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NEWS FROM THE DEPARTMENT OF OTOLARYNGOLOGY AT HARVARD MEDICAL SCHOOL

HARVARD Otolaryngology



Inner Ear OPTOGENETICS

Researchers use optogenetics
to transform cells in the inner ear
to respond to light
(page 14)



HARVARD
MEDICAL SCHOOL

DEPARTMENT OF
Otolaryngology

HARVARD Otolaryngology

News from the Department of Otolaryngology at Harvard Medical School

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← Cover design by Garyfallia Pagonis.

Large image: Active nerve cells, computer artwork.

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Dear colleagues and friends,

Optogenetics is a technology we often hear about. It's a biological technique that uses light to control cells in living tissue in order to genetically modify them to become expressed. Scientists have had success using this technology to enhance our understanding of the brain, especially in relation to mood and other neurological disorders, among other uses.

At Massachusetts Eye and Ear/Harvard Medical School, we have begun to explore its use in the inner ear. In our cover story starting on page 14, we discuss the work of Daniel J. Lee, MD, FACS, and his laboratory. They have successfully shown that neurons in the inner ear can become photoactive through the use of optogenetics. With this, we can learn more about how light drives an auditory response and perhaps use that knowledge to one day enhance cochlear implants.

In this issue, we also highlight surgical techniques pioneered by our surgeons to remove orbital tumors endoscopically through the nasal cavity. We showcase the unique prospective Boston Children's Hospital/Harvard Medical School takes on simulation courses for faculty and trainees. Lastly, we delve into a new hearing loss registry that is automatically populated from a patient's medical record with the intent to identify patients by genetic mutations.

We're excited to share with you more about our research advances and current progress across the field. Thank you for your interest in and support of the department's activities.

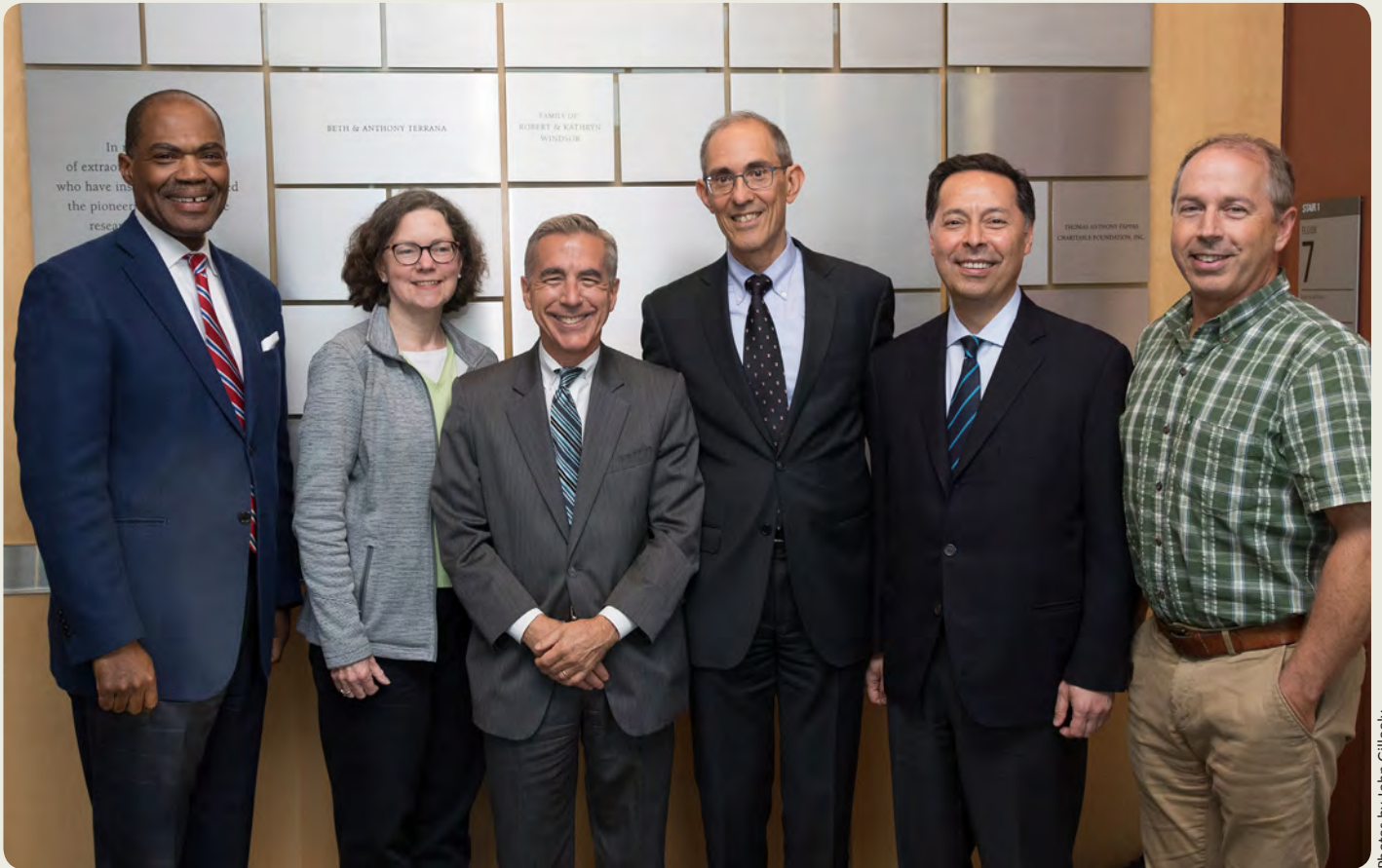
Sincerely,

D. Bradley Welling, MD, PhD, FACS

*Walter Augustus Lecompte Professor and Chair
Department of Otolaryngology
Harvard Medical School*

*Chief of Otolaryngology
Massachusetts Eye and Ear
Massachusetts General Hospital*

Sarah Fuller Chair in Neurotology Established at Boston Children's Hospital



Photos by John Gillooly.

From left to right: Dr. Kevin Churchwell, President and Chief Operating Officer at Boston Children's Hospital, and Harvard Medical School otolaryngology faculty Drs. Margaret Kenna, Michael Cunningham, Dennis Poe, Reza Rahbar, and Jeffrey Holt.

Dennis S. Poe, MD, PhD, Professor of Otolaryngology at Harvard Medical School and a neurotologic surgeon at Boston Children's Hospital, has been named the inaugural recipient of the **Sarah Fuller Chair in Neurotology** at Boston Children's Hospital.

Made possible by the generosity of the Sarah Fuller Foundation, this Chair honors the legacy of Sarah Fuller, a powerful advocate in caring for children who are deaf or hard of hearing.

Sharing Sarah Fuller's commitment to helping children with hearing loss, Dr. Poe was originally drawn to medicine by the opportunity to treat patients and find permanent fixes for them. He has focused a significant amount of his career investigating

the eustachian tube, which is the root to many problems of the middle ear, to find preventative measures and create new medical therapies and surgical procedures for treatment.

An underserved area of clinical importance, the eustachian tube is a small passageway that connects the upper part of the throat to the middle ears. Normally, it helps maintain equal pressure inside the middle ear by opening and closing like a valve. Sometimes, however, it becomes blocked, which can lead to common problems such as acute and chronic otitis media. Located in the back of the nasal passages and deep within the skull, the eustachian tube is challenging to access, thwarting attempts for successful interventions in the past.

Dr. Dennis Poe at a reception.



From left to right: Drs. Michael Cunningham, Dennis Poe, and Kevin Churchwell.



“I admire how Dr. Poe has taken the path less traveled to accomplish the feat of becoming the world’s most highly renowned expert in eustachian tube anatomy, pathophysiology, and treatment,” said D. Bradley Welling, MD, PhD, FACS, the Walter Augustus Lecompte Professor and Chair of Otolaryngology at Harvard Medical School. “Through his relentless pursuit of knowledge, he has already and will continue to benefit the care of millions of patients.”

Treating patients with eustachian tube dysfunction (ETD), Dr. Poe has built a practice dedicated to caring for some of the most challenging otolaryngology patients. In 2016, he developed the first FDA-approved device for treating and preventing ETD in adults. It’s a novel balloon dilation system specifically built to open the eustachian tube.

The Sarah Fuller Chair in Neurotology will support expertise in otology and neurotology that enhances the mission of the

Department of Otolaryngology and Communication Enhancement at Boston Children’s Hospital in providing world-class clinical care, research, and education. Its support will create opportunities to further the development of preventative and reconstructive treatments in these areas. As an initial effort, Dr. Poe is hoping to get a pediatric-friendly balloon device FDA-approved for use in children with ETD.

The Sarah Fuller Chair in Neurotology, which is now a permanently endowed fund at Boston Children’s Hospital, will help ensure that this work continues by investing in Dr. Poe, as well as his successors, for generations to come.

“This Chair establishes in perpetuity the unique role Dr. Poe has established as a board-certified neurotologist within a pediatric otolaryngology department,” said Michael J. Cunningham, MD, FACS, Otolaryngologist-in-Chief and the Gerald B. Healy Chair in Pediatric Otolaryngology at Boston Children’s Hospital. “He has greatly augmented the level of otologic care provided to our patients and serves as an invaluable resource of knowledge and technical skill to our team. This honor is equally a tribute to his clinical skills and contributions to the field.” ●

Simulation Scenarios

Surgeons use simulation courses in the operating room environment to provide scenario-based training

Teamwork and communication are key components of many tasks, especially in high-stake environments such as medicine and surgery.

In hospital operating rooms, failure in both are among the leading causes of medical mistakes. These mishaps can be driven by many influences, but an under-emphasis in communication and teamwork skills during medical education is considered to play a major role in such errors.

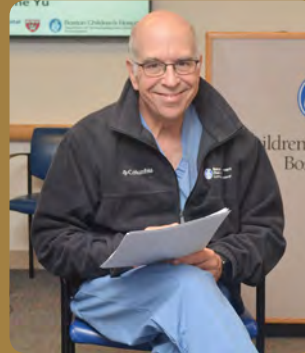
Seeking a solution, Gerald B. Healy, MD, FACS, Professor of Otolaryngology at Harvard Medical School and Emeritus Chair of Otolaryngology at Boston Children's Hospital, initiated the otolaryngology simulation program at Boston Children's Hospital. Now led by Mark S. Volk, MD, DMD, Assistant Professor of Otolaryngology at Harvard Medical School, this program has evolved into a multidisciplinary team-training course focused on improving human factor performance in the operating room.

The main course of the program, known as the Otolaryngology Crisis Resource Management (OCRM) course, is offered five times per year to otolaryngology residents and fellows,

anesthesiology trainees, and operating room nurses. It's the first of its kind to teach teamwork and communication skills to otolaryngologists in an authentic operating room setting.

Since 2008, roughly 50 trainees have taken the course each year, learning to work together when handling operating room emergencies.

"In most simulation courses, participants work on boosting their surgical skills. But with our course, we take it a step further," said Dr. Volk, who has devoted the academic aspect of his career to simulation. "Not only are participants working on their surgical and decision-making skills, but we also put them in situations where they have to work together with a multidisciplinary team to successfully complete the emergency scenario they've been given."



"Not only are participants working on their surgical and decision-making skills, but we also put them in situations where they have to work together to successfully complete the emergency scenario they've been given."

—Dr. Volk



A realistic operating room experience

Working with Peter Weinstock, MD, PhD, Associate Professor of Anesthesia at Harvard Medical School and Director of the Simulator Program at Boston Children's Hospital, Dr. Volk envisioned a course focused on perfecting the link between preparedness and high-quality pediatric care when first taking over the otolaryngology simulation program.

