**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.***

## Fox Chase Opens First Inflammatory Breast Cancer Clinic on the East Coast

PHILADELPHIA—Fox Chase Cancer Center, a world-renowned leader in research and treatment of women's cancers, announced the opening of its Inflammatory Breast Cancer Clinic, the first on the East Coast. The new clinic, led by noted breast cancer clinician and researcher Massimo Cristofanilli, MD, FACP, focuses on the treatment of patients with inflammatory breast cancer—one of the rarest and most aggressive forms of the disease. Fox Chase's new clinic is one of only three in the nation.

"Patients with inflammatory breast cancer often face challenging odds, first to be promptly and accurately diagnosed and then to receive the most effective treatment," says Dr. Cristofanilli, chairman of medical oncology at Fox Chase. "With the opening of this new clinic, Fox Chase is dedicating itself to improving both diagnosis and care for inflammatory breast cancer patients."

Inflammatory breast cancer (IBC) is a rare form of breast cancer, accounting for about one percent of all breast cancers diagnosed in the United States. IBC can be difficult to diagnose because it rarely causes a breast lump and may not show up on a mammogram. It is considered one of the most aggressive forms of breast cancer, making early diagnosis vital to saving lives.

Fox Chase's new IBC clinic offers patients a coordinated team of cancer care specialists who follow them through examination, care, and any continued monitoring.

"I believe in multidisciplinary team science as the most appropriate way to ensure that patients receive top quality care," says Dr. Cristofanilli.

In addition to leading the IBC clinic, Dr. Cristofanilli chairs the department of medical oncology at Fox Chase and plays a vital leadership role in the Women's Cancer Center, overseeing all breast cancer care, and co-directing the Women's Cancer Program—one of Fox Chase's six core research programs within the Center.

"Along with an outstanding clinical team, Fox Chase has the scientific resources needed to more closely investigate the etiology and molecular mechanisms of inflammatory breast cancer, which will help to improve the diagnosis and treatment of this disease," added Dr. Cristofanilli.

Dr. Cristofanilli came to Fox Chase from The University of Texas M. D. Anderson Cancer Center, where he founded and served as executive director of the Morgan Welch Inflammatory Breast Cancer Program and Clinic, which treats more cases of inflammatory breast cancer than any other hospital in the world. The program and clinic honor Morgan Welch, one of Cristofanilli's youngest patients. Welch was diagnosed with metastatic inflammatory breast cancer at the age of 24.

**Jefferson Scientists Identify a New Protein Involved in Longevity**

Researchers in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University have found that the level of a single protein in the tiny roundworm C. elegans determines how long it lives. Worms born without this protein, called arrestin, lived about one-third longer than normal, while worms that had triple the amount of arrestin lived one-third less.

The research also showed that arrestin interacts with several other proteins within cells to regulate longevity. The human version of one of these proteins is PTEN, a well-known tumor suppressor. The study, to be published in the online edition of the Journal of Biological Chemistry, was chosen by the journal as the "Paper of the Week" – considered in the top one percent of published articles.

Because most proteins in worms have human counterparts, these findings may have relevance to human biology and the understanding of cancer development, said Jeffrey L. Benovic, PhD, professor and chair of the department.

"The links we have found in worms suggest the same kind of interactions occur in mammals although human biology is certainly more complicated. We have much work to do to sort out these pathways, but that is our goal," said Dr. Benovic.

Researchers use the roundworm as a model because it offers a simple system to study the function of genes and proteins that are relevant to human biology. The worm, for example, has one arrestin gene, whereas humans have four. Worms only have 302 neurons compared to the 100 billion or so in the human brain. In addition, their short lifespan of two to three weeks allows for timely observation of effects on longevity.

Dr. Benovic and the study's first author, Aimee Palmitessa, PhD, a postdoctoral research fellow, studied signaling pathways activated by G protein-coupled receptors. These receptors bind to all kinds of hormones, sensory stimuli (such as light, odorants and tastants), neurotransmitters, etc., which then activate a cascade of signals inside the cell. They regulate many physiological processes and are the target for about half of the drugs currently on the market.

