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 Researchers Find New Method of Fixing Broken Proteins to Treat Genetic Diseases

Philadelphia— Researchers at Fox Chase Cancer Center have demonstrated the possibility to treat genetic diseases by enhancing the natural ability of cells to restore their own mutant proteins. In particular, they found that drugs called proteosome inhibitors could provide one way of manipulating cells into producing more of a so-called chaperone protein, named Hsp70, which helps amino acid chains fold into their proper protein form.

Their latest findings, presented in the journal *PLoS Genetics*, expand their previous research from yeast models of disease to human cell cultures and animal models. According to the researchers, if this approach works in humans, it could be a way to turn certain debilitating – or even fatal – genetic diseases into more treatable, chronic conditions.

"Hsp70 pulls misfolded mutant proteins apart like twisted rubber bands and allows them to snap back into place. Eventually a significant percentage of these proteins will snap back into something approaching a functional shape," Warren Kruger, PhD, leader of the study and professor in Fox Chase's Cancer Biology program. "If this can be done in humans, it could represent a way of reducing the severity – or perhaps correcting – certain hereditary diseases, even some familial cancers."

Genetic diseases are often caused by a specific type of genetic alteration called a missense mutation that makes cells add an incorrect amino acid into the protein chain. Since the shape of a protein depends on the specific arrangement of amino acids, even a single error amid a gene's very long stretch of DNA can cause the gene's protein product to become misshapen. Kruger and his colleagues studied ways to reverse the functional effects of missense mutations for three genetic diseases: two severe inherited metabolic disorders (CBS deficiency and MTHFR deficiency) and one inherited cancer syndrome (Li-Fraumeini).

In each case, the Fox Chase researchers found that it was possible to restore the function of the mutant proteins by tricking the cell into increasing levels of Hsp70. "We have shown that the more

opportunities we give Hsp70 proteins to try to fix mutants, the more likely it is that they will succeed," Dr. Kruger says.

While this approach has yet to be applied to clinical medicine, there are several drugs that are known to induce Hsp70 in humans. Dr. Kruger found that treating yeast and mammalian cells with a drug called bortezomib elevated the amount of available Hsp70 and rescued mutant proteins. Bortezomib is a member of a class of drugs called proteasome inhibitors, which decreases the effectiveness of enzymes that cells use to dispose of non-functioning proteins. Bortezemib (known under the brand name Velcade) is currently used to treat patients with multiple myeloma.

"We found that bortezomib can stabilize and restore mutants by tripling the amount of available Hsp70," Dr. Kruger says. "While we do not yet know the entire mechanism, we do know that bortezomib doesn't rescue mutants in cells that lack the gene for Hsp70."

Dr. Kruger and his colleagues are currently studying how to best adapt these findings to human disease.

"Of course, the big question we need to answer is one of safety – what are the long term effects of sustained Hsp70 elevation?" Kruger says. "The answer may be very disease-specific; one of how many mutant proteins must be restored to reduce the severity of a given genetic disease."

FDA Clears Penn Medicine's Trans Oral Robotic Surgery for Tumors of Mouth, Throat and Voice Box

A minimally invasive surgical approach developed by head and neck surgeons at the University of Pennsylvania School of Medicine has been cleared by the U.S. Food and Drug Administration (FDA). The da Vinci Surgical System has been cleared for TransOral otolaryngologic surgical procedures to treat benign tumors and select malignant tumors in adults.

Drs. Gregory S. Weinstein and Bert W. O'Malley Jr. of the University of Pennsylvania School of Medicine's Department of Otorhinolaryngology: Head and Neck Surgery founded the world's first TransOral Robotic Surgery (TORS) program at Penn Medicine in 2004, where they developed and researched the TORS approach for a variety of robotic surgical neck approaches for both malignant and benign tumors of the mouth, voice box, tonsil, tongue and other parts of the throat. Since 2005, approximately 350 Penn patients have participated in the world's first prospective clinical trials of TORS. These research trials compromise the largest and most comprehensive studies of the technology on record.

