Targeting the most-feared killer: research into the next generation of cancer treatment. See page 1.
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PUTTING THE BRAKES ON CANCER CELL SPREAD

Dr. Kam Yeung, associate professor in the Department of Biochemistry and Cancer Biology, is studying a protein called RAF kinase inhibitory protein (RKIP), which shows promise in slowing the growth and spread of cancers throughout the body.

Unlike normal cells, which continue to grow only when the environment is favorable, cancer cells don’t listen to the body’s commands. Instead, they grow out of control as a consequence of losing a tumor suppressor gene or because of an oncogene mutation, outgrowing the confines of surrounding cells and invading adjacent tissues. Eventually, such cancer cells enter the bloodstream and travel throughout the body, setting up widespread colonies of tumor cells that continue to grow. This process is called metastasis.

Dr. Yeung has spent the last decade studying RKIP, a protein that has been effective in suppressing cancer metastasis in breast and prostate cancers. He explains that RKIP acts on the RAF pathway similar to the way a brake system works on a car, slowing the progress of these cancers by halting their movement through the body. RKIP, first discovered in 1999 by Dr. Yeung and an international group of affiliated researchers, promotes apoptosis, the suicidal program in cells that causes them to die rather than to grow and migrate.

Dr. Yeung’s research is now focused on learning more about RKIP and how it functions on the molecular level. RKIP’s involvement in the central RAF pathway is of particular concern, since gain-of-function mutations in this pathway are often found in cancer cells. One study found that over 60 percent of patients with melanoma (a cancer of pigment cells in the skin) have a mutation in B-RAF in their tumors, and in studies with animal models, RKIP was found to inhibit this pathway and reduce the spread of tumors in melanoma patients.

In addition to its role in stopping cancer metastasis, RKIP has also been shown to be an effective biomarker in cancer patients. Cancer patients with low expression of the protein early in the course of their disease have a greater chance of their cancers metastasizing, making RKIP an effective predictor of survival rates. Numerous opportunities exist for translational research involving RKIP as researchers try to determine how the protein down-regulates metastasis. Further studies will address the question of how RKIP could be made to work more or less efficiently, producing information that could be harnessed for the development of new therapeutic methods.

Cancer cells can also be pathfinders; they can change shape to move around obstacles.
While Dr. Yeung’s research is focused on one protein that can stop tumor growth, another UT researcher, Dr. Kathryn Eisenmann, is researching a different aspect of cancer growth and movement.

For the past two years, Dr. Eisenmann, assistant professor in the Department of Biochemistry and Cancer Biology, has been researching properties of tumor cell known as plasticity (ability to change) and amoeboid motility. Cancer cells were once thought to be path creators, spreading through the body by using enzymes to generate their own paths through tissues. However, Dr. Eisenmann has discovered that cancer cells can also be pathfinders; they can change shape to move around obstacles. These cells can adapt their structural cytoskeletons to use amoeboid motility when it is advantageous for their spread. This plasticity, or ability to change shape and change the way these cancer cells move, shows that these cells are “smarter” than researchers initially believed.

When Dr. Eisenmann first discovered this adaptive movement ability of cells, she mistakenly believed that the cells were dying through apoptosis. Generally, cell movement involves filopodia: sticky fingers that cells grow and use to grip and move. However, when she blocked the ability of cells to move in this way, the filopodia appeared to be swallowed by blebs, or small protrusive bubbles, and drawn back into the cell. The process looked much like the process of apoptotic cell death. However, she also noticed that the cells were not dying as they typically would. Instead, they were changing shape and moving, thus demonstrating plasticity, or adaptability. She found this adapted ability to move to be present in melanomas as well as breast, prostate and some hepatic cancers.

In past clinical studies, researchers had sought to turn off proteins that allow cancer cells to use protease enzymes to create paths, with disappointing results. When Dr. Eisenmann inhibited the cells’ ability to degrade tissue with protease enzymes, she found that they simply changed the way they moved. This ability of cancer cells to adapt is likely the reason for the clinical failure of treatments based on stopping enzyme-based movement, without addressing the amoeboid movement. This discovery makes the treatment of cancer more complicated than previously imagined. Because the tumor cells are able to change the way they move, therapeutic treatments must be able to target both types of cell movement in order to fight cancer on multiple fronts.

Today, Dr. Eisenmann’s lab is focused on determining which biochemical pathways drive tumor cell plasticity and how these changes affect the way certain types of cancers invade tissues. Amoeboid motility, which is the way white blood cells move, requires less energy. Therefore, amoeboid movement might be responsible for more localized spread of breast cancers—for instance to adjacent lymph nodes—rather than for distant metastases resulting from cancer cells traveling throughout the body. Determining whether cancer cells demonstrate preferences for each type of cell movement may help us to understand how certain cancers metastasize. Dr. Eisenmann’s findings in the current studies will likely impact cancer treatment worldwide.

By finding innovative ways to halt the growth and spread of cancers, Drs. Yeung and Eisenmann contribute to the excellent research and patient care initiatives that create a higher degree of healing at UTMC.
RESEARCHER TARGETS LUNG CANCER DIAGNOSIS THROUGH SUSCEPTIBLE GENES

Chances are, those who smoke have heard it more times than they can count:
"If you don’t quit, you’ll get lung cancer."

The well-intentioned advisors might be surprised at what statistics reveal.

