infirmary. As you will see from reading this edition of THE SCOPE, our research program has continued to develop and expand. In April, Dr. Douglas Cotanche joined the Department to continue here his basic science work on inner ear hair cell regeneration. Dr. Cotanche is widely recognized as a leading investigator who is experimenting with mechanisms that might help to restore hearing for those individuals who have lost hearing or are born deaf. Dr. Susan Langmore, who joined our faculty one year ago, has now begun the NIH-funded multi-center clinical trial of an electronic device that shows promise of helping patients with head and neck cancer who have developed problems swallowing. Dr. Zimmern Wang, who originally came to our department with Dr. Stanley Shapshay in 2000, is the ADMINISTRATIVE OFFICE: 617-638-7933 • www.bumc.bu.edu/orl

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Dr. Douglas Cotanche Returns to BUSM

Douglas A. Cotanche, PhD, joined the Department of Otolaryngology – Head and Neck Surgery on April 1, 2008. Dr. Cotanche is a cell biologist/neuroscientist whose expertise is in the structural biology, development, and regeneration of hair cells in the avian and mammalian inner ear. His academic credentials include a BA in Zoology/Theatre from the University of New Hampshire, a PhD in Anatomy from the University of North Carolina at Chapel Hill, and a Postdoctoral Fellowship at the University of Pennsylvania in Cell Biology. He took his first faculty job in 1985 in the Anatomy Department at the Medical University of South Carolina in Charleston but soon moved back to New England in 1987 to accept a position in the Department of Anatomy & Neurobiology at Boston University School of Medicine. In 1998, he moved across town to serve as the Director of Research in the Department of Otolaryngology at the Harvard School of Medicine/Children’s Hospital before returning to BUSM to establish the Laboratory of Cellular and Molecular Hearing Research. Dr. Cotanche brings with him several NIH research grants among which is an ROI grant, Cell Form and Gene Expression in the Hair Cell Regeneration. The Deafness Research Foundation recently named Dr. Cotanche as one of the Ten Top Hearing Researchers to Watch. He has recently been appointed a member of the BUMC Institutional Animal Care and Use Committee, (IACUC).

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Douglas Cotanche, Ph.D.
Alumna Gives Back

Rebecca Stone, MD, (2007 Program Graduate) has donated $1,000 to the Resident Education Alumni “Give-Back” Fund. This fund was established in 2004 to supplement financial support available to residents to enable them to attend meetings or purchase educational materials throughout the five years of their residency. The concept of the Give-Back Fund is that graduates of our residency program make contributions that go directly to the residents currently in the residency program. Thus, those who have derived benefit from the contributions of graduates continually replenish the Give-Back Fund when they are in practice and have the financial means to help those who are coming behind them in the residency program.

Dr. Stone is an associate practicing General Otolaryngology-Head and Neck Surgery with a local practice, Boston ENT Associates. She works through Beth Israel Deaconess-Needham and the Faulkner Hospitals and is involved in teaching medical students and residents at both facilities. Thank you, Dr. Stone!

The Department of Otolaryngology- HNS

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and may represent a novel pharmacologic target to control the activity of these receptors in cancer cells. In addition, Dr. Spanjaard serves as the Chair of our Resident Research and Scholarly Activities Committee (RRSAC) and he serves as a Protocol Compliance Reviewer for the BUSM Institutional Animal Care and Use Committee (IACUC). To increase her role in research administration, Ms. Nina Leech, executive assistant in the department, has completed the first course, Good Clinical Practices in Clinical Research, of the Master’s Program in Clinical Investigation, in the BU Division of Graduate Medical Sciences.

While I am delighted with the output of research in the Department and proud of the fact that our scientists have been so successful in garnering extramural funding for their research, what pleases me most about research in our department is the culture that surrounds our research activities. Our team of scientists has always been endlessly approachable, generous with their time in mentoring our residents, helpful to BUSM students, and, in every way, team players within the Department. They are wonderful role models who demonstrate in their work the love of science and the joy of making new discoveries. We are extremely fortunate to have with us our team of scientists. After all, to be credible nowadays, an excellent Department of Otolaryngology at an academic medical institution must be dedicated as much to science, finding new and better ways to do things, and pursuing research, as it is devoted to patient care.

Kenneth M. Grundfast, M.D.

Dr. Miriam O’Leary Receives 2008 Jalisi Excellence in Teaching Award

Dr. Miriam O’Leary (2009 Program Graduate) was awarded the Qazi M.H. Jalisi Excellence in Teaching Award at the Otolaryngology Residency Training Program Graduation on June 14, 2008. Thanks to the endowment provided by Dr. Jalisi Sr. in honor of his son, Scharukh, who graduated from the Otolaryngology Residency Training Program in June 2004 and is now Assistant Professor of Otolaryngology - HNS in the Department, the Jalisi Award is awarded annually. All current Otolaryngology residents and BUSM medical students who rotated through the Department of Otolaryngology during the current academic year vote to determine the recipient of the Jalisi Award. The award inscription reads, “In appreciation for your eagerness and proficiency in imparting knowledge of otolaryngology to others – The Jalisi Excellence in Teaching Award is presented to Miriam O’Leary, M.D., June 14, 2008.”

Dr. Douglas Cotanche Returns to BUSM

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In addition to his research activities, Dr. Cotanche has a long history of teaching Gross Anatomy to first-year medical and dental students. During his first stint at BUSM, he taught in both the medical and dental gross anatomy courses and in 1993, received the Proctor and Gamble Teaching Award for Excellence in Teaching in the Basic Sciences at Boston University’s Goldman School of Graduate Dentistry. For the past six years, Dr. Cotanche has been teaching in the Human Functional Anatomy Course for first-year medical students in the Harvard/MIT Program in Health Sciences and Technology (HST). Last year, he received the coveted Award for Excellence in Teaching at Harvard Medical School (HMS). He will continue to teach in the HST Anatomy Course at HMS during the fall semesters but will also contribute to anatomy teaching here at BUSM.

