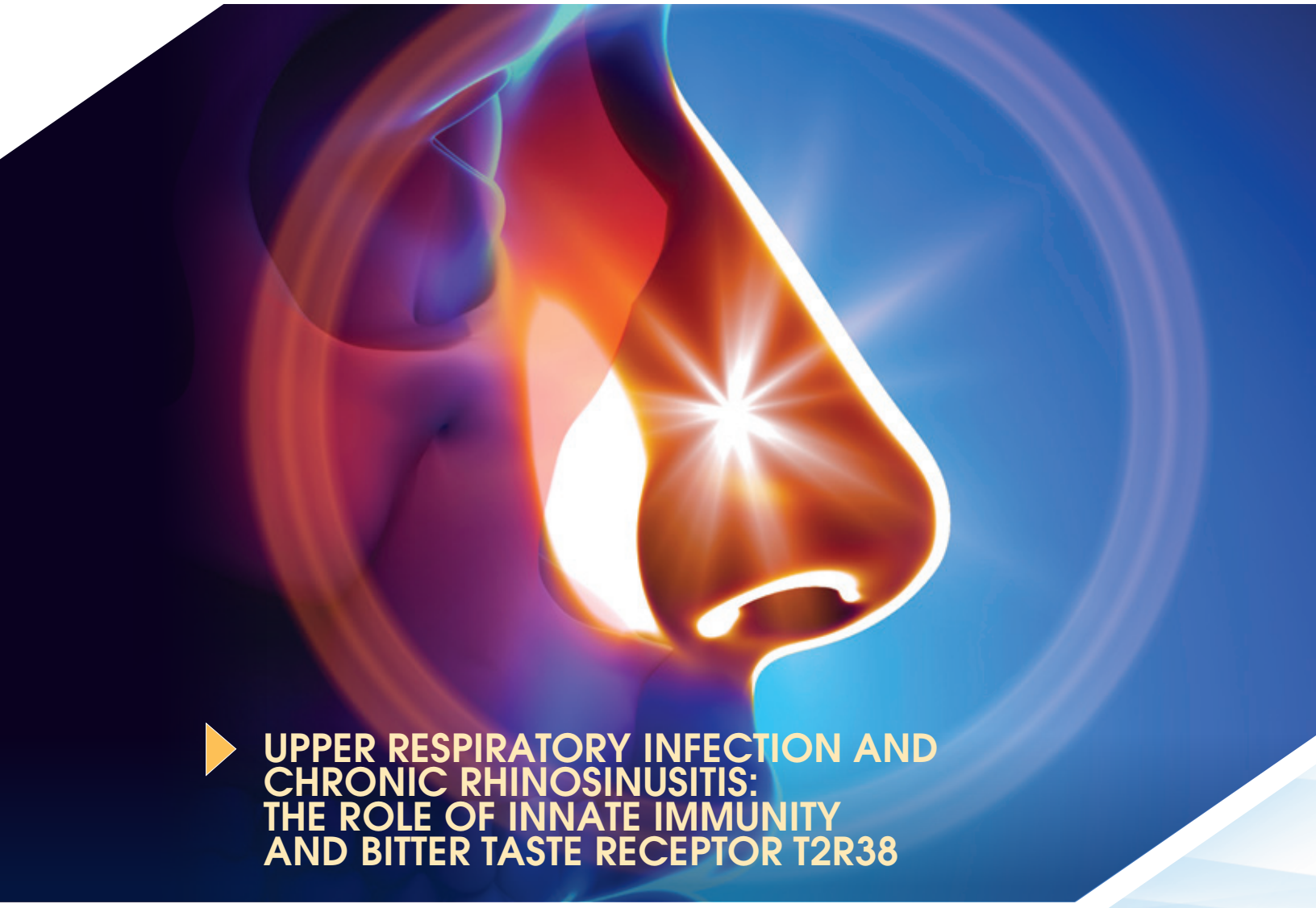
Penn Medicine

2016

PENN OTORHINOLARYNGOLOGY
HEAD AND NECK SURGERY



UPPER RESPIRATORY INFECTION AND CHRONIC RHINOSINUSITIS: THE ROLE OF INNATE IMMUNITY AND BITTER TASTE RECEPTOR T2R38

INSIDE

LETTER FROM THE CHAIR

Bert W. O'Malley, Jr., MD
Gabriel Tucker Professor and Chair
Department of Otorhinolaryngology – Head and Neck Surgery
Associate Vice President, University of Pennsylvania Health System

#4 in the Nation

Penn Otorhinolaryngology – Head and Neck Surgery at the hospitals of the University of Pennsylvania – Penn Presbyterian is **ranked #4** among the top Ear, Nose, and Throat departments in the nation by *U.S. News & World Report* for 2015.

EXCELLENCE IN PATIENT CARE, EDUCATION AND RESEARCH SINCE 1870

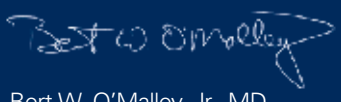
Dear Colleagues,

It's my great pleasure to bring to you this edition of the Penn Otorhinolaryngology – Head and Neck Surgery Newsletter. This latest edition provides an overview of the variety, depth, and focus of the clinical research taking place within the department, an examination of a novel surgical procedure at the vanguard of head and neck surgery, transoral robotic sialolithotomy, and the remarkable development of a device here at Penn inspired by smartphone technology and a pressing need for rapid access and sharing of endoscopic images.

