A recent laboratory study at The Ohio State University Comprehensive Cancer Center (OSUCCC) suggests that a new compound has potential value as a novel therapy for pancreatic cancer.

The compound, a derivative of celecoxib identified as OSU-03012, works by inhibiting activation of the Akt cellular pathway, which is involved in the development of pancreatic cancer.

Ching-Shih Chen, Ph.D., professor of pharmacy and OSUCCC researcher, developed the compound. Chen specializes in exploring signaling pathways that govern cancer cell survival as targets for drug discovery and design.

Investigators found that the agent caused a decrease in cellular proliferation in cultured human pancreatic cancer cell lines, says Dr. Peter Muscarella, co-author of the study and assistant professor of surgery in the Division of General Surgery.

The findings were published in the Feb. issue of the Journal of Gastrointestinal Surgery.

Muscarella says investigators are examining novel molecular targets for therapy because of the high mortality rate of pancreatic cancer patients.

“Pancreatic cancer has almost a 100 percent mortality,” he says. “The only survivors are those who are candidates for surgical resection, which is probably 10 to 20 percent of patients. Even with surgical resection and chemotherapy, the average survival is only 12 to 15 months.”

However, understanding of the processes involved in pancreatic tumor growth is growing, he says. “In the last 10 years, we’ve gained a significant understanding of the molecular events in pancreatic tumorigenesis. The Akt pathway is a complex intracellular pathway that is known to be involved in the development of many tumor types. Activation of the Akt signaling pathway is found in human pancreatic tumor specimens.

“Because Akt activation is commonly seen in pancreatic cancer development, we hypothesized that inhibition of the Akt pathway using this novel agent might be associated with decreased pancreatic cancer cell growth.”

In the study, the researchers cultured pancreatic cancer cell lines in media containing known concentrations of OSU-03012. They then compared cell proliferation of the pancreatic cancer cell lines in treated and untreated groups.

“We found that treatment with OSU-03012 induces a decrease in cellular proliferation, as opposed to the control group of cancer cells,” Muscarella says. “When we looked at the Akt pathway in the treated cells, we found that the decreased cell growth was also associated with an inhibition of Akt activation. So this confirmed our hypothesis that inhibition of this pathway could decrease pancreatic cancer cell growth.”

He says the findings of the study support further studies of the new compound. “We’re planning on evaluating the treatment in mouse xenografts within the next year, and if the inhibition is found to occur in animal models, we will likely develop a phase 1 trial here at the OSU Comprehensive Cancer Center.”

A phase 1 trial marks the first time a treatment is tried in human subjects.

The OSUCCC has a number of clinical trials open to patients with pancreatic cancer who are willing to try experimental therapies, he says.

Each year, about 30,000 Americans are diagnosed with pancreatic cancer, and almost as many die of the disease. ✤
LABORATORY OF MOLECULAR MEDICINE

Research suggests natural form of vitamin E protects against stroke

Recent research conducted in The Ohio State University Laboratory of Molecular Medicine suggests that a natural form of vitamin E protects against stroke and related damage to the brain and could be delivered orally to the people most at risk for certain neurological disorders.

The form of vitamin E examined in two studies, called tocotrienol (TCT), occurs naturally in palm oil. The oil is a common component of the typical diet of Southeast Asians, who tend to suffer fewer neurological disorders than Westerners.

One study identified the efficacy of TCT in minimizing stroke-related damage to the brain. The findings were published in the Oct. 2005 issue of Stroke. The other study investigated the transport of TCT to vital organs in the body. The findings were published in the Nov. 15, 2005 issue of Free Radical Biology and Medicine.

The primary vitamin E on drugstore shelves is another variety called tocopherol (TCP). Vitamin E occurs naturally in eight different forms. TCT, while not abundant in the American diet, can be found as a nutritional supplement in American health food stores, though not as commonly as TCP.

“One of the most striking features of these findings is that this neuroprotective property is seen in a nutrient known to be safe for human consumption,” says Chandan K. Sen, Ph.D., the principal investigator for the research.