“When it comes to receptors, worms are actually more complex,” said Dr. Benovic. “Humans have about 800 different kinds of G protein-coupled receptors while the worm has about 1,800. It relies upon these receptors to respond to sensory stimuli as well as various neurotransmitters and hormones.”

Arrestins were initially found to turn off the activation of G protein-coupled receptors inside cells. “Their name comes from the fact that they arrest the activity of receptors, so the worm offers a good way to study how its single arrestin protein interacts with protein receptors,” says Dr. Benovic. Two of the four arrestins that humans have are devoted to regulating receptors that respond to visual stimuli while the other two regulate most other receptors.

In this study, Dr. Palmitessa deleted the single arrestin gene in worms to see what would happen, and found, to her surprise, that these worms lived significantly longer. She also found that over-expressing arrestin in worms shortened their lifespan. “A little less arrestin is good – at least for worms,” Dr. Benovic reported.

This isn’t the first discovery made regarding longevity in worms. Researchers have already found that activity of the insulin-like growth factor-1 (IGF-1) receptor can influence longevity in worms – a finding that has also been replicated in fruit flies, mice, and humans. Like arrestin, a little less IGF-1 receptor activity is good, Dr. Benovic explained. Further research has shown that caloric restriction can also reduce IGF-1 receptor activation and, conversely, over-expression of the IGF-1 receptor is found in some human cancers.

In this study, Dr. Benovic and Dr. Palmitessa dug a little deeper and found that in the worms, arrestin interacted with two other proteins that play a critical role in its ability to regulate longevity. One of those proteins is the tumor suppressor PTEN; mutations in PTEN are involved in a number of different cancers.

Dr. Benovic said the connection between human arrestin and PTEN is not clear. “We don’t know at this point if human arrestins regulate PTEN function or if anything happens to arrestin levels during the development of cancer,” he said. “Do increasing levels turn off more PTEN, thus promoting cancer, or do levels decrease and allow PTEN to be more active?

“If it turns out to be the first scenario – that increasing amounts of arrestin turn off the tumor suppressor activity of PTEN, then it may be possible to selectively inhibit that process,” he says. “We have some interesting work ahead.”

The study was funded in part by the National Institutes of Health. The authors declare no conflict of interest.

**24 Temple Physicians Recognized in Philadelphia magazine's Annual "Top Doctors" Issue**

Included in *Philadelphia Magazine's* annual list of "Top Doctors" are 24 Temple University Hospital (TUH) physicians, each of whom holds a faculty appointment in Temple University School of Medicine.

The two dozen selected Temple "Top Docs" represent 17 different specialty services offered at Temple University Hospital - including Cardiovascular, Diagnostic Radiology, Gastrointestinal, Hematology, Infectious Diseases, Internal Medicine, Interventional Radiology, Otolaryngology, Neurology, Pulmonary, and Surgery (including the subspecialty areas of Colon & Rectal Surgery, General Surgery, Hand Surgery, Neurosurgery, Orthopaedic Surgery, Thoracic Surgery, and Vascular Surgery).

Below are the Temple physicians nominated by their peers as "Top Docs."

- S. Ausim Azizi, MD, Neurology
- Alfred A. Bove, MD, Cardiovascular Disease
- Gary S. Cohen, MD, Vascular & Interventional Radiology
- Gerard J. Criner, MD, Pulmonary Disease
- Daniel Dempsey, MD, Surgery
- Robert S. Fisher, MD, Gastroenterology
- Satoshi Furukawa, MD, Thoracic Surgery
- Sean P. Harbison, MD, Surgery
- Glenn C. Issacson, MD, Otolaryngology
- Douglas W. Laske, MD, Neurological Surgery
- Christopher M. Loftus, MD, Neurological Surgery
- Bennett Lorber, MD, Infectious Disease
- Kenneth F. Mangan, MD, Hematology
- James B. McClurken, MD, Thoracic Surgery
- Santiago J. Munoz, MD, Gastroenterology
- A. Koneti Rao, MD, Hematology
- William R. Reinus, MD, Diagnostic Radiology
- Joel E. Richter, MD, Gastroenterology
- Andrew B. Roberts, MD, Vascular Surgery
- John L. Rombeau, MD, Colon & Rectal Surgery
- Ellen M. Tedaldi, MD, Internal Medicine
- Joseph J. Thoder, MD, Hand Surgery
- John M. Travaline, MD, Pulmonary Disease
- F. Todd Wetzel, MD, Orthopaedic Surgery

