A Worldwide First in Otolaryngology: Investigating Gene Therapy for Hearing Loss

Hearing loss – acquired or genetic – is the most common sensory disorder in humans, with the majority of acquired hearing loss due to damaged or destroyed sensory hair cells in the inner ear. “These tiny, critical cells allow us to convert sound vibrations of the natural world into the electrical impulse that goes to the brain,” says Lawrence R. Lustig, MD, Otolaryngologist-in-Chief at NewYork-Presbyterian/Columbia University Medical Center and Chair of the Department of Otolaryngology – Head and Neck Surgery at Columbia University College of Physicians and Surgeons. “But once hair cells die – whether from trauma to the ear, aging, infection, noise exposure, or ototoxicity – they don’t grow back and you permanently lose hearing capability.”

And therein lies the challenge for reversing hearing loss...at least until now. The Department of Otolaryngology – Head and Neck Surgery at Columbia is one of three centers in the world conducting a clinical trial in which cellular regeneration is being used to treat hearing loss. For Dr. Lustig, it is the culmination of an interest and research in hearing loss that began while he was in medical school, where he took a year out of his... (continued on page 2)
Paving the Way to Gene Therapy

“...was well-known for years that birds could regenerate hair cells, but mammals couldn’t,” notes Dr. Lustig. “In 1999, a group of researchers identified a particular gene – the atonal gene – in fruit flies followed by the creation of a mouse knock-out of this gene. Everything else was totally normal in the ear, with the exception that they didn’t have any hair cells – either auditory or vestibular. That was the first clue that the atonal gene appeared to kick-start cell growth in a living organism,” says Dr. Lustig. “They further validated this work with another study where they deafened the mice using the aminoglycoside antibiotic, which kills hair cells, and then added back in the Atoh1 gene on the adenovirus. They were not only able to demonstrate hair cell regeneration, but also some hearing recovery – the degree of recovery being related to the number of hair cells that regrew. This demonstration of functional recovery was a turning point in the field and generated a lot of excitement.”

Hinrich Staecker, MD, PhD, an otolaryngologist with the University of Kansas Medical Center – the third center in the current clinical trial – then showed that you could do the same thing in the vestibular system using the same gene and virus. “Over the next several years, research led by Dr. Staecker in collaboration with Novartis focused on developing a translational study using the human version of the gene – Hath1 – on an adenovirus backbone,” says Dr. Lustig. “This work led to the hair cell regeneration gene therapy trial now underway. This is the first cochlea gene therapy trial ever done in the ear – the first one in otolaryngology – so it’s revolutionary in that regard.”

Candidates for the study, which began recruitment in late 2014, must be totally deaf and well within cochlear implant candidacy range, says Dr. Lustig. “One of the challenges is finding patients who have that level of hearing loss who haven’t had a cochlear implant. Once you’ve had a cochlear implant you’re no longer a candidate for the study. Hearing loss also has to be in both ears. Patients who have lost all hearing in one ear and have good hearing in the other ear don’t qualify either – at least not yet. And candidates must have intact vestibular function in the nonoperative ear.”

Will the treatment that worked in the mouse improve hearing in humans and, if so, how long will it work – a few months, a lifetime? These are critical questions the trial seeks to answer. “To deliver the therapy, we can either make a tiny little hole through the base of the stapes bone or do the injection through the round window membrane of the cochlea, a little membrane that we can access through the middle ear,” explains Dr. Lustig. “The delivery piece will not be the problem. The challenge is going to be developing the right vectors and the right genes and figuring out the best timing of treatment. If we can intervene before the onset of the hearing loss we could make a huge difference in patients’ lives. We are hopeful that this research will lead to treatment of patients with hearing loss of all types, possibly even supplanting the need for hearing aids and cochlear implants.”

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Sean Parker Institute for the Voice  (continued from page 1)

been a kind of cottage industry with everyone treating patients on their own – not as a team. It wasn’t so long ago that an individual with hoarseness might have been told he or she was guilty of ‘voice abuse,’ and told to undergo weeks, even months, of voice rest. Alternately, anti-allergy, anti-reflux medication, or endless repeated treatments with steroids might be prescribed instead of the patient undergoing a proper, sophisticated laryngeal evaluation.”

Not so at the Parker Institute. “Operating on the platform of an affiliation with NewYork-Presbyterian and Weill Cornell Medicine, our goal is to think critically about voice disorders in order to pursue treatment on a medically sound and rational basis,” says Dr. Sulica. “The larynx and vocal folds are highly specialized biological structures, and laryngeal problems are decipherable, treatable, and curable by means of scientific and medical principles. We do not need to rely on special gargles to help our patients. But we do need to continue to improve the science and to study the clinical evidence.”

