



PHILADELPHIA INTERNATIONAL MEDICINE® NEWS BUREAU

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For immediate release:

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Editors note: Research, new techniques and improved facilities by Philadelphia International Medicine hospitals and physicians may lead to new ways to treat some of our most challenging diseases. Below are just some examples from our hospitals.

Jefferson Appoints Director of Live Donor Liver Transplant

Philadelphia—Warren R. Maley, MD, joined the Department of Surgery at Thomas Jefferson University Hospital (TJUH), and will serve as the director of the Live Donor Liver Transplant Program. He also has been named an associate professor of Surgery at Jefferson Medical College of Thomas Jefferson University. Dr. Maley has performed extensive research in the fields of liver transplantation and surgical therapy to improve patient safety and care.

Dr. Maley received his medical degree from the University of Pittsburgh School of Medicine in 1984. He earned a bachelor of science degree from the University of Pittsburgh in 1980. Dr. Maley's postgraduate training began as an intern in the Department of Surgery at The Johns Hopkins Hospital from 1984-1985. He also completed a residency in surgery from 1985-1989.

As part of his surgical residency, Dr. Maley served as the surgical registrar at The John Radcliffe Hospital in Oxford, England. After six months in this position, he was appointed chief resident in surgery at The Johns Hopkins Hospital in Baltimore from 1990-1991. In 1991 he served as a gastrointestinal surgery fellow for one year, and then in 1992 began serving a two-year appointment as a transplant fellow. Prior to joining Jefferson, Dr. Maley served as surgical director of Liver Transplantation at The Johns Hopkins Hospital beginning in January of 2005. He also served as co-director of the Transplant Center at Willis-Knighton/LSU (Louisiana State University) Transplant Service in Shreveport, Louisiana from 2003-2005.

Dr. Maley is board certified by the American Board of Surgery and is a member of the Alpha Omega Alpha Medical Honor Society. He is also a member of the American Association for the Study of Liver Diseases, a member of the American Society of Transplantation, and a member of the American Society of Transplant Surgery. He has an extensive list of published research studies in such leading journals as

Transplant Proceedings, Transplantation, Liver Transplantation and Annals of Surgery; and has authored or co-authored eight book chapters.

Dr. Maley has an international practice and accepts new patients.

Temple Lung Center Has Adopted a New Tool for the Diagnosis and Treatment of Early-Stage Lung Cancer

The Temple University Hospital Lung Center has adopted a new tool for the diagnosis and treatment of early-stage lung cancer with a device that helps physicians navigate distant regions of the lungs using technology similar to the GPS in vehicle navigation systems. Temple is among the first academic medical centers to use the inReach™ System by superDimension, which enables pulmonologists to build a 3-D “roadmap” of a patient's lungs from a CT scan, and then navigate that map in real time using a flexible, steerable catheter and bronchoscope to take samples of hard-to-reach lesions.

“The new system is helping us extend our reach to biopsy lung abnormalities, and offer a greater opportunity to treat patients soon,” said John M. Travaline, MD, director of the Invasive Pulmonary Procedures Laboratory.

In the past, patients experiencing symptoms of lung disease or those who have suspected lesions could be examined and treated with standard bronchoscopic techniques, needle aspiration, or surgery. Using electromagnetic navigation coupled with flexible bronchoscopy, the inReach system offers patients a less invasive alternative.

This outpatient procedure, which takes from 30 minutes to about one hour, presents no additional risks beyond those associated with traditional bronchoscopy. And, because of the accuracy of the new technology, the inReach system can also aid doctors in the treatment of cancerous lesions with greater precision by enabling cancer staging in the lymph nodes.

“Lung cancer is the most common cancer-related death in men and women, claiming more lives than breast cancer, prostate cancer and colorectal cancer combined,” Dr. Travaline said.

In 2007, more than 200,000 Americans were diagnosed with lung cancer, and the present five-year survival rate is only 15 percent, according to the National Cancer Institute.

“Earlier diagnosis and treatment could increase the chance that patients live longer,” said Dr. Travaline. He added, “With the inReach System, we have the potential to help reduce the mortality rate for lung cancer.”