"About 10 to 15 percent of heavy smokers will eventually develop lung cancer. It is widely believed that a genetic component is the reason why a certain group of smokers develops lung cancer," said Dr. James Willey, professor of medicine and pathology. "While this rate may be surprising, it is at least 10 times the rate among non-smokers."

Willey strongly advocates against tobacco use. As a researcher whose career has been devoted to treating patients with serious pulmonary diseases, he articulates the ills of smoking clearly, from cancer, to heart disease, to pulmonary disease.

However, he believes that more can be done to reduce lung cancer deaths than simply advocating against smoking. For example, among the approximately 160,000 people killed annually by lung cancer in the United States alone, more than half are ex-smokers.

"Finding a way to identify individuals at greatest risk will enable closer and more effective monitoring to detect lung cancer early, when it is most curable," Willey said, noting his current research aims to do just that and may eventually contribute to better diagnostic and treatment methodologies not only for those expected to develop the disease from smoking, but also for the 10-20 percent of lung cancer victims who were never smokers.

In preliminary studies, Willey’s team at UT has already identified a test comprising a panel of 15 "protective" genes significantly associated with the likelihood of lung cancer diagnoses.

The team is in the midst of enrolling 785 subjects in a $1.6 million study funded by the National Cancer Institute to confirm the utility of this test. The goal is to determine whether the test will accurately predict which of the subjects will develop cancer.

"We all have certain protective genes that are designed to shield the lungs from damage caused by cigarette smoke and environmental toxins," Willey said. "Our belief is that this study will identify people who are predisposed because they are born with less robust protection mechanisms in the airway epithelium, which is where lungs cancers occur."

One group of genes protects the airway epithelium, or lining of the respiratory tract, from oxidants. Although a necessary gas for survival, oxygen is highly reactive and potentially damaging inside a cell. The airway epithelium is consistently exposed to oxygen in the atmosphere and has a robust expression of antioxidant genes, such as glutathione transferases, glutathione synthetases and superoxide dismutases, as a protective mechanism against damaging effects of oxygen.

"If a cell is less capable of protecting itself, the activated oxygen molecules are more likely to damage the cell’s DNA," Willey said. "Some people have less active antioxidant capabilities."

A second group of genes are responsible for repairing DNA damage. "Damage to DNA can lead to mutations that, in turn, cause cancer. Every time a cell divides, there is risk that DNA damage will lead to a mutation. To prevent this, we all have many different DNA repair genes. However, some people have less DNA repair activity than others."
"Hopefully, we’ll eventually validate this test or a similar one in a form that will be suitable for all people and all cancers."

A third group of key genes called transcription factors regulate activity of both DNA repair and antioxidant genes within the cells. Variation in activity of these genes is, in part, responsible for low activity of antioxidant and/or DNA repair gene activity.

In collaboration, the three groups of genes – which include 15 genes in total – protect the cells of the lungs from damage. When a sufficient number of these genes are compromised, the patient’s risk for developing lung cancer increases.

Patients enrolled in the study will be tracked at 16 hospitals across the United States, including The University of Toledo Medical Center, Toledo Hospital, Ohio State University, the University of Michigan, Mayo Clinic, Henry Ford Hospital, Vanderbilt University Medical Center, VA Tennessee Valley Healthcare System and Cleveland Clinic.

Evaluation will continue for two to three years, with regular examinations and diagnostic screens, including CT scans. Willey expects about 15 of the subjects to develop lung cancer during the study. Results, however, won’t be available until 2014, at the earliest.

“Our primary endpoint is to know whether our test will be associated with a five-fold or greater risk for lung cancer,” Willey said. “Based on our previous case-controlled studies, when we looked at people older than 50 with greater than 20 packs of cigarettes smoked per week, our test was associated with at least an eight-fold increased risk.”

He noted that many who are diagnosed with lung cancer are former smokers. "They're older adults who stopped smoking when the U.S. Surgeon General announced the risk, but the damage had been done."

A 10-year study conducted by the National Institutes of Health found that annual CT scans are effective in earlier lung cancer diagnoses if performed on people older than 55 who smoked more than 20 packs of cigarettes weekly for a number of years.

Early diagnosis at a stage when the cancer can be removed surgically, Willey said, will reduce deaths by at least 20 percent, but comes at a literal cost.

“The other side of the coin is that’s going to be expensive,” he said. “It could be $10 billion a year in a society not looking to spend more in Medicare costs.”

Willey’s test could further pare down the population of those needing CT scans to a pool of about 10 percent who are at highest risk. In addition to savings in the billions of dollars, focusing on those at highest risk for lung cancer will reduce the risk of screening. There are risks to screening because some positive findings on the CT scan turn out to be non-malignant, but sometimes this is discovered only at the time of surgery or after some other diagnostic test that also has risk.

Willey has seen advances in research, medical treatment and education improve outcomes for patients with lung cancer. He has personal reasons as well for pushing toward his goal.

On the day he discovered funding had been approved for the study, he diagnosed another patient with lung cancer — his 40-year-old niece.

“At this point, we are only validating our lung cancer risk test for smokers and ex-smokers,” he said. “Ironically, because my niece was a non-smoker, the test we are validating at this point wouldn’t have applied to her. About 10 percent of lung cancer deaths occur in never-smokers. It’s likely that such individuals are at that extreme end of genetic risk. Hopefully, we’ll eventually validate this test or a similar one in a form that will be suitable for all people and all cancers.”

