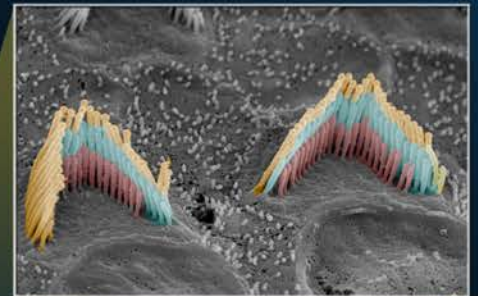


NEWS FROM THE DEPARTMENT OF OTOLARYNGOLOGY AT HARVARD MEDICAL SCHOOL

HARVARD

Otolaryngology

SPRING 2017 ■ VOL. 14, NO. 1



New Hope for **HEARING RESTORATION**

Improved gene delivery vector reaches inner and outer hair cells for the first time, restoring hearing and balance function (*page 14*)



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Dear colleagues and friends,

The idea of gene therapy has excited the medical community for decades. The promise that this technology holds in treating genetic disorders at their origin has inspired us to explore the viability of this as a therapeutic intervention for many diseases.

Within otolaryngology alone, its potential could mean that we find better treatments for some of the most demanding conditions our patients endure. As clinicians and researchers, we have to continue to challenge ourselves to advance new opportunities in gene therapy, as this technology could play an important role in treating conditions such as hereditary hearing loss, among several others.

In the Department of Otolaryngology at Harvard Medical School, we have several ongoing projects involving gene therapy. For genetic disorders causing hearing loss, such as Usher syndrome, we are starting to see promising advancements in hearing restoration when using therapeutic gene transfers. Recently, a group of our scientists successfully delivered corrected genes into the inner and, for the first time, the outer hair cells of mice using a new synthetic vector. In our cover story starting on page 14, we delve into this work, discussing how this vector came to fruition and how the research team restored both hearing and balance function in mice with Usher syndrome when using this vector.

In this issue, we're excited to highlight our progress in a number of research efforts including gene therapy, as well as Eustachian tube dysfunction and chronic rhinosinusitis.

Thank you for your interest in and support of the Department's activities.

Sincerely,

D. Bradley Welling, MD, PhD, FACS

*Walter Augustus LeCompte Professor and Chair
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*Chief of Otolaryngology
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Phillip C. Song, MD, Appointed Chief of Laryngology at Massachusetts Eye and Ear



Phillip C. Song, MD, has been named the Chief of Laryngology at Massachusetts Eye and Ear. In this new role, Dr. Song, who is also an Assistant Professor of Otolaryngology at Harvard Medical School and the Associate Director of the Voice and Speech Laboratory at Mass. Eye and Ear, will oversee clinical and research program development across the Laryngology Division.

Dr. Song's first initiative is to expand the scale of the Division clinically, within research, and in staffing. He plans to grow the laryngology research program by developing research protocols and exploring opportunities for collaboration. He also hopes to focus on neurolaryngology (management of neurogenic dysfunction of the larynx and pharynx), connecting laryngology to systemic and neurological diseases, and incorporating more swallowing services into clinical practice.

“The Division of Laryngology at Mass. Eye and Ear is historically significant. Dr. Harris Peyton Mosher was the first Harvard Chair to preside over two departments, Otolaryngology and Laryngology, and brought together these specialties to form modern day otolaryngology. Mass. Eye and Ear has since been known for being at the forefront of voice-related clinical care and research,” said Dr. Song. “This not only makes this role exciting, gratifying, and full of opportunity, but it also gives me the challenge of representing Mass. Eye and Ear in a way that continues our legacy in laryngology.”

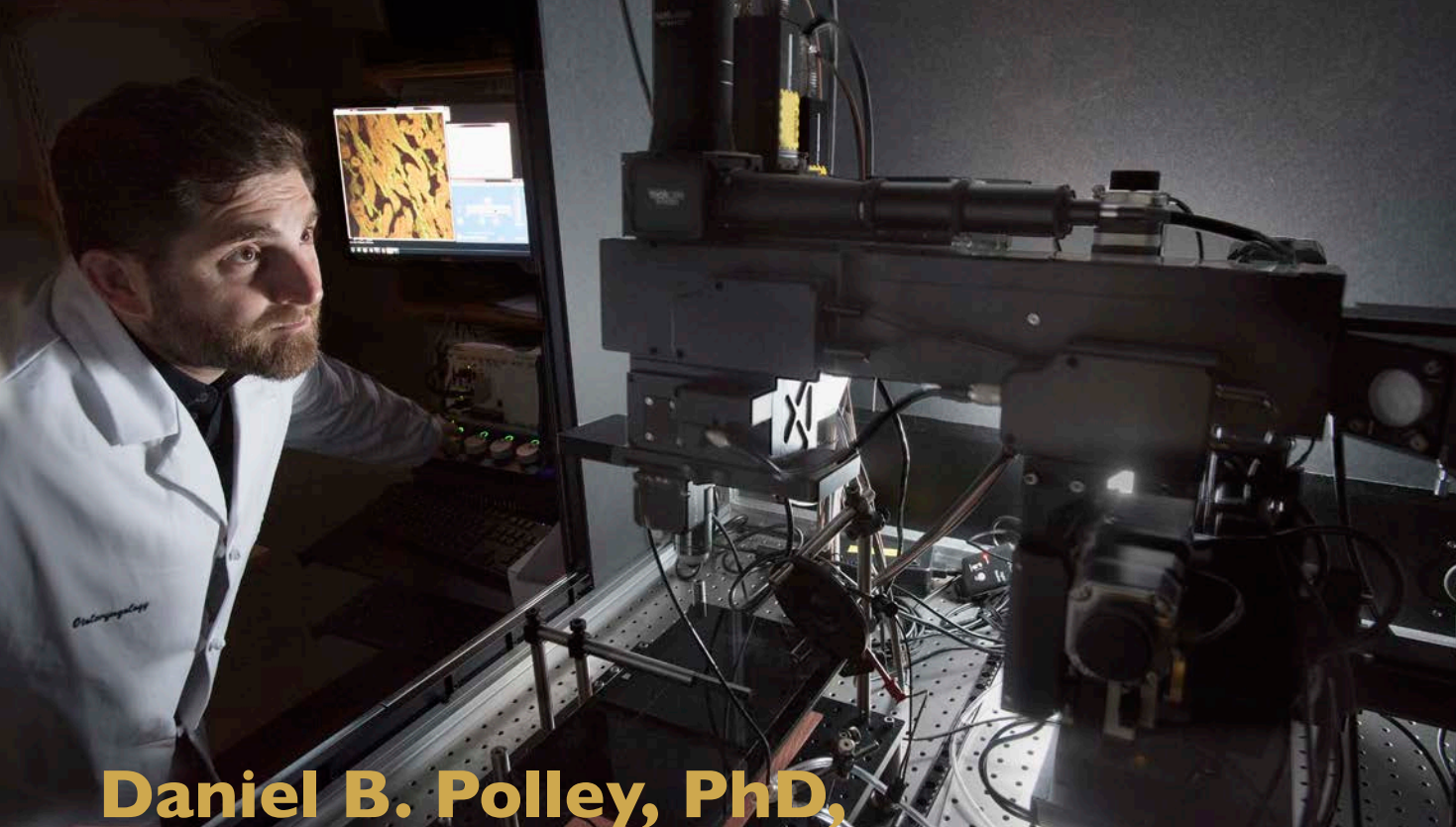
Dr. Song joined the Department of Otolaryngology at Mass. Eye and Ear in 2006 as a member of the laryngology team. Since then, he has built a busy clinical practice while working to promote the field of neurolaryngology and devising strategies to improve the treatment of voice and swallowing disorders.

Throughout his career, Dr. Song has been an invited speaker at national and international

meetings and has contributed to the field through a number of peer-reviewed papers. He also serves as the Curriculum Committee Chair for the Harvard Otolaryngology Residency Program.

In 2015, Dr. Song was the recipient of the William Montgomery Award for Excellence in Teaching, which is presented by the graduating class of Harvard Otolaryngology residents to a faculty member who was instrumental in their training.

“We are delighted to welcome Dr. Song into this leadership role,” said D. Bradley Welling, MD, PhD, FACS, the Walter Augustus LeCompte Chair of Otolaryngology at Harvard Medical School. “His vision for the future of the Division is inspiring, and his interest and expertise in neurolaryngology will greatly complement the work of our neuroscience researchers. I foresee great accomplishments being made under his leadership.” ●



Daniel B. Polley, PhD, Appointed Director of the Lauer Tinnitus Research Center at Massachusetts Eye and Ear

Neuroscientist and hearing researcher Daniel B. Polley, PhD, has been named the first Director of the Lauer Tinnitus Research Center at Massachusetts Eye and Ear. In this new role, Dr. Polley, who is also an Associate Professor of Otolaryngology at Harvard Medical School, an Amelia Peabody Scientist at Mass. Eye and Ear, and the Associate Director of the Eaton-Peabody Laboratories, will direct the Center's efforts to advance research to better understand and treat tinnitus.

The Center, which opened in 2015 through the generosity of Helene and Tom Lauer, brings together experts and resources to address the clinical problem of tinnitus, a condition affecting more than 50 million Americans and for which there are currently no widely effective treatments.

"The Lauer Center features an extraordinary team of neurotologists, hair cell biologists, audiologists, and auditory neuroscientists. Together, we have an opportunity to make real progress understanding this debilitating and enigmatic disorder," said Dr. Polley. "At the Lauer Center, we want to do more than catalog the physiological signatures of tinnitus. We aspire to identify root causes that will form the basis for new therapeutic approaches. By leveraging the combined power of leading-edge imaging methodologies and rigorous clinical scientific standards, we hope we can help move the field forward."

A leading expert in the function of the auditory cortex, Dr. Polley's research focuses on understanding plasticity in auditory processing centers in the brain after hearing loss. His work combines imaging and electrophysiological approaches in both animal models and human subjects to assess abnormalities in neural activity patterns that may generate tinnitus perception. His research examines the basic neural mechanisms that cause tinnitus and also focuses on how the plasticity of the brain might be engaged to reduce or eliminate the perception of phantom sounds.

The Center's investigators are also working to better understand the role of inner ear damage as the most common trigger in the development of tinnitus, while also developing new imaging strategies to visualize and repair synaptic contacts between cochlear hair cells and auditory nerve fibers.

"Dr. Polley is an expert in auditory brain plasticity who has made important contributions toward tackling the clinical problem of tinnitus," said D. Bradley Welling, MD, PhD, FACS, the Walter Augustus LeCompte Chair of Otolaryngology at Harvard Medical School. "I have no doubt that he and his team will lead the Lauer Center to achieve long-awaited breakthroughs to bring relief to patients with this frustrating condition." ●



**Michael J.
McKenna, MD,**
Named First
Incumbent of the
Joseph B. Nadol, Jr., MD,
Chair in Otolaryngology
at Massachusetts
Eye and Ear

Michael J. McKenna, MD, Professor of Otolaryngology at Harvard Medical School and Chief of Otology and Neurotology at Massachusetts Eye and Ear, has been named the inaugural recipient of the Joseph B. Nadol, Jr., MD, Chair in Otolaryngology at Mass. Eye and Ear.

A world-renowned neurotologic surgeon, Dr. McKenna first joined Mass. Eye and Ear/Harvard Medical School as an otolaryngology resident in 1984. He received his undergraduate degree from the University of California, San Diego, before earning his medical degree from the University of Southern California School of Medicine in Los Angeles. After his residency, he obtained further subspecialty training at the House Ear Institute in Los Angeles as a neurotology and skull base surgery fellow. In 1989, he returned to Boston for an academic appointment at Harvard Medical School and has since devoted his career to improving the lives of patients with ear disorders.

Over the course of nearly thirty years, Dr. McKenna has built a strong clinical practice that is strictly dedicated to caring for patients with needs in otology, neurotology, and skull base surgery. Considering patient care as his most important responsibility, Dr. McKenna sees more than two hundred patients with vestibular schwannomas and other skull base tumors per year. This experience has resulted in numerous clinical publications and invited presentations throughout the years.

Working in his National Institutes of Health (NIH)-funded laboratory, Dr. McKenna directs a robust research program aimed at better understanding the pathophysiology and pathogenesis of otosclerosis, a disease where abnormal deposits of bone form in the ear. The condition is among the most common causes of hearing loss in the general population. Recently, his focus has shifted to the development of better forms of





Top: Mass. Eye and Ear Chief of Otolaryngology Dr. Brad Welling, Dr. Michael McKenna, Dr. Joseph Nadol, Jr., Mass. Eye and Ear Board Chair Wyc Grousbeck, and Mass. Eye and Ear President and CEO John Fernandez

Bottom: Dr. Michael McKenna with his wife, Sue McKenna

Left: Drs. Joseph Nadol, Jr., (left) and Michael McKenna (right)

treatment for otosclerosis based on insights gained from his basic science investigations. Among his many successes, his laboratory was the first to discover an association between the measles virus and otosclerosis, which is considered to be one of the most significant contributions in the area of otosclerosis research in the last fifty years.