Expanding Expertise
Continuing to expand their capabilities, last year the Parker Institute welcomed Babak Sadoughi, MD, a fellowship-trained otolaryngologist skilled in laryngeal disorders, encompassing voice medicine and surgery for performers, treatment of benign diseases and malignant tumors of the larynx, and airway and swallowing rehabilitation surgery. Dr. Sadoughi brings special expertise in minimally invasive laryngeal surgery and in the use of lasers.

“Our primary mission is to deliver the highest level of clinical care for all the conditions that can affect the human larynx and its core functions,” says Dr. Sadoughi. “These conditions not only include benign disorders, such as polyps, nodules and cysts, but also less common and more ominous issues with cancers of the throat, as well as airway disorders that can cause obstruction of the respiratory pathways. We focus on any condition or problem that can affect those functions and rely on the best available scientific evidence to manage it.”

Dr. Sadoughi stresses the Institute’s multidisciplinary approach to care. “The Parker Institute laryngologists work in close association with the speech-language pathologists, but also with colleagues in other specialties, such as pulmonary, gastroenterology, oncology specialists, neurologists or thoracic surgeons, to name a few. The support of the highly experienced administrative and technical staff of the Institute is also essential to making the patient’s experience a smooth and effective one,” he says.

Research that Informs Clinical Care
Of equal importance, says Dr. Sadoughi, is advancing the field through research. “The overarching goal of our research is to improve the current fount of knowledge on these conditions in order to enhance patient outcomes and minimize the risks,” he says. An example of such research efforts was a recently published clinical study performed at the Parker Institute, which aimed at identifying the voice-related medical disorders specifically affecting performing artists, as opposed to the general population.

In another research endeavor, the Parker Institute examined the entity of vocal fold hemorrhage, an acute injury that results from the physical stresses of voice use or phonotrauma. It is not uncommon for a performer or other intensive voice user to experience this condition, which can be a source of considerable anxiety. “Vocal fold hemorrhage is a good example of the basic gaps in our knowledge,” explains Dr. Sulica. Hemorrhages are thought to result from enlarged blood vessels — the varices — on the vocal fold, which are believed to be especially fragile. “These hemorrhages are an archetype of the performer’s injury, occurring because of the physical stress of voicing on the vocal fold tissue. The perception, both among performers and many physicians, is that vocal fold hemorrhage is catastrophic and a potential career-ender.”

“Concentrating exclusively on voice disorders has taught us a great deal about how voice injuries happen and how they affect peoples’ lives. There are subtleties in voice rehabilitation that differ in each type of patient. Rehabilitating a teacher is different from rehabilitating a retiree, which is very different from rehabilitating a performer.”

– Dr. Lucian Sulica

“At the Parker Institute we have robust clinical experience to address that question,” continues Dr. Sulica. “We recently identified 46 patients with vocal fold hemorrhage to find out what their careers look like now years after their injury. It turns out that compared to patients with other voice disorders, hemorrhages represented no increase in risk to their careers. The clinical experience suggests the prognosis is not nearly as dire as is commonly thought. So now when a patient is paralyzed with fear having just learned they’ve had a vocal fold hemorrhage, we can tell them that it is extremely unlikely to affect their career based on solid clinical information. That’s when the entire visit becomes positive and focused on rehabilitation instead of on this dread that their career is about to end.”

Dr. Sulica notes that, interestingly, the more hemorrhages a patient had, the more confident they became about their vocal
Sean Parker Institute for the Voice  (continued from page 3)

health. “We think that is because each time they had a hemorrhage and recovered, it reinforced the message that there really is not a long-term consequence here. All they have to do is get through the acute episode. That reflects that performers, conventionally regarded as somewhat high-strung, are actually more levelheaded than they are given credit for – and maybe even more evidence-driven than many who take care of them!”

As each research effort answers another question about vocal fold hemorrhage and we know from our research that the chance of that bleeding is extremely small and that we don’t need to intervene,” says Dr. Sulica. “Before our investigation, there were six papers in the literature on how to operate on enlarged blood vessels, but not a single one on when to do such an operation. Those are the kinds of questions we are trying to answer. Our goal is simply to give patients and doctors accurate information about a given problem.”

In another study, the researchers investigated pseudocysts, which – like polyps – are frequently treated with surgery. They found that two in three patients – most of whom are performers – do not need surgery to continue at the level of voice use their profession demands. Voice therapy by itself appears to be sufficient. A follow-up study of surgical outcomes in the one-third of patients who ultimately chose to undergo surgery showed generally good results, but revealed a potential link to glottic insufficiency, a characteristic polyps do not share.

