Stop the Ringing

by Zack Butovich

“We are at a point in our research where I feel I can say that we are one million dollars away from a cure for tinnitus,” states Dr. Jonas Johnson, Chairman of our Department of Otolaryngology, where some of world’s leading research on the condition known as tinnitus takes place.

Making this bold statement in a room full of University of Pittsburgh alumni and friends in Naples, Florida, it was met with audible surprise. For anyone suffering tinnitus (over 10% of Americans), the prospect of a cure for the permanent ringing sound, which can sometimes be as severe as a loud crashing or exploding, is a dream come true.

In previous issues of Sight + Sound, we have mentioned the incredible progress Thanos Tzounopoulos, PhD, has made in his tinnitus research since arriving at the University of Pittsburgh in 2008 as part of the then brand new Auditory Sciences Center in our Department of Otolaryngology. He has helped to locate the source of tinnitus (the brain, not the ear); actually see it in action on a circuit and cellular level; identified possible causes of the “phantom sound” (a decrease of a specific potassium channel associated with the auditory control center within the brain); and recently, and most significantly, Dr. Tzounopoulos has hypothesized a way to prevent the development of tinnitus.

Dr. Tzounopoulos, in collaboration with the Drug Discovery Institute at the University of Pittsburgh, has identified at least a dozen molecules or combinations of molecules (essentially the chemicals that makes medicine and drug therapies), with the potential to restore the activity of the deficient potassium channel in the auditory center of the brain, thereby relieving the tinnitus effect.

This is the closest any research has ever gotten to finding an explanation and a potential cure for tinnitus.

Dr. Tzounopoulos is excited to begin working towards clinical trials with many of the molecules he has identified. Collaboration with Catherine Palmer, PhD, in the Department of Audiology, and Yael Raz, MD, in the Department of Otolaryngology, has begun, in an effort to identify how to test these potential treatments for tinnitus.

“My studies have elucidated the mechanisms underlying the induction of tinnitus; the next crucial step in my research is the determination of the mechanisms underlying the maintenance of long-term tinnitus,” says Dr. Tzounopoulos. This is an important distinction, because sometimes new onset tinnitus may have different origins or characteristics than tinnitus that has been maintained for a significant period of time. Furthermore, Dr. Tzounopoulos believes that the

continued on page 6
Re-Imagining Sight - Seeing with our Brain and Not With Our Eyes

by Carrie Fogel

Blindness, be it lifelong or gradual, represents a significant, life-altering impairment that can result in increased risk of accidents, depression, co-morbid disability, and even premature death. For any demographic, acquired blindness is a significant impediment to maintaining independence, yet, for children, absence or loss of sight is especially heartbreaking. In the United States, the National Federation for the Blind reports that there are currently more than 60,000 blind children.

Dr. Ken Nischal and the Department of Pediatric Ophthalmology at the University of Pittsburgh are currently working on near-term solutions to restore a sense of sight to the blind. Already, the first stage of this project has begun with the development of a research study that allows for children to experiment with a device that lets them ‘see’, and has, until recently, only been tested with adults. The BrainPort project is a promising research endeavor in the Louis J. Fox Center for Vision Restoration. Preliminary support has been provided by one of Pittsburgh’s most charitable organizations, the Jack Buncher Foundation. Bernita Buncher, Chair of the Jack Buncher Foundation, states, “as the daughter of a father who suffered with retinitis pigmentosa, a degenerative eye disease causing severe vision impairment, I am keenly aware of the profound effect the loss of sight has on one’s life.”

The BrainPort is a visual assistive device that provides some environmental awareness for those who have severe visual impairment or total blindness. The device operates by enabling perception of visual information using the sensitivity of the tongue. Generally, the device works by receiving visual input from a small camera attached to a pair of sunglasses, which then transmits the signal to a small handheld computer (about the size of a cell phone) and translates the visual information into an electrical impulse, sending it to a small tactile array that is placed on the tongue. The array, often called the “lollipop,” emits gentle electrical signals, similar to soda or champagne bubbles, in specific patterns based on the camera’s focus. The tongue is one of the most sensitive parts of the human body, with 10,000 points of discrimination per square inch. With appropriate training and motivation, users can learn to perceive shapes, sizes of objects, and even some large letters or basic words. Overall, the device can be utilized as a functional, non-surgical device, developed as an aid to the visually impaired.