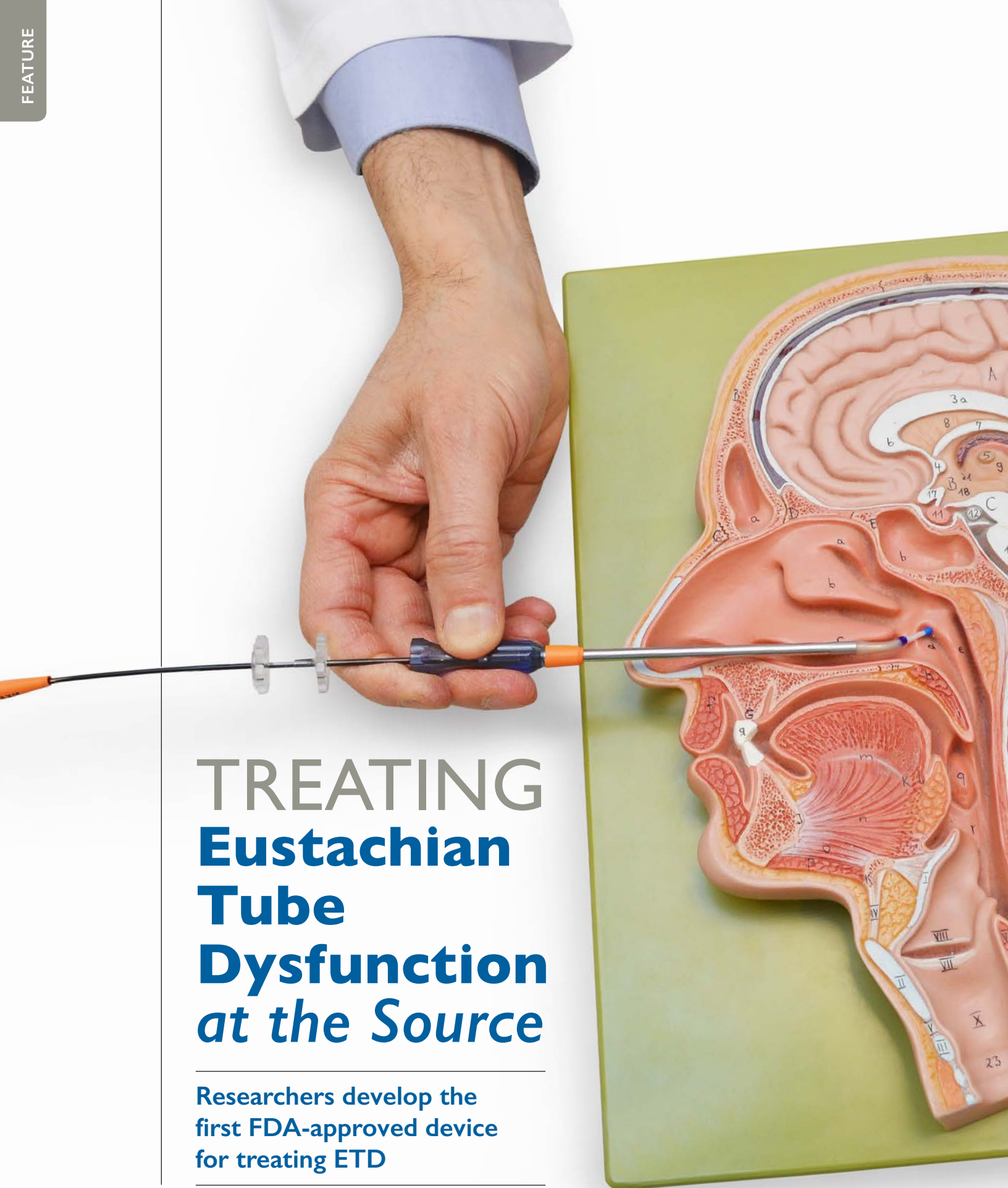
Dr. McKenna's focus has also recently involved developing improved methods for inner ear drug delivery to patients. With studies funded by an NIH Bioengineering Research Partnership grant in conjunction with Draper, a non-profit research development company in

Cambridge, Massachusetts, he is working to develop a versatile long-term drug delivery system for the treatment of inner ear disorders. If successful, this line of investigation could potentially benefit millions of individuals with degenerative inner ear disorders.

A dedication to patient care and research comes together through Dr. McKenna's teaching. From 1994 to 2015, he directed the Neurotology Fellowship Program at Mass. Eye and Ear. He provides young surgeons with advanced training in the diagnosis and treatment of diseases that affect the auditory and vestibular systems, facial nerve, temporal bone, lateral skull base, and related head and neck structures. He also assumes a primary responsibility for the surgical training of senior otolaryngology residents and has been instrumental in the training of more than 75 graduates of the otolaryngology residency program at Harvard Medical School.

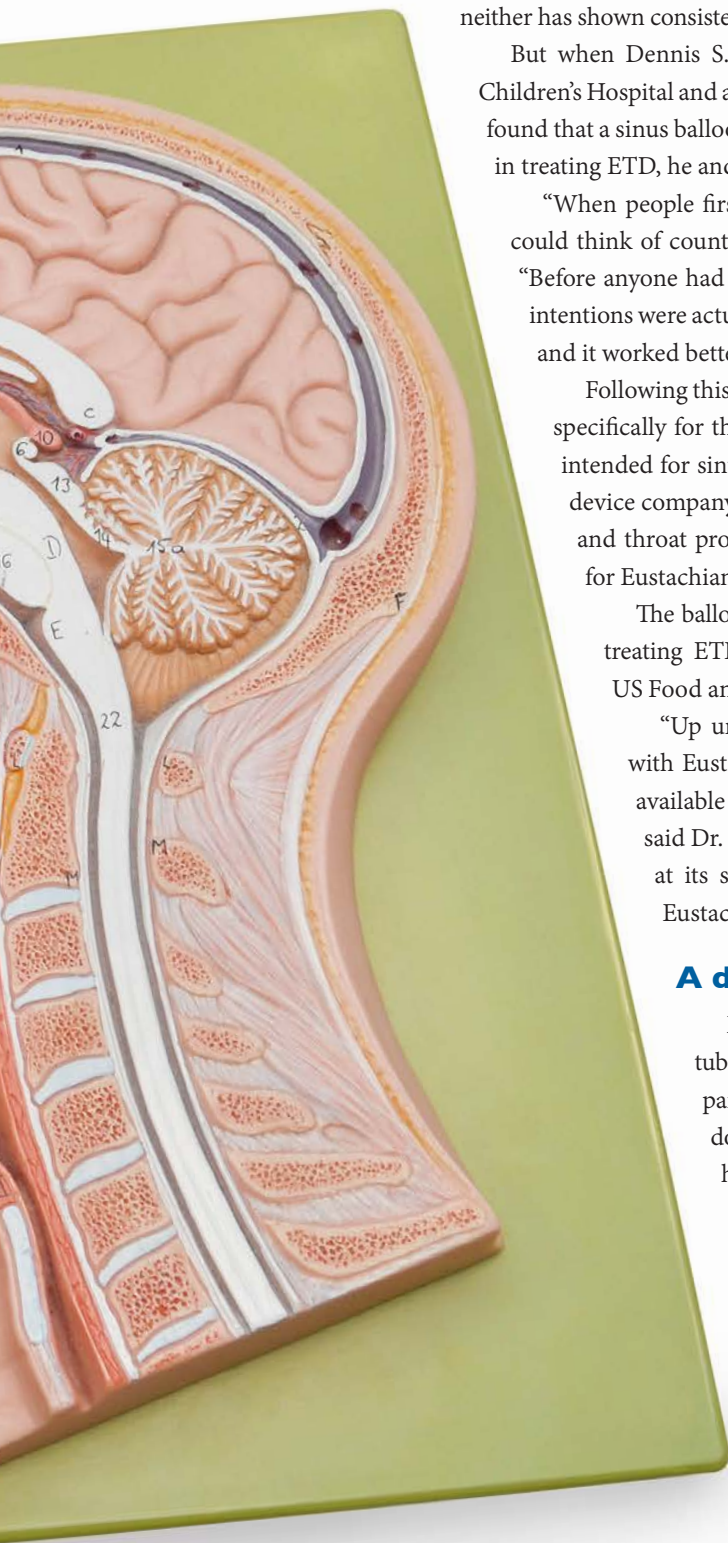
"This endowed chair is, in a sense, a recognition of a lengthy and thoroughly enjoyable relationship with Mass. Eye and Ear over the years and is immensely meaningful to me," said Joseph B. Nadol, Jr., MD, Walter Augustus Lecompte Distinguished Professor of Otolaryngology at Harvard Medical School and Director of the Otopathology Laboratory at Mass. Eye and Ear. "I could not be more pleased that the first incumbent of the Chair will be Dr. McKenna, who is internationally recognized for his many contributions to otology."

Named in honor of Dr. Nadol and made possible through the generosity of alumni, patients, and friends of Mass. Eye and Ear and Harvard Otolaryngology, this endowed chair honors Dr. Nadol's wonderful career as an esteemed leader, gifted researcher, dedicated mentor, and caring physician. ●



TREATING **Eustachian Tube Dysfunction at the Source**

Researchers develop the
first FDA-approved device
for treating ETD



Eustachian tube dysfunction (ETD), a condition often marked by ear pressure, decreased hearing, and ear infections, has always been challenging to treat. Traditionally, patients have been treated with ear tubes or medications, but neither has shown consistency in correcting the underlying problem.

But when Dennis S. Poe, MD, PhD, a neurotologic surgeon from Boston Children's Hospital and a Professor of Otolaryngology at Harvard Medical School, found that a sinus balloon placed into the Eustachian tubes proved to be effective in treating ETD, he and other surgeons began exploring dilation procedures.

"When people first suggested trying a balloon in the Eustachian tubes, I could think of countless reasons why it wasn't going to work," said Dr. Poe. "Before anyone had tried it, I decided to test the balloon in my lab, and my intentions were actually to show why it was a bad idea. But instead, it worked, and it worked better than it was supposed to."

Following this discovery, Dr. Poe set out to build a novel dilation system specifically for the Eustachian tubes, since surgeons were using balloons intended for sinus surgery. He partnered with Acclarent, Inc., a medical device company based in Irvine, California, that specializes in ear, nose, and throat products, to develop the first balloon dilation intervention for Eustachian tube dysfunction.

The balloon dilation device offers a minimally-invasive option for treating ETD and is the first device to receive approval from the US Food and Drug Administration (FDA) for this condition.

"Up until now, doctors have done their best to treat patients with Eustachian tube dysfunction, but unfortunately, the options available to them haven't addressed the root of the problem," said Dr. Poe. "Surgeons now have the option to treat the problem at its source and successfully restore proper function to the Eustachian tube for the first time."

A device that's safe and easy to use

Eustachian tube dysfunction occurs when the Eustachian tubes, which are small passageways connecting the upper part of the throat to the middle ears, become blocked or do not open properly. Normally, the Eustachian tubes help maintain equal pressure inside the middle ear by opening and closing like a valve. When they become blocked, airflow becomes obstructed and causes negative pressure to build up, often leading to pain, tinnitus, a feeling of fullness in the ears, and/or hearing loss.

The procedure uses a catheter to insert a small balloon through the patient's nose and into the

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Dr. Dennis Poe demonstrating how the dilation device is inserted through the nose and into the Eustachian tube.

Eustachian tube. When in position, the balloon is inflated for two minutes, allowing the pathway to re-open and regenerate airflow, releasing the built up pressure. Once the Eustachian tube is adequately dilated, the balloon is deflated and removed.

This system was designed to adapt to the Eustachian tube anatomy and help surgeons minimize trauma through precise access and positioning. Its flexible and appropriately angled distal end helps to insert the balloon component, and its lumen tubing vents air to prevent any buildup of backpressure from the balloon that could otherwise injure the middle and inner ear. Its balloon is designed to gently dilate the cartilaginous portion of the Eustachian tube, and its rounded end will restrict the instrument from passing into the bony portion.

“When designing the device, we had to think about how this is not an area many surgeons have been taught to operate on or even examine since surgery on the Eustachian tubes was condemned in the past from poor outcomes,” said Dr. Poe. “We knew we had to make it safe, but we also wanted to make the device easy to use and not technically challenging. After a lot of work, I think we landed on a good combination of both. It has all of the components that make it safe and easy to use.”