In the studies, the scientists compared the responses of hypertensive rats to TCT supplementation. One set of rats received moderate oral doses of TCT for 13 weeks before stroke was induced, and another group did not receive TCT. The group of rats that received TCT experienced significantly less stroke injury than the rats that did not receive the supplement.

“This suggests that the TCT form of natural vitamin E can be part of a regular diet to keep the brain enriched and more prepared to defend itself, particularly for people at a high risk for stroke,” says Sen, professor and vice chairman of surgery and deputy director of the Davis Heart and Lung Research Institute at Ohio State.

The scientists also separately observed that the neuroprotective abilities of TCT were more effective than the more common TCP.

In a parallel set of studies, researchers examined whether TCT could be taken by mouth and reach the brain and other vital organs effectively. They discovered that TCT can be taken orally and is carried to vital organs of the body by a mechanism independent of the currently known pathways involving tocopherol transfer protein (TTP). Oral TCT was efficiently transported to the organs of mice deficient in the TTP gene.

The same kind of defect in the TTP gene in humans causes a neurological disorder called ataxia, which interferes with muscle coordination and is associated with problems in speech, reflexes, and sensory function.

“Based on our findings that oral TCT may be transported to vital organs in the absence of TTP, it is important to test whether TCT benefits people suffering from defects in the TTP gene,” Sen says.

TCT restored fertility in TTP-deficient mice, which were infertile because of TCP deficiencies, suggesting that TCT reached relevant tissues and supported reproductive function.

The National Institutes of Health supported the research. Sen and his colleagues are currently planning a human study of TCT.

Sen co-authored the studies with colleagues in the laboratory of molecular medicine and in the departments of surgery, neurology, psychology, and internal medicine.
A recent clinical study at The Ohio State University Medical Center indicates that the immune-stimulating hormone known as interleukin-12 (IL-12) can be safely administered with interferon, another biologic drug, as an experimental therapy for some cancers.

Normally, interferon is used alone to stimulate the immune system to attack certain cancers. This strategy, a form of immunotherapy, is used to treat melanoma, advanced kidney cancer, and other tumors that respond poorly to chemotherapy or radiation therapy. But interferon can have serious side effects that limit its use.

In the study, a phase 1 clinical trial, using the two drugs in sequence caused no serious side effects in patients.

A phase 1 trial marks the first time a treatment is tried in human subjects. “Interferon can be quite toxic when used alone,” says Dr. William E. Carson III, principal investigator for the study. “We were initially concerned that the addition of IL-12 might increase that toxicity. Instead, we found that the two drugs can be used together without additional side effects.”

The findings were published in the Dec. 1, 2005 issue of the Journal of Clinical Oncology. They suggest that IL-12 primes white blood cells, so that a lower dose of interferon will stimulate the same level of immune activity as a higher dose of interferon when used alone.

The trial was conducted by Carson and a team of colleagues, including Dr. Michael J. Walker, associate professor of surgery in the Division of Surgical Oncology, who was also involved in developing the study.

The study involved 49 patients ages 23 to 84 with different types of advanced cancer, including melanoma and cancers of the colon, lung, kidney, and bladder.

On the first day of treatment, patients were given IL-12, initially by injection and then intravenously. Over the next five days, patients received injections of interferon. Patients received, on average, five such cycles over the course of the study.

The drug combination not only proved to be safe, which was the purpose of the study, but also stopped disease progression in five of the patients for at least six months. “Our findings were encouraging,” says Carson, associate professor of surgery in the Division of Surgical Oncology and associate director for clinical research at The Ohio State University Comprehensive Cancer Center. “They indicate that we can safely administer IL-12 in combination with interferon, that it enhances the action of interferon in some patients with advanced cancer, and that it can be an effective way to stimulate the immune system.”

Based on the study’s results, and the results of earlier animal studies led by the research group, Carson and his colleagues are conducting a national phase 2 clinical trial of the two drugs in patients with melanoma. Phase 2 trials are the first step in determining the effectiveness of a new therapy against a specific disease.