“If we can validate that our current test identifies a five-fold or greater risk of cancer based on genetics, that would go way beyond what anybody else has been able to do,” Willey stated. “This will be a pretty good starting point, but the work won’t end there.”
UT Autism Center opens

The University of Toledo Center for Excellence in Autism moved into its new location in the Kobacker Center in the spring. Located in a 2,700-square-foot renovated space in the north side of the Kobacker Center, the center is home to unique initiatives to meet the needs of adolescents and adults with autism spectrum disorders (ASD). By focusing on diagnosis, ongoing evaluation and individualized center- and community-based services, the center is positioned to facilitate meaningful outcomes in all areas of development across the lifespan.

The Adolescent Girl’s and Women’s Wellness Initiative is the first of its kind that will provide comprehensive medical, social and behavioral services for girls and women with ASD that also will include responsible sexuality health, development and abuse prevention opportunities.

"The center is unique in that it addresses the specific needs of adolescents and adults with Autism Spectrum Disorders," said Sherry Moyer, executive and research director of the UT Center for Excellence in Autism. "Through cutting-edge research and services, we will be able to address the more complex needs of individuals with ASD as they mature in order to improve the quality of life for everyone involved."

New VA clinic cements relationship with UTMC

The U.S. Department of Veterans Affairs broke ground on a new outpatient clinic for veterans at a March ceremony held on a Detroit Ave. site located on the UT Health Science Campus.

The 99,850-square-foot facility will be built on land purchased from the UT Foundation and will replace the existing clinic located on Glendale Avenue that the Ann Arbor Veterans Integrated Service Network leases from the University.

UT officials said the new clinic will provide opportunities for a closer relationship with the VA and new clinical training experiences for medical student rotations and resident education.

“Care for this nation’s veterans is a unique privilege and represents an outstanding educational opportunity for undergraduate and graduate medical education and across the range of health professions,” said Dr. Jeffrey Gold, chancellor and executive vice president for biosciences and health affairs.

“The ability for our learners to work closely with Veterans Affairs physicians and clinicians only increases the value of a University of Toledo health professional education,” added Gold, who also serves as dean of the College of Medicine and Life Sciences.
Evia pacemaker made U.S. debut at UTMC

When a 14-year-old girl was the first U.S. patient to receive a new generation of pacemaker, Dr. Blair Grubb, professor of cardiovascular medicine and pediatrics at UTMC, couldn’t be any closer to the process.

Dr. Grubb, recognized internationally as a bradycardia specialist, handled the surgical implant of the BIOTRONIK Evia pacemaker into 14-year-old Maria Stebbins of Washington, D.C., whose family traveled to UTMC with her for the surgery.

“The Evia pacemaker is also one of the smallest devices with remote monitoring capabilities as well as blood pressure monitoring ability,” Grubb said. “Once we tailored the device to Maria, she was able to return to D.C. and we’ll be able to monitor her heart and blood pressure from anywhere in the world.”

Grubb said Stebbins’ mother heard about UTMC from physicians in the nation’s capital after they were unable to diagnose her daughter’s condition. Her father, a colonel in the U.S. Army, received special dispensation to return from training police and military in Afghanistan.

“There are some truly outstanding hospitals in the Washington, D.C., area, and I think it speaks volumes about UTMC and Blair Grubb that patients are traveling across country to seek care,” said Dr. Jeffrey P. Gold, Health Science Campus provost, executive vice president for health affairs and dean of the College of Medicine. “When we talk about university-quality care and what sets it apart, this is a prime example.”

UT-hosted DNA repair symposium brought national experts to campus

It was a professional discussion at the cellular level, with special relevance to cancer research. The 13th Annual Midwest DNA Repair Symposium (AMDRS) was held on May 14-15 on UT Health Science Campus.

It was UI’s first hosting of the event that was originally conceived in 1999 as a forum to bring together DNA repair researchers from the Midwestern region to discuss ongoing research and stimulate collaborations. Dr. Kandace Williams, UT professor of biochemistry and cancer biology, one of the symposium’s co-chairs, explained the topic’s importance. “DNA repair is a critical process to maintain genomic stability and remove DNA damage that could result in genomic mutations,” she said. “Disruption of the DNA repair pathways has been linked to many inherited cancers as well as many sporadic cancers.”

Understanding these DNA repair pathways and how the body regulates them will have a significant impact on human health, she added.

The benefits of AMDRS attendance extend beyond seasoned researchers, providing students, postdoctoral fellows and beginning independent investigators with the opportunity to present their work to peers and interact with leaders in the field.
The Dean’s Club

On May 31, the UT College of Medicine and Life Sciences hosted the inaugural meeting of the Dean’s Club, the college’s premier annual giving society. The event featured Nader Abraham, Ph.D., Dr. H.C., FAHA, chair of physiology and pharmacology, who presented on the potential of regenerative medicine and UT’s leading efforts in this exciting new field of research. The first Ashel Bryan Distinguished Volunteer Award was presented by President Lloyd A. Jacobs to George Isaac. Mr. Isaac is a former chair of the MCO Board of Trustees and a noted philanthropist who has supported the college’s academic and clinical mission. Dr. Jacobs said, “Because of George Isaac’s visionary leadership and generosity, thousands of people have been better served by UTMC in an environment that is modern, comfortable and patient-centered.”