Ellen Mitchell, MD is continuing the BrainPort research begun by the Department of Ophthalmology approximately five years ago. Initially, Dr. Amy Nau’s research involved the BrainPort’s use in adults. Dr. Mitchell plans to continue this research in children; hoping that their ability to uptake new concepts and skills will help them to use the BrainPort in exciting, new ways. Once this information is gathered, Dr. Mitchell hopes that parents and practitioners can determine whether the BrainPort would be a good fit for their child. The support for the BrainPort project comes at an especially exciting time for the Department of Pediatric Ophthalmology. This year, the Department, along with several other community organizations (including the Western Pennsylvania School for the Blind), is developing a central hub of information, access, and rehabilitative care, called the Vision Enhancement Center (VEC). This center is a community-wide effort to alleviate some of the difficulties that families face in accessing information and the resources on caring for a visually impaired child.

This Vision Enhancement Center will provide crucial information on a broad range of services, resources, and visual assistive equipment for children and their parents, as well as host a mechanism to communicate with clinicians, therapists, and rehabilitation specialists, and manage educational spaces to help families learn how to live with their impairment. Dr. Nischal hopes that the center will allow children and parents to access the world in a way they never thought possible. Ms. Buncher is also hopeful at what possibilities lie in store, “I was shocked to discover that the World Health Organization estimates every minute one child in the world goes blind; I feel privileged to be able to help the Eye & Ear Foundation of Pittsburgh in their multi-faceted efforts to care for and cure people with diseases and disorders of the eye. As Helen Keller had said, ‘The only thing worse than being blind is having sight but no vision’.”

Please continue to refer to eyearound.org for updates on the BrainPort research and the Vision Enhancement Center. Once the VEC’s website is available, we will list the address on our website.
The Endoscopic Endonasal Approach (EEA), a type of skull base surgery, involves removing tumors at the base of the skull using the nasal passages as a corridor, thereby eliminating the need for external incisions. The EEA is a very complex technique, and due to its proximity to the brain, requires the combined expertise of a head/neck surgeon and neurosurgeon. For patients, however, the surgery is not always the most difficult part of their cancer treatment—the coordination of care among the various clinicians and specialists is often burdensome, costly, and ineffective.

From a business standpoint, the process of healthcare delivery used to be relatively uncomplicated. You became ill, saw a doctor, and paid for the treatment. But as our understanding of illness increased, and the vastness of medical knowledge grew, doctors became specialists, and the responsibility for healthcare gradually became centered in hospitals, clinics, and universities. Over time, as complex conditions presented in patients, treatments correspondingly evolved into multi-specialty efforts. For instance, a patient with a pituitary tumor may be evaluated by a head/neck surgeon, neurosurgeon, endocrinologist, ophthalmologist, and a number of other specialists, depending on the severity of their case.

Nonetheless, the business of healthcare delivery has been slow to catch up to new treatment necessities. Currently, the patient is responsible for managing the entire complex process of finding the proper specialist, coordinating appointments and sharing test results, often resulting in a frustrated patient and a less than optimal patient experience. What is needed is a new business model to improve patient care. Fortunately, Dr Carl Snyderman and Dr. Paul Gardner, Co-Directors of the Center for Skull Base Surgery, the leading center for such surgery and treatment in the world, have a plan to help alleviate some of these issues.

To help create more synergies and streamlined processes within healthcare delivery systems, the co-directors have come up with a simple solution: bring in a clinical coordinator whose primary responsibility will be to follow patients through their evaluation, treatment, and care process while diligently assessing any redundancies, prominent points of inefficiencies, and less than optimal uses of resources.

With a one-year timeframe, Drs. Snyderman and Gardner plan to evaluate the coordinator’s findings, and bring on part-time students from diverse disciplines, such as business, healthcare administration, and medicine to create new protocols and standards of practice aimed at increasing positive outcomes and experiences for patients. Finally, they aim to test these protocols in a pilot program to determine efficacy and quantify changes in the patients’ complete experience. If successful, Drs. Snyderman and Gardner will begin a process of working to integrate changes into larger hospital systems, with the hope of maximizing clinical outcomes, while also reducing costs and increasing patient satisfaction. While the process of change is never perfect, they are confident that improved patient flow from the perspective of the patient will drive better outcomes and create value for patients and the healthcare system.

