



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.

Dr. Mark Weiss Joins the Department of Medical Oncology at Jefferson

PHILADELPHIA – Mark Weiss, MD, will join the Thomas Jefferson University, Department of Medical Oncology as director of Hematologic Malignancies. Dr. Weiss will be professor of Medical Oncology at Jefferson Medical College of Thomas Jefferson University. He comes to Jefferson after a 19-year career at Memorial Sloan-Kettering Cancer Center in New York City.

“Dr. Weiss has a strong record as a leader in research, education and clinical hematology and oncology and will be a definite asset to our team,” said Neal Flomenberg, MD, chairman of the Department of Medical Oncology. “We are pleased that he has agreed to serve as director of Hematologic Malignancies here at Jefferson, as he is internationally known for his work in hematologic malignancies, particularly chronic lymphocytic leukemia and acute lymphocytic leukemia.”

Dr. Weiss earned his bachelor of arts from Cornell University in 1977. In 1983, he received his medical degree after completing the Medical Scientist Training Program at Cornell University Medical Center and Rockefeller University. He went on to complete a residency in internal medicine at Vanderbilt University Medical Center in Nashville. Dr. Weiss completed a fellowship in hematology and medical oncology at Memorial Sloan-Kettering Cancer Center in New York City.

After fellowship, Dr. Weiss remained at Memorial Sloan-Kettering for an additional 19 years, rising through the ranks to his current position of associate attending physician in the Division of

Hematologic Oncology and associate professor of Medicine at Weill Cornell Medical College of Cornell University Department of Medicine at New York Presbyterian Hospital.

Dr. Weiss is board certified in medical oncology, hematology and internal medicine. He is a member of the American College of Physicians, the American Society of Clinical Oncology and the American Society of Hematology. He is widely published in journals including *Leukemia*, *Cancer*, *the Journal of Clinical Oncology*, *Blood*, the *British Journal of Hematology*, *Nature Medicine* and *Clinical Cancer Research*. He has also served as a reviewer for *Blood*, *Cancer*, *Cancer Research*, *Clinical Cancer Research*, and the *Journal of Clinical Oncology*.

Fox Chase Cancer Center Appoints Massimo Cristofanilli, MD, FACP, Chairman of the Department of Medical Oncology

Noted breast cancer clinician and researcher Massimo Cristofanilli, MD, FACP, has been appointed chairman of the Department of Medical Oncology at Fox Chase Cancer Center and will hold the G. Morris Dorrance Jr. Endowed Chair in medical oncology. He will arrive at Fox Chase in January 2010.

In addition to his position in the Department of Medical Oncology, Cristofanilli will play a vital leadership role in Fox Chase's new Women's Cancer Center, overseeing all breast cancer care, and will co-direct the Women's Cancer Program, one of Fox Chase's six core research programs within the Cancer Center. He will also serve as associate director of clinical research for Fox Chase's Cancer Center Support Grant from the National Cancer Institute.

Dr. Cristofanilli comes 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 facility in the world. The program and clinic honor Morgan Welch, one of Dr. Cristofanilli's youngest patients. Welch was diagnosed with metastatic inflammatory breast cancer at the age of 24.

"The recruitment of Dr. Cristofanilli comes at an auspicious time for Fox Chase, which recently opened its new Women's Cancer Center to provide comprehensive women's cancer-related services," says Michael V. Seiden, MD, PhD, president and CEO of Fox Chase Cancer Center. "Dr. Cristofanilli's expertise in translational research and team-based collaborative science will compliment the strong breast cancer teams already in place at Fox Chase and will dovetail nicely with our robust ovarian cancer research program."

In addition to specializing in the treatment of patients with inflammatory breast cancer—one of the rarest and most aggressive forms of breast cancer — Dr. Cristofanilli also focuses much of his attention on a broad range of translational research around the disease. His research interests include the

use of molecular targeted agents in imaging and therapeutics, the study of breast cancer stem cells, the delivery of gene therapies to local regional recurrences of breast cancer, and the utility of monitoring, capturing, and studying circulating tumor cells in the management of women with inflammatory breast cancer.

“I am determined to improve the quality of diagnostics and care of cancer patients through the development of superb translational research,” says dr. Cristofanilli. “I believe in multidisciplinary team science as the most appropriate way to achieve this goal. Fox Chase Cancer Center has a vibrant, young and enthusiastic leadership that provides the ideal environment for rapid growth in this area. I am proud to be part of this leadership team and look forward to contributing my passion, vision and expertise.”