First anniversary of historic regional relationship

One year ago, The University of Toledo and ProMedica established the Academic Health Center to enhance clinical education and ensure that a new generation of health-care professionals will be ready to care for our community in the decades ahead.

In this short period of time, the Academic Health Center, or AHC, has made strong progress in its goal to create an environment for The University of Toledo and ProMedica to be recognized among the top-tier medical organizations in the country, as well as to increase recognition as a national authority in care, research and education.

The University of Toledo and ProMedica Health System agreed to the relationship to advance health education and research for both organizations. UT agreed to manage and oversee academic and clinical research endeavors across the ProMedica system under the guidance of a new joint Academic Health Center Board comprised of equal representation from ProMedica and the University.

Dr. Robert Gallo, founder of the Institute of Human Virology at the University of Maryland School of Medicine, presented Medical Grand Rounds on June 16 and the Vladimir Nigrovic Lectureship in Pharmacology and Anesthesia on June 17. Dr. Gallo presented “A Journey with Blood Cells and Cancer.” Dr. Gallo, the co-discoverer of HIV and winner of the prestigious Lasker Award, also holds an honorary doctorate from the former Medical College of Ohio.
Targeting the most-feared killer: research into the next generation of cancer treatment
In many ways, cancer cell behavior is akin to that of cells during fetal development: They grow, they divide and they migrate at a much faster rates than do adult cells.

**PROFESSOR OF BIOCHEMISTRY EXPLORES MODIFICATION OF CHROMATIN STRUCTURE FOR CANCER TREATMENT APPLICATIONS**

Rare but deadly. That’s melanoma, a form of skin cancer with a chilling mortality rate. It doesn’t respond to treatments that are successful for other forms of skin cancer. Once in the metastatic stage, it’s considered one of the most aggressive forms of cancer.

UT researcher Dr. Ivana de la Serna, assistant professor of biochemistry and cancer biology, is tackling the melanoma challenge on the molecular level, taking advantage of one critical characteristic of cancer cells.

In many ways, cancer cell behavior is akin to that of cells during fetal development: They grow, they divide and they migrate at a much faster rates than do adult cells. They’re also undifferentiated, with an immature, almost “primitive” appearance much different from that of the specialized (differentiated) mature cells in the tissues surrounding the cancer.

The development of cancer, then, is essentially a regressive process in which an adult (differentiated) cell becomes an embryonic (undifferentiated) cell.

Embryonic melanocytes (the skin cells responsible for pigmentation) are the focus of de la Serna’s research. Deep within their cellular structure are the familiar double strands of DNA molecules that carry genetic information. Within each cell, DNA is organized into chromosomes: structures made up of a single piece of coiled DNA. In eukaryotes (cells with nuclei), chromosomes in the nucleus are packaged by proteins into a condensed structure called chromatin. This packaging allows the very long DNA molecules to fit into the cell nucleus.

The formation of chromatin, de la Serna explains, is crucial for carrying information into cellular nuclei.

“Chromatin structure plays a critical role in the regulation of gene expression,” she said. “Chromatin is primarily an inhibitor, so by changing different parts of the chromosome, particular regions of the cell can be activated; that comes into play in replication.

“If mutation or DNA damage occurs, the chromatin can be modified so that the proper protein or enzyme can reach the DNA and repair it.”

Chromatin’s inhibitory role (wrapping particular genes to deny their expression) comes into play as embryonic cells develop into adult cells, a process that may shed light as to how cancers come into being. In de la Serna’s research, she examines certain genes that are active in the embryonic melanocytes that are turned off when the cells mature, but that are then expressed anew if and when cells make the transition to cancerous growth.
Chromatin regulates these embryonic genes' expressions by creating a barrier that makes stretches of DNA inaccessible to the enzymes that read the genes. This figurative wall of silence is permanent in normal cells, but is temporary in cells that turn cancerous.

"When we need to activate a gene (turn it on) we change chromatin structure and allow protein access to the DNA to say, make it into RNA, then ultimately into protein," de la Serna explained.

So modifying the chromatin, she noted, is key to understanding the process of regulation. "I work on chromatin remodeling — basically epigenetics, which involves changing gene expression and alterations in an organism's cells in ways that don't affect the DNA sequence.

"In this research, my team and I focus mainly on SWI/SNF enzymes, a complex of about a dozen different proteins that are involved in the wrapping and unwrapping of DNA sequences by chromatin. The enzymes were first discovered in yeast — very quickly they were found to be present in more complex organisms, including humans.

"In humans, the SWI/SNF enzymes regulate genes that are important in physical characteristics, in DNA damage repair and in the regulation of gene expression. They've also been shown to be involved in many different types of cancer."

From the melanocytes that are central to de la Serna's research, the most important cancer that can arise is melanoma, a tumor that results from transformation of normal melanocytes into cancer cells. One important protein shown to be involved in this transformation is called Microphthalmia-Associated Transcription Factor or MITF. This is a protein that is critical to the establishment of the melanocyte lineage from its precursors, and ultimately critical to its survival and proliferation.

The embryonic and carcinogenesis stories converge at this point: The MITF gene is key to a melanocyte becoming cancerous, chromatin is key to silencing or unsilencing MITF, and the SWI/SNF enzymes are key to wrapping or unwrapping the chromatin from the MITF gene.

"We think that different SWI/SNF complexes may be involved in regulating MITF activities, which is potentially important for promoting different aspects of the melanoma proliferation," de la Serna said. "We're looking at different genes in melanoma that are regulated by MITF and SWI/SNF.