To find out more about this pilot program, its progress, or the related efforts of the Center for Skull Base Surgery, please contact the Eye & Ear Foundation or find us online at www.eyeandear.org.
by Zack Butovich

Why fight biology when we are on the same team? Regenerative medicine approaches are shifting how we approach previously unsolvable problems like central nervous system regeneration. The University of Pittsburgh, the Louis J. Fox Center for Vision Restoration, and the McGowan Institute for Regenerative Medicine have one of the most comprehensive and successful regenerative medicine collaborations ever established. Within this collaboration, enthusiasm is now growing in developing functional optic nerve repair and regeneration strategies to prevent vision loss after injury or disease, as well as enabling a whole eye transplant (WET) procedure, an idea more fitting for science fiction just a decade ago.

Regenerating this optic nerve functionality is the goal of Michael Steketee, PhD and his lab, as part of the Fox Center for Vision Restoration.

The standard model for any regeneration tests typically involves severing the tissue and observing the scar response. While a scar on your arm or leg may have a permanent appearance, but otherwise makes no difference to your ability to use your arm or leg, a scar on your optic nerve completely interrupts blood flow and restricts the neural communication between the eye and the brain. Therefore, the key to rebuilding healthy, functional tissue, is to keep the occurrence of natural scarring at a minimal level. By utilizing extra-cellular matrix (ECM) from the labs of Dr. Steven Badylak, and bio-hybrid wraps designed by Dr. William Wagner (both of the McGowan Institute), Dr. Steketee has found remarkable success in reducing scarring and increasing regeneration in optic nerve models.

This success implies that repairing the optic nerve after trauma (which can be the result of physical force, but also degenerative diseases such as glaucoma), is possible. Furthermore it suggests ECM technology may be beneficial when used in conjunction with the WET project, as a way to replace lost ocular and optic nerve structures, potentially restoring communication between the eye and the brain, and restoring vision.

Success such as this has helped lend to the growing optimism for the previously unthinkable goal of whole eye transplant. Adding to that, is Kia M. Washington, MD, a physician-scientist with UPMC and the VA, and highly skilled plastic surgeon. Dr. Washington is the first surgeon in the world to successfully develop a vascularized ophthalmic transplant model in mammals – in other words, a full transplant of an entire eye from a donor to a recipient in a reliable, repeatable, and sustainable way that maintains tissue health, structural integrity, and connects the optic nerve from donor to recipient.

However, due to the eye's status of being one of the human body's most complicated systems, succeeding in the vascular transplant of the eye is not enough to restore a patient's sight (how can we be sure, that following transplant, the eye will actually see?). This embodies the next crucial step of the project: ensuring the transplanted eye can connect and then communicate visual information to the brain, which can only be achieved with a healthy optic nerve that transmits neural stimuli from the retina in the eye to the visual cortex in the brain, enabling usable perception.

Luckily, determining the functionality of ophthalmic structures, especially following degeneration, treatment, and potentially, transplant, is the expertise of Dr. Kevin C. Chan, PhD, whose lab in our Department of Ophthalmology, is pioneering new and innovative ways at imaging the structural integrity of the eye. Dr. Chan has designed ways to test vision in animal models, potentially creating a way to test the success of Dr. Steketee’s optic nerve regeneration techniques following trauma or transplant, as well as examine the viability of internal tissue integrity.

Yolandi Van Der Merwe, a master’s level student, is acting as a bridge between the labs of Dr. Steketee and Dr. Chan. Ms. Van de Merwe, whose background is in bioengineering, has developed an important model for evaluating the healing properties of ECM on retinal blood flow and structural integrity after injury in glaucoma and stroke models. Her efforts bring together the expertise of both robust research labs, allowing the necessary advances in regenerative medicine approaches to ocular repair to accurately tracked and evaluated in ways previously unimagined. This is an example of the power of the Louis J. Fox Center for Vision Restoration and the McGowan Institute for Regenerative Medicine.