Dr. Cristofanilli received his MD from the La Sapienza University in Rome, Italy, where he also completed a fellowship in medical oncology. After arriving in the United States, Dr. Cristofanilli completed an internship and residency in internal medicine at Cabrini Medical Center in New York. He later became a fellow in medical oncology at The University of Texas M. D. Anderson Cancer Center in Houston. Cristofanilli is board-certified by the European Society for Medical Oncology, the American Board of Medical Oncology, the American Board of Internal Medicine, and the Italian Certification in Medical Oncology.

“Dr. Cristofanilli is an enthusiastic and tireless clinician and researcher,” adds dr. Seiden. “He has an outstanding track record for building teams to execute cutting edge clinical trials designed to answer pertinent questions in the management of women with breast cancer.”

St. Christopher's Hospital for Children Appoints New Chief of Section of Hematology

Norma Lerner, MD, MPH, has been named chief of the section of Hematology and Calvin Bland Endowed Chair in Hematology and Sickle Cell Anemia at St. Christopher’s Hospital for Children.

Dr. Lerner specializes in pediatric hematology and oncologic disorders. Her areas of special expertise include sickle cell disease and clotting. Her clinical research investigations have included studies of sickle cell disease-associated cerebrovascular damage, aspirin prophylaxis, thrombosis in the intensive care setting, and newborn screening for hemoglobinopathies. She is a National Institute of Health (NIH) funded investigator.

Dr. Lerner comes to St. Christopher’s from the University of Rochester Medical Center in New York where she was a professor of pediatrics at the University of Rochester School of Medicine and Dentistry. She served as the director of the Pediatric Hemoglobinopathy Service and the Pediatric Vascular Hematology Center. She also served as medical director of the Hemoglobinopathy Genetics Service for nine county areas of upstate New York.

“Dr. Lerner has an excellent reputation within the pediatric hematology community. Her expertise and leadership, especially with sickle cell disease will continue our long tradition of excellence in managing this disease,” says Bernadette Mangan, chief executive officer.

“We are confident that Dr. Lerner will guide the Section of Hematology to continue providing excellence in clinical care, an excellent educational experience for the medical students, residents and fellows, and also grow its clinical research portfolio, ” says Daniel V. Schidlow, MD, physician-in-chief, St. Christopher’s Hospital for Children.

Dr. Lerner received her medical degree from Brown University and a master’s degree in public health from the University of Rochester. She completed her pediatric internship and residency at Boston City Hospital and Massachusetts General Hospital. She completed pediatric hematology/oncology fellowships at the Children’s Hospital of Philadelphia and the Memorial Sloan-Kettering Cancer Center in New York.

Dr. Lerner is board-certified in pediatrics and pediatric hematology/oncology. She is the author of many peer-reviewed journal articles and chapters, and has served on NIH study sections. Dr. Lerner is a member of the American Society of Hematology and the American Society of Pediatric Hematology/Oncology and serves as reviewer for several medical journals including the Journal of Pediatric Hematology/Oncology and the Journal of Pediatrics.

Penn Study Provides First Clear Idea of How Rare Bone Disease Progresses

An international team of scientists, led by researchers at the University of Pennsylvania School of Medicine, is taking the first step in developing a treatment for a rare genetic disorder called fibrodysplasia ossificans progressiva (FOP), in which the body’s skeletal muscles and soft connective tissue turns to bone, immobilizing patients over a lifetime with a second skeleton.

Reporting in the November issue of the Journal of Clinical Investigation senior authors Eileen Shore, PhD, professor of Genetics and Orthopedics, and Mary Mullins, PhD, professor of Cell and Developmental Biology, with scientists in Japan and Germany, demonstrated that the mutation that causes FOP mistakenly activates a cascade of biochemical events in soft tissues that kicks off the process of bone development. The linchpin of the cellular signaling gone awry is a receptor for a bone morphogenetic protein, or BMP.

The present study provides the first clear glimpse of how FOP might develop at a cellular level in the human body. Shore and co-author Frederick Kaplan, MD, the Nassau Professor of Orthopedic Molecular Medicine, and their research team, discovered the gene for FOP in 2006.

“If you think of BMP proteins as the hand that turns on a water faucet, the faucet, or receptor, should stay off if you never turn the handle,” Shore says. “What our experiments show is that in FOP patients the faucet is leaky, even when it is not actively turned on.” BMP receptors are protein switches that help determine the fate of stem cells in which they are expressed.