"Some people have more of a tendency to develop melanoma because they cannot respond to UV exposure by successfully tanning — rather, they get sunburn."

"The promising thing about these epigenetic regulators is that they're easier to modulate than trying to fix a mutation. If there's a faulty sequence in the DNA, you can sometimes bypass it by adding molecules, for instance. That's easier than gene therapy, which hasn't yet been perfected. With epigenetic mechanisms, you can add these small molecules to inhibit the functions of proteins like SWI/SNF or other such regulators."

This opens the possibility of cancer treatment that involves targeting the activity of regulating proteins like SWI/SNF, inhibiting them with different molecules.

"Some of our work may have preventative applications," said de la Serna, who's a member of the mentoring faculty for the UT Biomedical Sciences Graduate Program (Cancer Biology Track).

"The most important environmental factor for melanoma is UV exposure. Pigmentation is one of the most important protective mechanisms we have against UV. Some people have more of a tendency to develop melanoma because they cannot respond to UV exposure by successfully tanning — rather, they get sunburn.

"One receptor has been identified that binds a ligand and stimulates the tanning phenomenon, and protects skin in other ways. A $1.2 million NIH grant I received enabled our team to look at how that receptor then signals to transcription factors and chromatin-remodeling enzymes such as SWI/SNF, to regulate the specific genes that would protect the skin against UV exposure."

Those enzymes modify chromatin and regulate processes that include the body's response to UV. In cases where melanoma develops, the enzymes regulate its proliferation and thus the survival of melanoma cells.

Ultimately, understanding this most basic of cellular processes underlying the beginnings of cancerous growth could lead to new ideas on how to prevent or treat melanoma, and many different types of cancer.
DNA REPAIR PATHWAYS ARE EXPLOITED TO BOOST EFFECTIVENESS OF CANCER THERAPIES

When it comes to cancer, one might say that DNA repair pathways function too effectively. While they protect normal cells from many potentially DNA-damaging agents, they can also protect cancer cells from DNA-damaging drug treatments designed to kill these cells. Repair pathways, which are essential to general genome maintenance, can shield cancer cells as effectively as they do normal cells.

Conversely, these same pathways offer potential for new cancer treatments. Two researchers in the UT Department of Biochemistry and Cancer Biology — Dr. Kandace Williams, professor, and Dr. Steve Patrick, associate professor — are examining the mechanisms of DNA repair processes, with eyes on improving the effectiveness of cancer chemotherapies.

Dr. Patrick’s work focuses on multiple repair pathways that come into play in response to cisplatin, one of today’s most widely used chemotherapeutic drugs. Dr. William’s laboratory looks at a specific DNA repair pathway that interacts with the DNA-alkylating drug temozolomide, used to treat glioblastoma, a highly malignant brain cancer in adults. These highly toxic drugs treat cancer by damaging cellular DNA, causing cell death.

When such chemotherapeutic drugs enter the body’s system, DNA repair pathways immediately go to work, shielding both healthy and diseased cells targeted by the treatment.

On the one hand, repair pathways in normal cells are overwhelmed by the chemotherapeutic treatment, resulting in toxicity to the patient that includes damage to vital cells such as bone marrow. On the other hand, and despite considerable damage inflicted by the drug, some cancer cells continue to grow even as the disease enters remission. In most cases, these cells allow the cancer to eventually manifest itself again. When this happens, the growing tumor usually exhibits resistance to the original chemotherapeutic agent, and increased malignancy.

One mechanism of such resistance is enhanced DNA repair: an increased ability of the recurrent cancer cells to remove or repair the damaged DNA so cell division can continue. Another mechanism of cancer cell resistance is decreased DNA damage signaling within the cell, a process that normally leads to slowed growth or even cell death in response to the DNA damage. The work of Drs. Williams and Patrick intersect at this point, both with a goal of understanding these mechanisms of repair.

A clue may exist in the susceptibility of some cancer forms to chemotherapy. “There are some cancers, like testicular, that are curable, with an 80 to 90 percent survival rate,” Dr. Patrick noted. “Why are some forms so treatable and some are not? The link is DNA repair pathways.

“Testicular cancer, for example, has fewer DNA repair proteins, so they can’t remove the damaged DNA. When chemotherapeutic drugs target DNA, they bind to the DNA and block cells from growing, making the therapeutic agent more effective. I’m interested in learning how we can target the DNA repair pathways of other cancers to inhibit them, making the cancer curable.”

A UNIVERSITY OF TOLEDO COLLEGE OF MEDICINE AND LIFE SCIENCES PUBLICATION
"We’re hoping to identify cellular components that will ultimately help discover how to push tumor cells down their unique death pathway more effectively."
In a sort of mirror-image approach, Dr. Williams concentrates on how cancer cells manage to grow despite damage inflicted on their DNA. Her focus on glioblastoma has yielded a particular DNA adduct (a chemically modified molecule) generated by alkylating chemotherapy agents such as temozolomide. “This adduct is usually recognized by specific DNA repair proteins that, instead of repairing damaged DNA, push the cell toward cell death,” she explained.

“When the cells become resistant, it’s been found that the DNA repair pathway actually decreases in expression and cell death is no longer the result.

“We’re trying to figure out the mechanisms behind this, comparing normal cells to tumor cells to see if there are different cell death pathways.”

