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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.

Newly Discovered Esophagus Stem Cells Grow Into Transplantable Tissue

PHILADELPHIA— Researchers at the University of Pennsylvania School of Medicine have discovered stem cells in the esophagus of mice that were able to grow into tissue-like structures and when placed into immune-deficient mice were able to form parts of an esophagus lining. The investigators report their findings online this month in the *Journal of Clinical Investigation*.

“The immediate implication is that we’ll have a better understanding of the role of these stem cells in normal biology, as well as in regenerative and cancer biology,” says senior author Anil K. Rustgi, MD, the T. Grier Miller Professor of Medicine and Genetics and chief of Gastroenterology. “In the future, we will develop a panel of markers that will define these stem cells and use them in replacement therapy for diseases like gastroesophageal reflux disease [GERD] and also to understand Barrett’s esophagus, a precursor to esophageal adenocarcinoma and how to reverse that before it becomes cancer.”

Diseases of the esophagus are very common worldwide. “Benign forms include GERD which affects millions of people,” notes Dr. Rustgi.

GERD can sometimes lead to inflammation of the esophagus, called esophagitis. “In some of these cases esophagitis can lead to a swapping of the normal lining of the esophagus

with a lining that looks more like the intestinal lining and that's called Barrett's esophagus," explains Dr. Rustgi. "This can lead to cancer of the esophagus, which is the fastest rising cancer in the US, increasing by 7 to 8 percent a year."

The researchers set out to identify and characterize potential stem cells—those with the ability to self renew—in the esophagus to understand normal biology and how injured cells may one day be repaired. First, they grew mouse esophageal cells they suspected were adult stem cells. Those cells formed colonies that self renewed. These cells then grew into esophageal lining tissue in a three-dimensional culture apparatus. "These tissue culture cells formed a mature epithelium sitting on top of the matrix," says Dr. Rustgi. "The whole construct is a form of tissue engineering."

The investigators then tested their pieces of esophageal lining in whole animals. When the tissue-engineered patches were transplanted under the skin of immunodeficient mice, the cells formed epithelial structures. Additionally, in a mouse model of injury of the esophagus in a normal mouse, which mimics what happens during acid reflux, green-stained stem cells migrated to the injured lining cells and co-labeled with the repaired cells, indicating involvement of the stem cells in tissue repair and regeneration.

Eventually the researchers will develop genetically engineered mouse models to be able to track molecular markers of esophageal stem cells found in a micorarray study. The group has already developed a library of human esophageal cell lines and is looking for human versions of markers already identified in mice.

"The ultimate goal is to identify esophageal stem cells in a patient, grow the patient's own stem cells, and inject them locally to replace diseased tissue with normal lining," says Rustgi.

Penn co-authors are Jiri Kalabis, Kenji Oyama, Takaomi Okawa, Hiroshi Nakagawa, Carmen Z. Michaylira, Douglas B. Stairs, and J. Alan Diehl (Department of Cancer Biology), as well as Jose-Luiz Figueiredo and Umar Mahmood from Massachusetts General Hospital, Molecular Center for Imaging Research, Boston, and Meenhard Herlyn, from The Wistar Institute, Philadelphia.

Newly Formed Institute to Transform How Research Becomes Patient-Relevant Practice

Four notable medical and educational institutions have formed a landmark consortium that is expected to streamline the way bench science is translated into bedside practice that could benefit millions of people. Christiana Care Health System, Nemours/Alfred I. DuPont Hospital for Children, Thomas Jefferson University and the University of Delaware will pool their talents and expertise as the Delaware Valley Institute for Clinical Translational Science (DVICTS).

The Institute will bring together the capabilities of four primary medical and educational institutions with close affiliations to three other academic institutions, 33 hospitals, over 130 research and clinical specialty centers and 14 schools and colleges. Innovative collaborations will be established between experts in medical practice, health economics and policy, population sciences, public health and policy and material and biomedical sciences. The primary goal will be not only to develop new therapies and programs but also to improve when, how and where healthcare is delivered. The DVICTS will be led by a steering committee of 12 individuals—three representatives from each of the four lead institutions.

“We’re using our strengths, sharing our data, involving the communities and eliminating the usual compartmentalized infrastructure to open the doors to new ideas,” explains Robert L. Barchi, MD, PhD, President, Thomas Jefferson University. “Our education plan is a key component—being jointly developed with our partners. We’re training a new cadre of scientists who will understand both the clinical and translational side of medicine.”

“Discoveries that could fuel groundbreaking, real-world practices are limitless,” emphasizes Robert Laskowski, MD, President and CEO, Christiana Care Health System. “The DVICTS will have a direct impact on the lives of all our patients who utilize our facilities.”

Joint projects of member institutions are already underway. Molecular genetic markers are being developed to tailor and individualize cancer therapy and research is being carried out on the use and applications of proton beam therapy (housed at Jefferson) for cancer treatment. A biomathematics initiative is investigating the movement of fluid in bone tissue—an innovation that could revolutionize orthopedics. Medical informatics is giving patients a way to save all of their medical records on a single microchip. New devices such as a robotic exoskeleton will give individuals with limited movement freedom from their disabling conditions.

One of the goals of the DVICTS is to acquire new grants that could collectively fund greater research discoveries. “This is team science and team medicine,” says Patrick T. Harker PhD, President, University of Delaware, “that most certainly will have national and international

implications. This institute will combine the best doctors and researchers at these leading medical institutions with the University's researchers and scientists across a broad range of disciplines. What we can do together could change the practice of medicine."

Lower-dose Fractionated Stereotactic Radiotherapy for Acoustic Neuromas Results in Better Hearing Preservation

Researchers at Thomas Jefferson University have found that a lower dose of fractionated stereotactic radiotherapy for acoustic neuromas results in better hearing preservation and has the same tumor local control rate as a higher dose of therapy. The study appeared online in the *International Journal of Radiation Oncology*.

"We previously had not determined the optimal dose of fractionated stereotactic radiotherapy for acoustic neuromas," said David W. Andrews, MD, professor and vice-chairman of the Department of Neurological Surgery at Jefferson Medical College of Thomas Jefferson University, and the lead author. "This study was designed to compare the hearing preservation between the two doses. The lower-dose treatment resulted in a 100 percent tumor control rate, with the advantage of better hearing preservation."

Between 1994 and 2007, 101 patients with serviceable hearing were treated at Jefferson with fractionated stereotactic radiotherapy (FSR). Dr. Andrews and colleagues analyzed 89 patients within that cohort who had complete audiometric data available. Forty-three patients had received the high-dose of 50.4 Gy. Forty-six patients received the low-dose of 46.8 Gy.

The tumor local control rates were 100% for both the lower-dose cohort and the higher-dose cohort. The pure tone average was 33 decibels (dB) in the lower-dose cohort, which was significantly better than the 40 dB pure tone average in the high-dose cohort. The actuarial hearing preservation rate was also longer in the lower-dose cohort: 165 weeks vs. 79 weeks.

"This is a potentially practice-changing finding," Dr. Andrews said. "We are now working to design a study to directly compare FSR with other treatment options, including stereotactic single fraction radiosurgery."

According to Dr. Andrews, the tumor control rates for FSR are comparable to those of stereotactic single fraction radiosurgery, another treatment option for acoustic neuromas. But Dr.

Andrews and colleagues found in a previous study that FSR preserves hearing better, and does not cause trigeminal or facial neuropathies.

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