More than symptom management

To receive FDA approval, the device, which is known as the Aera™ system, underwent a randomized clinical trial of 299 patients with chronic ETD at institutions across the country. The study demonstrated a 99.7 percent technical success rate in dilating the Eustachian tube. Of the participants who underwent the surgical procedure, more than half had tympanogram (a method of measuring eardrum mobility and pressure) results within a normal functioning range at six and twenty-four weeks after the procedure. Researchers also noted improvement in quality of life measures across patients and that zero participating organizations reported serious adverse events related to the device or procedure.

Overall, the study went so well that results hit statistical significance, as determined by the FDA, before the original target date and the study ended early.

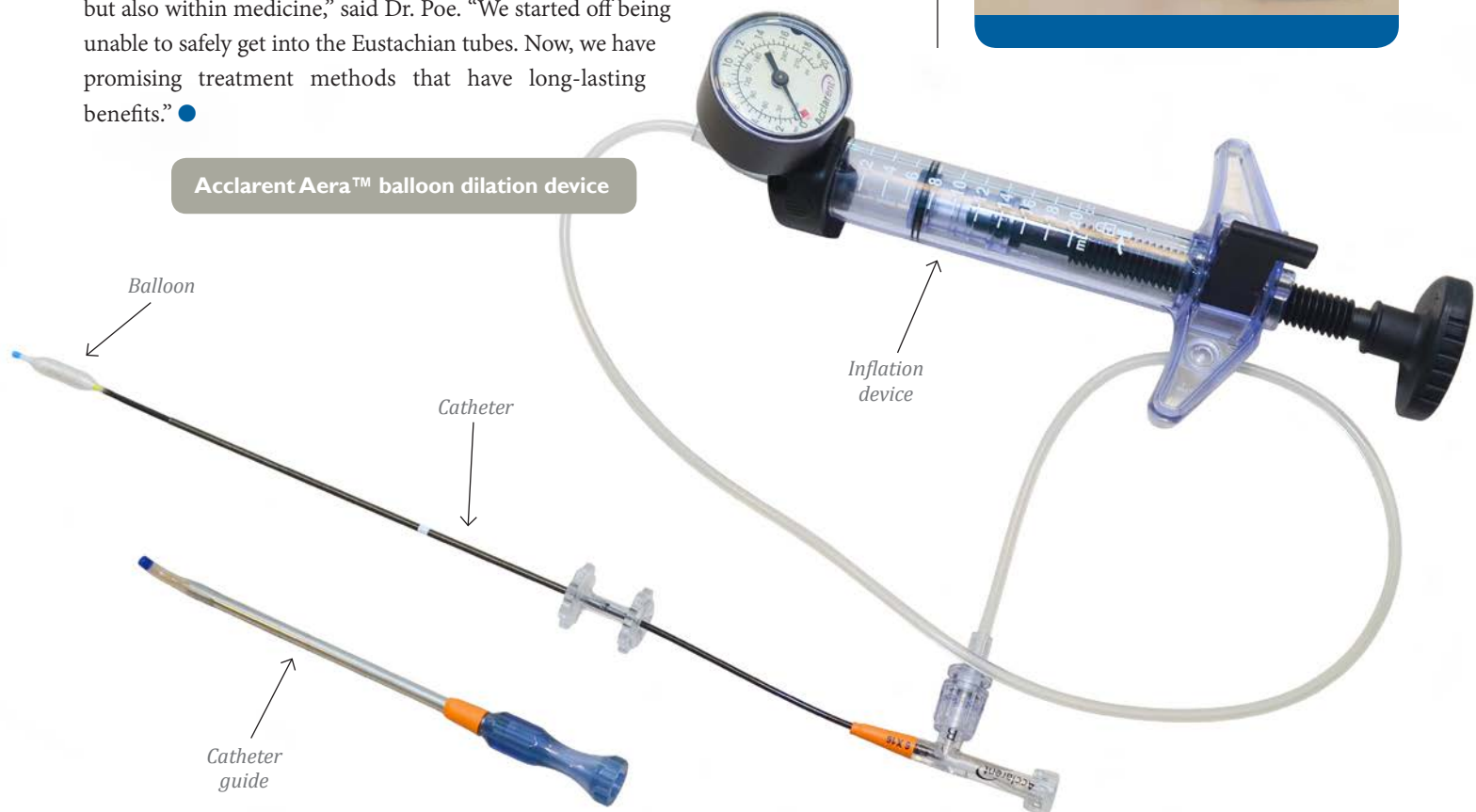
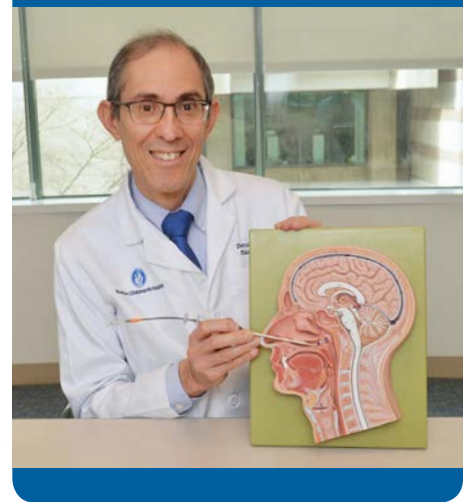
“Many thought that this would be a temporary treatment,” said Dr. Poe. “But it isn’t. Our clinical and histological (tissue) studies show that the benefits of balloon dilation hold up over time and that this device offers more than just symptom management; it successfully restores normal functionality for many patients.”

Looking ahead, the researchers are thinking about the device’s application in children and also beginning to develop a balloon dilation system that can be inserted through the ear. This procedure has allowed the researchers to learn more about the Eustachian tubes and identify a root cause of ETD, which they found to be inflammation in most cases. Knowing this, the researchers have also begun to think about how they can treat the inflammation with medical interventions.

“Balloon dilation of the Eustachian tube may cause a significant paradigm shift in the way we treat Eustachian tube dysfunction, not only from a surgical standpoint, but also within medicine,” said Dr. Poe. “We started off being unable to safely get into the Eustachian tubes. Now, we have promising treatment methods that have long-lasting benefits.” ●

“Many think of this as being a temporary treatment, but it isn’t. Our studies show that the benefits of balloon dilation hold up over time and that this device offers more than just symptom management; it successfully restores normal functionality for many patients.”

–Dr. Poe



Acclarent Aera™ balloon dilation device



Ahmad Sedaghat, M.D.
Department of Otolaryngology

Deconstructing Chronic Sinus Disease

Researchers assess
the manifestations of
chronic rhinosinusitis

*Dr. Ahmad Sedaghat
examining a patient.*

For most patients, the primary consequences of chronic rhinosinusitis (CRS), an inflammatory disease of the paranasal sinuses, are decreased quality of life and lost productivity related to missed work or school. As one of the more prevalent chronic illnesses in the United States, its symptoms can range from classic sinonasal symptoms such as nasal congestion to more subjective symptoms such as depressed mood.

Although previous studies have shown that these symptoms are often associated with quality of life detriments, CRS is a highly heterogeneous disease, meaning its clinical manifestations (disease behaviors or symptoms) may differ from patient to patient. This leaves a lot of variability, especially in what symptoms a patient may experience and the effects those symptoms have on the practical consequences of the disease.

A team of researchers, led by Ahmad R. Sedaghat, MD, PhD, a sinus surgeon at Massachusetts Eye and Ear and Assistant Professor of Otolaryngology at Harvard Medical School, has begun looking beyond what is known about CRS to characterize the disease and uncover its immunological mechanisms. By identifying connections between symptoms, patient characteristics, and how the disease develops, the researchers hope to find potential targets for treating the different symptoms.

“Past research has given us a good sense of what symptoms are associated with CRS, but until we understand how these symptoms arise and impact patients, we’ll be at a disadvantage when treating them,” said Dr. Sedaghat. “Rather than thinking about CRS as just CRS, we are characterizing specific outcome measures for the clinical manifestations of the disease to identify causative inflammatory pathways and their impact on quality of life and lost productivity.”

Understanding the symptomatology of CRS

For a long time, people have thought about the pathophysiology of CRS as a linear process—that inflammation causes symptoms, and that those symptoms can lead to quality of life impairments. However, CRS appears to be more complex than that. Dr. Sedaghat and his team of Harvard Medical School researchers from Mass. Eye and Ear and Beth Israel Deaconess Medical Center are finding that the impact of CRS is

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| Deconstructing Chronic Sinus Disease | continued

instead multi-dimensional, with several factors causing the underlying inflammation and leading to different disease behaviors.

To explore this notion, the researchers identified that the dominating symptoms of CRS tend to occur in four primary clusters: sleep, nasal, otologic, and emotional. In a study published in the *American Journal of Rhinology & Allergy*, they found that each cluster impacts the disease course separately. By studying each group independently, the researchers are beginning to show how these symptom categories differentially impact patients.

For instance, in subsequent studies published in *Rhinology* and *Annals of Allergy, Asthma & Immunology*, they found quality of life was most negatively affected by increased severity of sleep-related symptoms and otologic symptoms (such as ear pressure). Unexpectedly, they found the impact on lost productivity to be different—with depressed mood, and to a lesser extent nasal symptoms, most dominantly impacting the number of days that patients missed work or school due to CRS.

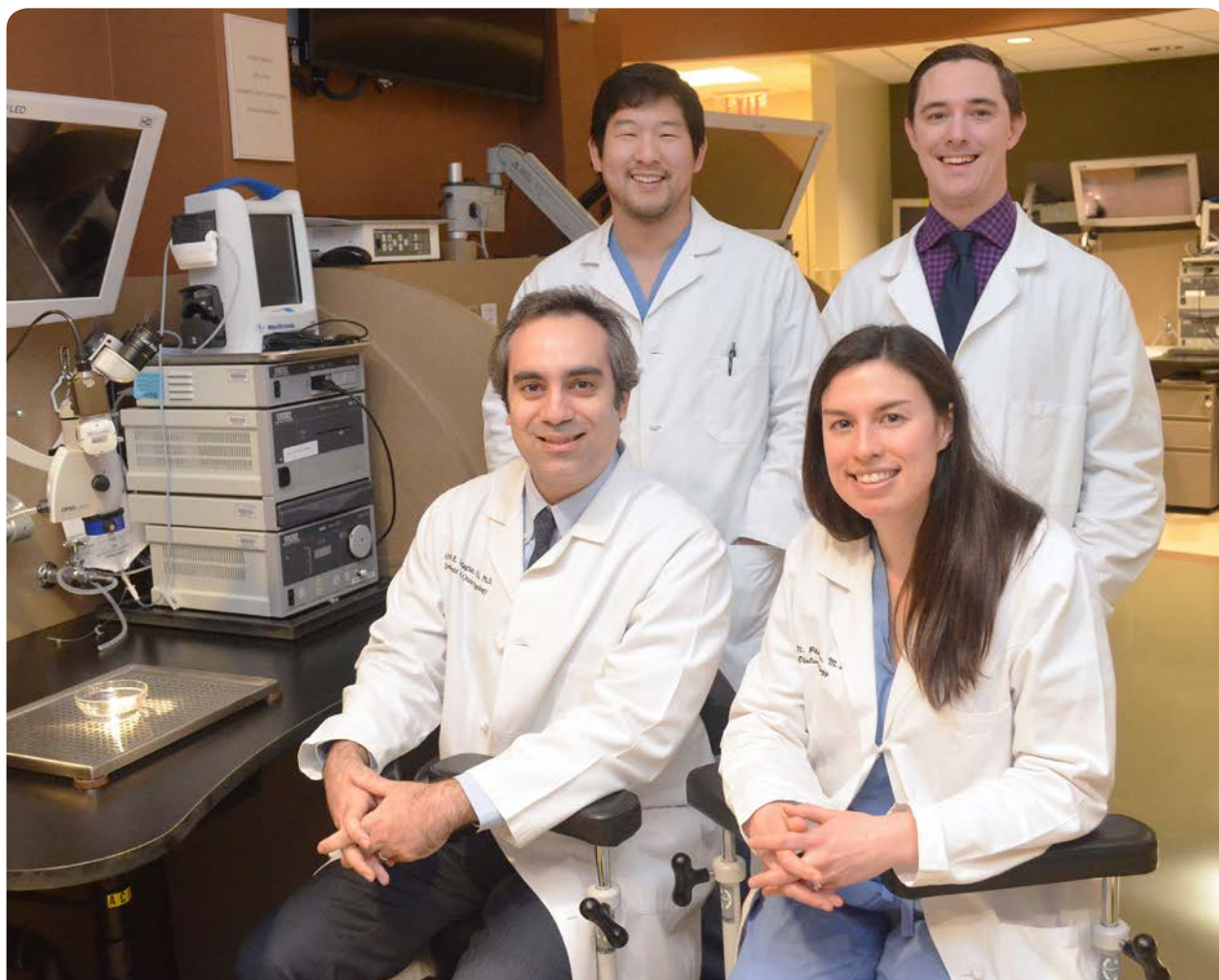
Findings like this could lead to novel insights for the care of patients by better informing physicians about the impact of CRS symptoms in a manner that can be applied on a patient-by-patient basis. Eventually, more specific treatments may be identified.