Together, Dr. Volk and Dr. Weinstock spearheaded the OCRM course, which now serves as a model for other specialties at institutions across the nation. With most simulation courses held in simulated operating rooms or clinics with actors, a realistic experience can be tough to achieve. This is why the OCRM course site simulation is done in the actual operating room or clinic room, with no actors.

"All participants play themselves," said Dr. Volk. "That's the big difference here. When the courses are in session, normal operating room time becomes simulation time, so it's extremely realistic. You are in the same operating room where real patients are treated, using the same exact equipment."

At the start of the course, participants are given a surgical task and at some point during the procedure, a "medical emergency" will occur. It is then up to the participants to work together to solve the problem appropriately while still providing optimum care to the "patient."



Left photo: OCRM participants work together to solve a medical emergency scenario.

Right photo: Dr. Mark Volk prepares for the OCRM course.

Each course involves two scenarios and after each scenario the participants undergo a debriefing, when any errors that occurred during the scenario are reviewed. Instructors who are specialized in debriefing training guide this process in a structured, non-judgmental manner.

"It lays the groundwork for participants to reflect on their simulated experience," said Dr. Volk. "They can then go on to discover ways to improve their teamwork and communication skills for actual critical situations in the future."

The positive influence of simulation courses

In addition to the OCRM courses, Dr. Volk also leads four Cardiac Intensive Care Unit (CICU) simulation courses, which are designed to enhance interactions between CICU and otolaryngology trainees and staff during the management of airway emergencies.

With the help of Gi Soo Lee, MD, EdM, Instructor in Otolaryngology at Harvard Medical School and Associate at Boston Children's Hospital, Dr. Volk co-directs a one-day program each summer for the incoming PGY-1 residents from all eight New England Otolaryngological Society residency programs. It provides hands on experience in urgent and emergent care techniques and clinical scenarios to enable new residents to function at a higher level during their first weeks on-call and in the clinics.

"The positive influence of these simulation courses has extended throughout our department, as well as to other members of our care team, exemplified by the mock code scenarios now run by our nursing staff," said Michael J. Cunningham, MD, FACS, Otolaryngologist-in-Chief and the Gerald B. Healy Chair in Pediatric Otolaryngology at Boston Children's Hospital.

Future simulation projects include developing a course using custom 3-D printed temporal bones, which will enable surgeons to practice on renditions of difficult cases prior to the actual operation.

"It's important for people to get trained in all aspects that make an operating room or clinic successful," said Dr. Volk. "I'm proud that we're unique in providing this type of training in an actual otolaryngology environment and hope to encourage others to adopt similar programs." ●

SEEING FURTHER: Endoscopic Orbital Surgery

Surgeons use endoscopic approaches to remove orbital tumors through the nose



*Dr. Benjamin Bleier (left)
and Suzanne Freitag (right)
in the operating room.*

Offering a means to illuminate and visualize the intricacies of the sinuses, endoscopic transnasal procedures became popular in the 1980s. Almost immediately, it was noted that if one can successfully access the sinuses through the nasal cavity with an endoscope, then they could likely access other structures around the sinuses as well.

These procedures have since been adapted to cover areas such as the pituitary gland and skull base, which have resulted in better outcomes for patients and increased understanding of the anatomy and physiology of these structures.

Surgeons have also used endoscopic transnasal techniques to address structures around the eye. Over the last two decades, much success has been had with adopting these techniques in orbital decompression and tear duct surgeries.

Using such approaches for tumors around the orbit, which protects, supports, and maximizes the function of the eye, however, has not taken off at the same rate.

Endoscopic orbital surgery offers the advantage of directly accessing lesions within the orbit while minimizing manipulation of normal structures. Since it is a nascent field, however, little has been documented in a systematic way, leaving the anatomy, optimal techniques, and outcomes involved in these procedures not fully fleshed out.

“There have been some case series on endoscopic orbital surgeries, but at low volumes,” said Benjamin S. Bleier, MD, FACS, Co-Director of the Center for Thyroid

“The traditional treatment for an orbital mass deep in the eye socket is either surgery through the eye socket or through a craniotomy approach. However, both are difficult procedures and have significant risks. Using an endoscopic procedure through the nose and sinuses can make this a lot easier.”

—Dr. Freitag



Dr. Benjamin Bleier (right) in the operating room with his fellow, Dr. George Scangas (middle), performing a multi-handed endoscopic technique to remove an orbital tumor.

Eye Disease and Orbital Surgery at Massachusetts Eye and Ear and Associate Professor of Otolaryngology at Harvard Medical School. “The thing is, these procedures can actually work quite well, but surgeons need to understand the anatomy first.”

Developing novel approaches

Things began to change when Suzanne K. Freitag, MD, also Co-Director of the Center for Thyroid Eye Disease and Orbital Surgery and Associate Professor of Ophthalmology at Harvard Medical School, had a patient present with a tumor in the inner part of the eye socket. Only eleven years old, the patient’s eye was bulging due to the location of the tumor and visual loss was noted.

“The traditional treatment for an orbital mass deep in the eye socket is either surgery through the eye socket or through a craniotomy approach,” said Dr. Freitag. “However, both are difficult procedures and have significant risks. The eye socket is a fixed bony cavity, so there is limited space in which to work. Using an

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| Seeing Further: Endoscopic Orbital Surgery | continued

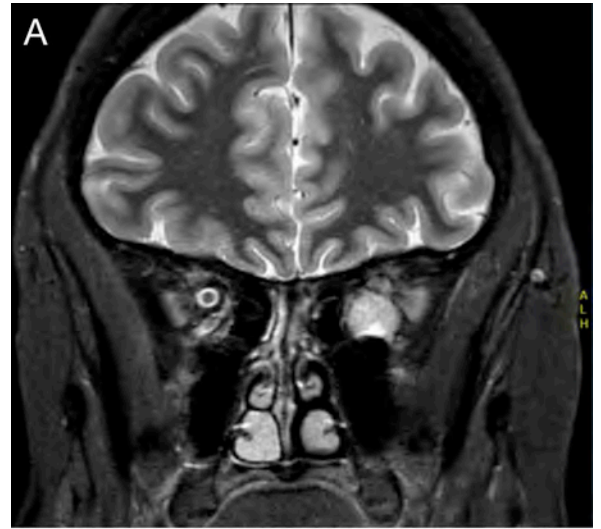
endoscopic procedure through the nose and sinuses can make this a lot easier.”

With this in mind, Dr. Freitag combined efforts with Dr. Bleier, who specializes in endoscopic sinus and skull base surgery. Together, they performed a novel, minimally invasive surgical technique to remove the complex tumor from behind the eye with an endoscope, making this among the first pediatric cases of its kind.

Unlike surgery that requires a large incision near the eye and removing part of the bone, endoscopic orbital surgery never touches the eye or even the brain. Surgeons can retract a few structures to get access to the growth and then remove it safely through the nasal cavity.

“A lot of people still don’t know that orbital tumors can be resected endoscopically through the nose. Our goal is to get that message out there and help grow this field so that more patients can benefit from these techniques.”

—Dr. Bleier



Pre- (A) and post- (B) operative MRI scans of a patient after endoscopic removal of a large orbital tumor (arrows demonstrate mucosal flap used to reconstruct the orbital wall).

Image used with permission from Thieme Publishers. Bleier BS, et al. Endoscopic Surgery of the Orbit: Anatomy, Pathology, and Management. Thieme, 2019.

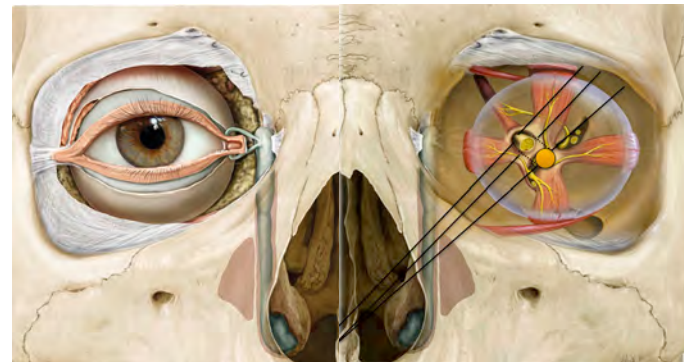


Illustration of how an endoscopic approach through the opposite nostril enables surgeons to follow a plane (black lines), which allows orbit tumors that extend to the lateral orbit to be removed without requiring retraction of the optic nerve.

Image used with permission from Thieme Publishers. Bleier BS, et al. Endoscopic Surgery of the Orbit: Anatomy, Pathology, and Management. Thieme, 2019.



Drs. Benjamin Bleier (left) and Suzanne Freitag (right).

This results in a shorter hospital stay, less pain, and improved function and appearance for patients.

“We performed a procedure that was more or less an extension of endoscopic transnasal surgery,” said Dr. Bleier. “Because there is not much out there on this type of surgery, we ended up performing it based on our combined experiences with more traditional surgeries around the eye. The patient did very well and the whole experience triggered this investigational thought on how we could help stimulate the field in a more methodical and prospective way.”

Since this surgery, Dr. Bleier and Dr. Freitag have begun collaborating on more cases and, as a result, have pioneered multiple techniques for the removal of orbital tumors entirely through the nose. They have also focused on building additional techniques in orbital decompression and tear duct surgeries.

“I like to think that we are leaders in codifying this field,” said Dr. Freitag. “We are pushing the boundaries of our techniques to develop more efficient processes to report on and improve outcomes.”

Getting the message out there

With endoscopic skull base surgery, what really helped grow the field was the realization that a team approach was necessary. In the operating room, having surgeons from different specialties made the initial difference. Then, standardizing outcomes reporting solidified interest.

Dr. Bleier and Dr. Freitag are taking a similar approach for endoscopic orbital surgery.

They started by establishing a dedicated center, the Center for Thyroid Eye Disease and Orbital Surgery, to bring together a collaborative group of surgeons who specialize in orbital lesions.

“Our team approach mirrors that of endoscopic skull base teams,” said Dr. Freitag. “We feel that it is important to disseminate to other surgeons that this type of surgery is possible. We travel the world to academic meetings and have lectured in Europe, Asia, the Middle East, and South America to teach these techniques.”

Additionally, Dr. Bleier and Dr. Freitag have published a variety of studies defining the anatomy of the orbit, developed early anatomic surgical approaches, and worked to optimize techniques. Working with ophthalmic plastic surgeons, they even pioneered an orbital reconstruction procedure.

“We adopted a technique from skull base surgery to rebuild the orbital wall after surgery in the event a patient loses orbital volume,” Dr. Bleier mentioned.

More recently, Dr. Bleier has instituted a training course at the Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery along with international colleagues. The team has also written a textbook published by Thieme, *Endoscopic Surgery of the Orbit: Anatomy, Pathology, and Management*, and has begun to draft a staging system manuscript to standardize endoscopic orbital procedures, laying the groundwork for proper diagnosis and eventual outcomes reporting.

