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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.

Philadelphia International Medicine Sees Record Growth; Selects Karp President and CEO

Philadelphia – Philadelphia International Medicine (PIM) has named Leonard Karp its president and chief executive officer, topping off a year of record growth and focused direction.

Karp, who has been acting president since September, had been the organization's chief operating officer and executive vice president since PIM was formed in 1999. He takes over as PIM completes a year that saw its three service lines mark significant growth.

For instance, patient care revenue from international patients choosing Philadelphia hospitals and physicians for their medical treatment increased by 25 percent in 2007.

PIM's Institute of Education, which provides advanced management and clinical training for international hospital administrators and physicians, completed in October a successful training partnership with Albert Einstein Hospital and IMBEC University, both in Sao Paulo, Brazil.

And, PIM's consulting and management subsidiary, Philadelphia International Medicine Management & Development (PIM-MD) signed a Memorandum of Understanding with the government of Jeju Island, South Korea that grants the organization an exclusive five-year option to build an international hospital on the resort island.

"All in all, PIM is proud of its accomplishments this year," said Karp. "But, when your organization is a combination of the best hospitals, physicians and staff in the world, it becomes a little easier to attract global attention."

Philadelphia International Medicine is a partnership consisting of The Children's Hospital of Philadelphia, Fox Chase Cancer Center, Pennsylvania Hospital, Temple University Hospital, Thomas Jefferson University Hospital and the University of Pennsylvania Medical Center.

In 2008, Karp said PIM will focus on building relationships in emerging markets, reinvigorate its marketing efforts, refocus the organization to provide an increased spotlight on the hospitals and physicians, and continue to expand global opportunities for the region and its health care organizations.

Penn Researchers Discover Link Between Chronic Kidney Disease and Oxygen-Deprived Tissue; Implications for New Approaches to Kidney Dialysis

Researchers at the University of Pennsylvania School of Medicine have discovered how low-oxygen conditions can worsen chronic kidney disease (CKD). The key player is a protein called hypoxia-inducible-factor (HIF-1) that, as its name suggests, is active when the kidney does not get enough oxygen, a condition known as hypoxia. The findings appear in a December issue of the Journal of Clinical Investigation.

CKD afflicts 20 million Americans who have hypertension, atherosclerosis, diabetes, and other conditions. The kidney has less oxygen reserves than other organs to start, and CKD is associated with less capillary blood flow, reducing oxygenation even further. As CKD progresses, kidneys become full of fibrous tissue and cannot filter wastes out of blood or regulate body salt. Eventually kidney dialysis, a form of renal replacement therapy, may be needed to carry out these processes. Ultimately, the clinical goal is to optimize treatment to halt or delay the progression of CKD by better understanding its molecular underpinnings.

"Fibrosis worsens when the kidney becomes hypoxic," states lead author Volker Haase, MD, assistant professor of Medicine, Renal Electrolyte and Hypertension Division. "We found that HIF-1 is more stable when oxygen is in short supply and that HIF-1 causes kidney epithelial cells to regress to a less-differentiated cell type. This transition is driven by HIF-1, a protein that turns on many genes that promote the synthesis of fibrous connective tissue, thus interfering with the kidney's normal filtering function," says Dr. Haase.

The study was conducted using mice that had been engineered to turn off expression of HIF-1 α (a critical subunit of HIF-1) in their kidneys. One kidney from each mouse was put under oxygen stress by obstructing the ureter, and the other kidney served as a control. As long as HIF-1 α was silenced, fibrosis was reduced in the oxygen-deprived kidney. This demonstrated that HIF-1 promoted the fibrotic process under reduced oxygen conditions.

Kidney biopsies from patients with diabetes who also suffer from CKD were tested for HIF-1 α levels. Normal kidneys had almost no HIF-1 α , whereas kidneys from diabetics had moderate to high expression of HIF-1 α . "This observation, along with increased expression of the genes controlled by HIF-1 in diseased kidneys in mice, shows that HIF-1 is the molecular link between hypoxia and CKD in humans as well as rodents," says Dr. Haase.

The next step is to test other models of CKD and identify additional molecular targets of HIF-1 that can promote fibrosis. “We also hope to study the inflammatory response to hypoxia in the diseased kidney,” concludes Dr. Haase. “We already know that some pro-inflammatory proteins are stimulated by hypoxia.” Someday, it may be possible to use HIF-1 and HIF-regulated genes as molecular markers to identify those patients that are at high risk for rapid progression of CKD requiring dialysis.

Jefferson Scientists See Breast Cancer Gene Activity from Outside the Body

Researchers at Jefferson Medical College and Jefferson’s Kimmel Cancer Center in Philadelphia have used PET imaging to see hyperactive cancer genes inside breast tumors in laboratory animals, marking the first time such gene activity has been observed from outside the body. This technology might someday help physicians to detect and classify cancer, enabling them to find cancerous breast tumors as early as possible, and determine the appropriate treatment.