Acute exacerbations and impact on pulmonary disease

Historically, the dominating symptoms of sinus disease have been considered to be the only factor that negatively impacts patients. However, in addition to identifying the behavior and specific contributions of those symptoms, the researchers have also sought to identify and characterize other clinical manifestations of CRS that suddenly occur.

For example, acute exacerbations of CRS (when symptoms acutely spike in severity, for instance, caused by an acute sinus infection) have been a known component of the disease for many years, but their impact on patients has not been previously reported. Dr. Sedaghat and his team have recently shown that

Dr. Ahmad Sedaghat (bottom left) with members of his research team, including: Harvard Otolaryngology residents Dr. Katie Phillips (bottom right) and Dr. Allen Feng (top left), and Harvard rhinology fellow Dr. Adam Campbell (top right).



the frequency of acute exacerbations in CRS patients significantly contributes to poor quality of life. Published in the *Journal of Allergy and Clinical Immunology: In Practice*, this work has identified acute exacerbations to be one aspect of CRS distinct from the four main symptom categories that can be specifically targeted.

They have also shown that in asthmatic CRS patients, the severity of CRS is directly associated with the control of the patient's asthma. These studies demonstrate how both acute exacerbations and the impact of CRS on comorbid asthma can affect patients in ways that are comparable to the impact of the more dominating, chronic symptoms.

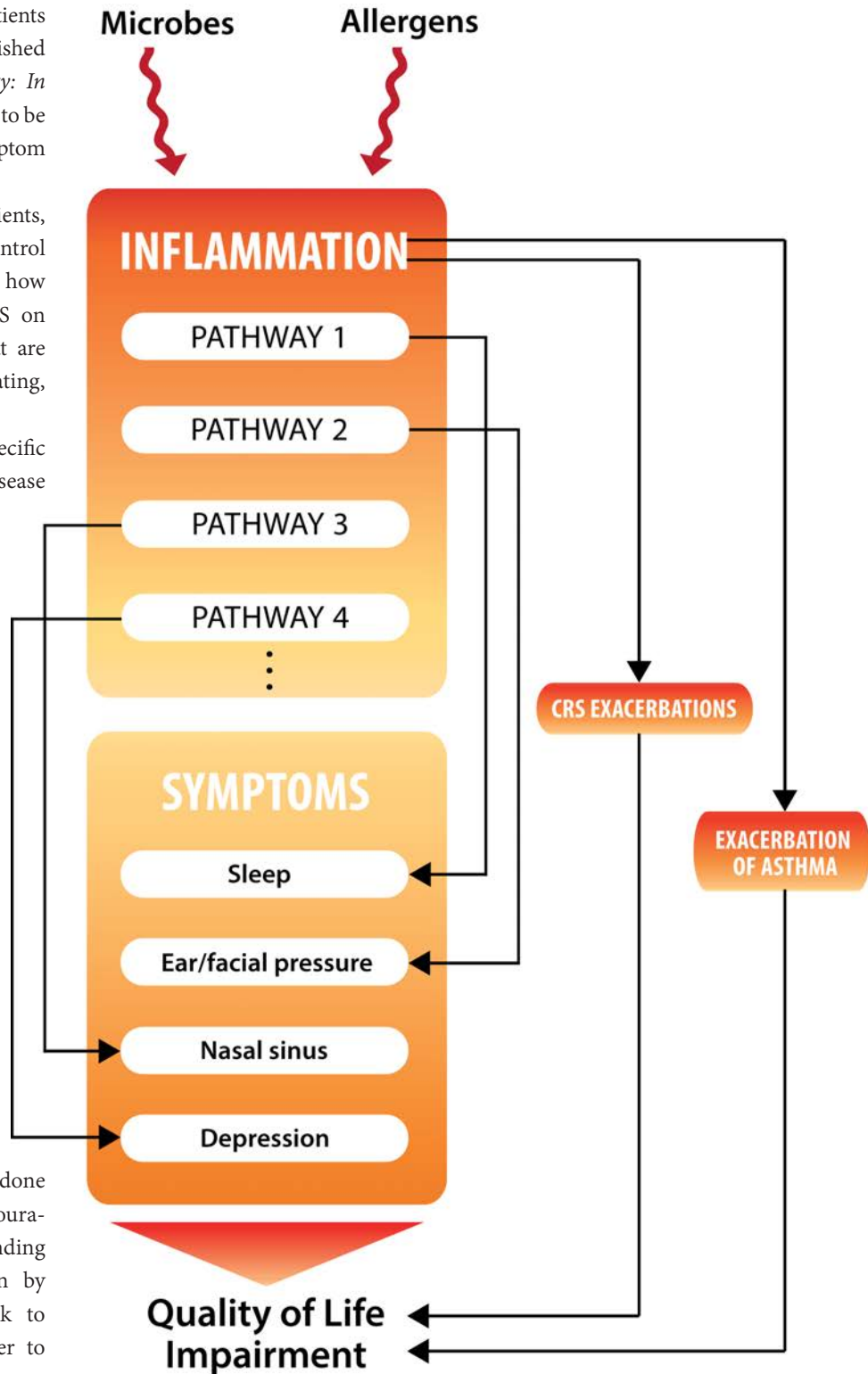
“Our findings so far point to the fact that specific elements of CRS may be driving specific disease manifestations or consequences,” said Dr. Sedaghat. “To specifically tailor our treatment to each patient, we have to be cognizant not just of the overall severity of the disease, but also of the severity of its individual aspects, symptoms, and characteristics.”

Looking ahead

Eighteen months in, this work is still in its early stages; however, the research team's findings are already paving the way for studying more individualized therapy options that could improve quality of life and reduce productivity losses in patients.

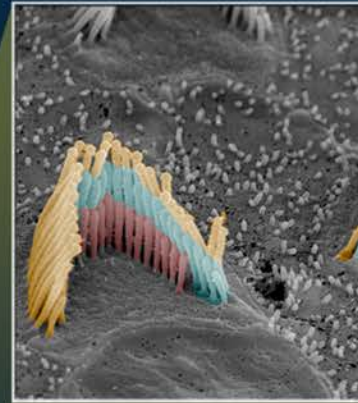
In addition to providing more insights on the disease's pathophysiology and the development of new treatment options, there is hope that this work could eventually lead to the development of preventative measures as well.

“We still have a long way to go until we fully characterize CRS, but the work that we've done is already informing my patient care, which is encouraging,” said Dr. Sedaghat. “We are understanding that each clinical manifestation is likely driven by distinct immunologic mechanisms. As we work to identify those mechanisms, we are coming closer to helping patients.” ●



A conceptual framework for characterizing the inflammatory mechanisms (causes) of CRS and translating them to their corresponding clinical manifestations (symptoms).

New Hope for **HEARING RESTORATION**

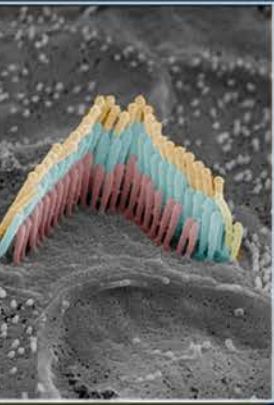


Pseudocolor image showing normal hair bundle morphology in mutant mice treated with Ush1c gene therapy.

Improved gene delivery vector reaches inner and outer hair cells for the first time, restoring hearing and balance function

Anc80L65 viral vectors targeted inner and outer hair cells after round window membrane injection in newborn mice. Top panel shows three rows of outer hair cells, with one row of inner hair cells (red) overlaying the bottom panel. Bottom panel shows green fluorescent protein expression (green), driven by the viral vector, is detected in a large number of outer and inner hair cells.

Often caused by the absence or dysfunction of hair cells, genetic hearing loss affects more than 125 million people worldwide. While research has shown that various genetic diseases can be cured in animals and humans using gene therapy, efforts to develop gene therapies for hearing loss haven't been as successful.



Many gene therapy approaches in the inner ear suffer from an inability to enter the cells of the cochlea, particularly a subset of cells known as outer hair cells, which amplify and tune the response to sound. Some methods have seen success in targeting inner hair cells, which detect sound waves and send information to the brain; however, these

methods can only recover partial hearing. In many cases of genetic deafness, delivery of genes to both cell types is needed to confer normal hearing ability.

Synthesized in the Grousbeck Gene Therapy Center at Massachusetts Eye and Ear, a synthetic virus, which is known as Anc80, has become one of the first viral vectors to reach both cell types successfully when injected through the round window. Presenting no adverse effects, this vector has safely transferred genes to both inner and outer hair cells when introduced into the cochlea.

“Up until now, it has been challenging to treat hearing loss with gene therapy,” said Lukas Landegger, MD, a research fellow in the Molecular Neuro-Otology and Biotechnology Laboratory at Mass. Eye and Ear/Harvard Medical School. “But now, by identifying a viral vector that can reach and transduce inner and outer hair cells, we have an encouraging means for reversing hearing loss completely.”

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“We have shown that Anc80 works remarkably well in transducing cells of interest in the inner ear. This is very exciting because it opens up possibilities to address many forms of genetic deafness by using a viral vector that appears to be better than what’s currently available.”

— Dr. Stankovic

Drs. Konstantina Stankovic (left) and Lukas Landegger (right)



Uptake in various cells inside the ear

Viral vectors are attractive potential vehicles for therapeutic gene transfer as viruses naturally infect by introducing their genetic information into cells in order to replicate and proliferate. However, when patients have been previously exposed to the virus, their immune system will likely target the gene therapy vector and inactivate it.

Hoping to overcome the challenges with immunity, Luk H. Vandenberghe, PhD, Director of the Grousbeck Gene Therapy Center and Assistant Professor of Ophthalmology at Harvard Medical School, reconstructed an ancient virus that is the predicted ancestor of currently available adeno-associated viruses (AAVs) to develop the synthetic AAV Anc80. This vector is unique as it is a made-by-design vector system as opposed to most AAVs, which are natural isolates. By engineering a new, benign virus, Dr. Vandenberghe aimed to render the vector less recognizable to the host immune system in patient populations that stand to benefit from gene therapy.

After successfully targeting the liver, muscle, and retina without producing toxic side effects, Dr. Vandenberghe had an idea of using Anc80 in the ear. To evaluate its effectiveness in transferring genes to the cochlea, Dr. Vandenberghe began working with Konstantina M. Stankovic, MD, PhD, FACS, an otologic surgeon at

Mass. Eye and Ear and Associate Professor of Otolaryngology at Harvard Medical School, and her research fellow, Dr. Landegger.

In a study published in *Nature Biotechnology*, the researchers evaluated cochlear gene transfer using commonly used AAVs alongside Anc80 *in vitro*. This demonstrated efficient inner and outer hair cell transduction (60 to 100 percent). Then, a research team at Boston Children's Hospital (BCH), led by Jeffrey R. Holt, PhD, Director of Research at BCH and Professor of Otolaryngology and of Neurology at Harvard Medical School, delivered Anc80 directly through the round window membrane. They found it to be highly effective in driving expression of green fluorescent protein (GFP) throughout the cells of the inner ear, reaching 90 percent of all inner and outer hair cells in the cochlea.

"Anc80 was developed to address an important immunological concern in gene therapy," said Dr. Vandenberghe. "However, in subsequent studies, we found that this first-of-its-kind designer viral vector also targets cells in a unique manner that allows it access to cochlear hair cells with an efficiency that was not observed to date."

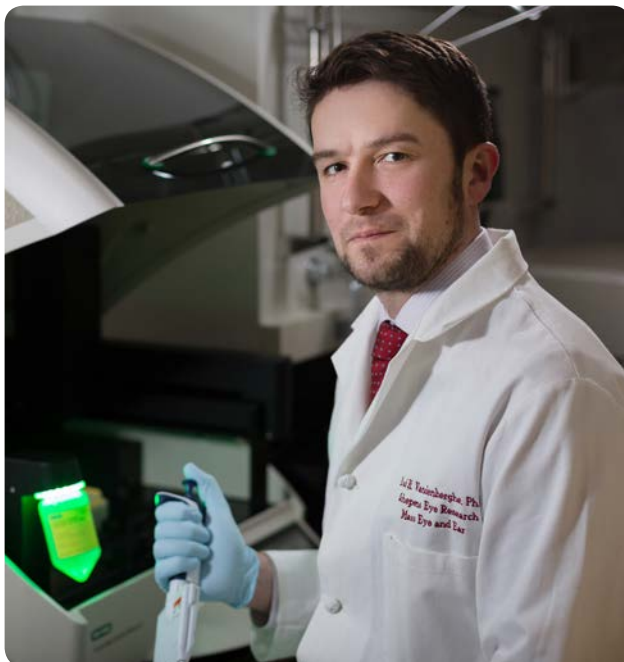
The vector was also able to target outer hair cells at high rates, an important component for restoring auditory function. Collaborating scientists at the University College London further tested the vector on human vestibular tissue in a dish and obtained the same results.