"TORS has dramatically improved the way we treat head and neck cancer patients, completely removing tumors while preserving speech, swallowing, and other key quality of life issues," said Bert O'Malley, Jr., MD, professor and chairman of Penn Medicine's Department of Otorhinolaryngology:

Head and Neck Surgery. “It is very exciting that a concept conceived at PENN, evaluated in pre-clinical experimental models at PENN, tested in clinical trials at PENN, and then taught to key surgeons and institutions both within the U.S. and internationally has been officially recognized by our federal governing agencies and peers around the world as a new and improved therapy for select neck cancers and all benign tumors.”

45,000 Americans and approximately 500,000 people worldwide are diagnosed with head and neck cancers each year. Head and neck tumor treatments often involve a combination of surgery, radiation therapy, and chemotherapy. In many cases, surgery offers the greatest chance of cure; yet conventional surgery may require an almost ear-to-ear incision across the throat or splitting the jaw, resulting in speech and swallowing deficits for patients. In comparison, the minimally invasive TORS approach, which accesses the surgical site through the mouth, has been shown to improve long term swallowing function and reduce risk of infection while speeding up the recovery time. Compared to traditional surgeries, patients have experienced a higher quality of life and shorter hospital stays. TORS outcomes are markedly improved when compared to standard chemotherapy, radiation or traditional open surgical approaches for oropharyngeal cancer.

“Based on our data and patient outcomes, coupled with the national and international enthusiasm and interest for TORS, we are changing the way oropharyngeal cancer and tumors will be treated now and in years to come,” noted Gregory Weinstein, MD, FACS, professor and vice chair of the University of Pennsylvania School of Medicine’s Department of Otorhinolaryngology: Head and Neck Surgery, director of the Division of Head and Neck Surgery and current president of The Society of Robotic Surgery. “We are already investigating new TORS treatments for other conditions such as sleep apnea, and collaborating with colleagues in Penn Neurosurgery to use TORS to remove skull base tumors and repair cervical spine disease.”

The Penn TORS program developed an international training program that has trained numerous surgical teams from 12 different countries, many of whom have started establishing TORS programs at their respective institutions. With the FDA clearance of the da Vinci System for transoral otolaryngology, Penn Medicine will immediately expand its well established training program to include surgical teams from the United States.

Drs. Weinstein and O’Malley have no financial ties or consulting agreement with the surgical company.

Christopher C. Dodson, MD, Joins Thomas Jefferson University Hospital’s Rothman Institute

Orthopedic Surgeon Christopher C. Dodson, MD, has joined the Rothman Institute at Jefferson. He has also been named an assistant professor of orthopedic surgery at Jefferson Medical College of

Thomas Jefferson University and joins the faculty after a fellowship in Sports Medicine and Shoulder Services at the Hospital for Special Surgery in New York.

Prior to joining Jefferson, Dr. Dodson served as a clinical associate in orthopedic surgery at Weill Medical College of Cornell University while completing his residency at the Hospital for Special Surgery.

Board certified in orthopedic surgery, Dr. Dodson will be specializing in shoulder, knee and elbow repairs including: rotator cuff tears, ACL reconstructions, shoulder injuries in young athletes and Tommy John ligament surgeries. Dr. Dodson's research has focused on joint repair and reconstruction. He is currently conducting a study on shoulder instability.

Over his career Dr. Dodson has published numerous articles, book chapters and abstracts, presented at several national conferences and serves as an editorial reviewer for *Clinical Orthopedics* and *Related Research*, *American Journal of Sports Medicine* and the *Hospital for Special Surgery Journal*.

Sports Medicine and orthopedics were a natural fit for Dr. Dodson. He was a star athlete, winning two Ivy League championships with the Brown University Men's Varsity Soccer Team. He remained active in sports medicine after his playing days were over, serving as an assistant to the team physician for the New York Mets baseball team, assistant physician to the players at the US Open tennis tournament, and as the current head team physician for Bensalem High School.

Dr. Dodson is a member of the American Academy of Orthopedic Surgeons and the American Orthopedic Society for Sports Medicine.

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