As Chair, I've had the good fortune to be surrounded by a superlative group of surgeons and clinician-researchers. This dedicated team has, by their efforts, expanded and provoked not only greater understanding of otorhinolaryngology and head and neck surgery, but pioneered procedures and therapies that are saving and extending the lives of patients who wouldn't have had a glimmer of hope just a decade ago.

I think you'll find the information herein both useful and interesting, and look forward to meeting or hearing from you, our greatest partners in care.

Best Regards,



Bert W. O'Malley, Jr., MD
Gabriel Tucker Professor and Chair, Department of Otorhinolaryngology – Head and Neck Surgery
Associate Vice President, University of Pennsylvania Health System

UPPER RESPIRATORY INFECTION AND CHRONIC RHINOSINUSITIS: THE ROLE OF INNATE IMMUNITY AND BITTER TASTE RECEPTOR T2R38

The evolving understanding of the role of bitter taste receptors (T2Rs) in the immune response and chronic rhinosinusitis (CRS) has been closely investigated by Penn Rhinology researchers James N. Palmer, MD (Chief), Noam A. Cohen, MD, PhD (Director of Research), Nithin D. Adappa, MD, David W. Kennedy, MD, Robert J. Lee, PhD, Laurel Doghramji, RN, Christine Reger, RN – a division of Penn Otorhinolaryngology – Head and Neck Surgery.

The taste receptors are among the most intensively studied phenomena in biology. The perception of bitterness in humans is exceptionally acute, as a result of the variety of taste receptors that respond to bitter compounds. Bitter tasting cells are known to discriminate among bitter compounds and to the many genes (~25) that code for these receptors. Bitter taste receptor type 2 member 38 (TAS2R38) has always been the focus of clinical interest. Recently, this interest has surrounded its contribution to sinonasal innate immunity and the pathology of chronic rhinosinusitis (CRS) and upper respiratory infection.

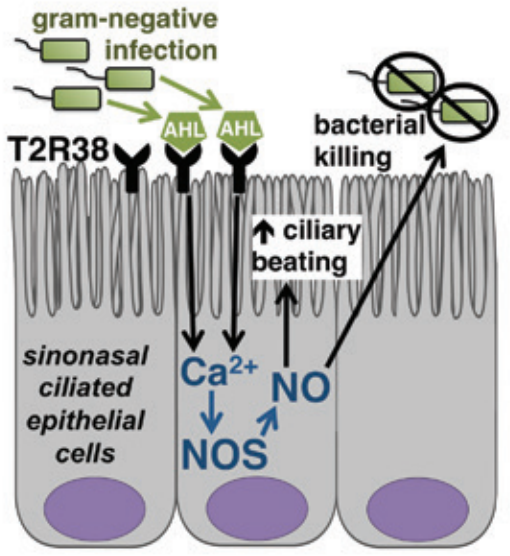
Innate Defense of the Sinonasal Cavity

Considered the front line of respiratory defense, the sinonasal cavity is home to a variety of innate immune mechanisms. The primary physical innate defense in the sinuses (as elsewhere in the respiratory system) is mucociliary clearance—coordinated ciliary beating that transports debris-laden mucus toward the oropharynx, where it is cleared by swallowing or expectoration. Mucociliary clearance is augmented by the secretion of antimicrobial peptides and the generation of reactive oxygen and nitrogen species that can have direct antibacterial, antifungal, and antiviral effects.

T2R38 in Sinonasal Innate Immunity

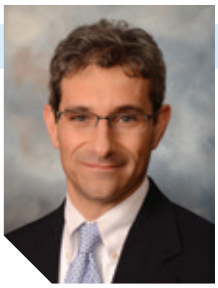
Within the last few years, researchers investigating bitter taste receptors (T2Rs) have discovered T2Rs in places outside of the oral cavity, where, presumably, their chemosensory role has nothing to do with taste perception. To date, these extraoral T2Rs have been found in the gastrointestinal tract, brain, testes, and bronchi, and importantly, in the sinonasal cavity, where epithelial cells express T2R38 within their motile cilia, and the recently defined solitary chemosensory cells (SCCs) express other T2Rs.

T2R38 in Sinonasal Innate Immunity



The role of the bitter taste receptor T2R38 in human sinonasal epithelial innate immunity. Reading from left to right, gram-negative bacteria secrete acyl-homoserine lactone (AHL) molecules to regulate quorum sensing. AHLs activate T2R38 in sinonasal cilia, initiating a calcium (Ca2+) signal that activates nitric oxide synthase (NOS)-dependent nitric oxide (NO) production. NO production has two distinct effects. The first is an increase in mucociliary transport caused by activation of the protein kinase G (PKG) pathway to increase ciliary beating. NO additionally diffuses directly into the airway surface liquid, where it directly permeabilizes and kills bacteria.

Nithin D. Adappa, MD



Noam A. Cohen, MD, PhD

David W. Kennedy, MD

Robert J. Lee, PhD

James Palmer, MD

If they had a role in immunity, the widespread distribution of the TR2s would make sense. In fact, research from Penn Rhinology has demonstrated that sinonasal T2R38 detects chemical signals arising from gram-negative airway pathogens and subsequently activates rapid innate immune responses mediated by the local production of nitric oxide (NO). A highly reactive radical, NO increases sinonasal ciliary beating and promotes mucociliary clearance (the principal physical airway defense), as well as producing chemicals that damage the bacterial DNA, membrane lipids and enzymes of many microbes.