"We have shown that Anc80 works remarkably well in transducing cells of interest in the inner ear," said Dr. Stankovic. "This is very exciting because it opens up possibilities to address many forms of genetic deafness by using a viral vector that appears to be better than what's currently available. With more than 100 genes already known to cause deafness in humans, there are many patients who may eventually benefit from this technology."

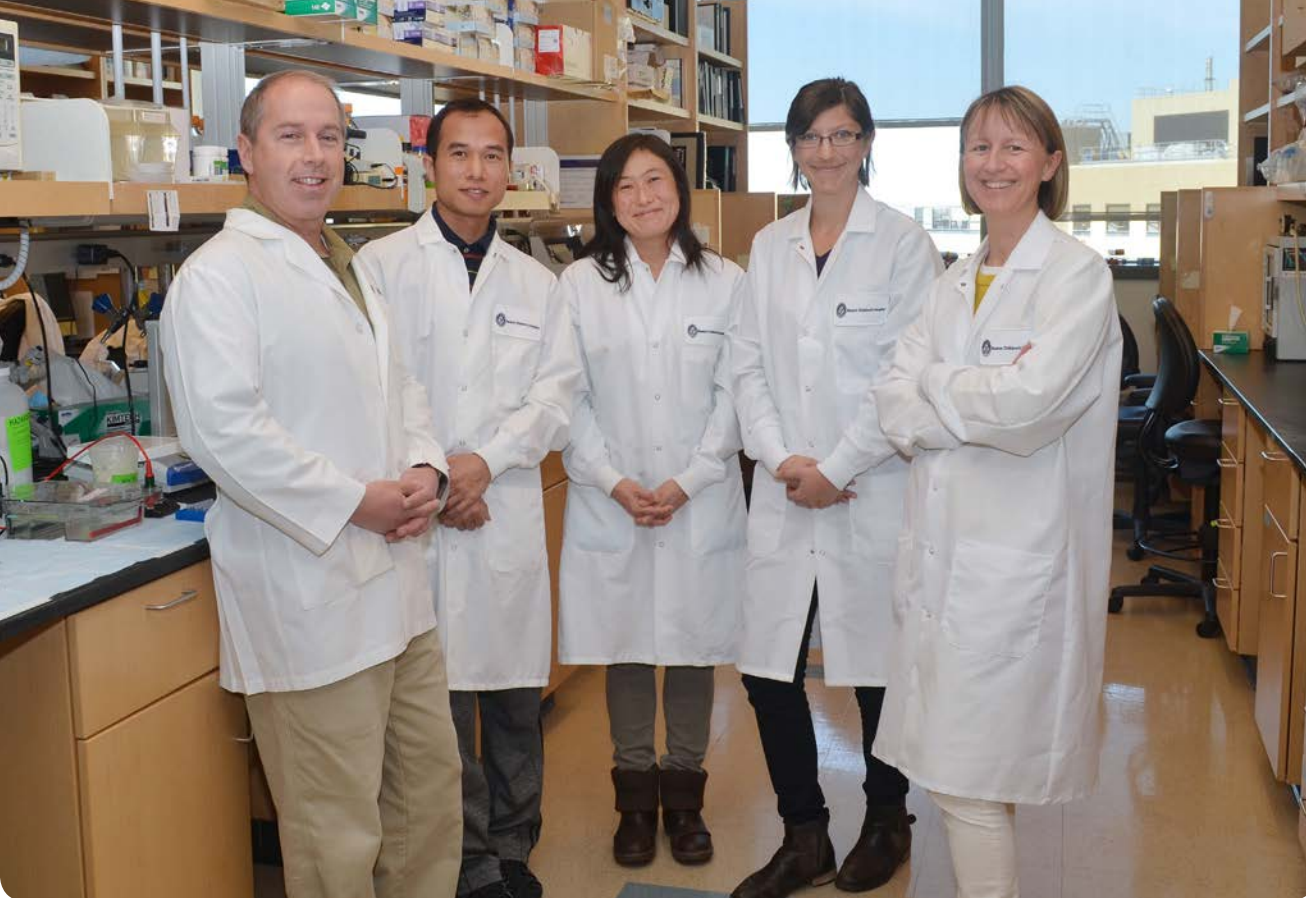
A potential for restoring hearing and balance

A research team led by Gwenaëlle Géléoc, PhD, Assistant Professor of Otolaryngology at Harvard Medical School and researcher in the Department of Otolaryngology and at the F.M. Kirby Neurobiology Center at Boston Children's Hospital, took this work a significant step further. Dr. Géléoc and her team used the vector to treat mice carrying a mutated gene responsible

Photo by Pierce Harman



Dr. Luk Vandenberghe in the Grousbeck Gene Therapy Center.



From left to right:
 Drs. Jeffrey Holt,
 Bifeng Pan, Yukako
 Asai, Sarah Gluck,
 and Gwenaëlle Géléoc

for Usher syndrome type 1C, a devastating genetic disorder that causes deafness, balance dysfunction, and blindness in children.

Dr. Vandenberghe had been working with Dr. Géléoc on this program, aiming for a gene therapy treatment for both the hearing and visual dysfunction of this type of Usher syndrome.

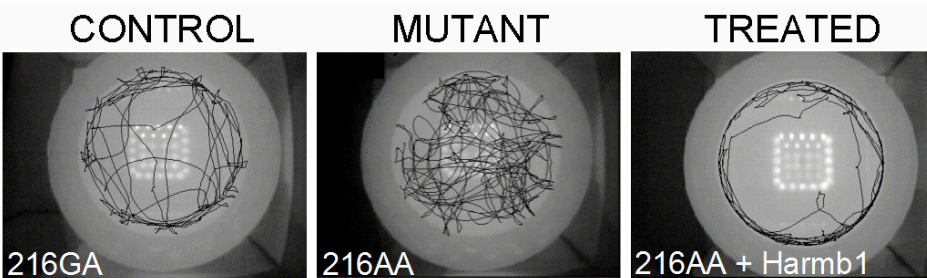
Also reported in *Nature Biotechnology*, the scientists inserted genes with the right coding sequence of the mutated DNA into the cochlea of newborn mice. This led to high levels of Ush1c protein in inner and outer hair cells (80 to 90 percent of sensory hair cells), a repair of damaged hair cell bundles, and a robust improvement in hearing and balance behavior.

The scientists first showed this using a “startle box,” which detects whether a mouse jumps in response to sudden loud sounds. When they measured responses in the auditory regions of the brain, a more sensitive test, the mice responded to much quieter sounds—19 of 25 mice heard sounds quieter than 80 decibels, and a few could hear sounds as soft as 25 to 30 decibels, like normal mice.

“The Ush1C gene is expressed in both inner and outer hair cells, and to obtain restoration of hearing and balance function in patients, gene delivery systems that target both auditory and vestibular sensory cells will be needed,” said Dr. Géléoc. “What we’ve accomplished is a proof of principle—that this approach can restore function to the level of normal hearing in mice. It’s the first time that we’ve got this level of rescue.”

“This is a landmark study,” said Dr. Holt, who was involved in both studies. “If we can continue to improve on our work and target different forms of genetic deafness, we could have biological treatments for hearing loss, which is something there’s never been before.”

continued on page 18



In an open arena, mice with Ush1c mutations display circling behavior, indicating balance dysfunction. Mutant mice treated with the vector that encodes the correct protein demonstrate normal balance function, similar to healthy control mice.

Pan B, Askew C, Galvin A, Heman-Ackah S, Asai Y, Indzhukulian AA, Jodelka FM, Hastings ML, Lentz JJ, Vandenberghe LH, Holt JR, Géléoc GS. Gene therapy restores auditory and vestibular function in a mouse model of Usher syndrome type 1c. *Nat Biotechnol.* 2017 Mar;35(3):264–272.

| New Hope for Hearing Restoration |

A promising future

While the Anc80 vector is a promising technology for treating hearing loss and balance dysfunction, both research teams will need to perform further studies before it can be brought to patients.

One caveat to these studies is the mice were treated right after birth. Although the effects of the treatment persisted for at least six months in the injected newborns, with only a slight decline between six weeks and three months, hearing and balance were not restored when the gene therapy was delayed 10 to 12 days.

Looking ahead, the researchers plan to investigate reasons for this and also test the technology in larger animal models. Also, knowing that Usher syndrome is only one of many genetic disorders causing deafness, the researchers plan to further investigate opportunities for therapeutic intervention in other forms of genetic hearing loss and eventually, develop novel gene therapies to treat these disorders.

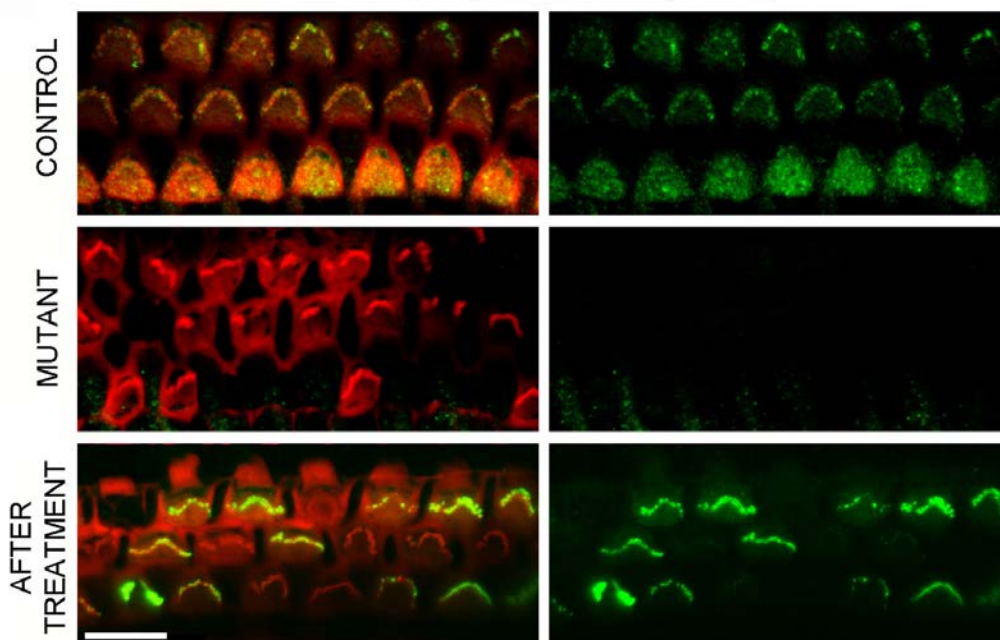
“Hearing loss, in general, is a huge problem,” said Dr. Landegger. “Ideally, we want to help patients by restoring their natural ability to hear, and this work hopefully brings us one step closer to that.” ●



“What we’ve accomplished is a proof of principle—that this approach can restore function to the level of normal hearing in mice. It’s the first time that we’ve got this level of rescue.”

— Dr. Géléoc

ACTIN (RED); HARMONIN (GREEN)



Harmonin protein encoded by the Ush1c gene is detected in healthy control mice, absent in Ush1c mutant mice, and is recovered after treatment with the viral vector in mutant mice.

This work was supported by Giving/Grousbeck, Ush2A Consortium, NIH 5DP1EY023177, the Bertarelli Foundation, the Kidz-b-Kidz Foundation, the Foundation Fighting Blindness, the Jeff and Kimberly Barber Gene Therapy Research Fund, and the Manton Center for Orphan Disease Research at Boston Children’s Hospital. Dr. Luk Vandenberghe is an inventor on Anc80 (patent #WO/2015/054653) and other gene transfer technologies, for which he receives royalties. These technologies are licensed to several gene therapy companies, some of which fund research in Vandenberghe’s laboratory (Selecta Biosciences and Lonza Houston).

*Pan B, Askew C, Galvin A, Heman-Ackah S, Asai Y, Indzhykuliaan AA, Jodelka FM, Hastings ML, Lentz JJ, Vandenberghe LH, Holt JR, Géléoc GS. Gene therapy restores auditory and vestibular function in a mouse model of Usher syndrome type 1c. *Nat Biotechnol.* 2017 Mar;35(3):264–272.*



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Alumni Giving Society

The Alumni Giving Society of the Department of Otolaryngology at Harvard Medical School

The Department of Otolaryngology at Massachusetts Eye and Ear/Harvard Medical School established the Alumni Giving Society in 2015 to recognize faculty and alumni who make gifts of \$1,000 or more during the fiscal year (October 1–September 30). Participation is a way to stay connected and to help deliver the finest teaching experience for today’s otolaryngology trainees.

Our alumni know from firsthand experience that support of the vital work of our students and faculty in the Department of Otolaryngology helps drive continued achievement across all areas of education, research, and patient care. To date, we have 30 members whom we thank for their generosity and for partnering with us to achieve our department goals and institutional mission.