“A lot of people still don’t know that orbital tumors can be resected endoscopically through the nose,” said Dr. Bleier. “Our goal is to get that message out there and help grow this field so that more patients can benefit from these techniques.” ●

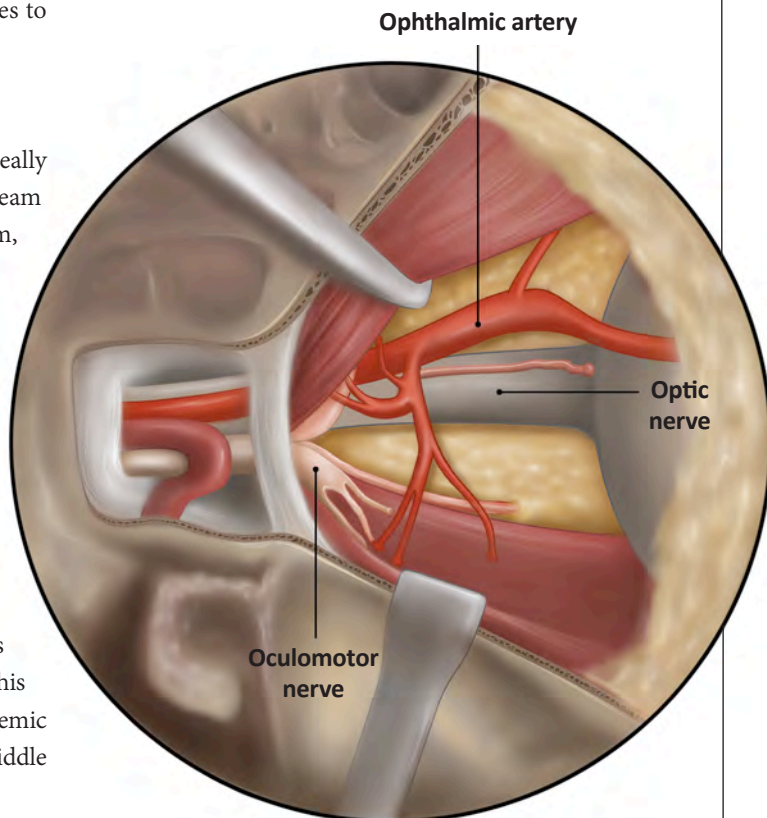


Illustration of an endoscopic view of a left orbit demonstrating the key anatomic structures, which must be preserved during surgery, including the optic nerve, ophthalmic artery, and oculomotor nerve.

Image used with permission from Thieme Publishers. Bleier BS, et al. *Endoscopic Surgery of the Orbit: Anatomy, Pathology, and Management*. Thieme, 2019.

EVOLVING

Hearing Loss Registries

Pediatric otolaryngologists develop new tool for data entry, storage, and analysis

Recent research estimates that 60 percent of hearing loss or deafness cases in infants are caused by inherited genetic defects. With more than 400 known genetic causes involving hearing loss—and more expected to be discovered—there is a need for better tracking of these patients.

For years, pediatric hearing loss patients have been placed under an umbrella diagnosis of sensorineural hearing loss (SNHL) when collecting and storing data. Although accurate, the mechanisms of SNHL go deeper than this. With several hundred gene mutations associated with hearing loss, not every case of this disease will be the same. Therefore, why should patients be classified as if they are?



*Dr. Leila Mankarious
with a patient.*

Being able to categorize these patients by the gene mutations causing their hearing loss instead would help create a framework that could make this information accessible and more usable.

“Now that we’ve found individual gene mutations responsible for hearing loss, how do we find them? How do you keep track of their individual etiologies in order to ultimately help them?,” asked Leila A. Mankarious, MD, Director of Hearing Registries at Massachusetts Eye and Ear and Associate Professor of Otolaryngology at Harvard Medical School.

With these questions in mind, Dr. Mankarious sought an opportunity to create a new data collection system. Working with the Mass. Eye and Ear Information Security team, Dr. Mankarious was able to use existing technology to create a tool that pulls information from

“Length is critical, especially when it interferes with face-to-face time with the patient,” said Dr. Mankarious. “What we found was that, for any survey or questionnaire longer than one page, usage by physicians dropped 50 percent. With each additional page, usage continued to drop by another 50 percent. We concluded that anything that lengthens the time of a visit wouldn’t be used.”

Ownership was another barrier to usage. Physicians and investigators felt that, if they didn’t “own” the data, they couldn’t use it. There were also concerns around preferences, as all intended users might have a different use in mind and may need certain features to best achieve their goals.

Dr. Mankarious developed the tools alongside her pediatric otolaryngology colleagues, so that the preferences of everyone who might use them would be

“I was aiming to develop a way that we could easily gather and use patient information, including specific genetic data, without the burden of endless hours of data entry and incomprehensible organization.”

—Dr. Mankarious

a patient’s medical record in Epic, an electronic health records software, and automatically upload it to a hearing loss registry.

Known as the Pediatric SNHL Registry, this collection of data is not only easy to access, modify, and analyze—but it can also be tagged and sorted based on genetic mutations, allowing users to find patients based on this information alone for the first time.

“I wanted to simplify the process,” said Dr. Mankarious. “I was aiming to develop a way that we could easily gather and use patient information, including specific genetic data, without the burden of endless hours of data entry and incomprehensible organization.”

Building a usable tool

Data registries can be valuable for collecting data for specific research questions. However, many fail due to faults within the user experience.

Noting this, Dr. Mankarious first investigated the biggest deterrents to usage. She found that the length of the tool, ownership, and preferences were the main problems physicians had with registries.

considered and that no one person had ownership over the data.

Furthermore, the tools were designed to automatically populate the database from medical records and to be modifiable, which is important, because research questions often change over time. In the past, once a registry was created, that was it. It could not be changed without losing or re-entering data. With this new system, physicians can add or remove elements as needed.

“Automating the collection of registry data is clearly the future,” said Richard E. Gliklich, MD, the Leffenberg Professor of Otolaryngology, Part-Time, at Harvard Medical School and Director of the Clinical Outcomes Research Unit at Mass. Eye and Ear. “It decreases investigator burden, cost, and potential enrollment bias. What Dr. Mankarious and colleagues have accomplished is state-of-the-art and has really propelled the field forward.”

Making patients discoverable

The main goals of the registry are to discover ways to fine-tune and personalize patient care and to learn more about the natural history of genetic hearing loss. With

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Dr. Leila Mankarious.

genetic forms of hearing loss being so broad and diverse, it can be difficult to track the different mutations and the patients associated with each.

In the new database, Dr. Mankarious decided to completely remove the previous system for searching for genetic information and replace it with a large dropdown menu of all gene mutations known to cause hearing loss. This menu is organized by frequency of occurrence and allows for the classification of patients based on their gene mutation and/or diagnosis rather than just their diagnosis alone.

“Before, our researchers would have to pull every SNHL patient chart and mine through them individually to find the patients who had the particular mutation they wanted to study. Now, they just have to click on the gene mutation through the menu to get a full list of patients,” she said.

Simplifying this process will help investigators more closely monitor specific patient behaviors, looking for trends and opportunities to inform treatment.

A big step toward personalized medicine

Since the registry launched, Dr. Mankarious has instituted three studies using the data collected. She has been tracking cytomegalovirus patients, investigating the natural history of unilateral large vestibular aqueduct syndrome (LVAS), and looking at the environmental factors affecting hearing performance of patients with LVAS.

Because the system was built for sharing, other pediatric otolaryngologists at Mass. Eye and Ear are also beginning to use the software for automated population and the registry for their research initiatives. There may

“Thinking about how to make each component of data collection, storage, and analysis better will hopefully lead to life-changing discoveries. These technologies are really a big step forward in the world of personalized medicine.”

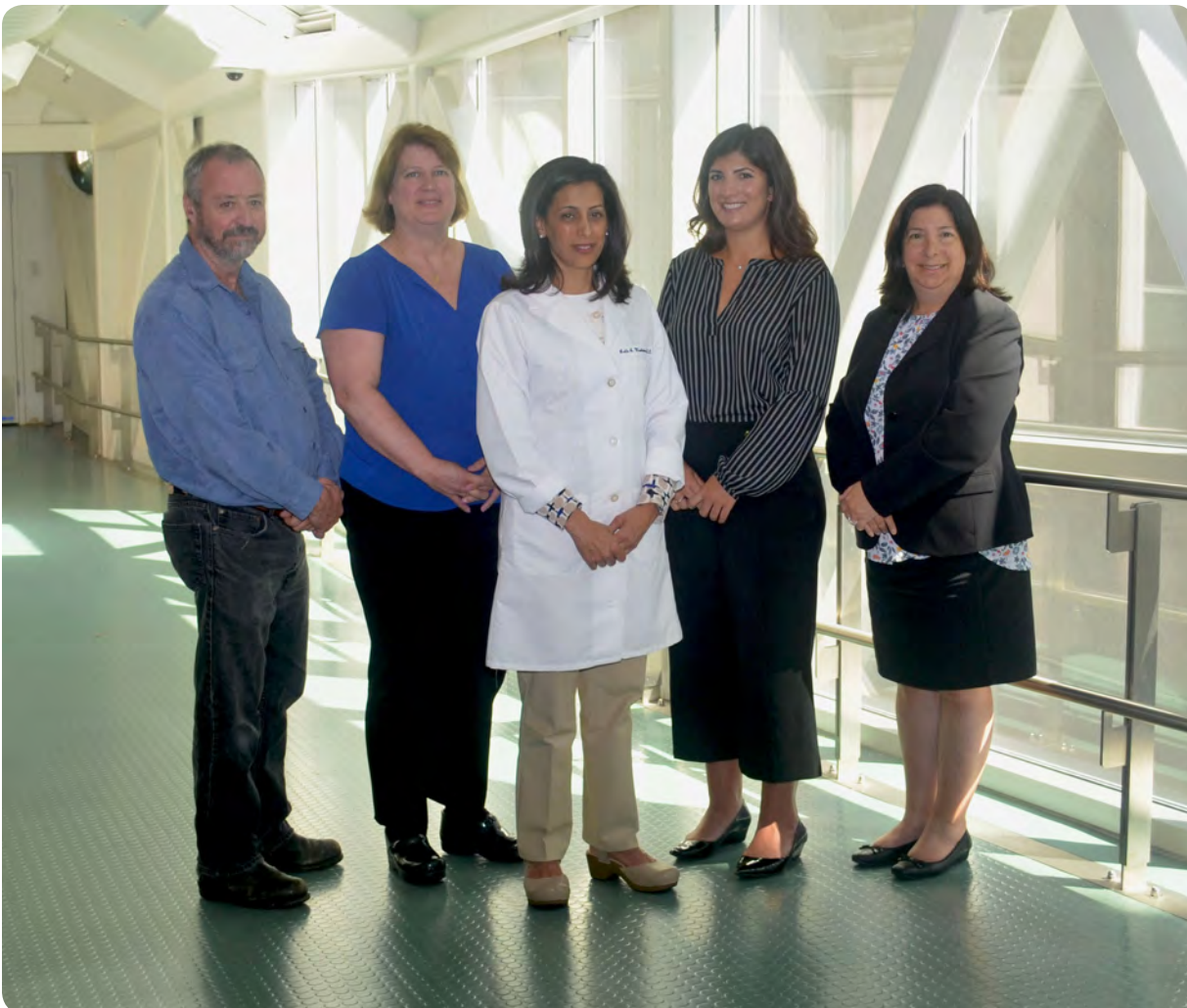
—Dr. Mankarious

also be opportunities for sharing of data with outside institutions in the future as information can be collated either with or without protected health information.

Even patients are responding positively. Dr. Mankarious mentioned that she finds her patients are “looking for ways to help make treatment better for their children and the generations to come” and “are eager to contribute however they can.”

Initial responses have been favorable, but as Dr. Mankarious and others continue to use the new software and database, they will also look for opportunities to improve. In fact, they are currently in the process of moving questionnaires onto iPads for patients to fill out themselves based on feedback received.

“The main point is finding and categorizing patients in order to help them in the long run,” said Dr. Mankarious. “It may seem simple, redesigning a registry for better genetic categorizations and improved workflow, but really thinking about how to make each component of data collection, storage, and analysis better will hopefully lead to life-changing discoveries. These technologies are really a big step forward in the world of personalized medicine.” ●



The Mass. Eye and Ear Information Security team with Dr. Mankarious. From left to right: William Goedicke, Diane Hampston, Dr. Mankarious, Lauren Winter, and Anne Murphy. Not pictured: DJ Farren.