These types of interdisciplinary collaborations, highly encouraged,
Over time, modern medicine has developed the capability to truly ‘flip the model’ of how patients consider their health. No longer is medical treatment only a reactionary measure to making a patient better. With the advancements in the understanding of how our individual genetic makeup influences our health over the course of our lives, doctors are able to engineer highly specific treatments that are not only reactionary, once a condition has presented itself, but are also preventative. Using one’s particular genetic sequence, doctors have the ability to track genetic markers that signify the risk or presence of disease before symptoms appear. Aside from the many overall benefits of personalized medicine, this method of treatment can be especially effective in the treatment of various types of cancer; arguably the deadliest and most pervasive disease to affect humankind.

In the Department of Otolaryngology at the University of Pittsburgh, physicians see patients who develop cancer of the head and neck. Cancer of the head and neck includes sites such as the mouth, throat, or voice box affects more than 50,000 people in the United States every year. Cancer of the head and neck can be attributed to environmental causes, such as tobacco use, or infections of the mouth caused by the proliferation of human papillomavirus (HPV). It can affect the form and function of the face, mouth and throat and is truly a terrible and life-altering disease.

As a former patient of Dr. Eugene N. Myers, Marian Mosites knew firsthand how disruptive head and neck cancer could be. In July of 1997, Marian noticed a lump in her neck, and while preliminary tests did not indicate a spread of cancer, she visited Dr. Myers in the UPMC Ear, Nose, and Throat offices to be sure. Initially not convinced that it was cancer, Dr. Myers performed a biopsy and discovered it was in fact cancer, which had spread from her tonsil into the lymph nodes of her neck. Surgical removal of the cancer, followed by radiation and chemotherapy proved to be successful for Marian, and she has been cancer free and enjoying a normal life for nearly 18 years.

“Dr. Myers was my knight in shining armor,” she says, “throughout the diagnoses, the surgery, the post-operative treatment and the follow-up care, Dr. Myers and the department were so very skilled, knowledgeable and on the cutting edge of [their] field, yet so very kind, caring and humble.” Marian and her family were so impressed with the treatment she received and grateful for saving her life that making a gift to the Eye & Ear Foundation of Pittsburgh was, as she calls it “a sure bet.” Marian and her husband, Steven, after hearing about the ways in which personalized medicine was the future of innovative treatment for head and neck cancer, decided to establish the Marian Mosites Initiative for Personalized Head and Neck Cancer Research.

Leading the Mosites Initiative will be Robert Ferris, MD, PhD, a member of the faculty in the Department of Otolaryngology at the University of Pittsburgh, who is not only treating cancers of the head and neck aggressively, but also working to understand why one’s immune system failed to reject this particular cancer. He strives to answer why the immune system was weakened, what weakened it, and how he can turn it back on to work for the patients he sees. Dr. Ferris is spearheading the effort to screen adults with HPV, a leading cause of cancer of the head and neck, by taking samples and studying how drugs that are already FDA approved can be used to change the way that HPV cells in humans with different genetic profiles proliferate as non-cancer conditions.

With enhanced screening opportunities in personalized medicine, the perceived inevitability of an invasive surgical removal, chemotherapy and radiation is becoming less and less. One specific goal of these personalized forms of therapies is the reduction of toxic substances and lowered appearance of negative side effects that often come hand in hand with these traditional treatments. This approach has already proven to be effective in clinical trials, and as enhanced screening opportunities are adopted, the world will see truly groundbreaking new options for curing cancers of the head and neck.

Marian and her husband, along with their family, are hopeful about this new venture into personalized medicine, and she states that, “it is incredibly exciting for someone who has experienced cancer treatment first hand. The idea that doctors and researchers can look to the genetics of the cancer to categorize it and to determine how best to prevent and treat it is awe-inspiring. With this commitment of funds over a five year period, we are hoping for a breakthrough in the research involving the genetic testing and categorizing of cancers to advance the treatment of head and neck cancer for patients everywhere.”

Robert L. Ferris, MD, PhD, FACS, Chief, Division of Head and Neck Surgery

Steven Mosites, Sr, Cindy Sunseri (daughter and EEF Board Member), and Marian Mosites
Ornial scarring affects millions of individuals around the world. The most common treatment for this blinding condition is a corneal transplantation. For more than a century, corneal transplants have been used to repair damaged and diseased corneas. Eye banks in the United States provide donor corneas to meet national demand, with over 48,000 corneal transplants performed in 2013. When a donor cornea is available, surgery is necessary to remove the damaged cornea and replace it with a healthy one. The patient who receives a cornea transplant then faces post-surgical follow-up care, a regimen of life-long medications, and a chance of rejection. Even with these complications, corneal grafting is the most widely carried out and most successful of organs transplants. World-wide, the situation is not so simple. As many as 6–8 million individuals endure corneal blindness with little hope of obtaining a transplant.