If you are not a member, please consider joining your colleagues today by making a gift with the enclosed envelope. As a member, you may designate your gift in the way that is most meaningful to you.

To learn more, please contact Julie Dutcher in the Development Office at 617-573-3350.

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Medical Director, Otolaryngology, Mass. Eye and Ear, Stoneham

Stacey T. Gray, MD, '04, '05

Program Director, Residency in Otolaryngology–Head and Neck Surgery, Harvard Medical School
Director, Sinus Center, Mass. Eye and Ear

Top: K. J. Lee, MD, FACS, and Robert C. Wang, MD, FACS

Bottom: Raj Sindwani, MD, Stacey T. Gray, MD, William C. Yao, MD, and Christopher D. Brook, MD



K. J. Lee, MD, FACS, HMS Otolaryngology Resident, Class of 1970

Blending great outcomes with compassionate care



Being introduced to ear, nose, and throat care at a young age helped influence K. J. Lee, MD, FACS, to pursue a career in otolaryngology.

“When I was a teenager, I developed facial paralysis due to an ear infection, which progressed into mastoiditis (an infection in the mastoid bone) and had to be treated with a mastoidectomy (a procedure removing diseased mastoid air cells),” said Dr. Lee. “This experience, coupled with my surgical interest in fine structures, is what led me down the path of becoming an otolaryngologist subspecializing in otology.”

Now an Emeritus Professor at Yale University and Co-Founder of The Patient Is U Foundation (TPIU), Dr. Lee has built a career using his experience as a patient to enhance the care he provides. Through his many publications and work in the field, he has dedicated himself to developing technologies and crafting guidelines that keep the patient at the forefront of healthcare.

Known as a world-renowned clinician, educator, author, innovator, and health policy advisor, Dr. Lee graduated from Harvard University before attending medical school at Columbia University. He completed his surgical residency at St. Luke’s Hospital/Columbia University

and his otolaryngology residency at Massachusetts Eye and Ear/Harvard Medical School.

As a first-year resident at Mass. Eye and Ear, he volunteered to help the former Harvard Medical School Chair of Otolaryngology, Harold F. Schuknecht, MD, with a project involving a rigorous study of more than 1,000 mastoidectomy tympanoplasty cases. Under the mentorship of Dr. Schuknecht, this work led to a landmark paper and was really the beginning of his career in otology.

“I distinctly remember standing in an elevator with Dr. Schuknecht and over-hearing a conversation that compelled me to volunteer for this project,” said Dr. Lee. “Working with Dr. Schuknecht showed me the importance of precise scientific method and how fascinating otology can be.”

In 1972, Dr. Lee joined Yale University and became the Chief of Otolaryngology at the Hospital of Saint Raphael, a position he held for more than 20 years. During this time, he served as the Hospital Medical Staff President, Chair of the Hospital Medical Board, Vice Chair of an HMO insurance company, and as the President and Treasurer of the American Academy of Otolaryngology—Head and Neck Surgery.

While at Yale, he also published the first of many editions of *Essential Otolaryngology*—a text that has been translated into several languages, is regarded as one of the most widely read textbooks in otolaryngology in the world, and is now in its 11th edition.

Well-known for his knowledge of health information technology and policy, Dr. Lee has always held a primary focus on creating technologies that simplify physician workflow and ensuring government mandates do not hinder

patient care. He has advised United States presidential candidates and Members of Congress on health policy, and in 2004, sponsored the Bipartisan Presidential Health Care Summit in conjunction with the Center for Congressional and Presidential Studies at American University. He has also designed a user-friendly interface for electronic medical records to improve efficiency and monitor pay-for-performance.

Dr. Lee’s latest venture has been co-founding The Patient Is U Foundation, which aims to bring the focus back on patients. To have success in healthcare, Dr. Lee believes that we need to concentrate on patient needs and work on bringing healthcare to those who need it most at a reasonable cost.

“When I started in the medical field, healthcare was between the patient and the doctor,” said Dr. Lee. “Now, because of the influx of business into healthcare, this has escaped us, and I want to change that.”

“TPIU is about educating doctors, healthcare providers, government officials, insurance companies, and anyone with patient contact to treat each patient as if the patient is you,” he continued. “By focusing on the patient and making healthcare more accessible, we will be able to treat patients with the service they deserve and achieve better outcomes.”

To foster education regarding how spirituality and compassion may influence medical care, he has endowed the C. T. Lee Lectureships (named after his parents) at Yale University, Columbia University, and, now, at Mass. Eye and Ear/Harvard Medical School.

Of all the successes Dr. Lee has seen throughout his career, he sees his family as his greatest accomplishment. ●

Anthony Wei Peng, PhD, Eaton-Peabody Laboratories at Massachusetts Eye and Ear/ Harvard Medical School, 2003–2006

Bridging the gap between biology and engineering

Combining his interests in biology and engineering with his desire to study sensory systems is what led Anthony Peng, PhD, to become an auditory neuroscientist.

“When studying electrical engineering in college, I took a neuroscience course and instantly became intrigued with biology,” said Dr. Peng, an Assistant Professor of Physiology and Biophysics at the University of Colorado (CU) Anschutz Medical Campus. “It was from there that I found a way to mix biology with my engineering background. I had become interested in the sensory systems, an area I realized biology and engineering could both be applied.”

Originally from the Washington, DC area, Dr. Peng received his bachelor’s of science in electrical and computer engineering from Cornell University before completing his PhD in the Speech and Hearing Bioscience and Technology program at Harvard Medical School/Massachusetts Institute of Technology. It was during his doctoral studies that he developed a strong background in auditory research, working in the Eaton-Peabody Laboratories with former Harvard Medical School faculty member Stefan Heller, PhD, who is now a Professor of Otolaryngology at Stanford University School of Medicine.

“I joined the Heller Lab because, like me, Dr. Heller was thinking about how to get auditory neurons to grow toward the electrodes of a cochlear implant in a controlled fashion,” said Dr. Peng. “But once I began working in his lab, I found myself taking a different path. I became interested in hair cells and how hair cells function, looking to find new proteins

that are important in the stereocilia hair bundle.”

Under the guidance of Dr. Heller, Dr. Peng focused his dissertation on using molecular biology techniques to investigate the genetic and developmental processes associated with the assembly and function of the hair bundles of the vertebrate inner ear. His work provided identification of new molecules that play an important role in hair bundle structure and function, which has influenced the work he now does.

“After completing my thesis, I decided that the best way I could help improve hearing loss was through the basic understanding of how the system worked,” said Dr. Peng. “Understanding the fundamental mechanisms will allow us to figure out what happens in disease and even ways of augmenting signals or helping to fix the issues.”

Dr. Peng continued his work as a post-doctoral fellow with Anthony Ricci, PhD, a Professor of Otolaryngology and of Molecular and Cellular Physiology at Stanford. Here, he completed his scientific circle by using his engineering background to explore sensory hair cell mechanotransduction (converting mechanical signals into electrical signals, a critical step in our ability to hear sounds and the major function of the stereocilia hair bundle) with electrophysiological and optical technologies. He focused on the mechanisms of hair cell adaptation, and this work could eventually result in new models of mechanotransduction being formulated.

In 2015, Dr. Peng moved to CU Anschutz to join the Physiology and Biophysics



Department and develop the Peng Lab. In his lab, his team has a strong focus on electrophysiology and continuing his research in understanding the molecular mechanisms of the mammalian auditory mechanotransduction process.

“Understanding these mechanisms will allow us to understand the roles they play in the amplification and processing of sound,” said Dr. Peng. “This line of work could be the first step in directly answering questions about how we sense sound and correcting problems that arise from failures in the system.”

“Sensory systems, in general, are very interesting. They’re how we interact with the world. Our sense of hearing alone requires a complex process of amplifying sound vibrations (mechanical) and converting them into electrical signals sent to the brain,” he continued. “In this process, the key mechanical-to-electrical conversion step remains poorly understood in our hearing organ and the ultimate goal of my work is to change that.” ●

News from every corner of the Department of Otolaryngology at Harvard Medical School.

New Faculty



Sukgi Choi, MD, joined the Department of Otolaryngology and Communication at Boston Children's Hospital/Harvard Medical School in March. Dr. Choi received

her medical degree from the Icahn School of Medicine at Mount Sinai prior to completing her otolaryngology residency at the Mount Sinai Medical Center and her pediatric otolaryngology fellowship at the University of Cincinnati Children's Hospital. Joining us from the Children's Hospital of Pittsburgh, she sees otolaryngology patients at both Boston Children's and Boston Medical Center.



Jason I. Kass, MD, PhD, is a head and neck surgeon at Brigham and Women's Hospital/Harvard Medical School and the Dana-Farber Cancer Institute. Dr. Kass completed his MD/PhD at

Boston University School of Medicine in anatomy and neurobiology prior to completing his residency in head and neck surgery at the University of Pittsburgh Medical Center. He then completed fellowship training in advanced head and neck oncology and microvascular reconstruction at the Icahn School of Medicine at Mount Sinai. His clinical expertise is in the multidisciplinary management of head and neck cancers, including transoral robotic surgery and microvascular reconstruction using free tissue transfer.

New Leadership



Benjamin S. Bleier, MD, has been named the Director of Endoscopic Skull Base Surgery at Mass. Eye and Ear.

Awards, Grants, and Honors

Neil Bhattacharyya, MD, FACS, chaired and first authored the American Academy of Otolaryngology—Head and Neck Surgery's clinical practice guideline on benign paroxysmal positional vertigo (BPPV).

Thomas Leigh Carroll, MD, is the Program Chair for the 2017 Fall Voice Conference in Alexandria, Virginia, and is the 2016–2017 Chair-Elect for the Laryngology and Bronchoesophagology Education Committee.

Jeffrey Tao Cheng, PhD, received an R01 grant award for his project titled, "Eardrum function in live and cadaveric ears: Research and clinical relevance."

Michael J. Cunningham, MD, FACS, was the Bryan Bailey Visiting Professor and Guest Lecturer for the Department of Otorhinolaryngology at the University of Oklahoma.

Bertrand Delgutte, PhD, Program Director of the Harvard Medical School/Massachusetts Institute of Technology Program in Speech and Hearing Bioscience and Technology (SHBT), announced the program's NIH training grant has been renewed.

Daniel G. Deschler, MD, FACS, is the President-Elect for the New England Otolaryngological Society (NEOS). He also received a nomination for the 2017 Excellence in Mentoring Awards given by Harvard Medical School.

Stacey T. Gray, MD, has been named the President of Otolaryngology Staff and the President-Elect for the Medical Staff at Mass. Eye and Ear. Additionally, she recently became a member of the editorial board for *International Forum of Allergy & Rhinology*.

Janani Iyer, Speech and Hearing Bioscience and Technology PhD student at Harvard Medical School/Massachusetts Institute of Technology, has won the National Defense Science and Engineering Graduate Fellowship from the Department of Defense to study optical imaging of the inner ear.

David H. Jung, MD, PhD, won an American Otolological Society research grant for 2017 in the amount of \$50K.

Margaret A. Kenna, MD, MPH, FACS, FAAP, wrote an editorial for *The New England Journal of Medicine* titled, "Acute Otitis Media – The Long and Short of It."

Sharon G. Kujawa, PhD, has been selected to receive the biennial Callier Prize in Communication Disorders. Presented by the Callier Center for Communication Disorders at the University of Texas at Dallas, the prize recognizes individuals from around the world for their leadership in fostering scientific advances and significant developments in the diagnosis and treatment of communication disorders.

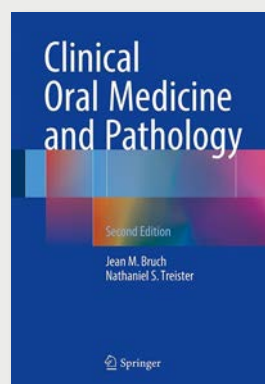
New textbooks:

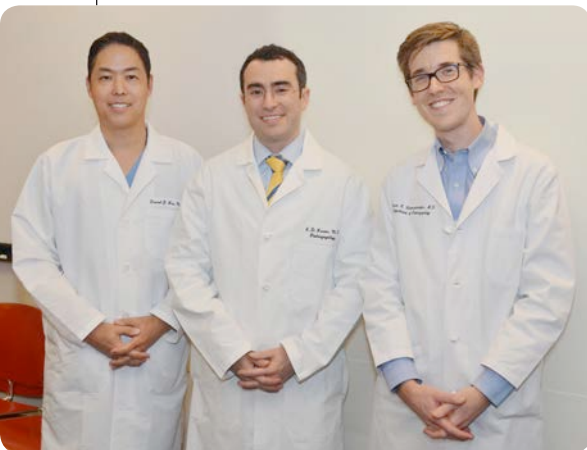
Clinical Oral Medicine and Pathology

Jean M. Bruch, DMD, MD, recently celebrated the release of the second edition of *Clinical Oral Medicine and Pathology*. This textbook serves as an authoritative contemporary resource for clinicians seeking guidance in the diagnosis and management of oral diseases.