Inner Ear OPTOGENETICS

Researchers use optogenetics to transform cells in the inner ear to respond to light

Best known for research applications in the brain, optogenetics is a technology that uses light-sensitive proteins (known as “opsins”) to change the properties of a cell so that it becomes photoactive. This allows for the photoactive cells in living organisms to be controlled with pulses of visible light, which investigators can use to precisely study circuits in the brain that govern perception, behavior, and disease conditions. This technology also provides a unique opportunity to directly activate or suppress a particular group of cells with millisecond precision.

In addition to being a powerful research tool in neuroscience, translational studies using optogenetic approaches are underway to develop new treatments for a range of conditions. Investigators are exploring the utility of optogenetics to restore vision in patients with inherited retinal disease, treat epilepsy, and to regulate heart activity, to name a few.

Optogenetic-based technologies may even have the potential to improve a person’s ability to hear.

“We believe that optogenetics could be used as an alternative stimulus paradigm for auditory prostheses such as the

cochlear implant,” said Daniel J. Lee, MD, FACS, Associate Professor of Otolaryngology at Harvard Medical School and Director of Pediatric Otology and Neurotology at Massachusetts Eye and Ear. “Unlike electricity, light can be focused to increase electrode density and reduce channel interaction with these devices, and theoretically provide a better hearing experience for implant users.”

In a recent study led by Dr. Lee, investigators showed that neurons in the inner ear can become photoactive through the use of optogenetics.

By changing the properties of these cells to react to laser light, the researchers hope that the technology may accelerate the development of a new kind of cochlear implant based on light as well as electricity. Modern cochlear implants use only electricity to provide a sense of sound.

“Most cochlear implant users enjoy meaningful sound and speech understanding, but there are some limitations that optogenetics may help us to overcome,” Dr. Lee noted.

One of the main limitations with cochlear implants is that electrical current generated by the electrodes can be difficult to focus, especially in a conducting medium of fluid. This reduces the number of channels of information that can be sent along the cochlear nerve.

Unlike electricity, using laser light to stimulate the spiral ganglion neurons may offer a more focused beam that restricts the path of light to the hundreds of cells that are photoactive, and ultimately convey sound through more channels than what today’s cochlear implants can provide.

“Optogenetics has revolutionized the field of neuroscience over the past decade, and its potential for focused stimulation has generated significant interest in the field of auditory implant research,” said Vivek Kanumuri, MD, Harvard Medical School otolaryngology resident and co-first author on the study.

A big challenge in the field, however, has been successful delivery of the necessary proteins into inner ear neurons.



“We believe that optogenetics could be used as an alternative stimulus paradigm for auditory prostheses such as the cochlear implant. Unlike electricity, light can be focused to increase electrode density and reduce channel interaction with these devices, and theoretically provide a better hearing experience for implant users.”

–Dr. Lee

Conveying a richer sound

While today’s cochlear implants have restored hearing to more than 320,000 people, patients often express difficulty hearing in noisy backgrounds and have limited music appreciation.

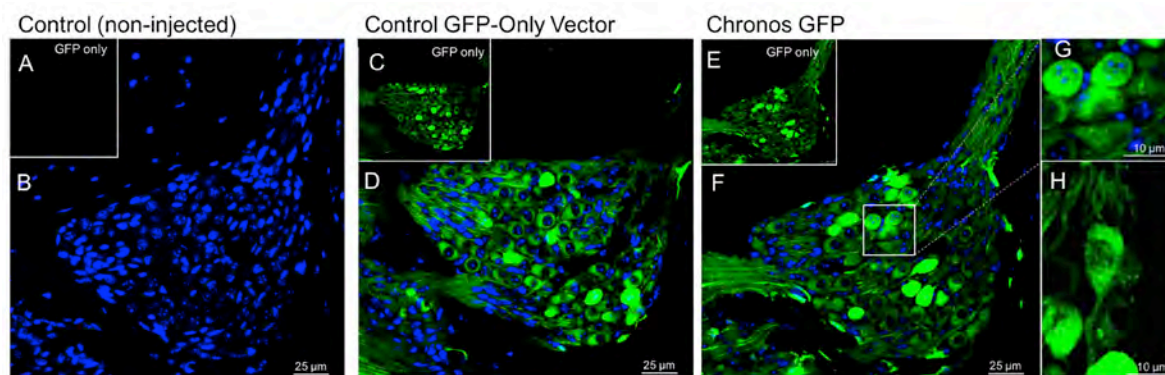
Current technology relies on a series of electrodes implanted in the fluid-filled inner ear that electronically activate cochlear neurons (spiral ganglion neurons). The surgically implanted receiver-stimulator receives electronic sound and speech information from an externally-worn microphone and speech processor. These electrical impulses are sent from the cochlea along the cochlear nerve to higher centers of sound processing in the brain.

Fortunately, recent research led by Luk H. Vandenberghe, PhD, of the Grousbeck Gene Therapy Center at Mass. Eye and Ear, introduced a new virus known as Anc80, which is ideal for this kind of gene therapy. More recently, Lukas Landegger, MD, PhD, and Konstantina M. Stankovic, MD, PhD, FACS, of the Molecular Neurotology and Biotechnology Laboratory at Mass. Eye and Ear, showed that this virus can effectively deliver proteins to the inner ear.

In an important advance described in *Molecular Therapy*, Dr. Lee’s group used Anc80 to efficiently deliver genetic material into the inner ear spiral ganglion neurons of mice to produce light-sensitive opsins. These cells are known to be difficult to genetically modify using established gene therapy approaches.

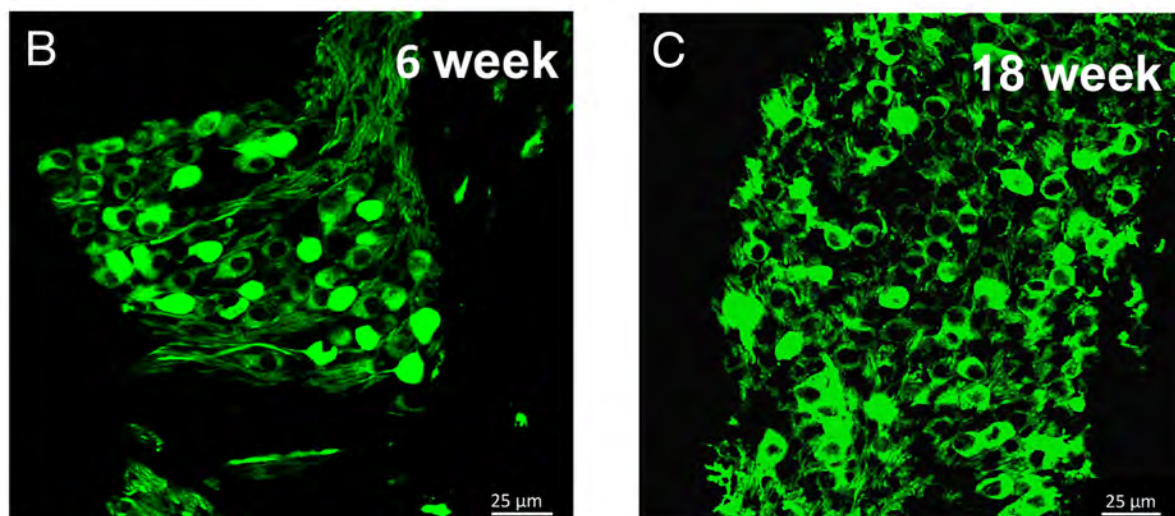
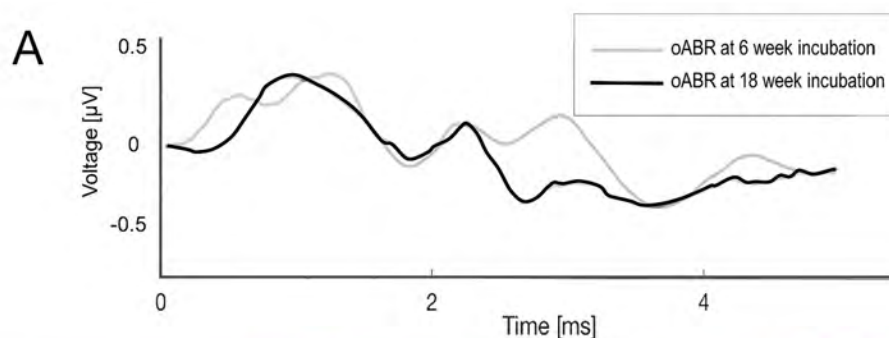
Following a six-week incubation period, an optical fiber was placed into the treated cochleas of mice to

continued on page 17



Cochlear histology comparing spiral ganglia at the middle turn of the cochlea in Chronos-expressing neurons versus controls. (A) Non-injected mice display no auto-fluorescence in the green channel. (B) For non-injected mice, an overlay of EGFP and DAPI images demonstrates only DAPI staining of neuronal nuclei. (C) Anc80L65 vector carrying EGFP only displayed high efficient transduction of spiral ganglion neurons, as seen in the green channel. (D) Overlay of EGFP and DAPI images. (E) Anc80L65 vector carrying Chronos demonstrated high transduction efficiency in a pattern very similar to the EGFP-only control. (F) Overlay of EGFP and DAPI images. (G) Enlarged image of neurons (outlined in F by white box) demonstrated cell membrane expression of Chronos. (H) Another neuron demonstrating cell membrane expression of Chronos in both the body and the axon. Overall, Chronos opsin was present in both the cell membrane and the cytosol of neurons. Scale bars, 25 μm (B, D, and F) and 10 μm (G and H).

Duarte MJ, Kanumuri VV, Landegger LD, Tarabichi O, Sinha S, Meng X, Hight AE, Kozin ED, Stankovic KM, Brown MC, Lee DJ. Ancestral adeno-associated virus vector delivery of opsins to spiral ganglion neurons: Implications for optogenetic cochlear implants. *Mol Ther.* 2018 Aug 1;26(8):1931–1939. Used with permission from the American Society of Gene & Cell Therapy (ASGCT).



Varying incubation periods yield similar opsin expression and electrophysiologic responses. (A) oABRs measured at 6 or 18 weeks both displayed multi-peaked waveform morphology. Histology at 6 weeks (B) and 18 weeks (C) demonstrates similar opsin expression levels (73.5 versus 72.9 percent). Scale bar, 25 μm .

Duarte MJ, Kanumuri VV, Landegger LD, Tarabichi O, Sinha S, Meng X, Hight AE, Kozin ED, Stankovic KM, Brown MC, Lee DJ. Ancestral adeno-associated virus vector delivery of opsins to spiral ganglion neurons: Implications for optogenetic cochlear implants. *Mol Ther.* 2018 Aug 1;26(8):1931–1939. Used with permission from the American Society of Gene & Cell Therapy (ASGCT).

deliver pulses of laser light, generating auditory brainstem responses (ABRs) in the brain. These light-driven ABRs were observed in seven out of eight mice tested. Following these experiments, the researchers analyzed the inner ear tissue and observed high levels of opsin expression in the spiral ganglion neurons.

“That’s the power of working in a place like Mass. Eye and Ear, where we have pockets of excellence that we can tap into to help advance fundamental questions for new treatments,” said Maria Duarte, MD, a 2018 Harvard Medical School graduate and co-first author on this study.

The potential to improve auditory implants

These findings may provide the basis for a new generation of cochlear implants based on light and electricity—and perhaps even a new generation of auditory brainstem implants (ABIs). ABIs are used in patients who are not eligible for cochlear implants because their cochlear nerve is absent or non-functional. Although they do provide hearing, their performance is very limited in most patients.