The role of T2R38 in sinonasal defense is supported by the finding that polymorphisms in the TAS2R38 gene that result in decreased T2R38 functionality may correlate with susceptibility to upper respiratory infection with gram-negative bacteria. Moreover, sinonasal cells stimulated with acyl-homoserine lactones (AHLs) of gram-negative bacteria have been found to produce NO in a T2R38-dependent manner, demonstrating that T2R38 in airway ciliated cells acts as a sentinel for invading pathogens.

TAS2R38 Polymorphisms in CRS

The polymorphisms in the TAS2R38 gene leading to impaired T2R38 function are the consequence of an anomaly in the human genome.

In the 1930s, a pair of researchers arrived at opposite conclusions about the taste of phenylthiocarbamide (PTC), a compound used at their laboratory. One found the crystals unbearably bitter; the other could taste nothing. It's now known that PTC tasters encode a functional version of TAS2R38; non-tasters encode a nonfunctional version. Because the functional T2R38 contains the amino acids L-proline (P), L-alanine (A), and L-valine (V), PTC tasters are said to have the PAV variant; the nonfunctional variant is known as AVI for the peptides L-alanine (A), L-valine (V) and isoleucine (I).

Not long after the identification of extraoral T2Rs, the Penn Rhinology research team discovered that human ciliated epithelial cells stimulated with PTC, AHLs or conditioned medium from *P. aeruginosa* responded in a way that correlated with the PAV or AVI polymorphisms. Epithelial cells from PAV variant tasters exhibited markedly enhanced nitric oxide production, MCC, and bacterial killing compared with cells from AVI nontasters. Further, cells derived from AVI nontasters had blunted nitric oxide responses that were not effective at killing *P. aeruginosa in vitro*, strongly suggesting that PAV individuals might be less susceptible to gram-negative infection.

Additional studies have confirmed a difference in susceptibility to gram-negative infection between patients having PAV functional and AVI nonfunctional variants. In these studies, samples taken from PAV functional patients under clinical conditions were clear of sinonasal gram-negative bacteria. Moreover, it now appears that the TAS2R38 gene is an independent genetic risk factor for CRS requiring sinus surgery. Lastly, a recent clinical study indicates that T2R38 genotype and/or PTC taste sensitivity correlate with surgical outcomes for a subset of CRS (non-polypoid) patients.

TR2s in the Development of Novel Therapies for Chronic Rhinosinusitis

The discovery of T2Rs in the sinonasal cavity and their potential role in defense mechanisms may have profound implications for researchers seeking the next generation of treatments for CRS. At present, conventional management of CRS involves antibiotics, a group of drugs that have been losing ground to resistant organisms for almost 50 years. The identification and confirmation of valid genetic factors controlling CRS susceptibility and/or patient outcomes could thus be the precedent for the development of novel therapeutic modalities. The T2R38 pathway is already a potential therapeutic target to promote endogenous immune responses in patients with upper respiratory infections.

Biological and Clinical Outcome	TAS2R38 Genotype AVI/AVI	PAV/PAV
Intracellular calcium response *in vitro*	▼	▲
NO production *in vitro*	▼	▲
Ciliary beat frequency/MCC *in vitro*	▼	▲
Bactericidal activity *in vitro*	▼	▲
Sinonasal gram-negative infection *in vivo*	▲	▼
CRS	▲	▼

Because there would likely be a large subset of patients with suboptimal responses to treatment with T2R38 agonists (i.e. AVI individuals), it will be necessary to further define T2R38 signaling mechanisms in airway cells, as well as to identify other T2Rs that activate similar responses. Other T2R isoforms expressed in other airway cell types may have important clinical relevance, as well. Current prospective clinical studies of T2R38 genotype and sinusitis risk, as well as patient outcomes, are ongoing in the Division and prospective therapeutic trials using T2R agonists are under review at the FDA. ▲

REFERENCES:

(1) Lee RJ, Cohen NA. Sinonasal solitary chemosensory cells 'taste' the upper respiratory environment to regulate innate immunity. Am J Rhinol Allergy. 2014 Sep-Oct;28(5):366-73. doi: 10.2500/ajra.2014.28.4077."

(2) Lee, RJ, Xiong, G, Kofonow, JM, Chen, B, Lysenko, A, Jiang, P, Abraham, V, Doghramji, L, Adappa, ND, Palmer, JN, Kennedy, DW, Beauchamp, GK, Paschalis-Thomas, D, Ischiropoulos, H, Kreindler, JL, Reed, DR, Cohen, NA. T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. J Clin Invest 122(11):4145-59 (2012).

(3) Lee, RJ, Kofonow, JM, Rosen, PL, Siebert, AP, Chen, B, Doghramji, L, Xiong, G, Adappa, ND, Palmer, JN, Kennedy, DW, Kreindler, JL, Margolskee, RF, Cohen, NA. Bitter and sweet taste receptor regulation of human upper respiratory innate immunity. J Clin Invest 124(3):1393-405 (2014).

(4) Adappa, AD, Howland, TJ, Palmer, JN, Kennedy, DW, Doghramji, L, Lysenko, A, Reed, DR, Lee, RJ, Cohen, NA. Genetics of the Taste Receptor T2R38 Correlates with Chronic Rhinosinusitis Necessitating Surgical Intervention. Int Forum of Allergy and Rhinology. 3(3):84-7 (2013).