At the University of Pittsburgh’s Louis J. Fox Center for Vision Restoration, scientists have been working for over 10 years to find a treatment for corneal scarring, which is simpler and cheaper than corneal transplantation. As a Professor of Ophthalmology at the University of Pittsburgh and the Associate Director of the Louis J. Fox Center for Vision Restoration, I am leading a research group to pursue the idea that stem cell-therapy may be able to reverse corneal blindness without the need for surgery. As part of this research, my associates and I have isolated stem cells from human corneas and shown that they can produce transparent tissue in the lab.

Two years ago, a donation from the Western Pennsylvania Medical Eye Bank Foundation was used by the Fox Center to support a collaborative research project between University of Pittsburgh and the LV Prasad Eye Institute in Hyderabad, India. This study was designed to bring laboratory research on corneal stem cells to a point where the cells could be used for therapy. The funding brought Dr. Sayan Basu, a corneal surgeon to the Fox Center laboratories to learn how to prepare corneal stem cells. Working with a team of Pittsburgh scientists, Dr. Basu was able to show that the stem cells could reverse corneal scarring in an animal model. The procedure that these researchers developed was very simple and could readily be adaptable to human use on an outpatient basis. Dr. Basu also found that the stem cells could be obtained from small tissue samples taken from a patient’s eye. Such a procedure will allow an individual to be treated with their own stem cells. The results of this exciting research were published in December 2014 in the prestigious journal, Science Translational Medicine, with Dr. Basu and Pittsburgh graduate student Andrew Hertsenberg as co-first authors.

Since his return to India, Dr. Basu has received approval to conduct the pilot study through India’s Institutional Review Board and he is performing stem-cell transplantation procedures on individuals with corneal blindness at the LV Prasad Eye Institute. In the U.S., translating the stem-cell procedure to human treatment faces some obstacles. It must be proven successful in human clinical trials, receive U.S. Food and Drug Administration approval, and be cost effective. It is our hope that success of the clinical trials in India will pave the way soon for corneal stem cell therapy in the United States.

The team behind the study includes co-lead author Andrew J. Hertsenberg, B.S., Martha L. Funderburgh, M.S., Sayan Basu, M.D., Jian Wu, Otero Fellow; (front row) Martha Funderburgh, Michael K. Burrow, B.S., Mary M. Mann, M.S., Yiqin Du, M.D., Ph.D., Kira L. Lathrop, M.A.M.S., and Fatima N. Syed-Picard, Ph.D., all of Pitt; and Sheila M. Adams, Ph.D., and David E. Birk, Ph.D., both of the University of South Florida.
Focus Turned to Otitis Media

by Zack Butovich

Dr. Charles D. Bluestone officially retired in June 2014 from the University of Pittsburgh’s Department of Otolaryngology as Distinguished Professor Emeritus of Otolaryngology in the School of Medicine, the highest possible honor that can be accorded to a faculty member at the University. A giant in the field of pediatric otolaryngology and former Chairman of the Department of Pediatric Otolaryngology at Children’s Hospital of Pittsburgh, Dr. Bluestone is an internationally respected otolaryngologist and specialist in middle-ear disease. Even though now retired from direct patient care, he remains active in the Society for Middle-Ear Disease (SMED), which he founded in 2012.

Middle ear disease occurs between the ear drum at the end of ear canal, and the inner ear, where the cochlea and other important auditory tissues are located. The most frequently encountered middle ear disease is otitis media, which is an infection that usually causes severe pain in young children, and is often related to dysfunction of the Eustachian tube and inflammation of the mucous membranes in the back of the throat.

While relatively common throughout the US (approximately 11% of the population is affected each year, of whom half are under the age of 5), otitis media is very treatable with a variety of options, ranging from medication to simple surgery. However, if left untreated, otitis media can cause long-term or permanent hearing damage, or most significantly, in some cases, death (in 2013, complications of otitis media resulted in approximately 2,400 deaths primarily in developing countries).