With the new knowledge that Anc80 can successfully transfer opsin genes into cochlear neurons, Dr. Lee and his team can further their studies to test this method in older

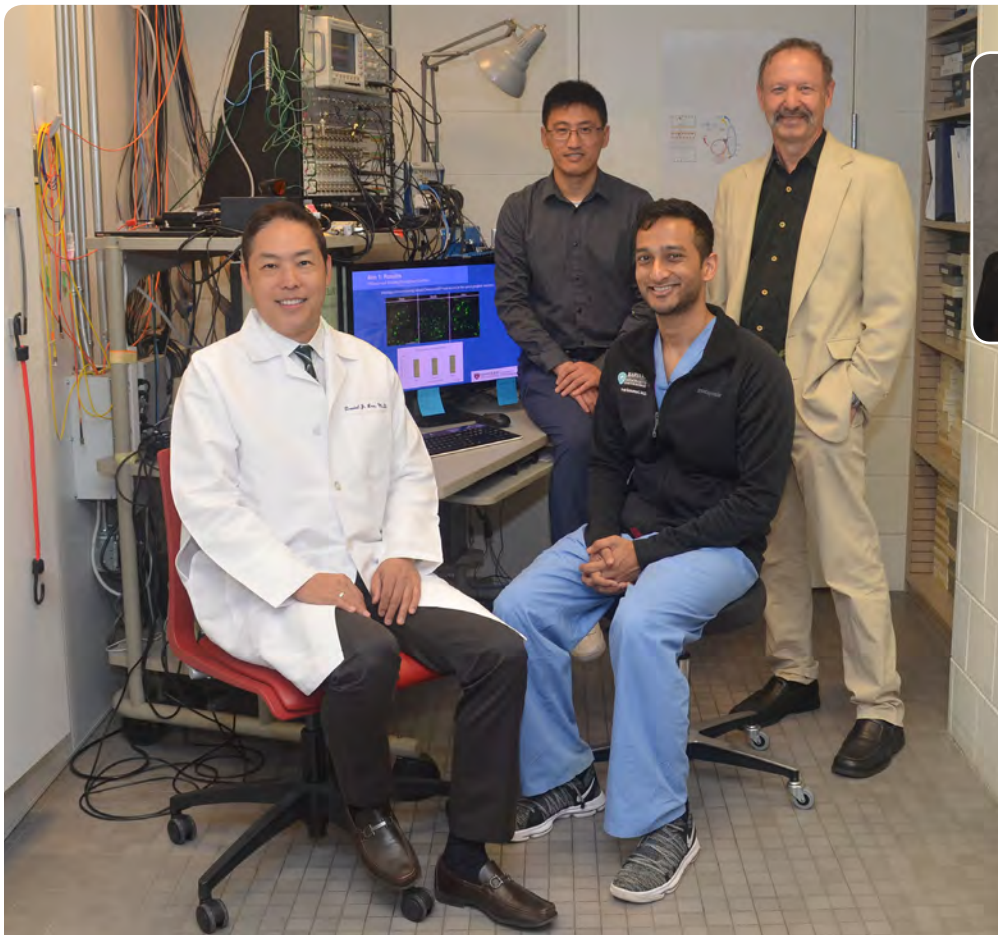
animals and examine how different types of opsins work.

In collaboration with Daniel B. Polley, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear/Harvard Medical School, Dr. Lee’s laboratory will also begin studying how these modified animals behave in response to sound or to light. “We will map the light responses to determine whether light applied to the apex of the cochlea is perceived as low-frequency sound and whether light applied to the base of the cochlea is perceived as high-frequency sound,” said M. Christian Brown, PhD, Associate Professor of Otolaryngology at Harvard Medical School.

“On the heels of our study, we can begin to investigate whether light-based cochlear implants can influence behavior similar to sound,” said Dr. Lee.

The traditional cochlear implant provides most deaf children and adults with sound awareness and speech perception, but it has performance limitations. A new generation device based on light as well as electricity could improve hearing outcomes in real-world situations, like at a restaurant or in a business meeting.

“The cochlear implant is not going away any time soon. It’s a great option for patients with severe to profound hearing loss who do not benefit from hearing aids and we’re excited about the potential to advance its technology even further,” said Dr. Lee. ●



From left to right:
Drs. Daniel Lee,
Xiankai Meng,
Vivek Kanumuri,
and M. Christian
Brown.
Inset photo:
Dr. Maria Duarte.

Farewell Class of 2018

Harvard Medical School Department of Otolaryngology Celebrates 2018 Graduation and Sixth Annual Meeting

Faculty and staff from the Department of Otolaryngology at Harvard Medical School gathered in the Meltzer Auditorium at Massachusetts Eye and Ear on Friday, June 22, to celebrate the 2018 graduating class of residents and fellows.

Four chief residents and 13 clinical fellows graduated from the program, which was led by Harvard Medical School Otolaryngology Residency Director Stacey T. Gray, MD, Associate Residency Director Kevin S. Emerick, MD, and Walter Augustus Lecompte Professor and Chair of Otolaryngology at Harvard Medical School D. Bradley Welling, MD, PhD, FACS, among others.

“It’s bittersweet to watch our residents and fellows, who’ve accomplished so much during their time with us, head on to the next chapter of their lives,” said Dr. Gray. “At the same time, we are proud of what they’ve done and excited to watch them move forward in their careers as otolaryngologists.”

The Joseph B. Nadol, Jr., lecturer and keynote speaker David E. Schuller, MD, Director Emeritus of The Ohio State University Comprehensive Cancer Center, CEO Emeritus of the James Cancer Hospital and Solove Research Institute, the Wolfe Chair in Cancer Research and Professor of Otolaryngology at The Ohio State University College of Medicine, and Vice President of Medical Center Expansion and Outreach at The Ohio State University Wexner Medical Center, delivered this year’s graduation address. In his speech, Dr. Schuller spoke about change and how one’s reaction to it will determine the impact they will have. He encouraged the graduates to be creators of change instead of victims of it.

Prior to the graduation ceremony, the day began with the department’s sixth annual meeting, an event that brings together our faculty, residents, and fellows. The meeting featured Chief Resident Research Talks on topics from reimagining the auditory brainstem implant to improving septorhinoplasty outcomes. These talks were followed by a poster session highlighting the work of all of our residents.

The annual meeting was concluded with faculty presentations by David A. Shaye, MD, FACS, Instructor in Otolaryngology at Harvard Medical School, and Ravindra Uppaluri, MD, PhD, Associate Professor of Otolaryngology at Harvard Medical School.

Awards and Honors

Annual Poster Session

Jennifer C. Fuller, MD

1st Place Poster Award (tied)

“FACE-Q patient perceived nasal appearance evaluation following functional septorhinoplasty with spreader graft placement”

Mentor: Robin W. Lindsay, MD

Alisa Yamasaki, MD

1st Place Poster Award (tied)

“Long-term improvement in nasal obstruction and global health-related quality of life after functional septorhinoplasty with and without turbinate surgery”

Mentor: Robin W. Lindsay, MD

Rosh Sethi, MD, MPH

2nd Place Poster Award

“Predictive value of single Photon Emission Computed Tomography (SPECT) for sentinel lymph node localization in the parotid and external jugular chain for cutaneous head and neck malignancies”

Mentor: Kevin S. Emerick, MD

Jeffrey P. Harris, MD, PhD, Research Prize

Presented to one of the graduating chiefs for his/her FOCUS research project.

Sidharth V. Puram, MD, PhD

“Mapping tumor heterogeneity in head and neck cancer”

Mentors: Derrick T. Lin, MD, FACS, and Bradley E. Bernstein, MD, PhD

Fellow Teaching Award

Joseph Zenga, MD

Chief Resident Teaching Award

Sidharth V. Puram, MD, PhD

William W. Montgomery, MD, Faculty Teaching Award

H. Gregory Ota, MD

Harvard Otolaryngology Resident Well-Being Award

Stacey T. Gray, MD

Trevor McGill Excellence in Teaching Award

Gi Soo Lee, MD, EdM



Dr. Sidharth Puram (middle) receives the Jeffrey P. Harris, MD, PhD, Research Prize, presented by Drs. Brad Welling (left) and Stacey Gray (right).

Graduating Class of 2018

Residents

Known for her thoughtfulness and tenacity, **Jennifer C. Fuller, MD**, started her residency with two strong interests: facial plastic and reconstructive surgery and global mission work. She continued to develop these interests throughout training and found a way to fold them into a scholarly niche. Working with Robin W. Lindsay, MD, she spent much of her time studying outcome evaluations for functional septorhinoplasty, hoping to find ways to improve outcomes. This work resulted in several presentations at national meetings, first-author publications, and awards. She also developed and patented a novel nasal model, which she piloted while on a mission trip to Ecuador. According to her peers, she strikes the perfect balance between confidence and humility. She is now pursuing fellowship training in facial plastic and reconstructive surgery at the University of Minnesota.

Deepa J. Galaiya, MD, is known for her inclusive nature and for always bringing people of different backgrounds together. She has an admirable ability to create positive learning environments for those around her. As a clinician, she is caring, considerate, and

compassionate. As a researcher, she is a divergent thinker. For her FOCUS project, she capitalized on her bioengineering background as she worked with Hideko Heidi Nakajima, MD, PhD, on inner ear mechanics in superior canal dehiscence. This work resulted in multiple national presentations. Inherently an advocate and activist, she was also involved in many national committees and surgical mission trips throughout residency. She is now at Johns Hopkins University pursuing fellowship training in neurotology.

Elliott D. Kozin, MD, joined our program as a seven-year research track resident. Working with Daniel J. Lee, MD, FACS, and M. Christian Brown, PhD, on optogenetic stimulation of the auditory pathway, he received grants from the American Academy of Otolaryngology–Head and Neck Surgery and New England Otolaryngological Society. Working with Aaron K. Remenschneider, MD, MPH, on 3-D printed biomimetic tympanic membranes, he received grants from the American Otological Society and the Ellison Foundation, among others.



The 2018 graduating class of Mass. Eye and Ear/Harvard Medical School residents. From left to right: Drs. Elliott Kozin, Deepa Galaiya, Jennifer Fuller, and Sidharth Puram.



Dr. Brad Welling (left) presenting Dr. David Schuller (right) with a certificate of appreciation for his keynote address.

Dr. Kozin has published more than 100 papers, given numerous presentations, and received several awards. He was our first resident to be named a Star Reviewer for the journal *Otolaryngology–Head and Neck Surgery*, as well as hold a position on their editorial board. He is also a member of the Board of Directors of the National Resident Matching Program. He is the current Neskey-Coghlan neurotology fellow at Mass. Eye and Ear/Harvard Medical School.

Celebrated for his enthusiasm toward teaching, **Sidharth V. Puram, MD, PhD**, was recognized by his fellow residents at graduation with the Chief Resident Teaching Award. During residency, he worked with Derrick T. Lin, MD, FACS, and Bradley E. Bernstein, MD, PhD, on mapping tumor heterogeneity in head and neck cancer. He received several grants and awards for this project. This work also led him to become the first resident in our program to be published in *Cell*. Outside of this project, he published more than 30 papers and gave numerous presentations. As a clinician, he is organized, reliable, and compassionate. He is known for his unique ability to make complicated concepts seem approachable. Dr. Puram is now the head and neck oncologic surgery fellow at The Ohio State University.

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The 2018 graduating class of Mass. Eye and Ear/Harvard Medical School clinical fellows. From left to right standing: Drs. Andrew Senchak, George Scangas, Mohamed Shama, and Edward El Rassi; sitting: Dunia Abdul-Aziz, Sarah Bowe, and Sarah Bouhabel. Not pictured: Drs. Joseph Dusseldorp and Joseph Zenga.