(5) Adappa, AD, Zhang, Z, Palmer, JN, Kennedy, DW, Doghramji, L, Lysenko, A, Reed, DR, Scott, T, Zhao, NW, Owens, D, Lee, RJ, Cohen, NA. The Bitter Taste Receptor T2R38 is an Independent Risk Factor for Chronic Rhinosinusitis Requiring Sinus Surgery. Int Forum of Allergy and Rhinology 4(1):3-7 (2014)

(6) Adappa, ND, Farquhar, D, Palmer JN, Kennedy, DW, Doghramji, L, Morris, SA, Owens, D, Mansfield, C, Lysenko, A, Lee, RJ, Cowart, BJ, Reed, DR, Cohen, NA. TAS2R38 genotype predicts surgical outcome in non-polypoid chronic rhinosinusitis. Int Forum of Allergy and Rhinology (in press).

(7) Farquhar, DR, Kovatch, KJ, Palmer, JN, Shofer, FS, Adappa, ND, Cohen, NA. Phenylthiocarbamide taste sensitivity is associated with sinonasal symptoms in healthy adults. Int Forum Allergy Rhinol. 5(2):111-8 (2015).

(8) Adappa, ND, Workman, AD, Hadjiliadis, D, Dorgan, DJ, Frame, D, Brooks, S, Doghramji, L, Palmer, JN, Mansfield, C, Reed, DR, Cohen, NA. T2R38 genotype is correlated with sinonasal quality of life in homozygous ΔF508 cystic fibrosis patients. Int Forum Allergy Rhinol. 2015 Dec 17. doi: 10.1002/alr.21675. [Epub ahead of print].

Review papers on the topic:

(1) Lee, RJ, Cohen, NA. Taste receptors in innate immunity. Cell Mol Life Sci. 72(2):217-36 (2015).

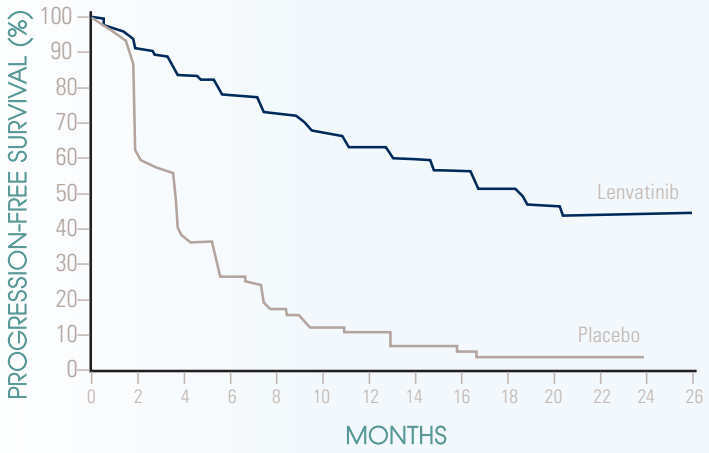
(2) Lee, RJ, Cohen, NA. Bitter and sweet taste receptors in the respiratory epithelium in health and disease. J Mol Med 92(12):1235-44 (2014).

(3) Workman, AD, Palmer, JN, Adappa, ND, Cohen, NA. The Role of Bitter and Sweet Taste Receptors in Upper Airway Immunity. Curr Allergy Asthma Rep. 2015 Dec;15(12):72. doi: 10.1007/s11882-015-0571-8.

(4) Lee, RJ, Cohen, NA. Role of the bitter taste receptor T2R38 in upper respiratory infection and chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 15(1):14-20 (2015).

(5) Lee, RJ, Cohen, NA. The emerging role of the bitter taste receptor T2R38 in upper respiratory infection and chronic rhinosinusitis. Am J. Rhinol. Allergy 27(3) 283-6 (2013).

CONTINUED PROGRESS WITH MULTIKINASE INHIBITORS IN DIFFERENTIATED THYROID CARCINOMA TREATMENT



Marcia Brose, MD, PhD, of Penn Otorhinolaryngology – Head and Neck Surgery, has devoted her career to spearheading the development of therapies for the treatment of patients with advanced radioactive iodine (RAI) refractory differentiated thyroid carcinoma (DTC).

Dr. Brose was the primary investigator for clinical trials leading to the 2013 FDA approval of the tyrosine kinase inhibitor sorafenib for the treatment of metastatic and advanced RAI-refractory DTC. Shortly before this time, Dr. Brose and colleagues from the United States, France, the United Kingdom, Japan, and Australia began recruiting patients for the phase III Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) to compare progression-free survival among patients with iodine-131–refractory thyroid cancer who received the oral, multitargeted tyrosine kinase inhibitor lenvatinib to patients who received placebo. Lenvatinib was approved for the treatment of progressive RAI-refractory DTC in February 2015.

Background

Papillary and follicular thyroid cancers are referred to as differentiated thyroid cancer (DTC), and together account for ~90% of thyroid cancers. The standard therapy for DTC is thyroidectomy with suppression of thyroid-stimulating hormone. In many patients, RAI is administered following surgery to eliminate remaining thyroid tissue or suspected micrometastases. RAI can be curative in the majority of patients with thyroid cancer. Up to 50% of patients with residual disease, however, will become refractory to RAI. This occurs either because their cells can no longer absorb RAI or are no longer inhibited by RAI. Prior to the introduction of sorafenib, patients with radioiodine refractory DTC were essentially beyond the scope of standard treatment. Their disease was defined by continuous progression, resulting in pulmonary, bone and brain complications, among others.