“We hope that the IL-12 will allow us to use lower doses of interferon in patients, which should result in fewer side effects and potentially a longer use of interferon, giving the immune system more time to fight the tumor.”
**CARDIOTHORACIC SURGERY**

**Specialists perform rare “domino” heart transplant operation**

Historic procedure involves youngest living heart donor, youngest heart recipient

Faculty of The Ohio State University Department of Surgery in January performed a rare “domino” heart transplant at Columbus Children’s Hospital, in an historic procedure involving the youngest living heart donor and the youngest heart recipient.

In a domino transplant, one patient undergoes heart-lung transplantation, receiving a new heart and lungs. The patient’s original heart is then given to a second heart-transplant recipient.

The procedure is made possible when the heart-lung recipient suffers from a primary pulmonary disease but has a functionally normal or near-normal heart.

For the recipient of the “domino” heart, the operation may be the only opportunity to receive a donor heart.

In the 12-hour procedure at Children’s Hospital, a four-month-old boy suffering from primary pulmonary hypertension and needing a new pair of lungs received a combined heart and double-lung transplant from a deceased out-of-state donor. Dr. Mark E. Galantowicz, associate professor of surgery in the Division of Cardiothoracic Surgery at Ohio State, operated on the four-month-old patient.

A heart-lung transplant was performed on the boy because at his age and size, the procedure presented a lower risk of airway complications, compared with a sequential double-lung transplant.

In turn, the boy’s healthy heart was donated to a 12-week-old girl suffering from congenital heart disease. Dr. J. Terrance Davis, professor of clinical surgery in the division, and Dr. Alistair B. M. Phillips, assistant professor of clinical surgery in the division, transplanted the “domino” heart into the 12-week-old patient.

As this newsletter went to press, both patients were progressing well, and the four-month-old patient had been discharged from the cardiac intensive care unit to the cardiac inpatient care unit, Children’s Hospital reported.

Davis has been a faculty member at Ohio State for 15 years. At Children’s Hospital, he has served since 1997 as chief surgical officer and administrative surgical director.

Galantowicz has been a faculty member at Ohio State since 2002. He is chief of cardiothoracic surgery, director of cardiopulmonary transplantation, and co-director of the heart center at Children’s Hospital.

Phillips joined the faculty at Ohio State in February, following a fellowship in pediatric cardiac surgery at Columbia University Medical Center, in New York, N.Y. He received his medical degree at Columbia University and completed his general and cardiothoracic surgery training at New York-Presbyterian Hospital and Weill Cornell Medical Center, in New York, N.Y.

The domino heart transplant at Children’s Hospital was the first such procedure performed in the United States since 1996, in any age group. Only 12 infant heart-lung transplants have been performed in the United States.
Eighteen Surgery faculty members included on Best Doctors list

Referral service asks physicians who they would go to for treatment in their clinical specialty

Eighteen faculty members in the Department of Surgery, about 25 percent of the department’s full-time faculty, were included on the Best Doctors in America list for 2005.

Best Doctors in America, an independent physician referral service that selects doctors through peer review, is considered one of the more credible guides for health-care consumers selecting a physician. The service asks physicians who they would go to for treatment in their specialty. Only physicians who earn the consensus support of their peers are included on the list.

Only 33,000 physicians in the United States, about four percent of all U.S. doctors, are listed as outstanding physicians by Best Doctors.

Dr. E. Christopher Ellison, the Robert M. Zollinger professor and chairman of surgery, associate vice president for health sciences, and vice dean of clinical affairs, says “The inclusion of so many Department of Surgery physicians on the list is a reflection of the outstanding clinical care they provide.”