Clinical Fellows, Mass. Eye and Ear

Dunia E. Abdul-Aziz, MD

Neurotology
 Fellowship Director: Daniel J. Lee, MD, FACS
 Future Plans: Otolaryngology Faculty, Mass. Eye and Ear/Harvard Medical School

Sarah Bouhabel, MD

Pediatric Otolaryngology
 Fellowship Director: Christopher J. Hartnick, MD, MS
 Future Plans: Faculty, McGill University Health Centre

Sarah N. Bowe, MD

Pediatric Otolaryngology
 Fellowship Director: Christopher J. Hartnick, MD, MS
 Future Plans: Pediatric Otolaryngologist, San Antonio Uniformed Services Health Education Consortium, Wilford Hall Ambulatory Surgical Center, and Brooke Army Medical Center

Joseph R. Dusseldorp, MD

Facial Plastic and Reconstructive Surgery
 Fellowship Director: Tessa A. Hadlock, MD
 Future Plans: Establish a facial nerve center in Sydney, Australia

Edward T. El Rassi, MD

Rhinology
 Fellowship Directors: Ralph B. Metson, MD, Stacey T. Gray, MD, Eric H. Holbrook, MD
 Future Plans: Assistant Professor, University of Oklahoma

George A. Scangas, MD

Rhinology
 Fellowship Directors: Ralph B. Metson, MD, Stacey T. Gray, MD, Eric H. Holbrook, MD
 Future Plans: Private Practice, Metson & Scangas

Andrew J. Senchak, DO

Vestibular
 Fellowship Director: Steven D. Rauch, MD
 Future Plans: Staff, Ear Institute of Texas

Mohamed Shama, MD

Thyroid and Parathyroid Surgery
 Fellowship Director: Gregory W. Randolph, MD, FACS, FACE
 Future Plans: Head and Neck Surgery/ Microvascular Reconstruction Fellowship, University of Florida

Joseph Zenga, MD

Head and Neck Oncology/ Microvascular Surgery
 Fellowship Directors: Daniel G. Deschler, MD, FACS, Jeremy D. Richmon, MD
 Future Plans: Head and Neck Oncology and Microvascular Reconstruction Faculty, Medical College of Wisconsin

Pediatric Otolaryngology Fellows, Boston Children's Hospital

Fellowship Director: Reza Rahbar, DMD, MD

Jennifer A. Brooks, MD

Future Plans: Thyroid and Parathyroid Surgery Fellowship, Mass. Eye and Ear/ Harvard Medical School

Jad R. Jabbour, MD

Future Plans: Staff, Charlotte Eye, Ear, Nose, and Throat Associates

Claire M. Lawlor, MD

Future Plans: Staff, Children's National Medical Center

Graham M. Strub, MD, PhD

Future Plans: Staff, Arkansas Children's Hospital



The 2018 graduating class of Boston Children's Hospital/Harvard Medical School pediatric otolaryngology fellows with Dr. Michael Cunningham (second to left) and Reza Rahbar (third from right). The fellows include (from left to right): Drs. Jad Jabbour, Graham Strub, Jennifer Brooks, and Claire Lawlor.

The Otolaryngology Residency Program at Harvard Medical School

The Department welcomes five new otolaryngology residents: **Ciersten A. Burks, MD, Christopher I. McHugh, MD, PhD, Lauren E. Miller, MD, MBA, Tara E. Mokhtari, MD, and Alan D. Workman, MD, MTR.**

Meet our PGY-I Residents

Ciersten A. Burks, MD, grew up in Indianapolis, Indiana, and graduated with a degree in biology from Indiana University. There, she was captain of the women’s soccer team and a member of Phi Beta Kappa honor society. Subsequently, she earned her medical doctorate at Indiana University School of Medicine, where she was presented with the Otolaryngology–Head and Neck Surgery Department research fellowship. This allowed her to work under the mentorship of D. Wade Clapp, MD, and Charles W. Yates, MD, studying genetically engineered, preclinical murine models of Neurofibromatosis types 1 and 2, with a special interest in vestibular schwannomagenesis. She is interested in translational, health disparities, and outcomes-based research as well as medical education and service to the community.



Originally from Livonia, Michigan, **Christopher I. McHugh, MD, PhD,** attended the University of Michigan where he earned his degree in biochemistry. He then enrolled in the combined MD/PhD program at Wayne State University. As a graduate student, he worked in the laboratory of Anthony F. Shields, MD, PhD, and studied the use of positron emission tomography (PET) imaging as a method for monitoring the response of cancer to chemotherapy. During his medical training, he participated in medical mission trips to Peru and Ecuador, and spent one month working in clinics in rural Bolivia. Dr. McHugh’s current research interests include intraoperative imaging and the development of sustainable models for international medical relief.



Lauren E. Miller, MD, MBA, grew up in Lima, Ohio, and graduated *summa cum laude* from the University of Pittsburgh with a degree in neuroscience. Following



her undergraduate studies, she completed her medical doctorate at the University of Pennsylvania as well as an MBA at the Wharton School, focusing on healthcare management. Dr. Miller has participated in a variety of research projects including nerve regrowth and regeneration, telemedicine, outcomes research in head and neck cancer patients, and women leadership in medicine. She is interested in both health outcomes research as well as biotech and medical device funding and innovation for surgical fields.

Tara E. Mokhtari, MD, grew up in Eden Prairie, Minnesota, and attended MIT for her undergraduate studies with research focusing on the development of platinum-based anticancer drugs. She graduated with a degree in chemistry and was inducted into the Phi Beta Kappa honor society. She went on to earn her medical doctorate from the Stanford University School of Medicine, where she spent one year as the bariatric and minimally invasive research fellow studying outcomes in bariatric surgery and a second year studying the role of the Wnt signaling pathway in cochlear development. Dr. Mokhtari is an accomplished violinist, having played in numerous orchestral and chamber music ensembles. Her primary research interests include clinical and surgical outcomes, quality improvement, and surgical innovation.



Alan D. Workman, MD, MTR, grew up in Westfield, New Jersey, and graduated *summa cum laude* from Cornell University with a degree in psychology. He matriculated at the University of Pennsylvania Perelman School of Medicine as a 21st Century Scholar. While there, he also earned his master’s in translational research and worked with Noam A. Cohen, MD, PhD, on several basic science and clinical research projects. He has received a grant from the National Institutes of Health to study airway innate immune defense and physiology. His research experiences include the study of cellular signaling and ciliary dynamics in the airway, development of diagnostics and therapeutics for chronic rhinosinusitis, and analysis of treatment and surveillance paradigms in sinonasal malignancy.



**New Clinical Fellows
Mass. Eye and Ear**



*Head and Neck Oncology/
Microvascular Surgery*
Joel Fontanarosa, MD, PhD



Laryngology
Sungjin Song, MD



Neurotology
Elliott D. Kozin, MD



Pediatric Otolaryngology
Christen L. Caloway, MD



Rhinology
Catherine G. Banks, MD



Rhinology
Qasim Husain, MD



*Thyroid and Parathyroid
Surgery*
Jennifer A. Brooks, MD

**Boston Children’s Hospital
Pediatric Otolaryngology**



**Jaime Doody,
MB, BCH**



Joshua Gurberg, MD



**Rounak B.
Rawal, MD**



Cher Xue Zhao, MD

Leonid Litvak, PhD, Eaton-Peabody Laboratories at Massachusetts Eye and Ear/Harvard Medical School, 1995–2001

Improving the cochlear implant experience



Coming from a family of musicians and engineers, Leonid Litvak, PhD, grew up with interests in sound and science. It came as no surprise when he chose to pursue his undergraduate degree in electrical engineering and applied mathematics.

During his time at Rice University in Houston, Texas, Dr. Litvak was assigned a project that involved cochlear implants and since then, he has set his mind on improving the user experience for patients with these devices.

“I thought it was really neat that cochlear implants combine biology, hearing, and engineering because those were all of my interests,” said Dr. Litvak, who is now the Senior Director of Research and Technology at Advanced Bionics, a cochlear implant manufacturer. “That is when I decided I wanted to focus on cochlear implants, especially since there is a lot of work to be done regarding music perception.”

Prior to graduation, Dr. Litvak was researching Master’s programs to continue his studies in electrical engineering when he came across the Harvard Medical School-MIT Speech and Hearing Bioscience and Technology (SHBT) doctorate program. He notes that it had “all of the elements that [he] was interested in.”

After being admitted into the program, he began his studies working with Donald K. Eddington, PhD, and Bertrand Delgutte, PhD, of the Eaton-Peabody Laboratories (EPL) at Massachusetts Eye and Ear. During this time, Dr. Litvak felt there was still much to be understood about the cochlear implant and how it worked.

He worked on projects that investigated alternative ways of stimulating cochlear implants, with the goal of improving naturalness of sound for cochlear implant users.

“Working in the EPL was quite an informative experience for me,” said Dr. Litvak. “When I got there, everyone was brilliant—I felt like I had a lot of catching up to do. But right from the start, I was treated like a colleague and given freedom to pursue my own research questions. It helped me learn and grow as a scientist and gave me the tools I needed to build my career.”

In 2002, Dr. Litvak began his tenure at Advanced Bionics, starting out as a systems engineer conducting research on frequency-to-electrode alignment.

Now, he directs the research and technology arm of the company,

leading research efforts in signal processing for biomedical applications, electric stimulation of the auditory nerve, electrode design, and big data. He oversees two teams: one that is responsible for materials and implant technology and the other focused on improving cochlear implant performance in challenging environments.

“I’ve had various roles at Advanced Bionics, but in each one, I’ve tried to always stay connected to research and the hands-on experience,” said Dr. Litvak. “With my teams, I try to give them the guidance and independence they need to do well in their work. It kind of reminds me of my experience at Mass. Eye and Ear in some ways. I want to make sure my teams are successful and that their work is impactful.”

Dr. Litvak also works on improving the way that cochlear implants are programmed in the clinic. He works on making the programming process for cochlear implants more objective through the use of neural responses in order to give audiologists more guidance when fitting patients.

Ultimately, Dr. Litvak hopes to have a significant impact on the use and performance of these devices.

“At the end of my career, if I find that I’ve contributed to people hearing better and that I’ve made a difference in their lives, then I would say that I had accomplished what I wanted,” he noted. ●

In memoriam

A mentorship with an everlasting impact



David J. Lim, MD



Robert S. Kimura, PhD

David J. Lim, MD, Professor-In-Residence at the University of California, Los Angeles (UCLA) David Geffen School of Medicine and Co-Director of the UCLA Pathogenesis of Ear Diseases Laboratory, passed away on June 29, 2018. Known for his contributions to defining human inner ear ultrastructure and cell biology, as well as the innate immunity of the middle and inner ear, Dr. Lim had an impact on many.

A founding member of the Association for Research in Otolaryngology, Dr. Lim began his work in electron microscopy, a technique he helped pioneer for inner and middle ear research as a postdoctoral fellow at Massachusetts Eye and Ear/Harvard Medical School. There, he spent much of his time working under the guidance of Robert S. Kimura, PhD, who co-founded and directed the Electron Microscopy Laboratory at Mass. Eye and

Ear and was also known for his work in the inner ear.

Following his training, Dr. Lim brought his wisdom and high spirits to The Ohio State University, where he served on faculty for more than 25 years before becoming the Scientific Director of the National Institute on Deafness and Other Communication Disorders of the National Institutes of Health. He then settled in Los Angeles, first heading scientific research for the House Ear Institute and later taking an appointment at UCLA.

Following in the footsteps of his mentor and friend Dr. Kimura, who passed away in April of 2017, Dr. Lim worked tirelessly to ensure that the most promising auditory and vestibular science was championed—especially as it related to the immunity and immunopathology of the middle and inner ear.

The impact Dr. Kimura had on Dr. Lim was so profound that in lieu of flowers, Dr. Lim's family asked for donations to Mass. Eye and Ear in honor of Dr. Kimura. All proceeds will go toward advancing inner ear research.