Pathogenic Mechanisms in DTC

The pathology of DTC is driven by a series of genetic mutations in growth factors and signalling pathways. The most common genetic change in papillary thyroid cancers involves the The B-RAF V600E somatic mutation. The B-RAF (or B-Raf proto-oncogene, serine/threonine kinase) gene contributes to chemical signaling from outside the cell to the cell's nucleus. The vascular endothelial growth factors (VEGFs) are signalling proteins that act to stimulate angiogenesis in the thyroid by binding to tyrosine kinase receptors (VEGFRs) on the cell surface. Expression of VEGF in DTC is associated with larger tumors and poorer prognosis. Platelet-derived growth factor (PDGF) also contributes to vessel formation in the thyroid; it, too, binds to tyrosine kinase receptors (PDGFRs). Some thyroid cancers involve mutations of the RAS gene (KRAS, HRAS, NRAS) mutations, and the fibroblast growth factor receptor (FGFR) family has been shown to have a role in DTC. FGFR-1 and -3 are expressed in most well differentiated tumor types. FGFR-4 is expressed in aggressive rapidly proliferating tumor types.

The Tyrosine Kinases in Thyroid Cancer

Genetic alterations within cancer cells can cause overexpression or mutation of the tyrosine kinases leading to activation of oncogenic signaling pathways. A subclass of the protein kinase, the tyrosine kinases contribute to cellular signal transduction in the cellular pathways that control proliferation, differentiation, migration, metabolism, and apoptosis. The primary kinase signaling pathways involved in thyroid cancer are represented clinically by acronyms that describe a serial cascade. They are the RET (rearranged during transfection) / PTC (papillary thyroid carcinoma)-RAS (rat sarcoma protein)-RAF (rapidly accelerated fibrosarcoma)-MAPK (mitogen-activated protein kinase) pathway and the PI3K (phosphatidylinositide 3-kinase)-AKT (protein kinase B)-mTOR (mammalian target of rapamycin) pathway.

Multikinase Inhibitor Therapy for DTC

The multikinase inhibitors target and directly inactivate the tyrosine kinase pathways in DTC. These agents include axitinib, lenvatinib, pazopanib, sorafenib, sunitinib, and vandetanib. Of these, only sorafenib, and lenvatinib have been FDA approved. Dr. Brose played a key role in both of these approvals, most recently as an investigator for the SELECT Trial.

The SELECT Trial

The Phase III Lenvatinib in Differentiated Cancer of the Thyroid (SELECT) trial was initiated to investigate progression-free survival in patients with RAI-refractory DTC receiving placebo or lenvatinib, an oral, multitargeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3, FGFRs 1 through 4, PDGFR, RET, and KIT signaling networks.

This trial took place as a multicenter, international, randomized, double-blind, placebo-controlled study from August 2011 — October 2012. The trial involved 392 patients, 261 of whom were randomized to receive lenvatinib (24 mg day in 28-day cycles) and 131 who received placebo by the same process. All patients had progressive RAI-refractory DTC. At disease progression, patients in the placebo group could receive open-label lenvatinib.

Patients were eligible for enrollment if they had measurable, pathologically confirmed DTC and evidence of RAI-refractory disease on the basis of several criteria. The primary end point of the study was progression-free survival, defined as the time from randomization until the first documentation of disease progression by independent radiologic review, or death. The secondary end points included the response rate and overall survival, defined as the time from randomization until death from any cause.

Results

There were substantial differences between the active and placebo arms of the SELECT study. The total response rate in the lenvatinib group was 64.8% (4 complete responses/165 partial responses), vs. 1.5% (2 partial responses) in the placebo group (P<0.001). At six months, 77.5% of lenvatinib-treated patients had progression-free survival vs. 25.4% in the placebo group. At the time of the primary analysis of progression-free survival (14 months), 93 (35.6%) patients in the lenvatinib group had disease progression versus 109 (83.2%) in the placebo group. The median progression-free survival in the lenvatinib group was 18.3 months versus 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001).

Thyroid cancer patient, Roseanne Nicewinter (left), talks with her physician Marcia Brose,MD, PhD (right).

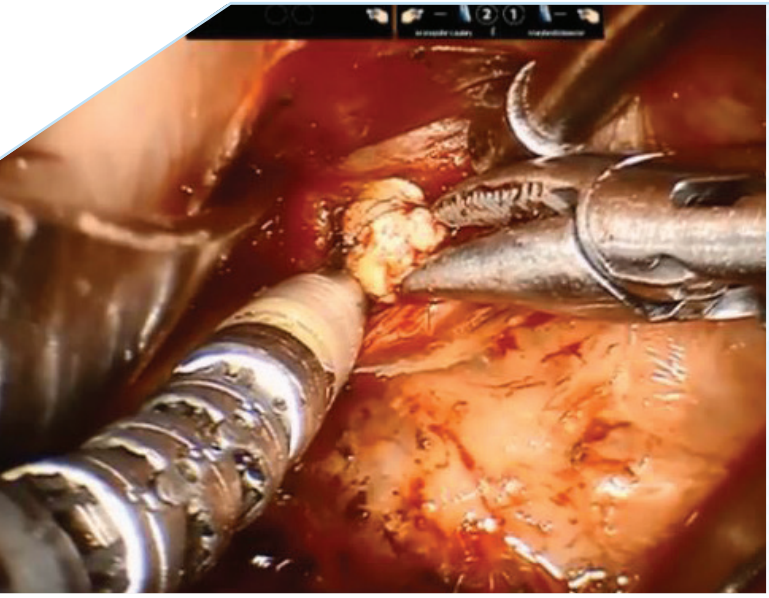
A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups, including patients who had received one prior tyrosine kinase inhibitor treatment. This is a key clinical consideration given the likely increased use of multiple therapies in patients with iodine–refractory thyroid cancer. Forty patients (15.3%) in the lenvatinib arm of the study had durable stable disease for >23 weeks vs. 39 patients (29.8%) in the placebo group. Progressive disease occurred in 18 patients (6.9%) in the lenvatinib group as compared with 52 patients (39.7%) in the placebo group.