“The mutation is mildly activating, and so it may take time or the right tissue environment to allow the signal to tip the balance to induce bone formation, explains Shore. “This is a very important finding, because it can help explain why the disease progresses.” The finding that the FOP mutation changes the BMP receptor such that it is effectively on most of the time gives Shore and colleagues a target to shoot for in potentially controlling the disease.

FOP is basically a case of biology run amok. During the process of normal bone formation, a temporary cartilage structure is laid down, and then is eventually replaced by bone. In the case of FOP, that normal process of bone formation occurs inappropriately in soft tissue, sometimes in response to injury, and sometimes spontaneously, typically beginning by age 5 or so. FOP occurs in about one in 2 million individuals.

The FOP mutation is a single replacement for a DNA building block in the gene for a receptor protein called ACVR1. In 2006, Kaplan and Shore’s team discovered that in the DNA of every patient with FOP they examined, the same mutation occurred: one building block in the protein-coding region of the ACVR1 gene is replaced by another, resulting in conversion of a single arginine amino acid in the sequence of the ACVR1 protein to histidine. The question the current study addresses is, what is the consequence of that change?

In experiments by Qi Shen, a postdoctoral fellow in the Shore-Kaplan lab and Shawn Little, a PhD student in the Mullins lab, the team found, using both cultured cells and zebrafish, that the specific mutation modifies ACVR1 in such a way that it acts as if it has been signaled by BMP, even when it hasn’t. The experiments further show that the mutant ACVR1 receptor alters the usual binding of an ACVR1 partner protein, FKBP1A, which normally keeps the ACVR1 receptor off in the absence of BMP. The result is activation of a cell-signaling cascade that culminates in changes in gene expression, and ultimately, in the formation of new bone.

“FKBP1A is like the safety pin in a hand grenade,” says Kaplan. “The FOP mutation damages the hand grenade in a very specific way that the safety pin does not work. When triggered by injury, the result is explosive new bone formation.”

Mullins’ participation in the study was serendipitous, says Shore. Mullins studies BMP signaling in zebrafish, and in these animals BMP plays many roles, including establishing an organism’s basic body plan. Mullins’ long time interest was a particular gene critical to this process, called Alk8. As it turns out, Alk8 is the zebrafish equivalent of human ACVR1.

Importantly, Mullins had already established a zebrafish genetic line that fails to express Alk8. When the team inserted the gene for human ACVR1 into those fish, their normal body plan was restored. But, when they used the FOP mutation instead, the effect was one of overcompensation

“The FOP form of ACVR1 causes too much BMP expression and we get a hyper-ventralized embryo, too much cell development in the tail region of the fish,” Shore explains. “So this confirmed our cell culture studies showing the mutant ACVR1 an activating mutation.”

Colleagues at the Max Planck Institute for Molecular Genetics in Berlin, Germany, conducted additional experiments demonstrating that the FOP form of ACVR1 can also enhance cartilage cell differentiation. In the presence of the mutation, mild activation of cartilage development was observed to occur without activation by BMP like a leaky faucet, but could be additionally stimulated by BMP, the fully turned-on faucet.

People with FOP have a mostly normal skeleton and no evidence of extra-skeletal bone at birth; after birth it can be several years before the disease develops, forming extra-skeletal bone either spontaneously or as a result of trauma. The bone formation then progresses in a series of periodic episodes. The current study suggests this periodic progression may occur because the FOP mutation does not turn the ACVR1 faucet on all the way.

“These studies are a good beginning at getting a grasp on what the mutation is and how it is affecting BMP signaling in the cells,” says Shore. “But there's a lot more to be understood.”

Philadelphia International Medicine is an organization that provides medical and patient support services to international patients. It also provides continuing medical education and health care training and education to international physicians, administrators and other practitioners. PIM is owned by the Fox Chase Cancer Center, Pennsylvania Hospital, Temple University Hospital, Thomas Jefferson University Hospital and the University of Pennsylvania Medical Center. It holds affiliation agreements with the Alfred I. duPont Hospital for Children and St. Christopher's Hospital for Children. As the international department of several Philadelphia-area hospitals, international patients gain access to physicians and hospitals rated among the best in the world through one telephone call. You can reach PIM by calling 1-215-563-4733; fax, 1-215-563-2777; or e-mail, physicians@philadelphiamedicine.com. You can find out more about PIM through its Website at www.philadelphiamedicine.com.