Dr. Sulica foresees that as computing power increases so will visualization technologies. “There is going to be an evolutionary

NewYork-Presbyterian/Columbia Broadens Areas of Expertise  (continued from page 5)

Justin S. Golub, MD
don’t have to remove bone in order to see into the middle ear. Bone removal takes time. There’s always the risk of injury when you’re using a drill, and it often results in a larger incision and more pain after surgery. Whereas with the endoscope you can slide past the obstructing bone making the surgeries less invasive. The endoscope also gives you an extremely magnified, panoramic view of the area you’re operating on.” The key to the successful application of endoscopes in ear surgery is defining which surgeries would be better performed with the endoscope versus those with a traditional microscope – an area of research that Dr. Golub will be pursuing.

In addition, Dr. Golub has studied the use of an ultrasonic bone aspirator with a goal of reducing postoperative headache in retrosigmoid vestibular schwannoma removal. “Bone dust that disperses into the cerebrospinal fluid during drilling could be responsible,” notes Dr. Golub. “This newer tool works like a drill, except that it has a suction port right at the tip. Most of the bone dust that is generated is shunted directly into the suction port so very little bone dust spills out into the field.” In studies conducted while Dr. Golub was with the University of Cincinnati College of Medicine, he and his colleagues found that using the ultrasonic bone aspirator with the suction component reduced bone dust dispersion approximately 25 times more than the otologic drill at optimized settings.

Dr. Golub is also very interested in age-related hearing loss and the implications of hearing on the aging process. "Because age-related hearing loss is one of the most common diseases, it is often just considered a normal part of aging and, consequently, it’s not treated," says Dr. Golub. "I want to look at this in a new light, treating hearing loss as a separate issue from aging itself, and exploring patterns of decision-making that will shed some light on why older adults don’t try to find treatment for hearing loss when there are effective methods available.”

Dr. Golub is the author of more than 30 peer-reviewed publications in otolaryngology and 20 book chapters. He has also co-edited three books, including the best-selling Otolaryngology-Head and Neck Surgery Clinical Reference Guide and the Otolaryngology Surgical Instrument Guide.

David A. Gudis, MD
than have previously been appreciated,” notes Dr. Gudis, who is collaborating with pulmonologists not only in the treatment of CF, but for asthma and bronchiectasis as well. “Patients who have cystic fibrosis almost always have sinus disease. Patients who have asthma frequently have nasal polyps. Patients who have bronchiectasis frequently have chronic sinusitis. In many cases, improving the sinuses may help the lungs, or at the very least, help patients feel better overall.”

With Marc L. Otten, MD, Director of Columbia Neurosurgery at NewYork-Presbyterian/Lawrence Hospital – a member of the NewYork-Presbyterian Regional Hospital Network, Dr. Gudis is developing an endoscopic skull base surgery program based at the Bronxville hospital. “The bottom of the skull and the top of the sinuses share a thin layer of bone, so we’re opening up the sinuses in order to access different intracranial areas,” says Dr. Gudis. “There are certain types of brain tumors that, anatomically, can be accessed endoscopically through the nose. We want to be able to make this endoscopic technology for the treatment of sinonasal and brain tumors accessible to the local community.”

Dr. Gudis has authored over 20 peer-reviewed publications and textbook chapters and has presented his research at national and international conferences. He is on several national committees for rhinology, pediatric otolaryngology, and humanitarian efforts. Dr. Gudis is the recipient of several grants funding surgical humanitarian missions in underserved regions around the world, including the Dominican Republic, Peru, Rwanda, Kenya, and Ghana. In 2015, he was part of the team performing the first endoscopic sinus surgery in Haiti, and he has recently become involved in the training of medical professionals there.

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NewYork-Presbyterian/Columbia Broadens Areas of Expertise

In 2015, the Department of Otolaryngology – Head and Neck Surgery at NewYork-Presbyterian/Columbia welcomed Justin S. Golub, MD, a fellowship-trained otologist/neurotologist with expertise in the medical and surgical treatment of hearing loss, ear disease, balance disorders, and tumors of the lateral skull base, and David A. Gudis, MD, a dual fellowship-trained rhinologist and pediatric otolaryngologist specializing in sinonasal, nasal disorders, and approaches to tumors of the anterior skull base. Both Dr. Golub and Dr. Gudis are part of the growing skull base program at NewYork-Presbyterian/Columbia.