Conclusion

Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival and the response rate among patients with iodine-131–refractory thyroid cancer. Median progression-free survival in the lenvatinib arm was 14.7 months longer than it was among those receiving placebo (P<0.001). This improvement is longer than that observed in other placebo-controlled clinical trials of kinase inhibitors involving patients with DTC, including trials of sorafenib, and the investigational agents sunitinib, axitinib, and vandetanib. This observation may be the result of the agent's inhibition of unique targets, including FGFRs. ▲

REFERENCES:

Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb 12;372(7):621-30. doi: 10.1056/NEJMoa1406470



EXPANDING THE APPLICATIONS OF TRANSORAL ROBOTIC SURGERY (TORS): SIALOLITHOTOMY AT PENN MEDICINE

Under the direction of Christopher Rassekh, MD, FACS, Penn Otorhinolaryngology – Head and Neck Surgery has introduced a new approach to sialolithotomy for the treatment of large (>7mm) sialoliths in the posterior (hilar) compartment of the submandibular gland – the incorporation of TransOral Robotic Surgery. The procedure complements the thriving sialendoscopy program at Penn Medicine.

Approved by the Food and Drug Administration in 2009, TransOral Robotic Surgery (TORS) was invented at Penn Medicine by Bert W. O'Malley, Jr., MD, and Gregory S. Weinstein, MD, FACS. TORS consists of a group of minimally invasive techniques that enable surgeons to perform procedures that formerly involved extensive cutting of bone and tissue to reach tumors deep within the head and throat.

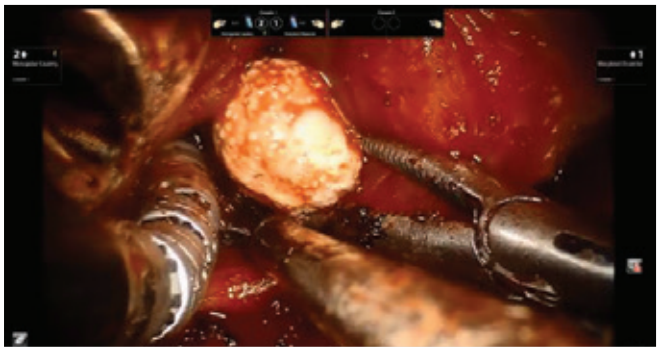
"The transoral robotic sialolithotomy program here at Penn combines two of the greatest advances in head and neck surgery in this century—TORS and sialendoscopy," Dr. Rassekh says. In fact, Dr. Rassekh was asked by the inventors of TORS, Dr. O'Malley and Dr. Weinstein to direct a collaboration with the world's foremost leader and pioneer in sialendoscopy, Francis Marchal, MD. This collaboration began with a cadaveric study in the Penn Otorhinolaryngology – Head and Neck Surgery department TORS laboratory where Dr. Marchal was being trained in robotic surgery in September of 2014. Following this laboratory session, Dr. Marchal has invited Dr. Rassekh to write a chapter on the topic for his recently published book and also invited Dr. Rassekh to speak in Prague on the topic and most recently transmit a live surgery session from Penn through Geneva, Switzerland where Dr. Marchal is on the faculty. This was presented at the International Sialendoscopy Hands-On Course, attended and viewed by surgeons from more than 50 different countries in collaboration with surgeons from India and Hong Kong.

About Robotic Sialolithotomy

The objective of submandibular gland stone extraction is to save the gland, if possible. "This is almost always possible with smaller stones using sialendoscopy," Dr. Rassekh says, "But with stones greater than 7mm in size, particularly stones deep in the hilar portion of the gland, surgical excision of the gland becomes a possibility."

Removal of the submandibular gland is associated with some significant risks. The gland is attached to the major sensory nerve to the tongue, (the lingual nerve) and the major motor nerve is just deep to the gland (the hypoglossal nerve). In order to approach the gland from the outside, surgeons must dissect very close to the lower branches of the facial nerve, making lip paralysis a possible consequence. Patients usually desire to preserve their gland and also avoid these risks as well as the neck scar. However, removal of the gland is necessary for tumors and for obstructions of the duct that cannot be removed.

And then there are the stones. Some 80% of sialoliths occur in the submandibular gland, primarily at the distal portion of the Wharton duct or hilum, and of these, one in five is invisible to radiography. The stones are primarily mineral in composition, can be smooth or ragged at the surface, and grow at a rate of 1-1.5 mm per year. Twelve percent have grown to a size >10mm. These larger stones impede the duct, impinge the nerves and often cause misery until they're removed and usually lead to infection if not treated.



Large stone being removed from submandibular duct hilum using Maryland forceps. The spatula tip cautery is at 9 o'clock and the lingual nerve can be seen gently retracted between the spatula tip cautery and the suction.