“Everyone benefited from knowing Dr. Lim and Dr. Kimura. Together, their knowledge and authority on elucidating the ultrastructure of the inner ear was unparalleled,” said D. Bradley Welling, MD, PhD, FACS, the Walter Augustus Lecompte Professor and Chair of Otolaryngology at Harvard Medical School. “The loss of both of them sits heavy in our hearts, but the impact that they had and the legacies they left behind, both individually and collectively, will continue to move science forward for generations to come.” ●

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 43 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.

Alumni Giving Society Leadership

D. Bradley Welling, MD, PhD, FACS
Walter Augustus Lecompte Professor and Chair of Otolaryngology, Harvard Medical School
Chief of Otolaryngology, Mass. Eye and Ear/
Massachusetts General Hospital

Michael B. Rho, MD, FACS, '05
President, Harvard Otolaryngology Alumni Society
Medical Director, Otolaryngology, Mass. Eye and Ear, Stoneham

Alumni Leaders

Daniel G. Deschler, MD, FACS
Richard E. Gliklich, MD, '93, '94
Donald G. Keamy, Jr., MD, MPH
Paul M. Konowitz, MD, FACS
John B. Lazor, MD, MBA, FACS, '95, '96
Jon B. Liland, MD, '72
Derrick T. Lin, MD, FACS, '98, '02
Leila A. Mankariou, MD
William W. McClerkin, MD, '73
Ralph B. Metson, MD, '87
Michael M. Paparella, MD
Herbert Silverstein, MD, FACS, '66



From left to right: Drs. Nicolas BuSaba, Joshua Silverman, Carol Lewis, Vicente Resto, Andrew Scott, Eric Holbrook, Brad Welling, Stacey Gray, Michael Rho, Matthew Dedmon, Matthew Naunheim, and Kiran Kakarala.

Current Alumni Giving Society members for fiscal year 2018 from October 1, 2017, to September 30, 2018, are listed below. With your gift of \$1,000 or more, you will be included in the 2019 Alumni Giving Society.

CHAMPION: Gifts of \$25,000 or more
Michael S. Cohen, MD
Ralph B. Metson, MD

VISIONARY: Gifts of \$10,000 to \$24,999
Daniel J. Lee, MD, FACS
Michael B. Rho, MD, FACS

INNOVATOR: Gifts of \$5,000 to \$9,999
Nicolas Y. BuSaba, MD, FACS
Stacey T. Gray, MD
Thomas J. Kereiakes, MD
John B. Lazor, MD, MBA, FACS
Jon B. Liland, MD
In Seok Moon, MD, PhD

PIONEER: Gifts of \$2,500 to \$4,999
Barry J. Benjamin, MD
Frank P. Fechner, MD
Richard E. Gliklich, MD
Wade W. Han, MD
Lukas Landegger, MD, PhD
Leila A. Mankariou, MD
Cliff A. Megerian, MD
David E. Nash, MD
H. Gregory Ota, MD
Steven D. Rauch, MD
Jonathan Y. M. Ting, MD

FRIEND: Gifts of \$1,000 to \$2,499
Megan E. Abbott, MD
Samir M. Bhatt, MD
Benjamin S. Bleier, MD
Sarah N. Bowe, MD
Daniel G. Deschler, MD, FACS
Ruth Anne Eatock, PhD
Peter N. Friedensohn, MD
Paul E. Hammerschlag, MD, FACS
Christopher J. Hartnick, MD, MS
Eric H. Holbrook, MD
Paul M. Konowitz, MD, FACS
Eugene N. Myers, MD, FACS, FRCS Edin (Hon)
Brian J. Park, MD, MPH, FACS
Adrian J. Priesol, MD
Sunil Puria, PhD
Edward J. Reardon, MD
Mark F. Rounds, MD
Jennifer Setlur, MD
Herbert Silverstein, MD, FACS
Phillip C. Song, MD
Mark A. Varvares, MD, FACS
D. Bradley Welling, MD, PhD, FACS

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

New Faculty

Daniel L. Faden, MD, has joined Mass. Eye and Ear/Harvard Medical School as an investigator and specialist in head and neck cancer. He earned his medical degree from Boston University School of Medicine before completing residency



training in otolaryngology—head and neck surgery at the University of California, San Francisco. He then pursued fellowships in advanced head and neck oncologic surgery and cranial base surgery at the University of Pittsburgh, where he also completed a postdoctoral research fellowship through the National Institutes of Health. His research focuses on how acquired genomic alterations and viral infections affect the behavior of head and neck cancers, with the goal of translating findings into advancements in precision head and neck oncology care.

Craig A. Jones, MD, is the Medical Director of Otolaryngology at Mass. Eye and Ear's new Cape Cod practices in Mashpee and Harwich. Dr. Jones earned his medical degree from the University of Maryland School of



Medicine, before completing his residency in otolaryngology—head and neck surgery at Mass. Eye and Ear/Harvard Medical School. He has been practicing on Cape Cod for 18 years and has interests in otology and allergy.

Srinivas Vinod Saladi, PhD, has joined Mass. Eye and Ear/Harvard Medical School as a research investigator in head and neck cancer. He earned his PhD from the University of Toledo College of Medicine and Life



Sciences in biochemistry and cancer biology prior to completing postdoctoral training in cancer epigenetics and signaling at the Massachusetts General Hospital Cancer Center. The primary research interests of his lab focus on understanding the mechanism by which epigenetic reprogramming contributes to cellular plasticity in tumors.

New Leadership

Jean Bruch, DMD, MD, Director of the Norman Knight Hyperbaric Medicine Center, Mass. Eye and Ear.

Konstantina M. Stankovic, MD, PhD, FACS, Director of Otolaryngology and Neurotology, Mass. Eye and Ear.

Awards, Grants, and Honors

Benjamin S. Bleier, MD, FACS, received an R01 grant from the National Institutes of Health for his work, "Direct CNS delivery system for BDNF antagoNATs using heterotopic mucosal grafting for the treatment of Parkinson's disease."

Zheng-Yi Chen, D.Phil., received a new Department of Defense hearing restoration grant for his work, "Hair cell regeneration in mature mammalian inner ear." He also received a multi-investigator grant from the National Institutes of Health for his work in developing genome editing.

Michael J. Cunningham, MD, FACS, gave the Sylvan E. Stool Memorial Lectureship at the University of Colorado's Department of Otolaryngology—Head and Neck Surgery 2018 Midwinter Meeting.

Daniel G. Deschler, MD, FACS, was appointed Chair of the Patient Care Division of the American Head and Neck Society and to their Executive Council.

Kevin S. Emerick, MD, is the recipient of the 2018 Chris O'Brien Traveling Fellowship, which is presented by the Research and Education Foundation of the American Head and Neck Society.

Xiying Guan, PhD, received the R21 Exploratory/Developmental Research Grant Award from the National Institutes of Health, which will be dedicated to studying the mechanisms of conductive hyperacusis.

Gerald B. Healy, MD, FACS, has been selected to be a member of the first class of the Master Surgeon Educators of the American College of Surgeons.

Jeffrey R. Holt, PhD, chaired the Auditory System Gordon Research Conference in July 2018. Seven podium and poster presentations were featured from the Holt/Géléc Lab. He is also the recipient

of the Harvard Medical School SIM Excellence in Student Mentoring award.

Artur A. Indzykilian, MD, PhD, received a grant through the National Institute On Deafness and Other Communication Disorders of the National Institutes of Health for his work, "Molecular basis of hair cell stereocilia bundle morphology." He has also received a Bertarelli Collaborative Research Award within the Bertarelli Program in Translational Neuroscience and Neuroengineering.

David H. Jung, MD, PhD, received a \$30K Emerging Research Grant from the Hearing Health Foundation for his work, "Mechanisms and development of novel small molecule treatments for cochlear synaptopathy."

Vivek Kanumuri, MD, Mass. Eye and Ear/Harvard Medical School resident, received a 2018 American Academy of Facial Plastic and Reconstructive Surgery Leslie Bernstein Resident Research Grant for his work, "Optogenetic stimulation of the facial nerve."

Margaret A. Kenna, MD, MPH, FACS, FAAP, co-authored the textbook *Pediatric Sensorineural Hearing Loss: Clinical Diagnosis and Management*, published by Plural Publishing. She also co-chaired the 2018 International Symposium on Usher Syndrome held in Germany alongside **Gwenaëlle S. Géléc, PhD**.

Elliott D. Kozin, MD, the Mass. Eye and Ear Neskey-Coghlan fellow in neurotology, received the 2018 CORE American Neurotology Society/American Academy of Otolaryngology—Head and Neck Surgery Herbert Silverstein Otolaryngology and Neurotology Research Award for his proposal, "Otopathologic changes following head injury." He is also a 2018 Star Reviewer for the journal *Otolaryngology—Head and Neck Surgery*.

Daniel J. Lee, MD, FACS, received a research grant from the Department of Defense for his work, "Improving hearing in NF2 patients who use the Auditory Brainstem Implant (ABI)."

Richard F. Lewis, MD, received a new National Institutes of Health R01 grant for his work, "Temporal synthesis of vestibular and extra-vestibular signals."

Robin W. Lindsay, MD, will co-chair the American Academy of Facial Plastic and Reconstructive Surgery Meeting at COSM

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in May 2019. She has also been selected to chair the WIO Research and Survey Committee for the American Academy of Otolaryngology–Head and Neck Surgery.

Suresh Mohan, MD, Mass. Eye and Ear/Harvard Medical School resident, received a 2018 American Academy of Facial Plastic and Reconstructive Surgery Leslie Bernstein Resident Research Grant for his work, “Enhancement of axonal penetration through cross-facial nerve grafts.”

Reza Rahbar, DMD, MD, has been elected Secretary of the American Society of Pediatric Otolaryngology.

Gregory W. Randolph, MD, FACS, FACE, has been elected Chair of the Endocrine Surgery Section of the American Head and Neck Society.

Steven D. Rauch, MD, received an honorary professorship at the Annual Vestibular Conference of the Guangdong Academy of Medical Sciences in Guangzhou, China. He was also appointed as a member of the Ménière’s Disease Advisory Board of the Hearing Health Foundation.

Jo Shapiro, MD, was awarded an honorary fellowship from the Royal College of Surgeons in Ireland in recognition of her contribution to professionalism, leadership, and surgery.

Mark G. Shrime, MD, MPH, PhD, FACS, has been awarded the 2018 Arnold P. Gold Foundation Award for Humanism in Medicine by the American Academy of Otolaryngology–Head and Neck Surgery. This award recognizes members committed to practicing otolaryngology with compassionate, patient-centered care.

Kristina Simonyan, MD, PhD, Dr. med., was invited to serve on the Scientific Advisory Board of the Tourette Association of America.

Anne E. Takesian, PhD, received a Bertarelli Collaborative Research Award within the Bertarelli Program in Translational Neuroscience and Neuroengineering for her project, “Targeting VIP interneurons to enhance auditory cortical plasticity.”

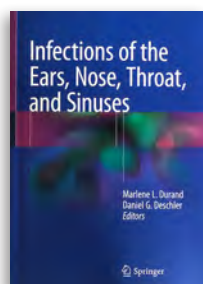
Ravindra Uppaluri, MD, PhD, has been appointed the inaugural Distinguished Chair in Otolaryngology at Brigham and Women’s Hospital.



Mass. Eye and Ear has launched a Center for Global Surgery Evaluation. Led by **Mark G. Shrime, MD, MPH, PhD, FACS**, and **Blake C. Alkire, MD, MPH**, the center investigates impacts on health, financial well-being, equity, disparities, and the macroeconomic health of countries. Through the development of innovative research techniques, it strives to ask questions of relevance to ministries of health, global surgery implementers, and, most importantly, patients themselves.