“It turns out that in the presence of temozolomide and sufficient expression of this DNA repair pathway, tumor cells appear to die differently from when a normal cell is pushed toward genetically programmed cell death. We’re hoping to identify cellular components that will ultimately help discover how to push tumor cells down their unique death pathway more effectively.”

In the case of the anti-cancer drug cisplatin, research has suggested that DNA adducts alone may not be responsible for the drug’s cancer-killing activity. More likely cisplatin’s effect involves the interplay of proteins within a cell that can bind to and alter the metabolism and repair of the DNA adducts. Patrick’s work with cisplatin zeroes in on interstrand cross-links (ICLs) in DNA, and on proteins that bind to and initiate a DNA repair pathway. By understanding the role of these proteins and the mechanisms underlying cisplatin ICL DNA damage recognition, the improvement and development of new cancer treatments may be possible.

Their 2009 paper, “Prolonged cell cycle response of HeLa cells to low-level alkylatation exposure,” focuses on the how exposure of tumor cells to alkylators has become a useful tool in deciphering the mechanisms that limit the efficacy of chemotherapeutic alkylating drugs, including temozolomide.

Both researchers, who are members of the mentoring faculty for the Biomedical Sciences Graduate Program (Cancer Biology Track), took a moment from discussing their work to mention the 13th Annual Midwest DNA Repair Symposium, which was held on UT’s Health Science Campus in May. “It’s always a high-profile event offering a chance for graduate students to hear world-class speakers,” said Dr. Williams, who is also program director for Cell Biology and Pathogenesis Program of the UT College of Medicine Cancer Center and — along with Dr. Patrick — served as co-chair of the symposium.

"In the case of the anti-cancer drug cisplatin, research has suggested that DNA adducts alone may not be responsible for the drug’s cancer-killing activity."
Although advanced breast and prostate cancers are independent of hormones, they are still able to activate the hormone receptors that support cancer growth.

**UT PROFESSOR’S RESEARCH LEADING TO NEW THERAPIES FOR BREAST, PROSTATE CANCERS**

Although breast cancer and prostate cancer are significantly different diseases, there are distinct similarities.

By the numbers, the comparison is particularly interesting. According to the American Cancer Society, breast cancer is the most common malignancy in women and prostate cancer is the most common carcinoma in men, aside from skin cancer for both.

The ACS reports that slightly fewer than one in eight women will develop breast cancer. The statistic for prostate cancer is one in six men.

Dr. Manohar Ratnam is keenly aware of the numbers. However, the professor in UT’s Department of Biochemistry and Cancer Biology is more interested in another vital link between breast cancer and prostate cancer.

“These two types of cancer are similar in that their developments and growths are largely supported, at least initially, by sex hormones,” Ratnam said. “They are also similar in that the growth of cancer cells, especially in advanced stages, becomes independent of these hormones.”

About 80 percent of breast tumors, he explained, contain a receptor that can bind to estrogen, the female sex hormone. The cancer cells are stimulated and depend on the presence of the hormone to grow.

Prostate cancers dependent on testosterone, the male sex hormone, work similarly, by binding to its receptor on the cancer cells.

Initial treatment of both breast and prostate cancers generally involves the removal of malignant growths, if possible, along with chemotherapy and radiation treatments to extinguish residual cancerous cells.

Subsequent treatments often include adjuvant therapies to reduce or block the effects of the hormones that stimulate cancer growth.

“In both breast cancers and prostate cancers that are found to be hormone-receptor positive, adjuvant therapy uses medication to block the female and male sex hormones,” Ratnam said. “Hormonal adjuvants are typically administered over many years. It’s a long-term therapy with several undesirable side effects.”

Ratnam explained that hormone therapy tends to halt the progress of breast and prostate cancers for a few years, but nearly half of hormone-receptor positive breast cancers and slightly fewer than half of hormone-receptor positive prostate cancers develop resistance after three to five years.

“Even as hormone therapy is administered, research shows cancer cells are still growing at a lower level than before, but the progression hasn’t been entirely stopped,” Ratnam said.

Hormone-receptor positive cancers also acquire features that mimic the stimulating effects of hormones in their absence.

“Although advanced breast and prostate cancers are independent of hormones, they are still able to activate the hormone receptors that support cancer growth,” Ratnam explained.

Aside from the fading effectiveness of adjuvant therapy, patients also experience severe side effects from long-term use.

“Hormones are important for aspects of normal physiology. They help maintain bone density and have important roles in cardiovascular health and maintaining muscle mass,” Ratnam said. “Estrogen and testosterone may also be required for brain health.”
Ratnam and his research team have targeted hormone therapy with goals of increasing its effectiveness and developing medications devoid of side effects that plague current drugs.

"By understanding the specific aspects of how hormones support cancer cells, we believe it's possible to target those actions without interfering with the actions of the hormones in normal tissues," he said.

Ratnam's research, funded by a $1.25 million grant from the National Cancer Institute, has yielded vital information regarding malignant tumor growth.

"We've found there is a protein, a vitamin A receptor, that plays a major role in a low-level multiplication of cancer cells even as the patient is treated with adjuvant hormone therapy," Ratnam said. This retinoid acid receptor type alpha 1 is doing something at a very low level that stimulates the cancer cells.

"We've found, under conditions of adjuvant therapy, the malignant cells depend on this protein to maintain a state of growth necessary for further changes to occur in the cells to aid in their progression into an aggressive tumor. However, normal adult tissues don't need this protein, as other proteins can compensate for its loss."