Dr. Cotanche currently lives in Southborough MA with his three children, son Kalvin (14), twin daughters Molly and Maggie (12), his beloved golden retriever Rosie, his deaf cat Santiago, and his daughters’ pet chinchillas Howard and Tony. In his “spare” time, he sings in three different choral groups and is the MC and house manager for the Steeple Coffeehouse, a charity benefit folk music venue whose proceeds help support the outreach mission of its host, the Pilgrim Congregational Church in Southborough.
Dr. Chung was born and raised in New York City. After earning his undergraduate degree at Brown University in Providence, Rhode Island, he returned home to attend New York University School of Medicine. Dr. Chung first became interested in otolaryngology after seeing big head and neck resections and as he continued to explore this field, he found that he was just as excited about mastoidecomies and FESS as about free flaps. As with many who are drawn to otolaryngology, Dr. Chung is attracted by the specialty’s combination of surgery and broad clinic experience. He proclaims otolaryngology to be “the perfect specialty!”

Wayne is an enthusiastic runner and is excited to be in Boston with its rich running tradition. He hopes to continue training and some day run in the Boston Marathon. During medical school, he helped to develop the medical Chinese language program which is now used as a resource at other medical schools throughout the country. Dr. Chung hopes to similarly contribute to the community during his time at BMC.

“I look forward to joining the Otolaryngology – Head and Neck Surgery family at the Boston Medical Center,” says Dr. Chung. He continues, “Don’t worry Red Sox Nation, I am from Queens and a Mets fan!”

Dr. Elackattu was born in India but moved to Chicago when he was two years old. He graduated in three years from the University of Chicago with degrees in Biology (with a neuroscience specialization) and Psychology. At U of C, he was active in the Lambda Phi Epsilon fraternity and participated in intramural basketball and flag football, volunteered at the children’s hospital, and worked in a neuroscience research lab.

After college, Dr. Elackattu began to seriously explore a future in health care by taking a year to work as an EMT-B in the Chicago-area where he was able to interact with healthcare providers on all levels and with people in multiple fields while at the same time accepting responsibilities for patient care. Dr. Elackattu says that this experience drove him to pursue medicine as a career.

Dr. Elackattu began his medical education at St. George’s University in Grenada and St. Vincent’s, West Indies, and then transferred to Northeastern Ohio University College of Medicine where he completed his last two years. He has worked for the past year as research fellow in the BUSM Department of Otolaryngology with Drs. Wang and Grillone (among others) on a variety of projects. He hopes to continue his research momentum throughout his residency.

Alphi enjoys playing sports (basketball, weightlifting, boxing) when time affords it and says, “I will be preparing for my biggest challenge yet – marriage, which will take place September 2008.” Alphi will be marrying Anita Pachikara, MD, who is currently a second-year pediatric resident at Metro Health/Case Western in Cleveland, Ohio. Dr. Pachikara will complete her training in 2010.

Bharat Yarlagadda, MD

Dr. Yarlagadda was born in India and has lived in Canada, Buffalo, Houston, and the Capital District of New York. He graduated magna cum laude from the Accelerated Medical Program at the Rensselaer Polytechnic Institute in Troy, NY, with a major in Biology. He then moved across the Hudson River to the Albany Medical College where he graduated cum laude. Dr. Yarlagadda says that he has always had an interest in surgery and developed an interest in otolaryngology during his third year of medical school when he found the procedures very interesting and the people were great to work with. An away rotation at BUMC during his fourth year convinced him that this program was to be his top choice.

Bharat enjoys playing tennis, grilling hamburgers and ribs outside with his friends, listening to music, sitting on the beach, “trying” to ski, and spending time with the people he loves. He says, “I’m really looking forward to living in Boston. I lucked out with a great apartment in the Back Bay by the Prudential Center. I can’t wait to explore the city and take advantage of everything it has to offer.”

Michael P. Platt, MD.

Dr Platt joined the Department of Otolaryngology – Head and Neck Surgery at BMC in July 2008. Dr. Platt specializes in rhinology, which focuses on diseases of the nose, paranasal sinuses, and related structures. In addition to his clinical practice at Boston University Medical Center, Dr. Platt performs basic science research on nasal polyps and chronic sinusitis at the Massachusetts Eye and Ear Infirmary. He is studying genomic alterations in chronic sinusitis with the use of molecular techniques and microarray gene chip technology. A native of Pennsylvania, Dr. Platt attended the University of Scranton, where he graduated summa cum laude and won the Hyland Award for Excellence in Biology. He became interested in diseases of the head and neck at Jefferson Medical College in Philadelphia before pursuing a residency in Otolaryngology – Head and Neck Surgery at Albany Medical Center in Albany, NY. He was awarded the Steven M. Parnes Chairman’s Award from his fellow residents at the conclusion of his chief resident year. Most recently, he completed a Rhinology Fellowship at the Massachusetts Eye and Ear Infirmary. Dr. Platt has traveled on several medical missions to Haiti and Honduras to provide surgical care to those in greatest need and hopes to continue this service throughout his clinical practice. In his free time, Michael enjoys sailing, woodworking, and playing tennis with his wife, Judy, who is a family physician specializing in women’s health and maternity care at Tufts University Family Medicine Residency Program.
Centers for Research in Otolaryngology

Research activity in the Department of Otolaryngology – Head and Neck Surgery is robust and expanding. Areas of investigation include basic science, technological, translational, and clinical research.

The Otolaryngology Head and Neck Cancer Molecular Biology Laboratory (OMBL) was established in 1998 by Dr. Remco Spanjaard to primarily study the basic science associated with cancers found in the head and neck region. His current work is also increasingly involving him in translational research components. Dr. Spanjaard has built on his years of laboratory work in the OMBL to achieve current discoveries that will profoundly contribute to the diagnosis of melanoma and treatment of head and neck and other cancers. Dr. Spanjaard continues to closely collaborate with Dr. Douglas Faller, Director of the Cancer Research Center at BUSM, to develop new anticancer drugs and therapies.

Dr. Zimmern Wang came to BUSM with Dr. Stanley Shapshay in 2000 to continue his work in chemoprevention, laser technology, and spectroscopy as a means of early detection and treatment of cancers of the head and neck. The Otolaryngology Center for Innovative Technology (OCIT) which Dr. Wang directs is now engaged in a broadening range of initiatives to find diagnostic and treatment applications for evolving technologies.