Christopher Rassekh, MD, FACS, featured with the robot used for TORS-assisted sialolithotomy.

Stones up to 5mm can be removed with simple basket extraction. Stones between 5 and 7 mm can usually be removed either with a combined approach or using laser. Stones larger than that and/or far back in the duct near the hilum or partially inside the gland traditionally required removal of the gland. Now, combined approaches with sialendoscopy are feasible to remove even these large and posterior stones. TORS facilitates these combined approaches.

According to Dr. Rassekh, robotic surgery is not only simpler than previous techniques, but safer and faster.

"After the location of the stone has been identified, I use the robot to enter the gland transorally through a small incision," Dr. Rassekh explains. "It's easier to visualize the lingual nerve and the duct with the robot, so I carefully avoid these and advance to the stone. Then, after cutting the tissue over the stone, I expose and grasp it with one of the instruments and extract it. Then we do sialendoscopy to confirm that the duct is open and that there are no additional stone fragments."

The Benefits of TORS for Sialolithotomy

According to Dr. Rassekh, robotic surgery is set apart by several unique benefits, including the capacity to perform 4-handed surgery. "One of the principal problems every surgeon encounters when operating in a small or contained field is having to maneuver around the hands of an assistant or a device to get a clear view. Using the robot, I can do everything from a remote console while our bedside assistant helps with retraction and suction," Dr. Rassekh says.

Transoral robotic sialolithotomy also has the advantage of removing larger stones intact. Outside of open surgery and its inherent risks, other methods (e.g., extracorporeal lithotripsy, laser lithotripsy) have been introduced to sialolith extraction that rely on breaking the stones into fragments that can then be extracted or flushed from the gland. Both procedures can contribute to a slight increase in the risk of injury and also add substantially to operative time, particularly if the fragments become embedded in the ducts.

In the event that the stone cannot be removed, the TORS approach also facilitates removal of the gland through the mouth, another operation that has been investigated in the laboratory collaboration with Dr. Marchal and which has been performed by Drs. Rassekh, Weinstein and O'Malley. This avoids the risks of removing the gland through the neck mentioned before, as well as patient's concerns regarding the risk of lower lip paralysis and unsightly scarring. "For efficacy and safety, there's just no comparison between any of these procedures and the practical simplicity of TORS," Dr. Rassekh says.

When asked, Dr. Rassekh refuses to limit the possibilities for transoral robotic sialolithotomy. "We're at the frontier of robotic and endoscopic sialolithotomy here at Penn," he says. "I know we'll continue to use the sialendoscope in other novel applications in the future. Beyond that, all I can say is that there are great things ahead." ▲

"The transoral robotic sialolithotomy program here at Penn combines two of the greatest advances in head and neck surgery in this century—TORS and sialendoscopy."

HOW MOBILEOPTX® GOT TO MARKET

Four years ago two surgeons in the department of Otorhinolaryngology – Head and Neck Surgery at Penn became innovators and inventors. This, admittedly, was a notion somewhat outside of their clinical experience. Natasha Mirza, MD, is an otorhinolaryngologist and director of the Penn Center for Voice and Swallowing. Still, she had discovered the ingredients for the genesis of all great inventions: an unmet need, and a simple, cost-effective, imaginative means to fill that need.

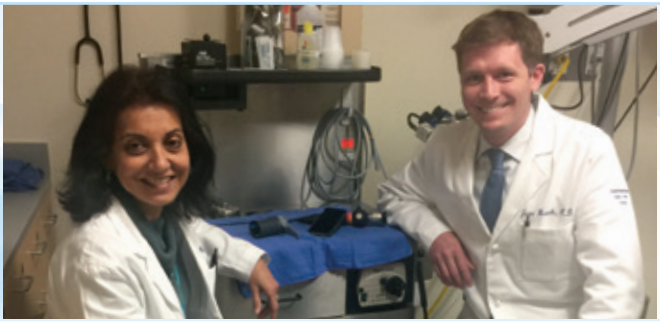
Dr. Mirza's specialty is airway and laryngeal pathology, a field that depends upon the constant transmission of laryngeal pathology images from the bedside and emergency room in real-time in order to communicate findings to patients, their providers and families. Unfortunately, the advances in real-time communication most of us enjoy every day on our cell phones has not been translated to the field of endoscopy.

The equipment currently used for mobile endoscopy in hospitals is called a "tower". It consists of a computer screen, a computer, a keyboard, a laryngoscope, a light and camera stacked on a movable trolley that is wheeled from room to room. The cost of the stack and its components runs to $60,000 at the low end—and this cost doesn't account for time loss, part replacement and storage.

Arriving at bedside, the equipment is assembled while the computer boots up. The images are then taken, recorded, and processed with a typed description before transmission. If all goes well, the images are stored or copied on discs. All this takes approx. 10 to 15 minutes. If there's a glitch anywhere in the system, though, it can take much longer or it may not be possible to store the images at all.

One evening in 2011, it occurred to her that the process could be further improved if she simply attached her phone directly to the endoscope. The quality of the camera in her smartphone was sufficient to ensure a high-resolution image, and with adequate storage and a vastly enhanced capacity to transmit information, it could replace much of the burden, space and time imposed by her existing equipment.