Dizziness: Why You Feel Dizzy and What Will Help You Feel Better

Gregory T. Whitman, MD, recently released his book, *Dizziness: Why You Feel Dizzy and What Will Help You Feel Better*, which explores the different conditions that can cause dizziness, offering insights on the types of dizziness people can experience and describing what people with dizziness can do to feel better.





From left to right: Drs. Daniel Lee, Elliott Kozin, and Aaron Remenschneider

Daniel J. Lee, MD, FACS, Elliott D. Kozin, MD, and Aaron K. Remenschneider, MD, MPH, were awarded an American Hearing Research Foundation grant titled, “Application of diffusion tensor imaging to evaluate central auditory pathways in patients with congenital deafness” for 2017–2018.

Dr. Kozin (Mass. Eye and Ear/Harvard Medical School resident) and **Dr. Remenschneider** also received funding from the Ellison Foundation for their project titled, “Three-dimensional printed eardrums for repair of traumatic perforations.”

Brian M. Lin, MD, Mass. Eye and Ear/Harvard Medical School resident, has been selected by the *American Journal of Epidemiology* (AJE) and the Society for Epidemiologic Research (SER) as one of ten 2016 AJE Reviewers of the Year.

Robin W. Lindsay, MD, became a member of the editorial board for *JAMA Facial Plastic Surgery*. She was also on the faculty at the Advances in Rhinoplasty meeting in Chicago this spring.

Katie M. Phillips, MD, Mass. Eye and Ear/Harvard Medical School resident, received the John J. Conley, MD Resident Research Award from the Eastern Section of the Triological Society.

Sidharth V. Puram, MD, PhD, Mass. Eye and Ear/Harvard Medical School resident, was the recipient of Richard J. Bellucci, MD Resident Research Award from the Eastern Section of the Triological Society and received the Broad Next10 Translation research grant with Co-PI and fellow resident **Anuraag Parikh, MD.**

Reza Rahbar, DMD, MD, FACS, founded the International Pediatric Otolaryngology Group of the European Society of Pediatric Otorhinolaryngology, which has been responsible for three publications to date and provides consensus guidelines for pediatric otolaryngology care. Other faculty members who’ve been involved include **Karen F. Watters, MB, BCh, BAO, MPH;** **Christopher J. Hartnick, MD, MS;** and **Margaret A. Kenna, MD, MPH, FACS, FAAP,** as well as former pediatric otolaryngology fellows **Julie Strychowsky, MD,** and **Matthew T. Brigger, MD, MPH.**

Gregory W. Randolph, MD, FACS, FACE, received the Triological Society Southern Section Vice President Citation and is the Chair-Elect of the American Head and Neck Society Endocrine Section 2017. He was also recently elected to the International Thyroid Oncology Group Board of Directors.

David A. Shaye, MD, received a grant from the AO Alliance Foundation to run facial trauma educational courses for surgeons in Africa. Dr. Shaye has been directing these courses in Rwanda and Zimbabwe, using plating principles and wiring techniques to account for availability of materials. The courses have been a success, and his work is evolving into the creation of an international facial trauma curriculum for developing countries.

Mark G. Shrime, MD, MPH, PhD, FACS, is the recipient of the 2017 Damon Runyon Clinical Investigator Award.

Konstantina Stankovic, MD, PhD, FACS, had her grant, “Prospective, randomized, placebo-controlled phase 2 trial of aspirin for vestibular schwannoma” recommended for funding by the Department of Defense. The goal of this multi-institutional clinical trial is to test if systemic aspirin therapy prevents vestibular schwannoma (VS) growth and if changes in serum biomarkers predict and reflect the response to aspirin treatment in VS.

Derek J. Stiles, PhD, Boston Children’s Hospital (BCH) Audiology Program Director, oversaw a poster presentation given by the BCH fourth year audiology externs, which received the Best Audiology Poster award at the Early Hearing Detection and Intervention Conference in Atlanta, Georgia.

HMS Promotions

Benjamin S. Bleier, MD,
Associate Professor of Otolaryngology

Eric H. Holbrook, MD,
Associate Professor of Otolaryngology

Jeffrey R. Holt, PhD,
Secondary Appointment as
Professor of Neurology

Felipe Santos, MD,
Assistant Professor of Otolaryngology

Jennifer J. Shin, MD,
Associate Professor of Otolaryngology

Karen F. Watters, MB, BCh, BAO, MPH,
Assistant Professor of Otolaryngology

Department of Otolaryngology Vice Chairs Update

Daniel G. Deschler, MD, FACS, continues as Vice Chair for Academic Affairs (Mass. Eye and Ear and Mass General).

Christopher J. Hartnick, MD, MS, continues as Vice Chair of Quality and Safety.

M. Charles Liberman, PhD, continues as Vice Chair and Director of Research.

Steven D. Rauch, MD, has accepted a new role as Vice Chair of Clinical Research.

Jennifer J. Shin, MD, has newly accepted the position of Vice Chair for Academic Affairs (Beth Israel, Boston Children’s, and Brigham and Women’s).

The following are select research advances from the Department of Otolaryngology at Harvard Medical School.

Basic Science

Fast-spiking GABA circuit dynamics in the auditory cortex predict recovery of sensory processing following peripheral nerve damage

Hearing abilities vary widely after selective damage to inner hair cells or auditory nerve



fibers. To address how these plasticity processes are coordinated over the course of functional recovery, researchers **Jennifer Resnik, PhD**, and **Daniel B. Polley, PhD**, from the Eaton-Peabody Laboratories at Mass. Eye and Ear/Harvard Medical School, induced either a moderate or massive loss of cochlear afferent synapses in adult mice and tracked the day-

by-day recovery of sound processing in the auditory cortex. In doing so, the researchers developed a new approach to record from individual neurons over a several month period while monitoring dynamic changes in the strength of inhibition from a select class of fast-spiking parvalbumin-containing inhibitory cells.

Whereas the status of brainstem-evoked potentials did not predict whether auditory processing eventually recovered in the cortex, homeostatic adjustments in cortical inhibition during the first days following injury could predict the eventual recovery of cortical sound processing months later. These findings underscore the potential importance of self-regulated inhibitory dynamics for the restoration of sensory processing following peripheral nerve injuries.

Resnik J, Polley DB. Fast-spiking GABA circuit dynamics in the auditory cortex predict recovery of sensory processing following peripheral nerve damage. eLife. 2017 Mar 21;6.

New technique generates high volume of sensory cells needed for hearing

The death of cochlear hair cells, which do not regenerate, is a cause of hearing loss in a high percentage of the population. In 2013, Mass. Eye and Ear/Harvard Medical School researchers successfully regenerated hair cells and restored partial hearing in mice by converting cells found in the inner ear into hair cells. However, the success of restoring hearing through this approach was limited by the small number of cells that could be turned into hair cells.

In a study recently published in *Cell Reports*, a research team from Mass. Eye and Ear, Brigham and Women's Hospital, and Massachusetts Institute of Technology, led by Senior Author **Albert Edge, PhD**, has shown that Lgr5+ cells can be augmented to a much higher volume and then converted into hair



cells, lending hope that full hearing can be restored to those with hearing loss due to damaged hair cells. From a single mouse, the team generated more than 11,500 hair cells (compared to less

than 200 hair cells generated without efforts to augment). The newly generated hair cells have bundles and molecular machinery for transduction, synapse formation, and specialized hair cell activity. Targeting supporting cells capable of proliferation and cochlear hair cell replacement could lead to the discovery of hearing loss treatments.

McLean WJ, Yin X, Lu L, Lenz DR, McLean D, Langer R, Karp JM, Edge AS. Clonal expansion of Lgr5-positive cells from mammalian cochlea and high-purity generation of sensory hair cells. Cell Rep. 2017 Feb 21;18(8):1917–1929.

Identification of induced and naturally occurring conductive hearing loss in mice using bone conduction

A significant fraction of the genetic defects in mouse models of hearing loss affects both the inner and middle ear. A common method used to separate sensory-neural

from conductive pathologies in the hearing clinic is the combination of air-conduction and bone-conduction audiometry.

A team of researchers from the Eaton-Peabody Laboratories at Mass. Eye and Ear/Harvard Medical School, including **John J. Rosowski, PhD**,

described a new technique to measure air- and bone-conducted hearing responses in mice and use them to separate



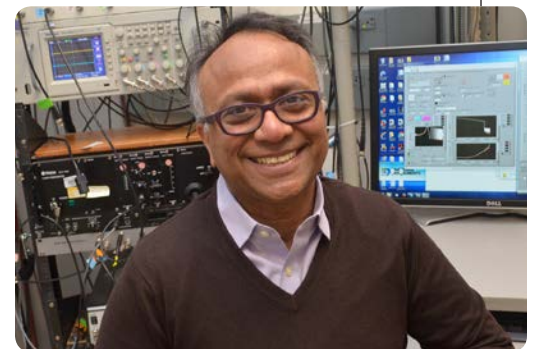
conductive and sensory-neural losses. They stimulated the mouse ear both acoustically and via whole-head vibration to demonstrate the presence of an age-related conductive

hearing loss in a common mouse model of presbycusis, the BALB/c mouse.

Chhan D, McKinnon ML, Rosowski JJ. Identification of induced and naturally occurring conductive hearing loss in mice using bone conduction. Hear Res. 2017 Mar;346:45–54.

Attenuating the ear canal feedback pressure of a laser-driven hearing aid

Microphone placement behind the pinna, which minimizes feedback but also reduces perception of the high-frequency pinna cues needed for sound localization, is one reason why hearing-aid users often complain about poor sound quality and difficulty understanding speech in noisy environments. Mass. Eye and Ear/Harvard Medical School researcher **Sunil Puria, PhD**, in collaboration with Earlens Corporation, has investigated strategies for minimizing the feedback pressure and developed finite element models of the human middle ear



using stapes velocity, cochlear pressure, ear canal impedance, and middle ear power reflectance from living and cadaver temporal bones.

These models have applications in the design of improved hearing aids that mechanically drive the umbo (the central, most inverted portion of the ear drum). Such design applications could reduce feedback pressure using acoustic dampers in the canal tip. This new design paves the path towards placing the microphones of future devices that mechanically stimulate the middle ear into the ear canal.

Khaleghi M, Puria S. Attenuating the ear canal feedback pressure of a laser-driven hearing aid. J Acoust Soc Am. 2017;141(3):1683–1693.

The curious case of gerbil hearing

Analogous to a prism decomposing white light into a spectrum of colors, the mammalian cochlea mechanically decomposes incoming sound into component frequencies. According to Nobel laureate Georg von Békésy, this results from the changing width, thickness, and collagen volume of the basilar membrane (BM) along its length, assuming a beam model, but this fails for mammals with atypical BM geometry.

A new model, developed by a team of researchers including **Sunil Puria, PhD**, of the Eaton-Peabody Laboratories at Mass. Eye and Ear/Harvard Medical School, correctly predicts the frequency-to-place mappings for gerbil and mouse by incorporating their flat and arched cross-sectional BM regions. The model shows that the flat (non-arched) region is the most important determinant for BM tuning, which allows improved tuning estimates from fossil records since the distance between bony supports only provides the total BM width.

Kapuria S, Steele CR, Puria S. Unraveling the mystery of hearing in gerbil and other rodents with an arch-beam model of the basilar membrane. Sci Rep. 2017 Mar 22; 7(1):288.

Healthcare Economics

Industry Sponsorship of Research in Otolaryngology

A team of researchers from Mass. Eye and Ear/Harvard Medical School, including otolaryngology resident **Vinay K. Rath, MD**, conducted an analysis of payment disclosures released under the Physician Payments

Sunshine Act to characterize industry sponsorship of research in otolaryngology and compare the field to other surgical specialties. The researchers found that otolaryngology had both the second-lowest proportion of funded surgeons and median payment per compensated surgeon among all surgical



specialties. However, there was wide variation within otolaryngology, with a small subset of top earners funded by companies focused on otologic and sinonasal conditions accounting

for much of the total payment value. This study suggests that otolaryngology may have a lower potential for research bias due to financial conflicts of interest as compared to other specialties, though patients may benefit from collaborations between otolaryngologists and industry to advance clinical science in presently underrepresented otolaryngologic disease areas.

Rathi VK, Abt NB, Kozin ED, Naunheim MR, Gray ST. Industry sponsorship of research in otolaryngology: An examination of the Centers for Medicare & Medicaid services open payments database. JAMA Otolaryngol Head Neck Surg. 2017 Apr 6.