In the last year, two additional centers for otolaryngologic research have been added to the Department. Dr. Susan Langmore became a faculty member of the Department in July 2007 and Director of the newly designated Center for Voice and Swallowing within the Department. Supported by an NIH grant, Dr. Langmore has set up a national multi-center clinical study to determine the effectiveness of a therapeutic modality for patients post-treatment for head and neck cancer. In March 2008, Dr. Douglas Cotanche relocated his Laboratory of Cellular and Molecular Hearing Research to BUSM. His pioneering work on hair cell regeneration for the restoration of hearing loss proffers new hope for many patients seen in the otolaryngology practice.

All of the centers for otolaryngology research provide opportunities for Boston University students (from both campuses) and BMC otolaryngology residents to engage in original and cutting-edge research under the tutelage of experienced and dedicated practitioners and researchers. In addition to the dedicated research efforts described above, all faculty members in the Department conduct independent research which attracts the interest of students and colleagues in the Boston University community and beyond. For detailed descriptions of research in the Department, please visit our website www.bumc.bu.edu/orl

Otolaryngology Center for Innovative Technology (OCIT)

Zimmern Wang, MD, Director, Professor of Otolaryngology

Early Diagnosis of Cancer of the Oral Cavity and Upper Aerodigestive Tract with Laser Induced Fluorescence.

Principle Investigators: Zimmern Wang, MD, Gregory Grillone, MD; NIH grant

In collaboration with Professor Michael Feld and his group of engineers at the MIT Harrison Spectroscopy Laboratory, Drs. Wang and Grillone are directing the application of tri-modal spectroscopy to the early diagnosis of cancer of the oral cavity and the upper aerodigestive tract. Dr. Elizabeth Stier of BMC Obstetrics/Gynecology Associates is the project co-investigator for application of this technology to the early diagnosis of cervical cancer. The dynamic of ongoing development and refinement of this innovative diagnostic technology is facilitated by monthly meetings of the engineers from MIT, Dr. Stier, and the group from the BUSM Department of Otolaryngology. The MIT engineers have observed the procedures of the clinical practitioners involved in the study to invent and adapt a spectroscopy machine that extrapolates the parameters obtained through a noninvasive fiberoptic wand into patterns of reflected light and fluorescence that digitally map normal, dysplastic, and cancerous sites by color. The wand consists of a light source and a camera that records readings but does not come into physical contact with the patient at all. The maps are compared with pathological findings from traditional biopsy results of the same tissue to confirm their accuracy. In addition to use for clinical diagnosis, the spectroscopy machine has been brought into the operating room by the otolaryngologists to collect intraoperative readings during cancer surgery. These findings are also later compared with traditional pathology biopsy findings to determine the potential application of spectroscopy for establishing clean surgical margins in real time intraoperatively.

Spectroscopic technology uses a white light and a laser pumped series of dyes to excite reflectance and fluorescence, respectively, from the oral, upper aerodigestive tract and cervical mucosa of patients with suspicious lesions prior to biopsy. The findings from this research will determine if this optic technology can provide a non-invasive supplement or alternative to biopsy which is the standard diagnostic procedure. The first report from this study, Non-invasive detection of oral cancer using spectroscopic-based algorithms, has been submitted to Ann Otol Rhino Laryngology for publication.

Laser Atraumatic Treatment of Vascular Lesions on Vocal Folds

Principle Investigator: Zimmern Wang, MD; Investigators: Gregory Grillone, MD; Peak Woo, MD; NIH grant

Small vascular malformations (SVM) on the vocal fold are a common problem in patients seen by otolaryngologists. SVM can disrupt the voice and is currently treated with endoscopic microsurgery using the CO2 laser or other microsurgeries. However, current treatments are unsatisfactory because of their invasive nature and the aim of this study is to find an alternative treatment. The pulsed dye laser (PDL) has been successfully used for treatment of microvascular lesions in cutaneous tissue because its high selectivity for destroying targeted blood vessels enables the surgeon to spare normal tissue. Although the PDL has been studied over the past five years for these types of lesions, there are no studies that directly compare PDL treatment with the current conventional treatment – CO2 laser
or “cold” microinstrument. Dr. Wang and Dr. Grillone have designed a study that compares the laser group and the traditional surgery group by evaluating voice recovery among patients. To increase patient enrollment and maximize the statistical power of the study findings, Dr. Peak Woo of the Mount Sinai Medical Center Grabscheid Voice Center in New York City has joined in the protocol of the study. By offering an alternative treatment for SVM, Drs. Wang and Grillone expect to develop a treatment that provides better and quicker voice improvement than the current conventional surgeries.

**Voice-preserving treatment for laryngeal papilloma.**

Principal Investigator: Zimmern Wang, MD; NIH grant

Recurrent respiratory papilloma (RRP) is among the most common tumor diseases afflicting the vocal cords or other regions of the voice box. This disease is linked to the human papilloma virus (HPV) and can cause significant distress for people including changes in their voice and impairment of their ability to breathe. Particularly troubling is the high incidence of recurrence after treatment resulting in a mean number of 1.6 surgeries per year for each patient. Approximately 16,000 procedures at a cost of more than $100 million are performed in the United States yearly. Current surgical treatment can result in scarring and damage to the vocal organs.

RRP is vascular in nature and its progression is highly dependent on the underlying blood supply. While the Pulse Dye Laser (PDL) has been successfully used for RRP treatment because of its ability to target blood vessels, new studies show a potential role for Celecoxib due to its inhibitory effect on vascular growth by inhibiting the COX-2 enzyme. Combining these two treatment modalities to create a novel, less invasive long-term strategy for the treatment of laryngeal papillomas is the goal of this study. This human subject study design follows earlier animal students of chemoprevention conducted by Dr. Wang that established the safety and benefit of this combined therapy in reducing recurrence of RRP.