“Drs. Golub and Gudis have added tremendous ability for our department to care for specialized ENT problems,” says Lawrence R. Lustig, MD, Otolaryngologist-in-Chief and Chair of the Department of Otolaryngology – Head and Neck Surgery at NewYork-Presbyterian/Columbia. “Dr. Golub brings a wealth of experience in the area of ear surgery and skull base surgery and will be anchoring the research wing of the Otolaryngology Division. Dr. Gudis will be heading up the Rhinology Division, providing exceptional care in problems relating to the sinuses and diseases of the anterior skull base. With dual training in both pediatric ENT and rhinology, Dr. Gudis is uniquely trained to handle the most complex sinus cases involving both adults and children.”

Justin S. Golub, MD

Justin S. Golub, MD, joined NewYork-Presbyterian/Columbia in 2015 after completing a two-year fellowship in otology, neurotology, and skull base surgery at the University of Cincinnati and Cincinnati Children's Hospital Medical Center. Following medical school at Emory University School of Medicine, Dr. Golub spent an additional year performing research in regenerative medicine at the Georgia Institute of Technology. He then pursued otolaryngology-head and neck surgery training at the University of Washington in Seattle, where he did an additional year of research on an NIH T32 grant on studies to regrow the inner ear hair cells that die – work he continues at Columbia under Dr. Lustig. Dr. Golub is now pursuing a Master’s degree in patient-oriented research through the Biostatistics Department at Columbia University Mailman School of Public Health.

David A. Gudis, MD

David A. Gudis, MD, joined NewYork-Presbyterian/Columbia after completing two fellowships at the Medical University of South Carolina. His first fellowship was in pediatric otolaryngology and craniofacial surgery. This was followed by fellowship training in rhinology in advanced endoscopic sinus and skull base surgery – both adult and pediatric – ranging from treatment of chronic sinus problems, nasal polyps, problems breathing through the nose, and constant nasal drainage, to endoscopic skull base surgery, including removal of sinonasal tumors and brain tumors that can be accessed endoscopically through the nose.

Dr. Gudis pursued his medical education at the University of Pennsylvania and the Children’s Hospital of Philadelphia for his residency in Otorhinolaryngology – Head and Neck Surgery. During that time, Dr. Gudis received a resident research award for his studies of allergic fungal rhinosinusitis from the Pennsylvania Academy of Otolaryngology, and was also awarded the American Academy of Otolaryngology – Head and Neck Surgery Humanitarian Resident Award for his volunteer work in cleft palate and cleft lip surgery in Accra, Ghana, and the Synthes Resident Humanitarian Travel Award for a surgical mission in Cange, Haiti.

At Columbia, Dr. Gudis’s clinical practice focuses on medical and surgical treatment of chronic sinusitis, including revision sinus surgery, sinonasal tumors, skull base tumors, endoscopic skull base surgery, and pediatric otolaryngology, including chronic otitis media, hearing loss, sleep-disordered breathing, rhinosinusitis, velopharyngeal insufficiency, and cleft palate.

Dr. Gudis also cares for patients in the Hospital’s cystic fibrosis program who have chronic nasal polyps and other sinus pathology – a frequent problem with this disease. “In fact, we are now understanding that patients with pulmonary disease often have concomitant sinonasal disease, and the two are probably interacting in ways greater...”
The Show Must Go On

“Concentrating exclusively on voice disorders has taught us a great deal about how voice injuries happen and how they affect peoples’ lives,” says Dr. Lucian Sulica. “There are subtleties in voice rehabilitation that differ in each type of patient. Rehabilitating a teacher is different from rehabilitating a retiree, which is very different from rehabilitating a performer.”

While the Sean Parker Institute for the Voice treats individuals from all walks of life, performing artists are a special focus. “We work in close cooperation with individual performers and, in some cases, with productions,” says Dr. Sulica. “Performers have a very intense schedule – particularly in the musical theatre world – with immediate needs that must be addressed. They have a specific range of injuries that wouldn’t necessarily make much of a difference to you or me, but which can have a significant impact on them.”

That ability to respond quickly is critical. “They can’t be seen next week; they need to be seen now. We understand that,” says Dr. Sulica. “We also understand that that need does not represent an overreaction, or a so-called ‘high maintenance’ patient. It is based on the needs of their profession.”

The Parker Institute collaborates with The Center for the Performing Artist at NewYork-Presbyterian/Weill Cornell, which offers specialized expertise in performing arts medicine in combination with the clinical resources of an academic medical center.

In addition, Dr. Sulica often addresses performers at vocal health events at performing arts training programs. “We want to work with young performers to help them prevent injury, and when it happens, not to be afraid to seek care,” he says.