Ratnam's research is progressing toward the development of a new class of medications that will target the retinoid acid receptor for destruction within the cells. Negating the protein will likely increase the effectiveness of hormone therapy, increasing the frequency and duration of disease-free survival.

The new drugs would be used in combination with currently existing hormone therapy medications.

Potential medications based on Ratnam's findings are currently being tested on mouse models, with a goal of conducting clinical trials on humans within two years at medical centers across the United States.

"We've already gained fundamental new insights into hormonal signaling pathways, both in early and advanced stage breast and prostate cancers," Ratnam said. "If we can improve the effectiveness of adjuvant therapy so it has a better than 50 percent success rate, that would save a significant number of lives."

Eventually, Ratnam believes medications culled from his research could help improve treatments for a variety of cancers, as well as other diseases.

His research team, however, doesn't tend to think too far into the future. After more than 25 years in the field of biochemical research, he's learned that his work can diverge in many unforeseen directions.

"Our reality in the lab is solving the problem at any given point," Ratnam said. "You're almost entirely focused on the process, then we follow where the research leads us."

"We've already gained fundamental new insights into hormonal signaling pathways, both in early and advanced stage breast and prostate cancers."
PROFESSOR OF BIOCHEMISTRY AND CANCER BIOLOGY EXAMINES GENE-BASED STRATEGY TO KILL GLIOBLASTOMA CELLS

For about a decade, Dr. William Maltese, chair and professor of Biochemistry and Cancer Biology, has studied glioblastoma, a type of brain cancer.

When glioblastoma tumors are surgically removed from the brain, tumor cells that remain around the margin of the tumor grow, causing the tumor to recur and spread to other portions of the brain. Normal cells have mechanisms to prevent such spread by bringing about apoptosis, a common form of cell death. However, glioblastoma cells often carry mutations in the genes that cause apoptosis; therefore, treatments intended to kill these cells through apoptosis are ineffective for glioblastomas.

Dr. Maltese’s lab came across a study demonstrating that RAS, a gene which was considered to be an oncogene that promotes cancer growth, could actually cause glioblastoma cells to die. The method of cell death brought on by RAS, however, is much different from apoptosis. Instead of dying in a natural, sequenced pattern, the cells treated with RAS died through “cell drinking.” The cell would take in fluid from the surrounding area and form large vacuoles. Instead of recycling or disposing of the excess fluid as would normally happen, the fluid-filled vacuoles would merge and eventually cause the cell to burst. As the first to discover this mechanism of cell death, Dr. Maltese and his co-investigators named it methuosis.

Methuosis has proven to be an effective method for killing glioblastoma cells in culture, but now Dr. Maltese is researching ways to make it effective for treating brain tumors in patients. His lab, collaborating with Dr. Paul Erhardt in the Center for Drug Design and Development in the College of Pharmacy and Pharmaceutical Sciences, has identified a compound called MOMIPP that can bring about methuosis in drug-resistant glioblastoma cells. They are working with Dr. Andrew Ditto, a postdoctoral fellow in Dr. Maltese’s laboratory, to package MOMIPP in a biodegradable nanoparticle that releases the compound slowly over time; such a package could potentially be used to treat glioblastoma. One problem so far is that MOMIPP, like other cancer treatments, can also cause healthy cells to die because the treatment lacks specificity. Their current focus is to resolve this specificity issue so that cancer cells can be targeted by the treatment and normal cells can be left unaffected. In order to accomplish this, peptides are placed on the surface of the nanoparticle that delivers the drug. These peptides are designed to react only with the cancer cell so that the methuosis-inducing compound is absorbed by these cells and ignored by the healthy cells. If this strategy proves to be effective, it could eventually open the door for early-stage clinical trials of MOMIPP or related compounds for treatment of glioblastoma.

Like Dr. Maltese, Dr. Steve Selman is focused on treating cancer through non-traditional methods. Dr. Selman spends many of his clinical hours diagnosing and treating patients with bladder cancer and patients with prostate cancer. His research team has spent years exploring innovative approaches to treating these disease states.
Like Dr. Maltese, Dr. Steve Selman is focused on treating cancer through non-traditional methods.

Recently his UT urologic research team, which includes medical students, urology residents and faculty, has found that EGCG, a polyphenolic catechin found in green tea, is lethal to bladder cancer cells while having little effect on normal cells. This makes it a very attractive treatment for some bladder cancer patients. For these patients, direct instillation of EGCG into the bladder could have beneficial effects in both the prevention and treatment of their disease.

The use of a "natural" substance to treat bladder cancer led Dr. Selman and his group to the work of Dr. Channing Hinman, a retired faculty member in Pharmacy. Dr. Hinman has been exploring the use of cobra toxin and its derivatives for a number of blood cancers. The two researchers decided to look at urologic cancers and recently found that a part of the cobra venom called cardiotoxin was effective in killing prostate cells. Interestingly, this toxin may also prove beneficial in the treatment of a benign growth of the prostate called BPH: benign prostatic hyperplasia.

Finally, the urologic cancer research group has begun a collaboration with Dr. Maltese in his pursuit of a new method of causing cancer cell death through methuosis. Pioneered by Dr. Maltese's group, the use of compounds causing methuosis could have clinical applications for the treatment of bladder cancer patients with cancerous growths limited to the lining of urinary bladder.