From left to right: Drs. Ronald de Venecia, Nicholas Dewyer, Daniel Lee, and Felipe Santos.



Daniel G. Deschler, MD, FACS, and **Marlene L. Durand, MD**, have published a new textbook, *Infections of the Ears, Nose, Throat, and Sinuses*.

The Department of Otolaryngology at Harvard Medical School held its first annual Mastoid Bowl this summer. Hosted by **Daniel J. Lee, MD, FACS**, this competition evaluated otolaryngology residents as they performed mastoidectomies (canal-wall-up with facial recess) on cadavers in the Joseph B. Nadol, Jr., MD, Surgical Training Laboratory at Mass. Eye and Ear. The winner was otolaryngology Chief Resident **Katie M. Phillips, MD**.

HMS Promotions



Thomas L. Carroll, MD, Assistant Professor of Otolaryngology



Kosuke Kawai, ScD, Assistant Professor of Otolaryngology



Kristina Simonyan, MD, PhD, Dr. med., Associate Professor of Otolaryngology



Anne E. Takesian, PhD, Assistant Professor of Otolaryngology

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

Basic Science

The essential role of TMC1 in the hearing process confirmed

The proteins that form the permeation pathway of mechanosensory transduction channels in inner ear hair cells have not been definitively identified. Genetic, anatomical, and physiological evidence support the role for the sensor protein transmembrane channel-like protein (TMC1) in hair cell sensory transduction, but the molecular function of such proteins has been unclear.



In a study led by **Jeffrey R. Holt, PhD**, of Boston Children's Hospital/Harvard Medical School, researchers confirmed TMC1's essential role in the conversion of sound or movement into

electrical signals, ending a 40-year quest. Published in *Neuron*, they mapped out the working parts of TMC1.

Working with living hair cells in mice, the team made substitutions in 17 amino acids within the TMC1 protein, one at a time, to see which ones altered the hair cells' ability to respond to stimuli and allow the flow of ions. Twelve amino acid substitutions altered the influx of ions, and five did so dramatically, reducing ion flow by up to 80 percent. One substitution blocked calcium flow completely, thereby revealing the location of the pore within TMC1 that enables ion influx.

The data provide compelling evidence that TMC1 is a pore-forming component of sensory transduction channels in auditory and vestibular hair cells, which could have implications for reversing hearing loss in the future.

TMC1 forms the pore of mechanosensory transduction channels in vertebrate inner ear hair cells. Pan B, Akyuz N, Liu XP, Asai Y, Nist-Lund C, Kurima K, Derfler BH, György B, Limapichat W, Walujkar S, Wimalasena LN, Sotomayor M, Corey DP, Holt JR. *Neuron*. 2018 Aug 22;99(4):736–753.e6.

Synaptopathy in the aging cochlea

A fairly universal communication problem for middle aged and older listeners is an increasing difficulty understanding speech in noisy conditions. The discovery by Mass. Eye

and Ear investigators in 2009 of dramatic age- and noise exposure-related cochlear synaptopathy, i.e., the loss of synaptic connections between the inner hair cell and the auditory nerve fibers that carry their information toward the brain, has suggested a possible contributor to these performance declines.

In a recent study funded by the Department of Defense and published in the *Journal of Neuroscience*, **Aravindakshan Parthasarathy, PhD**, and **Sharon G. Kujawa, PhD**, of Mass. Eye and Ear/Harvard Medical School, used a combination of electrophysiologic, pharmacologic, and histologic techniques to show evidence for temporal coding abnormalities that are present at the earliest stages of the auditory neural pathway. These deficits in



representation of fast timing cues that are essential for speech-in-noise processing are highly correlated with the age-progressive loss of cochlear synapses and are largest at higher sound levels relevant to real world communication.



Although the standard clinical audiogram is silent to this synaptic loss, the additional, noninvasive tests used

in these studies could be adapted for future diagnostic approaches to assess "hidden" hearing loss in a clinical setting.

Synaptopathy in the aging cochlea: Characterizing early-neural deficits in auditory temporal envelope processing. Parthasarathy A, Kujawa SG. *J Neurosci*. 2018 Aug 8;38(32):7108–7119.

Sensory overamplification in layer 5 auditory corticofugal projection neurons following cochlear nerve synaptic damage

Layer 5 (L5) cortical projection neurons innervate far-ranging brain areas to coordinate integrative sensory processing and adaptive behaviors. In a study led by **Daniel B. Polley, PhD**, and **Meenakshi Asokan** of Mass. Eye and Ear/Harvard



Medical School, a plasticity in L5 auditory cortex (ACTx) neurons that innervate the inferior colliculus (IC), thalamus, lateral amygdala, and striatum were categorized.



The research team tracked daily changes in sound processing using chronic wide-field calcium imaging of L5 axon terminals on the dorsal cap of the IC in awake, adult mice.

Sound level growth functions at the level of the auditory nerve and corticocollicular axon terminals are both strongly depressed hours after noise-induced damage of cochlear afferent synapses. Corticocollicular response gain rebounded above baseline levels by the following day and remained elevated for several weeks despite a persistent reduction in auditory nerve input. Sustained potentiation of excitatory ACTx projection neurons that innervate multiple limbic and subcortical auditory centers may underlie hyperexcitability and aberrant functional coupling of distributed brain networks in tinnitus and hyperacusis.

Sensory overamplification in layer 5 auditory corticofugal projection neurons following cochlear nerve synaptic damage. Asokan MM, Williamson RS, Hancock KE, Polley DB. *Nat Commun*. 2018 Jun 25;9(1):2468.

An engineering model to test for sensory reweighting

Quantitative animal models are critically needed to provide proof of concept for the investigation of rehabilitative balance therapies (e.g., invasive vestibular prostheses)



and treatment response prior to, or in conjunction with, human clinical trials. In a study led by **Richard F. Lewis, MD**, of Mass. Eye and Ear/Harvard Medical School, a novel approach to modeling the nonhuman primate postural control system is described.

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Previously, system identification methodologies and models were only used to describe human posture. However, using pseudorandom, roll-tilt balance platform stimuli to perturb the posture of a non-human primate in normal and mild vestibular (equilibrium) loss states, the researchers found that the relationship between trunk sway and platform roll-tilt in the subjects was determined via stimulus-response curves and transfer function results. When a feedback controller model was used to explore sensory reweighting (i.e., changes in sensory reliance), it prevented the subject from falling off the tilting platform.

Conclusions involving sensory reweighting for a normal sensory state and a state of mild vestibular loss led to meaningful insights. This first-phase effort to model the balance control system in nonhuman primates is essential for future investigations toward the effects of invasive rehabilitative (balance) technologies.

An engineering model to test for sensory reweighting: Nonhuman primates serve as a model for human postural control and vestibular dysfunction. Thompson LA, Haburcakova C, Goodworth AD, Lewis RF. *J Biomech Eng*. 2018 Jan 1;140(1).

The neuroregenerative capacity of olfactory stem cells is not limitless: Implications for aging

It's estimated that more than 60 percent of people between the ages of 65 and 80 have olfactory (smell) impairment. Not only is this a hazard in the inability to detect smoke from a fire, natural gas leaks in the home, or spoiled food, but it also significantly impacts quality of life and appreciation of food flavor.

It's known that loss of olfactory neurons occurs with age, but our understanding of what causes this has been limited. Close examination of the nasal membranes in human autopsy specimens and biopsies has revealed areas where the neurons are absent, but the underlying stem cells that have the ability to divide and replace these neurons remain in a suspended state.

In collaboration with Tufts University School of Medicine, **Eric H. Holbrook, MD**, of



Mass. Eye and Ear/Harvard Medical School, developed a mouse model that displays a nasal olfactory membrane that mimics what is found in human tissue.

In this model, mice undergo rapid loss of the olfactory neurons, which causes the underlying immediate precursor stem cells to increase cell division and regenerate dying neurons at a high rate. Through this, the research team found that these cells have a limited capacity under such conditions and eventually disappear, leaving a membrane without neurons. However, a population of reserve basal stem cells remains but are stuck in an inactive state. Experimental activation of these basal stem cells in mice has been shown to result in regeneration of new neurons and forms the basis of potential therapeutic treatments in human smell loss.

The neuroregenerative capacity of olfactory stem cells is not limitless: Implications for aging. Child KM, Herrick DB, Schwob JE, Holbrook EH, Jang W. *J Neurosci*. 2018 Jun 22. pii:3261-17.

Fluorescent reporter mice for nerve guidance conduit assessment: A high-throughput *in vivo* model

Conventional neurohistology techniques for assessment of peripheral nerve regeneration are resource-intensive, rendering assessment of tissue-engineered devices for nerve repair cumbersome. A team of researchers including otolaryngology resident **Suresh Mohan, MD**, and **Nate Jowett, MD, FRCS**, of Mass. Eye and Ear/Harvard Medical School, recently developed



a platform for rapid and low-cost assessment of nerve guidance conduit performance. This model employs transgenic reporter mice for stain-free axon visualization.



Interposition repair of sciatic nerve gaps was performed by sutureless entubulation of nerve stumps within guidance conduit ends, and axonal ingrowth was assessed at three and six weeks using

epifluorescent microscopy following rapid cryosection. Procedural time was reduced to less than three minutes per animal and direct costs were kept under \$25.00. Axonal ingrowth into various types of bioengineered conduits was readily quantified, permitting classification of conduit environments as ingrowth-permissive, semi-permissive, or restrictive. This approach offers a rapid and

cost-effective means for assessing the next generation of bioengineered neural conduits, which carries potential to circumvent the need for nerve autografting and its associated morbidity for patients suffering from facial and other peripheral nerve deficits.

Fluorescent reporter mice for nerve guidance conduit assessment: A high-throughput *in vivo* model. Mohan S, Hernández IC, Wang W, Yin K, Sundback CA, Wegst UGK, Jowett N. *Laryngoscope*. 2018 Aug 10.

Clinical Practice

Opioid prescription patterns after rhinoplasty surgery

Facial plastic surgeons from Mass. Eye and Ear/Harvard Medical School, including **David A. Shaye, MD, MPH**, **Linda N. Lee, MD**, and otolaryngology resident **Rosh Sethi,**



MD, MPH, performed a study of 173 rhinoplasty patients over a one-year period to examine opioid prescription patterns using the Massachusetts opioid registry. The study showed a near-negligible rate of refills were required after surgery and 11.3 percent of patients never filled their opioid prescription at all.

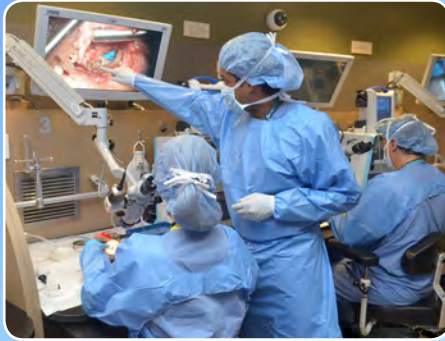


Recently published in *JAMA Facial Plastic Surgery*, the results suggest patients experience less pain than expected and that the optimal number of opioid tablets to manage postoperative rhinoplasty pain may be lower than expected.

A reduction in narcotic prescriptions after rhinoplasty may limit the opportunity for opioid abuse, an epidemic in the United States, where less than five percent of the world's population consumes two-thirds of the world's opioid supply.

As a result of their findings, the authors have reduced the number of opioid tablets they prescribe to patients by at least 50 percent.

Opioid prescription patterns after rhinoplasty. *JAMA Facial Plastic Surgery*. 2018 Sept 6. Sethi RKV, Lee LN, Quatela OE, Richburg KG, Shaye DA.



Upcoming Events

oto.hms.harvard.edu/event-calendar

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



Check out our new Harvard Otolaryngology website at oto.hms.harvard.edu.

HARVARD Otolaryngology

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