Department of Surgery faculty members included on the list are:

- Dr. Mark W. Arnold, professor of clinical surgery in the Division of General Surgery.
- Dr. Robert R. Bahnson, the Dave Longaberger professor of surgery and chief of the Division of Urology.
- Dr. Ginny L. Bumgardner, professor of surgery in the Division of Transplantation.
- Dr. Donna A. Caniano, the H. William Clatworthy Jr. professor of surgery and chief of the Division of Pediatric Surgery.
- Dr. William E. Carson III, associate professor of surgery in the Division of Surgical Oncology.
- Dr. J. Terrance Davis, professor of clinical surgery in the Division of Cardiothoracic Surgery.
- Dr. E. Christopher Ellison, the Robert M. Zollinger professor and chairman of surgery.
- Dr. William B. Farrar, professor of surgery and chief of the Division of Surgical Oncology.
- Dr. Ronald M. Ferguson, professor of surgery and executive director of the Comprehensive Transplant Center.
- Dr. Mark E. Galantowicz, associate professor of surgery in the Division of Cardiothoracic Surgery.
- Dr. William B. Farrar, professor of surgery and chief of the Division of Transplantation.
- Dr. Gerard S. Kakos, clinical associate professor of surgery in the Division of Cardiothoracic Surgery.
- Dr. Denis R. King, clinical associate professor of surgery in the Division of Pediatric Surgery.
- Dr. Stephen A. Koff, professor of surgery in the Division of Urology.
- Dr. W. Scott Melvin, professor of surgery, chief of the Division of General Surgery, and director of the Center for Minimally Invasive Surgery.
- Dr. Robert L. Ruberg, professor of surgery in the Division of Plastic Surgery.
- Dr. William L. Smead, associate professor of surgery in the Division of General Vascular Surgery.
- Dr. Steven Teich, clinical assistant professor of surgery in the Division of Pediatric Surgery.
Clinical specialists, research scientist join Surgery faculty

A general surgeon, a pediatric cardiothoracic surgeon, and a research scientist in general vascular surgery recently joined The Ohio State University Department of Surgery faculty.

Dr. Sidney F. Miller, previously professor of surgery at Wright State University and director of the regional adult burn center at Miami Valley Hospital, in Dayton, Ohio, on Feb. 1 was appointed professor of surgery in the Division of General Surgery and director of the burn center at The Ohio State University Medical Center.

A diplomate of the American Board of Surgery and a fellow of the American College of Surgeons, Miller is an active clinician, educator, and researcher, with a specialty interest in burns and a research interest in wound healing.

He is a member of many national and regional professional societies, including the American Burn Association, the American Trauma Society, and the American Association for the Surgery of Trauma. He is a past president of the Ohio Chapter of the American College of Surgeons and the Dayton Surgical Society.

Miller has written or co-written 85 refereed publications and five book chapters. He serves on the editorial boards of the Journal of Burns and the Journal of Burn Care and Rehabilitation and as a reviewer for the Journal of Surgical Research.

Miller received his undergraduate and medical degrees at Indiana University and completed his residency at Miami Valley Hospital.

Following his training, he served at the U.S. Air Force Hospital at Mather Air Force Base, near Sacramento, Calif., where he was named chief of surgical services.

In 1975, Miller joined the surgery faculty at Wright State. During 30 years there, he served as director of postgraduate and continuing education and as acting chairman of the department of surgery.

At Miami Valley Hospital, Miller was director of the regional adult burn center, medical director of the biosciences center, and associate director of education in the department of surgery.

Dr. Alistair B. M. Phillips, previously a fellow in pediatric cardiac surgery at Columbia University Medical Center, in New York, N.Y., on Feb. 1 was named assistant professor of clinical surgery in the Division of Cardiothoracic Surgery.

A surgeon with a specialty interest in pediatric cardiothoracic surgery, Phillips is certified by the American Board of Surgery and the American Board of Thoracic Surgery. He has written or co-written nine scholarly publications.

Phillips received his medical degree at Columbia University and completed his general and cardiothoracic surgery training at New York-Presbyterian Hospital and Weill Cornell Medical Center, in New York, N.Y.

He received a bachelor of science degree in biomedical engineering with honors at Johns Hopkins University, in Baltimore.

Pedram Ghafourifar, Ph.D., previously associate professor of pharmacology and physiology at Marshall University, in Huntington, W. Va., on Jan. 15 was appointed research associate professor of surgery and director of basic science research in the Division of General Vascular Surgery. He was also named associate investigator in the Davis Heart and Lung Research Institute.