Fox Chase Study Finds Enzyme Inhibitor that Takes an Unexpected Approach toward Blocking Cancer-Promoting Protein

Scientists at Fox Chase Cancer Center have discovered a unique method of attack that may be used to inhibit signaling enzymes called kinases, which often have a role in sustaining drug-resistant cancerous cells. They have confirmed that IPA-3, a small molecular inhibitor of a kinase called PAK1, targets the

enzyme's regulatory domain, mimicking how enzymes are naturally regulated within cells.

"Typically, research has focused on ways of blocking the active site of enzymes, the part of the enzyme that performs a particular task," says Jeffrey R. Peterson, PhD, an assistant professor Fox Chase's Cancer Genetics and Signaling program and co-author of the article. "The structure of active site, however, is often shared among kinases, which makes it tough to target a particular kinase without accidentally inhibiting a related enzyme.

"By targeting PAK1's specific regulatory domain, IPA-3 is highly selective molecule that takes a more-or-less backdoor approach to shutting down a kinase," Peterson says. "If we can create drugs that take advantage of this mechanism, we could create new combination therapies that will allow doctors to kill what might otherwise be drug-resistant cells."

Peterson and Julien Viaud, postdoctoral researchers in the Peterson lab, published their findings in the journal *Molecular Cancer Therapeutics*. The researchers previously identified IPA-3 from a screen of 33,000 candidates, and the molecule has since gone on to become an important subject of study by cancer laboratories around the world. In the article, the researchers use a variety of techniques to define how IPA-3 interacts with PAK1.

"We found definitive proof that IPA-3 fit into and binds to PAK1's autoregulatory domain, the part of the enzyme where it can, essentially, shut itself off when necessary," Peterson says. "Our tests also demonstrate that IPA-3 is highly selective for PAK1, which means that it is less likely it will also turn off other kinases unintentionally."

The idea is not entirely without precedent; the cancer drug Gleevec, for example, is unusually selective for its target by binding to a region outside of the active site that is less common among kinases. By defining the regulatory domain as a useful target for inhibition, however, researchers now have a specific place to look when trying to develop new therapeutics for protein regulation.

According to Peterson, small molecule inhibitors such as IPA-3, are promising tools for drug discovery. While IPA-3 itself might not be a suitable as a drug for use in humans, the molecule could form the conceptual basis of a new targeted therapeutic.

Jefferson Hospital Among First To Offer New, Non-Invasive Tinnitus Treatment

The Jefferson Balance and Hearing Center of the Department of Otolaryngology – Head and Neck Surgery at Thomas Jefferson University Hospital is among the first hospitals to offer the FDA-cleared Neuromonics Tinnitus Treatment. This therapy is proven to interact, interrupt and desensitize tinnitus by delivering a customized neural stimulus, embedded in clinically modified music.

"Tinnitus is an awful, debilitating condition that can have a devastating impact on a patient's quality of life," said medical director Thomas Willcox, MD. "This new treatment represents a significant step

forward for a condition with traditionally limited therapeutic options. By targeting underlying neurological and psychological causes, it has been proven to offer long-lasting benefit.”

Tinnitus is the perception of sound in the ears or head when no external source is present. Often described as "ringing in the ears," it affects as many as 50 million people in the United States. The Centers for Disease Control and Prevention report that one million new cases of tinnitus are identified each year, 200,000 of which are severe. Tinnitus symptoms can negatively impact normal daily activities and can lead to additional medical conditions, such as anxiety, depression, sleep deprivation and elevated stress.

Tinnitus is not simply an auditory problem, but also has a neurological and psychological basis. While most tinnitus cases are preceded by hearing loss, neurological factors often contribute to the deterioration in symptoms. First, the brain attempts to compensate for the hearing loss by “turning up” sounds internally. Ultimately a psychological component emerges, when the sufferer develops a “fight-or-flight” stress response to the debilitating sounds. The patient then focuses more attention on the tinnitus, perceiving it as louder and louder. Tinnitus takes increasingly significant control over their life. Thus begins a vicious cycle involving neurological, psychological and auditory factors.