But having had her eureka moment, Dr. Mirza faced the conundrum confronting all first-time inventors—translating an idea into a tangible product. Fortunately, one of her colleagues in the department, Jason Brant, MD, with an undergraduate degree in biomedical engineering, and an interest in innovation was intrigued by the idea, which was something he had also been considering. Within a month, he had created a prototype that proved that the phone could be coupled to the endoscope in a real-time setting to take and transmit images. This piece, put together with basic hardware from Home Depot by Dr. Brant, was the basis of the device that is now available. The inventors filed their patent through Penn and are the first in this arena to do so.



MobileOptx co-inventors Natasha Mirza, MD (left), and Jason A Brant, MD (right).

By using MobileOptx, clinicians, wherever they might be, can contact specialists here and at other academic medical centers for second opinions and emergent assistance.

Now the hard work began. With the assistance of engineers at Penn Engineering school, Drs. Brant and Mirza began a process of refining the device through 3D printing. Eventually, the design involved two pieces, a unique case to fix and stabilize the phone, and, a universal spring-loaded adapter that attaches to any endoscope. "It was beautiful," Dr. Mirza says, reflecting on the moment. "Because now we had something we could demonstrate." The idea of forming a company to manufacture and market the device had been simmering on the back burner and, with the much-improved second-iteration in hand, Drs. Mirza and Brant approached UPstart at the University of Pennsylvania.

With UPstart's help, the inventors formed MobileOptx®, a name that now identifies both the company and the device. Bringing the product to market would involve a substantial infusion of capital. So, again with an innovative approach and support from the department of Otorhinolaryngology – Head and Neck Surgery at Penn, the inventors secured a grant and were able hire a private engineering firm to finalize the device.

To prove that the MobileOptx smartphone coupler could provide images suitable for diagnosis of laryngeal pathology, the inventors initiated a clinical study among residents and clinicians, to assess the efficacy of the device. The findings were overwhelmingly positive, with more than 90% concurrence between the conventional naked eye endoscopic view and that obtained through MobileOptx. The next step, and one that didn't involve a great deal of intuition, involved the smartphone platform.

In April 2015, MobileOptx was one of five finalists in the Upenn AppITUP Challenge from the Penn Center for Innovation and PCI Ventures. SemperCon, a company that develops smartphone apps for business and consumers, won the deal with MobileOptx and have developed an app that is now in the Apple store.

"What we were trying to do from the start was save time, capture images, allow review of these images and eventually share them with other providers and even with the patients themselves. A picture is worth a thousand words," Dr. Mirza says. "And that's where MobileOptx will help me. But, there's no reason that MobileOptx should be restricted to airway endoscopy. It can be used wherever there's an endoscope."

For Dr. Brant, whose interests include otology as well as laryngeal endoscopy, the device offers access to a greater realm of potential. "Many small rural hospitals in this country and other parts of the world don't have access to our endoscopy equipment, let alone the capacity to record and transmit images," he notes. "By using MobileOptx, clinicians, wherever they might be, can contact specialists here and at other academic medical centers for second opinions and emergent assistance. It's a phone, after all. It was made to communicate.

In an interview soon after the launch of MobileOptx, Steven E. Sobol, MD, MSc, FRCS(C), FAAP, of the Children's Hospital of Philadelphia, and associate professor in the Department of Otorhinolaryngology – Head and Neck Surgery at Penn's medical school offered a final word MobileOptx.

"MobileOptx will revolutionize the training of residents and fellows in the academic setting," Dr. Sobol said. "And, at last, gone are the days of needing to repeat endoscopic procedures in order to validate findings." ▲

Penn Medicine
3600 Market Street | Suite 210
Philadelphia, PA 19104

PENN OTORHINOLARYNGOLOGY – HEAD AND NECK SURGERY

Founded in 1870, Penn Otorhinolaryngology – Head and Neck Surgery is one of the oldest departments and residency programs in the country. The legacy and tradition of excellence in patient care, education, and research continues to grow and flourish today.

Penn's multidisciplinary team of board-certified otorhinolaryngologists specializes in the evaluation, diagnosis and treatment of a spectrum of ear, nose and throat disorders, as well as areas within the head and neck.

SERVICES INCLUDE:

- Audiology
- Balance Center
- Center for Head and Neck Cancer
- Center for Implantable Hearing Devices
- Cranial Base Surgery/ Skull Base Surgery
- Facial Plastic and Reconstructive Surgery
- General Otolaryngology
- Head and Neck Surgery
- Hearing Aid Dispensing
- Otology/Neurotology
- Rhinology
- Smell and Taste Center
- Speech-Language Pathology and Rehabilitation
- Thyroid Program
- Tinnitus
- TransOral Robotic Surgery (TORS)
- Voice, Speech and Swallowing Disorders

EXCELLENCE IN PATIENT CARE, EDUCATION AND RESEARCH SINCE 1870

Penn PhysicianLink®

Consults • Referrals • Transfers

Penn PhysicianLink provides facilitated access to, and simplifies the lines of communication between referring physicians and Penn Medicine. This comprehensive, coordinated collection of support services expedites and facilitates both direct physician communication as well as patient transfers.

Exclusive, Physician-Only Telephone Line:

877.937.PENN (7366)

This dedicated, physician-only telephone line offers direct access to facilitate:

- Emergent and non-urgent transfers to Penn Medicine
- Physician consults and referrals
- Information about medical education and clinical programs

Physician Liaison Services:

Penn Medicine physician liaisons will facilitate meetings between and among referring physicians and Penn providers for Grand Rounds, CME and education programs and other professional meetings.

877.937.PENN (7366) • PennMedicine.org/PhysicianLink

FY16 6990 2/16