**Voice preserving therapy of laryngeal papilloma in children**

Principal Investigator: Zimmern Wang, MD; Co-Investigator: Kenneth Grundfast, MD; NIH grant

Recurrent respiratory papilloma (RRP) is one of the most commonly occurring head and neck tumors in children. In 1995, there were 2,354 new cases and 5,970 active cases of pediatric RRP. Although RRP is histologically benign, the disorder has a tendency to be devastating to those affected because of relentless recurrence and a tendency to progressively cause worsening voice quality the longer the disease is present. Significantly, more surgical procedures are performed each year for treatment of laryngeal RRP in children than in adults. Children with RRP almost always present with lesions on their vocal cords or other regions of the larynx which causes poor voice. As with other RRP diseases, high incidence of recurrence after treatment is typical. The need for repeat surgical procedures, doctor’s office visits, and hospitalizations carries a psychological and financial burden for affected children and their families. RRP involving the larynx can lead to life-threatening problems if the airway is blocked by lesions. Growth of papilloma within the larynx depends, in part, on vascular supply to the lesions.

Current methods of treatment are less than optimum and there continues to be a world-wide search for improved methods of management. The Pulse Dye Laser (PDL) has been successfully used for treatment of RRP because it selectively destroys small vessels that supply blood to the RRP lesions. Recent studies have also shown a potential role for Diindolemethane (DIM), a safe dietary product, in the inhibition of the growth of RRP lesions. The aim of this study is to develop a novel, less invasive, and long-term effective strategy for treatment of RRP in children that combines a laser microvascular targeting (MVT) technique using the PDL with orally administered DIM. We expect that this combination treatment will control of the disease better than the control achieved with using the PDL alone. As a first step in the research process, animal studies have been completed to establish the safety of administering DIM to children. The new findings from this work, Safety study of DIM in sexually immature rats, has been submitted to the 2009 Triological Meeting Eastern Section for consideration of presentation and research award.

**Functional MRI Study with Caloric Stimulation of the Vestibular System**

Principal Investigator: Kenneth Grundfast, MD; Co-Investigators: Zimmern Wang, MD, Dae-Shik Kim, MD

Functional MRI (fMRI) is a powerful tool utilized in both research and clinical areas since the early ’90s. It offers the opportunity to study brain function and the vestibular system in a noninvasive way by correlating oxygen consumption with neuron activity through imaging blood oxygenation level dependent (BOLD) contrast.

Currently, there is no uniformly defined area in the cerebral cortex that is identified as a single control center. In this study, vertigo is elicited by introducing cold water stimulation into the ears of healthy volunteers. Subjective reporting and tracking of nystagmus with an eye tracking device verify the experience of vertigo. Analysis of fMRI data has implied that vestibular response in the volunteers is a combination of several parallel physiological processes which were separated and represented by different independent components. New findings from this study were presented at the 2008 Combined Otolaryngology Spring Meeting (COSM) in Orlando, Florida, in May 2008. The work on this project represents the first time that scientists have successfully imaged such small targets as the human vestibular nucleus with fMRI technology. Drs. Wang and Kim are currently expanding on this study and are involved in new research to utilize fMRI in studying other areas of the brain.

**Head and Neck Cancer Molecular Biology Laboratory (MBL), BUSM Cancer Research Center**

Remco Spanjaard, PhD, Director, Associate Professor of Otolaryngology

The American Cancer Society estimates that in the US in 2008, 12,250 new cases of laryngeal cancer will be diagnosed and 3,670 people will die from the disease. There are an additional estimated 2,400 cases of hypopharyngeal cancer and 2,000 cases of nasopharyngeal cancer totaling about 16,650 patients—a substantial patient group. Advances in multi-
Cancer patients due to tobacco use. This insight has lead to an increasing interest in identifying biologic agents that stop the progression of premalignant lesions and prevent the development of a second primary malignancy. Retinoids, compounds that are derived from Vitamin A, have been shown to suppress premalignant lesions of the oral cavity and to decrease the incidence of a second primary in patients treated for squamous cell carcinoma of the head and neck. Retinoids are also effective differentiation-inducing agents in many other tumor types. However, in clinical trials, these compounds have been noted to have prohibitive toxic side effects such as mucocutaneous dryness, headaches, nausea/vomiting, bone/joint pains, and hypertriglyceridemia. Moreover, some of the retinoids such as all-trans retinoic acid (RA) have a short plasma half-life, requiring frequent oral dosing. This has necessitated the search for alternative biologic agents that are less toxic and have more favorable pharmacokinetic profiles.

For over a decade, the MBL has investigated the molecular actions of RA and its receptor (RAR) in various tumor types. RARs are members of a large superfamily of nuclear receptors (not the cell surface) that function as hormone-dependent transcription factors. This means that in the absence of RA, they cannot induce gene expression but when activated in the presence of RA, they can induce a genetic cascade that can result in cessation of tumor growth. So far, RA is the only drug that has resulted in clinically-proven chemopreventive and antitumor effects in head and neck cancer. Successful treatment has been shown to be correlated with re-expression of RAR, one of three types of RARs. It is therefore of considerable importance to understand and boost the activity of RA and its corresponding nuclear receptor. Two major current projects exploring the potential implications of RA and RARs in the treatment of cancer and two current projects to develop methods of early cancer detection are summarized below.

To better understand the RAR-signaling pathway, a new biochemical coactivator pathway that contributes to RAR and other nuclear receptor activity has recently been discovered by Dr. Spanjaard in the MBL. This exciting development is particularly pivotal because this newly identified pathway is not controlled by a protein but by a noncoding RNA. Two provisional patents have been filed on behalf of the BUSM resulting from this work because this pathway may represent a novel pharmacologic target to control the activity of these receptors in cancer cells. In 2007, The Department of Defense awarded its Theme Award to Dr. Spanjaard for this work and he is continuing to further develop a RNA-based drug that may be used as a therapeutic agent. The early work that led Dr. Spanjaard to this discovery was funded by the NIH. The following two published articles describe this work:


To find new drugs that can re-sensitize cancer cells to the growth-inhibitory and differentiation-inducing effects of RA. In collaboration with Douglas V. Faller, MD, Director of the BUSM Cancer Research Center, Dr. Spanjaard is exploring development of a new generation of so-called histone deacetylase inhibitors (HDACi). Histones are proteins in the cell nuclei around which DNA is wound. These histones can be chemically altered by a group of enzymes called HDACs so that transcription factors such as RARs cannot bind to the DNA and activate a growth-inhibitory genetic program after addition of RA. To overcome this block, Drs. Faller and Spanjaard are exploring the possibility of designing highly specific and non-toxic HDACi that stop the activity of these enzymes in epithelial cancers, thereby re-sensitizing the tumor cells to the beneficial effects of RA. Moreover, these new drugs may also result in lowering the required dosage of RA to achieve its antitumor effects which may help to overcome its toxic side-effects. Funding for these experiments is currently pending.