Clinical Practice

Patients with severe chronic rhinosinusitis show improvement with Verapamil treatment

A clinical trial studying the use of Verapamil, a drug currently in use for cardiovascular disease and cluster headache, in alleviating chronic rhinosinusitis (CRS) with nasal polyps revealed significant improvement in the symptoms of this subset of patients.



Led by Senior Author **Benjamin S. Bleier, MD**, from Mass. Eye and Ear/Harvard Medical School, it is the first study of its kind to explore treatment for CRS by inhibiting P-glycoprotein, a protein pump within the nasal lining that Mass. Eye and Ear researchers previously identified as a mechanism for severe cases of CRS marked by the presence of nasal polyps. The clinical trial results, which are published

in the *Journal of Allergy and Clinical Immunology: In Practice*, suggest that Verapamil represents a promising novel therapy for the treatment of CRS with nasal polyps.

The study authors conducted a randomized, double-blind, placebo-controlled clinical trial studying the use of low-dose Verapamil in 18 patients with CRS with nasal polyps. An analysis of these patients demonstrated improved outcomes for those in the Verapamil group in relation to those in the placebo group. However, the researchers also observed that the treatment effect was significantly limited among patients with higher body mass indices. Future studies are being planned to determine if a higher dose of Verapamil may be needed to be therapeutic for some patients.

Miyake MM, Nocera A, Levesque P, Guo R, Finn CA, Goldfarb J, Gray ST, Holbrook EH, BuSaba NY, Dolci JE, Bleier BS. Double-blind placebo-controlled randomized clinical trial of Verapamil for chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2017 Jan 11.

Clinically significant improvements following functional septorhinoplasty detected with global health-related quality-of-life instrument

Nasal airway obstruction is a common presenting complaint among patients in



otolaryngology practices and its treatment necessitates critical outcomes evaluation and cost-utility analysis. A team of researchers from Mass. Eye and Ear/Harvard Medical

School, including **Robin W. Lindsay, MD**, evaluated the utility and applicability of the EuroQol 5-Dimension (EQ5D) global health-related quality-of-life (HRQoL) questionnaire for the assessment of clinical outcomes in functional septorhinoplasty and found that nasal obstruction impacts both disease-specific and global quality of life.

A total of 135 patients completed EQ5D and NOSE surveys preoperatively and postoperatively. Of these, 117 completed the two-month survey and 64 completed their last survey at six or more months. Overall, the nasal valve correction improved not only disease-specific quality of life but also global HRQoL. The ability to calculate health utility

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values from the EQ5D and its low response burden make it an attractive tool for septorhinoplasty outcomes research.

Fuller JC, Levesque PA, Lindsay R. Assessment of the EuroQol 5-dimension questionnaire for detection of clinically significant global health-related quality-of-life improvement following functional septorhinoplasty. *JAMA Facial Plast Surg*. 2017 Mar 1;19(2):95–100.

Facial nerve sacrifice during parotidectomy: A cautionary tale in pathologic diagnosis

The parotid gland harbors 85 percent of all salivary gland neoplasms. Though the majority of tumors are benign, complete surgical resection remains the mainstay of treatment. Along with adequate tumor removal, facial nerve preservation is a critical objective. Given the significant negative



effects on quality of life following facial nerve sacrifice, every effort should be made to spare the nerve until conclusive evidence mandates its removal. In a study completed

by a team of clinicians from Mass. Eye and Ear/Harvard Medical School, including **Daniel G. Deschler, MD, FACS**, they shared their observations from a case where facial nerve sacrifice was considered, but ultimately deferred due to lack of definitive intraoperative pathologic diagnosis.

In their report, they highlighted a challenging clinical scenario of identifying a tumor that is behaving as if it were a malignancy requiring significant life-changing intervention, such as sacrifice of the facial nerve. Although often warranted, physicians seek to avoid this when not required. This case indicates how an initial clinical scenario could lead a well-intended practitioner down such a pathway and ultimately have the diagnosis be benign. By reviewing the sequence of events of this patient, the authors seek to highlight critical aspects of the decision-making process, which affords the patient the best ultimate care and protects the well-intended efforts of thoughtful practitioners from inadvertently causing harm.

Abt NB, Derakhshan A, Naunheim MR, Osborn HA, Deschler DG. Facial nerve sacrifice during parotidectomy: A cautionary tale in pathologic diagnosis. *Am J Otolaryngol*. 2017 Jan 18.

A novel classification system to improve coordination and scheduling of operative cases in a tertiary pediatric medical system

The number of ambulatory procedures has steadily increased over the past two decades, enabling main operating suites to be utilized for more complex patients and procedures. In 2010, a team of researchers from Boston Children's Hospital/Harvard Medical School, including **Reza Rahbar, DMD, MD, FACS**, began implementing a surgical scheduling



categorization system (SSCS) to delineate patients appropriate for ambulatory surgery centers (ASCs) and those who require main operating suites. The SSCS consisted of four categories:

(1) American Society of Anesthesiologists (ASA) physical status classification I/II patients (appropriate for institution's suburban ASCs), (2) ASA I/II patients with social or transportation issues, (3) ASA I/II patients requiring coordination with other medical or surgical departments, and (4) patients of any ASA class who were deemed higher complexity by the surgeon. Patients in categories two, three, and four were believed to require a main operating suite.

The objectives of this study were to describe the clinician's experience utilizing the SSCS for all surgeries performed in otolaryngology between July 2012 and June 2013 and to provide guidelines on how to use this classification system to improve the efficiency of scheduling for main operating suites and ASCs.

Of 7,198 procedures, 48 percent were category one, 13.6 percent were category two, 1.9 percent were category three, and 36.5 percent were category four. Of note, 39.6 percent of all ASA II patients were classified as category four due to social and complexity factors that were not adequately reflected in the ASA classification. This additional level of specificity makes the SSCS an effective tool to communicate with surgical schedulers as well as the anesthesia and operating room team to determine operative location and perioperative care. The SSCS represents

a first step toward developing a true risk stratification system, which will require a detailed evaluation of surgical complications to optimize patient safety.

Gantwerker EA, Bannos C, Cunningham MJ, Rahbar R. Surgical scheduling categorization system (SSCS): A novel classification system to improve coordination and scheduling of operative cases in a tertiary pediatric medical system. *Int J Pediatr Otorhinolaryngol*. 2017 Jan;92:156–160.

A motion sickness drug worsens vestibular perception

Despite the vestibular contribution to motion sickness, little is known about how motion sickness drugs modify the perception of vestibular stimuli. A team of researchers from Mass. Eye and Ear/Harvard Medical School and Massachusetts Institute of Technology, including Senior Author **Faisal Karmali, PhD**, studied how oral promethazine (brand name Phenergan) modifies vestibular perceptual thresholds. These thresholds measure the smallest motion that can be reliably perceived and have been shown to be a sensitive measure of vestibular precision. In this test, subjects sit in a chair and repeatedly experience small motions to the left or right,



and report their perception of the direction of each motion. The researchers found that tilt thresholds increased 31 percent after ingestion of promethazine, indicating a worsening of vestibular perception. These results could have important functional implications since recent studies show that higher tilt thresholds are associated both with a higher risk of failing a balance test and worsening performance in a piloting task.

Diaz-Artiles A, Priesol AJ, Clark TK, Sherwood DP, Oman CM, Young LR, Karmali F. The impact of oral promethazine on human whole-body motion perceptual thresholds. J Assoc Res Otolaryngol. 2017 Apr 24.

Duration of analgesic use and risk of hearing loss in women

Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen are the most commonly used medications in



the United States. Frequent use of analgesics has been associated with higher risk of hearing loss. However, the association between duration of analgesic use and risk of

hearing loss is unclear. Therefore, a team of researchers from Mass. Eye and Ear/Harvard Medical School and Brigham and Women's Hospital/Harvard Medical School, including otolaryngology resident **Brian M. Lin, MD**, prospectively investigated the relationship between duration of analgesic use and self-reported hearing loss among 55,850 women in the Nurses' Health Study.

Over a 22-year follow-up period (1990–2012), longer duration of NSAID use was associated with a ten percent increase in risk of hearing loss (>6 years of use compared to <1 year of use), and longer duration of acetaminophen use was associated with a nine percent increase in risk of hearing loss (>6 years of use compared to <1 year of use). Duration of aspirin use was not associated with hearing loss. In this cohort of women, longer duration of NSAID and acetaminophen use were associated with slightly higher risk of hearing loss, but duration of aspirin use was not. Considering the high prevalence of analgesic use and the high probability of frequent and/or prolonged exposure in women of more advanced

ages, these findings suggest NSAID use and acetaminophen use may be modifiable risk factors for hearing loss.

Lin BM, Curhan SG, Wang M, Eavey R, Stankovic KM, Curhan GC. Duration of analgesic use and risk of hearing loss in women. Am J Epidemiol. 2017 Jan 1; 185(1):40–47.

Benign temporomandibular joint lesions presenting as masses in the external auditory canal

The external auditory canal (EAC) and the temporomandibular joint (TMJ) share an intimate anatomical relationship. Both



neoplasms and infections arising from the EAC can involve the TMJ, but rarely the reverse. In this study, a research team led by **C. Eduardo Corrales, MD**, of Brigham and Women's Hospital/

Harvard Medical School, presents six cases of benign TMJ disorders, which presented as EAC masses from two academic centers.

The overall objective is to alert clinicians of this possibility when evaluating an occluding EAC lesion and to be aware of the diagnosis and management implications for these complex lesions.

These TMJ lesions are uncommon and, therefore, identification can be challenging. Patients often present vague and non-specific symptoms such as hearing loss, otalgia, TMJ pain, painless swelling, headaches, and trismus. It's important to keep a broad differential of common primary EAC tumors including squamous cell carcinoma antigen (SCCA). In most circumstances, it is prudent to obtain imaging (HRCT, MRI with contrast, or both) before biopsy of an EAC mass. The mainstay of treatment for these lesions is surgical excision and the goals of surgery include restoring patency of the EAC, alleviating medial canal entrapment cholesteatoma, mitigating potential TMJ herniation, retaining mandibular motility and alignment, and avoiding injury to the overlying facial nerve.

Williams RA, Jackler RK, Corrales CE. Benign temporomandibular joint lesions presenting as masses in the external auditory canal. Otol Neurotol. 2017 Apr; 38(4):563–571.

Residency Training

Educational cadaveric module for teaching osteotomies in rhinoplasty

Facial plastic surgeons from Mass. Eye and Ear/Harvard Medical School, including Senior



Author **Linda N. Lee, MD**, and otolaryngology residents **Jenny X. Chen, MD**, and **Elliott D. Kozin, MD**, studied outcomes of osteotomies performed for rhinoplasty in an educational cadaveric module.



Lateral osteotomies performed during rhinoplasty can be done through percutaneous or intranasal approaches. Both techniques can be difficult for trainees to learn, as they rely heavily on tactile feedback. In this study, surgical trainees performed both techniques in a cadaveric lab and the results of the



osteotomies were compared. After the hands-on portion of the training, trainees reported significantly increased confidence in performing both intranasal and percutaneous osteotomies. Rates of successful and complete osteotomies with correct placement were similar between the two techniques. Intranasal periosteal disruption was higher in the intranasal technique.

Based on these findings, which were accepted for publication in *Otolaryngology—Head and Neck Surgery*, the researchers stress the importance of an educational cadaveric skills lab as a powerful tool, particularly for teaching surgical techniques, which rely heavily on tactile feedback.

Chen JX, Kozin ED, Shaye DA, Hadlock TA, Lindsay R, Lee LN. Educational cadaveric module for teaching percutaneous and intranasal osteotomies in rhinoplasty. Otolaryngol Head Neck Surg. 2017 Apr. 1.

OTOs on the Run



Noah S. Siegel, MD, Medical Director of Otolaryngology at Massachusetts Eye and Ear's Longwood location and Instructor in Otolaryngology at Harvard Medical School, brought his idea of hosting a 5K race at the annual American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) meeting to fruition last fall.

After suggesting the idea to the Academy and volunteering to champion the race, Dr. Siegel and his team successfully hosted the inaugural "OTOs on the Run" last September. Now, the second annual race is being planned for the 2017 AAO-HNS meeting in Chicago. It will be held on **Monday, September 11, from 6:00–7:00 am**. Those interested in participating can sign up when completing the conference registration.



"I felt hosting a race would be a great way to not only support the professional needs of members but to also promote healthy lifestyles," said Dr. Siegel. "Our first race was a great start—it provided an opportunity to build community, further enjoy the national meeting, and explore our host city. And now, we have the opportunity to see how it will grow at the second race this fall."

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In a report released by *U.S. News & World Report* and the physician network Doximity, the Department of Otolaryngology at Mass. Eye and Ear/Massachusetts General Hospital was ranked #1 in the nation for otolaryngology care.



Upcoming Events

MassEyeAndEar.org/ENTCalendar

Please visit the online calendar for information on upcoming events in the Harvard Medical School Department of Otolaryngology.



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