Neuromonics’ non-invasive, FDA-cleared device is customized to the patient's unique hearing and tinnitus profile. It delivers a customized neural stimulus that promotes neural plastic changes, allowing the brain to filter out the disturbing tinnitus sound. This stimulus is delivered within spectrally modified, customized music, which engages the brain's emotional response center, the limbic system, and thereby reduces tinnitus-related disturbance.

The therapy is delivered via a compact, lightweight and uniquely designed medical device. Treatment typically occurs over an approximately six-month period, with daily use recommended for two or more hours per day, especially when the tinnitus is most disturbing. The treatment can take place during regular activities such as reading, relaxing or computer work. It involves a multi-stage process designed for optimal clinical results.

Cell-Regeneration Molecules Essential Signals for Early Lung Development, Penn Study Finds

A tissue-repair-and-regeneration pathway in the human body, including wound healing, is essential for the early lung to develop properly. Genetically engineered mice fail to develop lungs when two molecules in this pathway, Wnt2 and Wnt2b, are knocked out. The findings are described this week in *Developmental Cell*.

“We wanted to know the answer to a seemingly simple question: What is required to generate the lung in mammals?” asked senior author Edward Morrisey, PhD, Associate Professor of Medicine and Cell and Developmental Biology at the University of Pennsylvania School of Medicine.

“Wnt molecules are important for lung growth and we think that some of the molecules in the Wnt

pathway are needed to specify lung progenitor cells and if not enough cells are ‘told’ to make a lung, an animal develops a faulty, smaller organ or even no lung,” says Dr. Morrisey, who is also the scientific director of the Penn Institute for Regenerative Medicine.

Several molecular signals are important for proper lung development but not much is known about the early signals that turn on the genes needed to specify the lung at the right place and time in the embryo. Clinically, understanding how a lung develops is important in treating or preventing a host of lung and pulmonary diseases in children. “Premature babies in particular often develop respiratory problems which can lead to health issues not only during infancy but also later in life” says Dr. Morrisey.

He also points out that pulmonary and cardiac development is intricately connected, “One thing that is coming out of these studies is that the lung and heart form together which is an important point to remember as pathways affecting one organ system can affect the other.” In fact, one of the Wnt knockout mice the team developed also has profound cardiovascular defects, he notes.

In the developing embryo, the lung, pancreas, liver, thyroid, and stomach all come from the foregut region, which starts out looking like a long tube. “These organs bud from this undifferentiated tube and go on to develop into specific tissue types,” explains Dr. Morrisey. “The lung is one of the last to bud off the foregut during development.”

The team focused on the Wnt pathway to see where and when Wnt molecules were expressed along the foregut tube, even before the lung starts to become a recognizable organ. “The lung is a relative late arriver,” says Dr. Morrisey. “The liver, pancreas, and other organs begin developing days earlier.” They found that the Wnt proteins Wnt2 and Wnt2b are expressed in the cells surrounding the foregut, right where the lung will eventually form. When they are knocked out, the animals completely lacked lungs.

Dr. Morrisey surmised that Wnt2 and Wnt2b were required to specify the early progenitors for the lung in the foregut. “We found that the *Nkx2.1* gene, which is expressed in both lung and thyroid progenitor cells in the foregut, were absent only in the region where the lung was supposed to form and not in the thyroid progenitor cells.”

They confirmed this fine tuning of lung development by knocking out an additional gene in the Wnt pathway called *beta-catenin* in the early foregut, and these mice also did not develop lungs, but all the other foregut-associated organs developed properly. “This says that these two Wnt molecules are essential for specifying the lung but not other foregut-derived organs” explains Dr. Morrisey.

The Morrisey lab also showed that activation of the Wnt pathway resulted in formation of lung progenitors in both the esophagus and stomach where they are normally excluded. “The ability of Wnt to program esophagus and stomach endoderm to a lung fate points to the critical role this pathway plays in lung development and suggests the possible use of Wnt in generating lung epithelium from non-lung sources.”

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