Despite its treatability with simple interventions, otitis media is very often under-treated in developing nations and in impoverished regions, such as South-Central Asia and Aboriginal Australia. Adding to the lack of available care, access to it, or awareness of the disease, is the fact that many of these populations are highly genetically susceptible to otitis media. Australian Aborigines, for example, have a nearly 50% chance of developing otitis media in their childhood. Inuit populations in Alaska have a similar rate of infection. Populations in Eastern Africa, Thailand, Malaysia, and the Asian Sub-Continent all exhibit high risk factors for otitis media.

Identifying this prevalent issue around the world, Dr. Bluestone, in the years leading up to his retirement, worked to create SMED to help provide information on, bring awareness to, and ultimately unite physicians around the world on the issues of otitis media, middle-ear disease, and the need for greater education and care worldwide. SMED is a not-for-profit international advocacy society with leading experts in middle-ear disease from around the world as its advisors. Relying upon support from the Eye & Ear Foundation, Children’s Hospital Foundation, the DePaul School for Hearing and Speech, the University of Pittsburgh, and a vast consortium of clinical specialists from all over the world, SMED is dedicated to helping provide resources for those suffering from middle-ear disease, their families, and their care providers.

The Society for Middle-Ear Disease is now working directly with the Eye & Ear Foundation of Pittsburgh to establish funding for an International Visiting Scholars Program. This program would grant physicians from developing nations the chance to learn from experts in middle ear disease at the University of Pittsburgh, thereby enabling them to provide the best quality care and information for the patients in their country suffering from middle-ear diseases, especially otitis media. This Visiting Scholars program may be a crucial first step in delivering important treatment and prevention of middle ear disease to developing areas around the world in a way that is sustainable and self-perpetuating.

More information on the Society for Middle-Ear Disease, including information on advances in middle ear evaluation and treatment, can be found at societyformiddleeardisease.org. Donations in support of the Society can be made at eyeandear.org.

Optic Nerve Regeneration continued from page 4

and more importantly, supported at the University of Pittsburgh, not only advance the capability of Dr. Steketee and Dr. Washington’s labs, but advance the field closer toward clinical translation. As Dr. Joel S. Schuman, Chairman of the Department of Ophthalmology, has quoted time and again, “The idea of the lone scientist working in his lab no longer applies. It’s not how you can succeed in science anymore. Collaboration is the key to everything.” It is also the cornerstone to the optimism surrounding optic nerve repair and the WET project. With so many brilliant researchers, working together in so many open and collaborative ways, optimism prevails in that we may just have the keys to success.
Our good friend and Ambassador to the Louis J. Fox Center for Vision Restoration, Melody Goodspeed, sent me a podcast that has inspired me to share some thoughts with you. The podcast is from an NPR program and, if any of you are interested in listening to it, the URL is www.thisamericanlife.org/radio-archives/episode/544/batman#play. The topic is about setting expectations and overcoming obstacles. The context of the program refers to seeing without your eyes, as the subject of the editorial, Mr. Daniel Kish, the real life Batman, a blinded individual who has learned to see by using echo location. The overarching message is about never lowering expectations for ourselves and others. Mr. Kish states the reason he was able to develop echo location, to the point where he can ride a bike and hike in the woods without the use of his eyes, is because nobody ever set limits on him and, therefore, he has never set limits on himself. This is an amazing true story and it does remind us that we can truly accomplish anything, even if it others believe it to be impossible.

The clinicians and scientists we are working with in the Departments of Ophthalmology and Otolaryngology are not limiting themselves. They are actively expanding their ideas to find better treatments or cures for disorders such as hearing loss, macular degeneration, glaucoma, poor balance, tinnitus (ringing in the ears), corneal blindness, or cancers of the head and neck. What is often the only limiting factor in their research is resources. Your support is what allows our scientists to set their sights on doing what no one else thought possible. Why not be the first to transplant an eye? Why can’t surgeries of the head and neck all be closed procedures? Daniel Kish’s story reminds me that we cannot limit ourselves. We need to continue to find a way to see the world beyond our limitations. Thank you for helping us make all things possible with your donations to the Eye & Ear Foundation of Pittsburgh.