To improve treatment for melanoma. Approximately 20% of melanomas occur in the head and neck region and this is one of the few cancers for which the rate of incidence is rising rather than falling. Moreover, there are no effective treatments for advanced stage melanoma. Dr. Spanjaard has identified a new unique melanoma-specific cell surface signaling molecule called TROY. TROY promises to be a novel diagnostic tool to detect circulating melanoma cells in patient serum. This finding was patented and currently a US company is assessing whether an immunological blood test, similar to that for prostate cancer, can be developed to detect melanoma. No such test exists for melanoma so that, if successful, the clinical impact for melanoma patient care could be significant. TROY also presents a potential novel pharmacologic target because its activity appears to be important for melanoma cell proliferation. With funding from two private foundations, Dr. Spanjaard is currently further evaluating the biological role of TROY in melanoma. The following published article describes this work:


To apply DNA microarray technology to identify novel head and neck cancer-associated genes that may play an important role in the disease development. The DNA microarray method, or gene chip, allows simultaneous detection of differentially expressed genes between two or more tissue samples. Gene expression of normal mucosal tissue was compared with that of a tumor of the oral cavity. Many new candidates have emerged that were specifically associated with the tumor, but two metalloproteinases, MMP11 and MMP12, are of particular interest. Preliminary research suggests that these two metalloproteinases are co-expressed in at least a subset of head and neck cancer patients which may greatly alter their tumorigenic properties. Because relatively much is known about the biological activity of MMPs and their role in cancer, continuing to focus on the role of MMP11 and MMP12 in head and neck cancer is expected to be promising. This work has received pilot funding in the past and development into a major research project is awaiting further funding.

Otolaryngology Center for Voice and Swallowing

Susan Langmore, PhD, Director, Professor of Otolaryngology. Dr. Susan Langmore came to Boston Medical Center from the University of California at San Francisco in July of 2007. With her, she brought an NIH-funded multi-center clinical research study entitled The Efficacy of Electrical Stimulation for Dysphagia in Head and Neck Cancer Patients, which is designed to determine the efficacy of a treat-
ment modality typically used in orthopedic rehabilitative settings and recently applied to swallowing disorders.

The inception of this study began on a pile of napkins at a Starbucks Café. Several years and gallons of coffee later, the first year of a $2.7 million 5-year NIH/NCI R01 funded clinical trial has been completed. It is a nationwide multi-center clinical trial with fourteen recruiting institutions in five states, a data coordinating center, central lab, two consultants, 80+ research and administrative staff, and a central research coordinator. It is a study of massive proportion and much of the first year has been dedicated to building a framework required for its successful implementation.

The core of this study aims to address the disparity between advances in medical treatment of head and neck cancer and the advances in subsequent rehabilitation. Twenty-first century improvements in local/regional control of cancer with radiation therapy – often coupled with surgery and/or chemotherapy – have decreased mortality rates. Unfortunately, elimination of the cancer can leave devastating side effects – both physiological and quality-of-life – exemplified by the inability to eat and swallow normally. Despite an extremely high incidence of dysphagia in this patient population, conventional swallow therapies are limited and yield only minor and often unknown benefit. Insufficient rehabilitative (or preventative) modalities for head and neck cancer survivors have left many desperate for a solution for their dysphagia.

Recently, a new therapy has been introduced for dysphagia called e-stim or Neuromuscular Electrical Stimulation (NMES). A device delivers a low voltage current through the skin and excites motor nerves causing muscle contraction. An aggressive marketing campaign has turned e-stim into a highly sought after (and expensive) therapy for dysphagia. Despite its explicable popularity, only anecdotal evidence and a few poorly designed studies have demonstrated its true benefit.

This randomized controlled trial will compare NMES therapy combined with exercise therapy to sham NMES combined with the same exercise therapy. The protocol will be used by head and neck cancer patients who have moderate to severe dysphagia and are 3-6 months post-XRT (or post-XRT/CRT) to determine whether NMES is efficacious. The study will also reveal whether the exercise therapy is effective by itself.

The goal of this study is to determine whether e-stim represents a truly beneficial treatment or whether our resources should be redirected. This study is exciting and unique in that it has both clinical and health policy implications. If e-stim is determined to be effective, this new treatment may represent the first real hope for improved swallowing for a growing population of cancer survivors. If determined ineffective, its growing use and concomitant cost will be re-examined. Equally exciting is the multitude of research, both clinical and analytical, that will emanate from this landmark study.

As the second year of the study progresses, the faculty and staff in the Department of Otolaryngology – Head and Neck Surgery at BMC are excited to begin patient recruitment. BUMC is the core site for this trial and the Data Coordinating Center at the BU School of Public Health will process data from all sites. Seven other major medical centers in Boston are participating, as well as four major medical centers in New York, and one in Illinois, Iowa, and Wisconsin.

Information about patient enrollment and the study can be found on the web at ClinicalTrials.gov and will be linked to the BUMC Otolaryngology home page www.bumc.bu.edu/orl.