Reporting in the *Journal of Nuclear Medicine*, scientists led by Eric Wickstrom, PhD, and Mathew Thakur, PhD, used a DNA “probe” – a modified nuclear medicine agent – to detect the hyperactivity of CCND1, a common breast cancer gene. The gene is copied thousands of times in most breast cancer cells. The high concentration makes CCND1 copies easier to image with the genetic PET probe. The research team found a much higher concentration of the cancer gene activity in estrogen receptor-positive breast tumors in mice than in normal tissue.

“Less than one-fourth of lumps found in mammograms are really cancer,” notes Dr. Wickstrom, professor of Biochemistry and Molecular Biology at Jefferson Medical College of Thomas Jefferson University. “Our new technique will let us see what is really going on in a suspicious lump. We will see if a lump is malignant or something safe.”

“Patients with benign lumps could avoid invasive procedures if active cancer genes could be identified from outside the body,” says Dr. Thakur, professor of Radiology and Radiation Oncology at Jefferson Medical College. “Observing the cancer gene activity of a breast tumor will permit physicians to determine the best way to treat it.”

The new technique to visualize sites of cancer gene activity, which the investigators call radiohybridization imaging (RHI), might help physicians find out whether lesions found in mammograms are cancerous or non-cancerous without a biopsy. The genetic imaging agents are intended to find cancer gene activity as quickly as possible and guide the choice of therapy based on which genes are most active.

The American Cancer Society estimates that approximately 40,000 women in this country will die from breast cancer in 2007. Yet, clinical examination and mammography can miss almost half of the breast cancers in women under 40, approximately one-quarter of cancers in women ages 40 to 49 and one-fifth of cancers in women over age 50.

“When suspect lumps are discovered, biopsies are necessary to determine if the lumps are

cancerous,” Dr. Thakur points out. “However, more than three-fourths of the lumps are found to be benign. Mammography, an invaluable screening technique, sees shapes but not gene activity. Genetic PET scanning is a minimally invasive, sensitive and specific technique that might detect cancers with high efficiency in adult women and young women without breast compression.” The researchers expect that RHI will be tested in clinical trials in suspected cases of breast cancer.

Dr. Wickstrom, Dr. Thakur, and their co-workers have found that RHI works for detecting the activity of other cancer genes in other types of tumors as well. “Early detection saves lives,” Dr. Thakur says. “Several other cancers show characteristic activated genes that we might be able to use for early diagnosis, such as pancreatic cancer, prostate cancer, lymphoma, and colon cancer.” The investigators are also exploring genetic agents designed for magnetic resonance imaging and fluorescence imaging.

These experiments were supported by grants from the Department of Energy and the National Cancer Institute.

Men Unaware of Their Risk of Cancer

When Female Family Members Test Positive for Cancer-Causing Gene Mutation

Men whose mothers, sisters or daughters test positive for a cancer-causing gene mutation also have an increased risk of developing the disease but are unaware of that risk. That is the conclusion of a study at Fox Chase Cancer Center exploring how families communicate genetic test results.

Like their female relatives, fathers, sons or brothers can also harbor a mutation in the BRCA 1 or 2 genes. Male carriers of these mutations, more commonly called the “breast cancer genes,” face a 14 percent lifetime risk of developing prostate cancer as well as a 6 percent lifetime risk of developing breast cancer.

“Despite these health implications, we have found a lack of understanding of genetic test results among men in these families,” said Mary B. Daly, MD, PhD, senior vice president for population science at Fox Chase and lead author of the new research presented at the San Antonio Breast Cancer Symposium.

Dr. Daly and her colleagues interviewed 24 men, each with a first-degree female relative who tested positive for having a BRCA1 or BRCA2 mutation. The women reported telling the results of their genetic test result to the male relative in the study, though only 18 of the men remember receiving the results.

Dr. Daly said what they learned demonstrates a level of cognitive and emotional distance that men experience from the genetic testing process. Nearly half of the men (seven) who remembered receiving results did not believe that the test results increased their own risk of cancer. Only five (28 percent) could correctly identify their chance of being a mutation carrier.

“We devote a significant amount of time learning how best to communicate genetic test results to women, but this study shows we also need to help them communicate the information to their male family members who may be impacted by the test results,” concluded Dr. Daly.

Fourteen of the 18 men who recalled receiving the results expressed some level of concern about the meaning of the test result, but most (11) directed their concern toward other family members, primarily

daughters and sisters.

“Based on the responses, we were not surprised to learn that the level of interest in genetic testing was relatively low. Of the six men who did express interest, half said they’d do it for their children’s sake.”

Fox Chase Cancer Center was founded in 1904 in Philadelphia as the nation’s first cancer hospital. In 1974, Fox Chase became one of the first institutions designated as a National Cancer Institute Comprehensive Cancer Center. Fox Chase conducts basic, clinical, population and translational research; programs of cancer prevention, detection and treatment; and community outreach.

Philadelphia International Medicine is 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 to PIM. 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.