"We are proud of the well deserved recognition given to these outstanding Temple doctors, who reflect the quality of care and comprehensive specialty services that Temple University Hospital is privileged to provide to the communities it serves – from our patients in Philadelphia to our patients around from different countries," said Sandy Gomberg, RN, MSN, chief executive officer of Temple University Hospital.

"Such independent recognition of Temple's clinical excellence is a testament to not only the individual specialists cited, but to the comprehensive nature of advanced medicine and research for which Temple physicians are known," added John M. Daly, MD, dean of the Temple University School of Medicine.

**Rare Disease in Amish Children Sheds Light on Common Neurological Disorders**

So often the rare informs the common. Penn researchers investigating a regulatory protein involved in a rare genetic disease have shown that it may be related to epileptic and autistic symptoms in other more common neurological disorders.

A team of researchers from the University of Pennsylvania School of Medicine, led by Peter B. Crino, MD, PhD, associate professor of Neurology and director of the Penn Epilepsy Center, demonstrate how mutations in the STRAD-alpha gene can cause a disease called PMSE (polyhydramnios, megalencephaly, and symptomatic epilepsy) syndrome, found in a handful of Amish children. PMSE is characterized by an abnormally large brain, cognitive disability, and severe, treatment-resistant epilepsy.

Specifically, in an animal model, they found that the lack of the STRAD-alpha protein due to genetic mutations causes activation of the signaling pathway involving another protein called mTOR. In humans, this in turn may promote abnormal cell growth and cognitive problems in the developing brains of children. STRAD-alpha and mTOR proteins are part of a complex molecular network implicated in other, more common neurological disorders, many of which have autism-like symptoms as a component.

"The identification of a new gene that regulates mTOR provides fascinating insights into how mTOR pathway dysfunction may be associated with neurological disorders," says Dr. Crino. "Each new mTOR regulatory protein that is identified provides a new possible therapeutic target for drug development and treatment."

The research on PMSE – published this month in the Journal of Clinical Investigation – reveals clues about more common neurological disorders characterized by benign tumors and malformations of the brain, the most common of which is tuberous sclerosis complex (TSC). The root cause of TSC also lies in mutations in proteins along the mTOR pathway, however a different protein is affected compared to PMSE.

"It is quite compelling that TSC, a relatively common disorder, and PMSE, a rare disorder, are linked by a common cellular pathway, and exhibit similar severe neurological features," notes Dr. Crino. "In our study, we found that we could reverse some of the cellular features that result from STRAD-alpha deficiency in cell culture models of PMSE. This provides important conceptual support for more widespread treatment approaches that modify mTOR signaling in neurological disorders associated with epilepsy, autism, and cognitive disability."

Current estimates place tuberous sclerosis complex-affected births at one in 6,000. Nearly 1 million people worldwide are known to have TSC, with approximately 50,000 in the United States. PMSE, on the other had, has only been described in 25 people in Lancaster County, PA. It's incidence among other Amish populations, let alone the rest of the country, is unknown. PMSE is also known as pretzel syndrome in the Amish community, because the lax joints of patients fold over easily. PMSE was identified in an Amish, or Old Order Mennonite pediatric population in 2007 by researchers from Penn and the Clinic for Special Children in Lancaster, PA, a genetic clinic devoted to the needs of the Amish.

The mTOR pathway normally controls cell growth, but in PMSE uncontrolled mTOR signaling leads to increases in brain size and areas in which the cerebral cortex is malformed. To prove this, the researchers knocked down the activity of the STRAD-alpha protein in a mouse model and caused malformations of the developing brain. The structure of these malformations was similar to what is seen in human PMSE and TSC and supports the conclusion that normal brain development in part depends on normal STRAD-alpha function. Localized brain malformations are among the most common causes of epilepsy and neurological disability in children.

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