Laboratory of Cellular and Molecular Hearing Research (CMHR)

Douglas A. Cotanche, PhD, Director

The major focus of the research in the Laboratory of Cellular and Molecular Hearing Research (CMHR) is to explore hair cell regeneration in the vertebrate inner ear and determine how it can be applied to the human cochlea as a treatment for hearing loss. More than 36 million Americans suffer from some form of hearing loss that negatively impacts their lifestyle and/or their ability to work. While up to 26 million of these people acquire their hearing loss from exposure to loud sounds at work or in leisure activities, the remainder are either born deaf or are affected by other non-noise related causes. Two to three out of every 1000 children are born deaf or hard-of-hearing and half of these impairments have a genetic basis. In humans and other mammals, all of the hair cells needed for auditory function are born during embryonic life and cannot be replaced if lost or damaged by noise, ototoxic drugs, aging, or genetic mutations. In 1986, the CMHR discovered that birds, unlike mammals, are able to regenerate hair cells in the cochlea throughout their lifetimes. However, this regeneration is not continuously occurring. It only happens when the existing hair cells are damaged or die. Since first discovering hair cell regeneration, the CMHR has been focused on defining the mechanisms that regulate hair cell death and regeneration in the avian cochlear sensory epithelium and have recently also begun to explore the capability of mouse and human neural stem cells to regenerate the damaged cochlea and cochlear nerve in the mammalian inner ear. The CMHR has been characterizing gene expression in both mouse and human neural stem cells to compare them with genes expressed in other stem cell lines and with genes expressed

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in cochlear tissues. In addition, they have carried out transplantation studies where mouse neural stem cells have been introduced into the noise-damaged mammalian cochlea in vivo and in vitro.

**Apoptosis and Regeneration of Hair Cells in the Avian Cochlea**

Principal Investigators: Douglas Cotanche, PhD, Christina Kaiser, PhD (BUSM), Cathie Klapperich, PhD (BU Biomedical Engineering) Zheng-Yi Chen, PhD (Mass Eye & Ear Infirmary); NIH Funding

This study focuses on the regeneration of hair cells in the avian cochlea because it is the only vertebrate auditory epithelium that exhibits a proficient and robust regeneration after trauma. Hair cells in the avian cochlea die by apoptosis following either gentamicin treatment or sound damage. Apoptosis is a genetic program that is activated in traumatized cells to initiate a pathway that actively leads to their death and elimination from the tissue. Findings by the CMHR have demonstrated that hair cells in the chick cochlea respond to sound damage or aminoglycoside treatment by undergoing apoptosis and that this leads to the elimination of the damaged hair cells from the sensory epithelium. They have been able to identify and define the expression patterns of several key proteins of the hair cell apoptotic cascade and are now exploring potential ways to inhibit these proteins, block cell death, and prevent hair cell loss.

Death of the cochlear hair cells induces a regenerative response in the surviving supporting cells, so that they either undergo a direct transdifferentiation into hair cells without dividing, or they proliferate and make new hair cells and supporting cells to repopulate the damaged sensory epithelium. The earliest response to hair cell death involves the activation of a subset of supporting cells to undergo a direct transdifferentiation into new hair cells. This results in the loss of one supporting cell for each cell that becomes a hair cell without dividing. The transdifferentiation process actually begins even before the dying hair cells are ejected from the sensory epithelium. In fact, as soon as the hair cells begin to respond to gentamicin, some of the supporting cells begin to enter the earliest stages of differentiating into hair cells, as determined by Math1 labeling. However, current CMHR data suggest that not all of the supporting cells that initially express Math1 will become hair cells. Some seem to go back to a resting state, or else they switch into the mitotic pathway. At present, the CMHR group is testing which of these options is being utilized.

In addition to the extensive CMHR studies on hair cell regeneration in vivo, the group has developed an in vitro model for studying apoptosis and hair cell differentiation in a whole organ culture preparation of the chick cochlea. This organ culture preparation can be maintained for several days in normal media without extensive hair cell loss or signs of damage. Yet, when these cultures are exposed to gentamicin at doses equivalent to that used in animal studies, the hair cells undergo programmed cell death in a pattern and time frame equivalent to that seen in the cochlea in vivo. This organ culture model system of gentamicin-induced cell death in the chick cochlea has enabled the CMHR group to directly study the individual steps in hair cell death and regeneration in vitro and will allow them to experimentally block or manipulate the progression of apoptosis, something they cannot readily do in the whole animal.

In their recent experiments, the CMHR group has been working in collaboration with faculty in the Biomedical Engineering Department at BU to develop appropriate biomatrices for culturing the chick cochlear sensory epithelia. They have greatly increased the quality of the hair cell survival and the longevity of the culture system by combining the defined biomatrices with a newly developed two-chambered culture system that allows the upper surfaces of the hair cells to be bathed in an endolymph-like solution, while the basolateral surfaces are immersed in a perilymph-like solution. This represents a significant advance in their ability to work with long-term cultures of the mature cochlear sensory epithelium. Moreover, further experiments with inhibitors of cell motility have shown that the cytoskeleton of the supporting cells plays a direct and active role in physically ejecting the dying hair cells from the cochlear sensory epithelium.

The CMHR has also initiated a genechip microarray study in collaboration with Dr. Zheng-Yi Chen at Massachusetts Eye and Ear Infirmary examining the genes that are up or down regulated during specific time points in the regeneration response. The collaborative group is using the Affymetrix chicken gene arrays to examine genes expressed in control ears and at various time points during regeneration. With this technique, they should be able to pinpoint the function of key molecules controlling supporting cell proliferation and hair cell differentiation.