A research scientist specializing in vascular biology and cardiovascular disease, Ghafourifar is a member of two National Institutes of Health study sections: one on mitochondria and neurodegeneration and another on neurodegeneration, neuroinflammation, oxidant stress, and mitochondria.

He serves on the editorial boards of the journal Antioxidants and Redox Signaling and the journal Rejuvenation Research and is an ad hoc reviewer for more than a dozen other journals.

Ghafourifar received doctoral degrees in pharmacy and pharmacology at Tehran University, in Tehran, Iran. He was a postdoctoral fellow at the Swiss Federal Institute of Technology, in Zurich. ✤
**MMSP CORNER**

**Dr. Michael Go**

Dr. Michael Go, chief resident in the Division of General Surgery, completed the Department of Surgery’s Master of Medical Science Program (MMSP) in 2004, and he says this achievement has set him apart in important ways.

“The master’s degree, along with my publications, is another tangible piece of evidence of my productivity during my research time,” Go says. “I only fully appreciated this two years after the fact, when that degree would surface during all of my fellowship interviews and set me apart from others.

“The Master of Medical Science Program was a profitable experience in several ways. Although I have been involved in clinical and basic science research projects throughout my medical career, my formal research education had mostly been ‘on the job.’ The MMSP offered an opportunity for me to formally study research methods in a systematic fashion. In doing so, I recognized what has made me successful in my research efforts in the past, and also what I could do to improve the quality of my science and writing.

“Similarly, I was able to take a formal biostatistics course, again empowering me with the full use and understanding of statistical tools that I have used for years, but perhaps without maximal efficiency.

“I believe that other useful course work, for example a series on grant writing, exists that others may want to explore to enrich their research experience.

“Overall, the MMSP is a nice asset of our residency that can be as flexible and useful as each individual makes it.”

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**GRANTS**


**PRESENTATIONS**


Pakistan Cardiac Society, 17th Biennial Congress, National Institute of Cardiovascular Diseases, Karachi, Pakistan, Dec. 16–18, 2005.

**IN THE NEWS**

Dr. Donna A. Caniano, the H. William Clatworthy Jr. professor and chief of the Division of Pediatric Surgery, was listed in the Jan. 13 issue of the Columbus Dispatch as a recipient of a YWCA Women of Achievement award. Caniano was one of six among 37 nominees who received the honor April 5. A former director of the medical humanities program at Ohio State, she was recognized for expanding the curriculum to include cultural diversity, disability, and gender issues.

Dr. E. Christopher Ellison, the Robert M. Zollinger professor and chairman of surgery, associate vice president for health sciences, and vice dean of clinical affairs, and Dr. Vipul R. Patel, associate professor of surgery and director of robotics and minimally invasive surgery in the Division of Urology, were quoted in the Dec. 2005 issue of Columbus Monthly, in a story about the transformation of University Medical Center by Dr. Fred Sanfilippo, senior vice president and executive dean for health sciences and CEO of the Medical Center.

Dr. Bradley J. Needleman, assistant professor of surgery in the Division of General Surgery and director of the bariatric surgery program at University Medical Center, was quoted Dec. 16, 2005, by the Columbus Dispatch, in a story about a patient who had bariatric surgery at the Medical Center.

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Changes of Address
Please address correspondence about changes of address to the editor.
INSIDE:

1 Study suggests new compound may inhibit pancreatic cancer growth

2 Research suggests natural form of vitamin E protects against stroke

3 Recent study shows combination of biologic drugs safe

4 Specialists perform rare “domino” heart transplant operation

Dr. J. Terrance Davis (right), professor of clinical surgery in the Division of Cardiothoracic Surgery, and Dr. Alistair B. M. Phillips (center), assistant professor of clinical surgery in the division, remove the defective heart of a 12-week-old patient during a rare “domino” transplant procedure at Columbus Children’s Hospital. See story on page 4. Photo courtesy of Columbus Children’s Hospital.