**Stem Cell Transplantation for Mammalian Cochlear Repair**

Principal Investigators: Douglas Cotanche, PhD (BUSM), Mark Parker, PhD (Mass Eye & Ear Infirmary); Philanthropic Funding

The CMHR has been exploring regeneration in the mammalian inner ear by transplanting neural stem cells into a gentamicin-damaged or sound-damaged guinea pig cochlea. They have shown that mouse neural stem cells will infiltrate the surviving cochlea, respond to local microenvironmental cues, and differentiate into neurons and glia within the spiral ganglion, as well as hair cells and supporting cells in the organ of Corti. Two weeks after transplantation, the neural stem cells can be identified in the cochlear tissues by labeling of marker genes that have been transfected into these cells. By 4 or 6 weeks after transplantation, the stem cells can no longer be identified by these genetic markers, as the differentiating cells seem to downregulate the inserted genes. However, they have been able to identify the mouse neural stem cells in the guinea pig cochlea using an X/Y chromosome tag. The neural stem cells were derived from male mice and can be labeled by fluorescent in situ hybridization for the Y chromosome, while the host guinea pigs that they transplanted the stem cells into were all female. Thus, any cells in the experimental ears that labeled with a Y chromosome marker were from the transplanted mouse neural stem cells. Animals survived for 6 weeks, then the cochlear tissues were sectioned and processed for X/Y fluorescent in situ hybridization followed by immunocytochemical labeling for cell-type specific markers. The CMHR group were able to identify numerous cells in the spiral ganglion that were derived from the mouse stem cells and demonstrated that they had differentiated into either neurons or glial cells and expressed Apoptosis and Regeneration of Hair Cells in the Avian Cochlea...
Summary of Current Faculty Research

Clarke Cox, PhD, Associate Professor & Director, Division of Audiology


Anand Devaiah, MD, Assistant Professor

Research Interests: skull base surgery (endoscopic, anterior and lateral); otologic disease and physiology; head and neck cancer; outcome analyses; general otolaryngology

Recent Research Protocols: outcomes analyses in paranasal sinus/skull base tumors; anatomic studies for endoscopic skull base approaches; fMRI in tumors of the anterior and lateral skull base


Stucken CL, Andreoli SM, Friedberg MD, Devaiah AK. Opioid analgesics and respiratory complications following tonsil and adenoid surgery in young children. Poster presentation, Association for Pediatric Otolaryngology subsection (ASPO), COSM, May 2008. First place, ASPO Research Poster Award.


Gregory A. Grillone, MD, Associate Professor & Department Vice Chairman

Conducting a pilot study on the efficacy of the DaVinci robot in transoral resection of tumors of the oropharynx, hypopharynx and larynx with the goal to set up time, surgical time, and physiology; head and neck cancer; outcome analyses; general otolaryngology

First place, ASPO Research Poster Award.


Kenneth M. Grundfast, MD, Professor & Department Chairman

Pilot and Exploratory Projects in Palliative Care of Cancer Patients and Their Families, American Cancer Society, KM Grundfast PI (submitted)

A study to Evaluate the Effectiveness of the Slide-on(TM Endosheath/4 Vs. Traditional Disinfection of Flexible Naso-Pharyngo-Laryngoscopes, Medtronic, KM Grundfast PI (submitted)

Scharukh Jalisi, MD, Assistant Professor

Scharukh Jalisi, MD, Tiffany Ainsworth, MD, Michael LaValley, PhD. Comparing prognostic outcomes of tall cell variant to normal variant papillary thyroid cancer - a meta-analysis

Rohail Haider, Scharukh Jalisi, MD, Alphi Elackattu, MD, Lawrence Chin, MD. Melanoma of the anterior skullbase

Scharukh Jalisi, MD, Ilan Mizrahi, BA, Alphi Elackattu, MD, Lawrence Chin, MD. Intracranial meningioma with extracranial extension presenting as nasal mass

Scharukh Jalisi, MD and Alphi Elackattu, MD. Intracranial cholesteatoma presenting with facial twitching

Scharukh Jalisi, MD, Leslie K. Winter, MD, Rebecca Stone, MD. Sarcoidosis masquerading as carotid body tumor

Scharukh M. Jalisi and Varan A. Mardirossian, MD. Prevertebral Abscess – A New Otolaryngology Diagnosis

Elizabeth Mahoney, MD, Assistant Professor


Roberts DS, Mahoney EJ, Hutchinson CT, Aliphas A, Grundfast KM. Analysis of Recurrent ACE Inhibitor-Induced Angioedema. Laryngoscope, accepted for publication June 2008.

J. Pieter Noordzij, MD, Associate Professor

Survival properties of injected human cartilage slurry in a nude mouse model. The state-of-the-art treatment of unilateral vocal cord paralysis, a cause of significant dysphonia, is surgical medialization of the immobile vocal fold, allowing better apposition with the non-paralyzed vocal fold. One of the most popular medialization techniques involves the injection a substance into the paralyzed fold. The purpose of this protocol is to examine the viability and volume retention characteristics of human cartilage slurry when injected into a living organism.

Jeffrey H. Spiegel, MD, Associate Professor, Medical Director & Chief, Facial Plastic and Reconstructive Surgery


Spiegel JH, Winter L. Ear Stapling for Weight Loss. (accepted for publication)

Spiegel JH, Bortniker E. Congenital Absence of the unilateral lower lateral nasal cartilage. (accepted for publication)

Spiegel JH, Rodriguez G. Chondrolaryngoplasty under general anesthesia using flexible fiberoptic bronchoscope and laryngeal mask airway. (accepted for publication)

Spiegel JH, Yang J. Forehead shape as a determinant of gender identity. Supported by NIH (currently ongoing)

Spiegel JH, Lee M, Sakai O. CT anatomy of the frontal sinus; relevance to cranioplasty. (currently ongoing)

Spiegel JH, Shah P. Standard cosmetic use of Botox and its variance from published recommendations. (manuscript in preparation)
genes particular to these two cell types. A smaller number of stem cells migrated out to reach the organ of Corti where they differentiated into inner phalangeal cells, pillar cells, Deiter’s cells, and outer hair cells. Since these stem cells positioned adjacent to one another within the organ of Corti or spiral ganglion could express different cell-specific genes, it suggests that the transplanted cells are able to recognize and respond to local signals within the cochlea and differentiate into a variety of cell types needed to repair the cochlear ganglion or sensory epithelium.

The CMHR has also utilized gene microarrays, RT-PCR, and immunocytochemistry to characterize the genetic profile of these stem cells. They have shown that the mouse neural stem cells express a number of genes characteristic of other stem cells, such as embryonic stem cells, hematopoietic stem cells, and neurosphere stem cells. However, their neural stem cells also exhibit several genes expressed in hair cells and supporting cells of the developing and mature cochlea. In addition, CMHR findings have shown that these neural stem cells, which are normally maintained as a stem cell line, will begin to express a number of glial genes when grown as neurospheres and that only a few of the cells in the neurospheres retain stem cell-like properties. Recently, they have transfected neural stem cells with a constitutively expressed Math1 gene, which is a key early gene in hair cell differentiation. When this Math1 gene is expressed, the neural stem cells stop dividing, begin to differentiate, and initiate the development of surface projections that resemble stereociliary bundles. This suggests that the induction of Math1 in the neural stem cells can direct these cells down a hair cell developmental pathway and may be very useful for directed transplantation of new hair cells into the inner ear.

The CMHR has also begun working with a human neural stem cell line and is currently defining the gene expression patterns of these cells in their undifferentiated and differentiated states using genechip microarrays and RT-PCR for identifying the patterns of gene expression and immunocytochemical evaluation of protein expression in these cells. They will also attempt to direct these cells to differentiate down a hair cell pathway in vitro by transfecting them with a plasmid containing a conditionally-activated Atoh1 gene. In addition, they will be transplanting these human neural stem cells into noise-damaged guinea pig cochleas in their undifferentiated form or after differentiating them down a cochlear pathway to determine whether they can be targeted to integrate into the spiral ganglion or the cochlear sensory epithelium and differentiate into neurons, hair cells, and/or supporting cells and glial cells.

Recent publications describing work by the CMHR include the following:

Visit the CMHR website www.bumc.bu.edu/cotanchelab

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**Otolaryngology Babies**

**Devan Devaiab, born August 30, 2007**

**Noah Aliphas, born May 18, 2007**
2008 Otolaryngology Graduates

Teresa Chan, MD

Five years ago it hardly seemed possible that this day would come so quickly. I will certainly miss the familiar faces I have grown to know and love throughout my training. I would like to extend my deepest gratitude to the faculty at BMC and all of the affiliates. Thank you for the honor of caring for your patients and learning from you. Thank you for your patience and dedication to training us all. I understand this in some small way now, but I will soon have a new appreciation for just what that takes as I start on faculty at the University of Texas Southwestern in Dallas in August. I will certainly miss your banter and your guidance across the OR table and in my day-to-day practice, but I know your lessons will not leave me. Wish me luck as I learn to do what you all do so well.

To my friends from all walks of life and fellow residents who have provided the necessary distractions and inspirations to make these past five years fly – thank you all for making work and life much more fun.

Mom and Dad, thank you for setting the example of hard work in the first place. Thank you for your love, generosity and unconditional support in all my endeavors. You have never failed me.

Mir, I could not have asked for a better co-resident and friend to spend the last five years with. We have shared countless good memories and laughs from all of our (mis)adventures over the years. I will miss you dearly.

Finally, Matt, you continue to challenge me to learn more, to work harder, to have a better purpose and to be a better being. From the noisy nights of call to enduring two years apart -- thank you for your patience, love, and support throughout it all. I am very much looking forward to starting to live life again with you.

Miriam O’Leary, MD

I’m honored and proud to be graduating from the Boston University Otolaryngology Residency program. Many great otolaryngologists over the past 40 years have shaped the program in which I trained and I have been taught their tradition of excellence. My experiences at Boston Medical Center, Lahey Clinic, the VA, UMass, and Children’s Hospital have all complemented each other and have encompassed the full spectrum of the practice of otolaryngology. The dedication of our attendings to their patients, to the advancement of our field, and to the education of their residents is second to none. I have been given the tools to meet every challenge that I may encounter as a practicing otolaryngologist. My immediate and extended family have provided unwavering support and encouragement throughout my residency. And I couldn’t have asked for a better co-resident or friend than Teresa over the past 5 years! I’m honored and proud to be graduating from the Boston University Otolaryngology Residency program. Many great otolaryngologists over the past 40 years have shaped the program in which I trained and I have been taught their tradition of excellence. My experiences at Boston Medical Center, Lahey Clinic, the VA, UMass, and Children’s Hospital have all complemented each other and have encompassed the full spectrum of the practice of otolaryngology. The dedication of our attendings to their patients, to the advancement of our field, and to the education of their residents is second to none. I have been given the tools to meet every challenge that I may encounter as a practicing otolaryngologist. My immediate and extended family have provided unwavering support and encouragement throughout my residency. And I couldn’t have asked for a better co-resident or friend than Teresa over the past 5 years! After graduation, I will begin a Fellowship in Head and Neck Oncologic Surgery and Microvascular Reconstruction with Dr. Francisco Civantos at the University of Miami. I hope to return to the Massachusetts area after completing my fellowship for an academic position.

Dr. Jalisi Completes BU Clinical Research Programs

Scharukh Jalisi, MD, Assistant Professor of Otolaryngology, has successfully completed the Clinical Research Training Program at Boston University. Dr. Jalisi, the first surgeon-clinician-scientist in this program, was supported by an NIH-funded K30 program. Concurrently, he is also completing the Masters of Arts in Clinical Investigation through the Boston University Division of Graduate Medical Sciences. These training programs have focused on clinical research design, management, and outcomes evaluation of clinical research. Dr. Jalisi’s ultimate goal is to initiate meaningful clinical research in all aspects of head and neck surgery with an emphasis on quality of life measures after chemoradiation therapy versus ablation followed by microvascular free tissue transplantation in head and neck oncology and skullbase surgical patients.
Boston University Otolaryngology Alumni Association

We are pleased to announce the creation of the Boston University Otolaryngology Alumni Association (BUOAA). The Association will benefit both the alumni and the current residents and will sponsor an Annual Alumni Day Scientific Program, develop a networking resource for both alumni and residents, and much more!

All alumni will soon receive an invitation to join the BUOAA. Please take a moment to either reply to the letter or email OTOalumni@bmc.org with your updated contact information.

Thank you!

Image from article, Tracheotomy: Historical Review, by Drs. Loring Pratt, Alfio Ferlito, and Allessandra Rinaldo [V118(9) p1598] to appear on the cover of the September 2008 issue of Laryngoscope. Dr. Pratt is a longtime associate of the BUMC Department of Otolaryngology and serves annually as an interviewer for the Otolaryngology Residency Program candidate selection process, (used with permission of Lippincott Williams & Wilkins)

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