Dr. Selman's group has been supported over the years by the National Institutes of Health, the Stranahan Foundation, the Harold and Helen McMaster Foundation and the Gieger Family Foundation for Cancer Research.
COLLEGE OF MEDICINE CLASS NOTES

John R. Perfect MD (MED '74), professor of medicine and associate professor of molecular genetics and microbiology at Duke University, was honored with a Distinguished Faculty Award by the university's medical alumni association. Lead author of the "2010 Guidelines for the Treatment of Cryptococcosis," issued by the Infectious Diseases Society of America, he also serves as interim chair of Duke's Division of Infectious Diseases and director of the Mycology Research Unit.

Robert A. May MD (UTCTC '75, Univ Coll '79, MED '82), medical director of the respiratory care program at UT, was presented the annual Albert H. Andrews Jr. MD Award by the National Board for Respiratory Care (NBRC) for service to the professional community. The U.S. Air Force veteran and former flight surgeon also served as president of the NBRC board of trustees.

John A. Russ MD (MED '80), Toledo, attended the Air Force Academy Class of 1970 reunion in the fall, when the class unveiled its gift to the academy in Colorado: a $1 million memorial dedicated to graduates killed in Vietnam and to the Air Force's legacy in that region.

Kim Bowen MD (MED '87), part of the medical staff of Medina (Ohio) Hospital, was named 2010 Humanitarian Physician of the Year by fellow medical staffers who honored his assistance in founding and supporting the Medina Health Ministry for underserved individuals.

Viki Christopoulos MD (A/S '88, A/S '88, MED '92) opened an ophthalmology practice in McKeesport, Pa., with a clinic and an optical dispensary called Eyopolis.

Krista Dobbie MD (MED '98) is medical director for the Sentara Medical Group Palliative Care Program and a palliative care practitioner at Virginia Beach (Va.) General Hospital.

Aaron Wittenberg MD (MED '00), Scottsdale, Ariz., who practices interventional radiology, was named the Rising Young Doctor of the Year by the John C. Lincoln Hospitals of Phoenix.

Nicholas J. Wilson MD (MED '01), a board-certified radiologist, joined Geisinger Medical Center in Danville, Pa.

Yogesh P. Patel MD (Res '06), assistant professor for the UTMC radiology residency program, was elected president of the Ohio State Radiological Society, the Ohio chapter of the American College of Radiology.

Emma Hostetter MD (MED '07) joined Amnville (Pa.) Family Medicine in August. She's working on her master's degree at Johns Hopkins School of Public Health, Baltimore.

Laura Wills MD (MED '07) joined the staff of Adena Pediatrics in Chillicothe, Ohio.

Marriages & Unions

Roy Colllaco PhD (PhD '00) & Joyce Bevington MD, PhD (MED '09, PhD '09), Toledo.

Benjamin J. Bregmaa MD (MED '06) & Landi Coltrian. He began a Fellowship in pulmonary critical care at Wake Forest University Baptist Medical Center in July, Winston-Salem, N.C.

Josef Froehlich MD (A/S '06, MED '10) & Mary Anne Bafunno PharmD (Pharm '07, PharmD '09). He's completing his residency in psychiatry at the University of Louisville Hospital; she's a clinical pharmacist at Jewish Hospital in Louisville, Ky.

Births

Dawn Zientack MD (MED '00) and Will Collier MD (MED '00), Delaware, Ohio, celebrated the birth of their second child Paxton John in December.

Kate J. (Jennings) Willks MD (MED '08) and her husband Joseph welcomed Isaac David to their Morgantown, W.V., family in November.

Death notices

Robert C. Bobo MD, Sylvania, longtime associate professor in the College of Medicine and volunteer professor in clinical pediatrics, Jan. 25 at 68.

Marios Boucouras MD, Naples, Fla., clinical assistant professor in MCO Department of Surgery's Division of Orthopedics from 1970 to 1987, Dec. 20 at 89.

Ashel G. Bryan, Bowling Green, longtime benefactor of the Health Science Campus, Sept. 26 at 89. He served as a board trustee with the former MCO from 1976 to 1985 (chair for four years) and with the MUO Foundation from 1984 to 1995 (president for three years). A member of the Presidents Club and Heritage Oak Society, he and his wife Dorothy funded an outdoor commons area on the Health Science Campus, supported various construction projects and instituted a number of scholarships and professorships in their names, including an emergency hardship fund for UTMC nurses. In 1987, MCO named him a Distinguished Citizen; he was awarded an honorary degree from MCO in 1996. The donated artwork of Dorothy, who died of cancer in 2001, is on display at several UTMC locations.

John T. "Jack" Cairns, Toledo, Jan. 23 at 81. After a newspaper career, he joined MCO from 1984 to 1994 as a communication specialist in the Executive Office of Communications.

Bernard J. Cullen MD, Maumee, professor emeritus of pediatrics and noted expert on child abuse, Aug. 19 at 91. While in private practice in Toledo, he founded the Family and Child Abuse Prevention Center in 1973. He joined the faculty at MCO in 1977 and became director of the Regional Child Abuse and Neglect Prevention Program. For more than 30 years, Cullen served as chair of the Ohio chapter of the American Academy of Pediatrics Committee on Child Abuse and Neglect. His work as a founding member of the Lucas County Sexual Abuse Task Force resulted in the establishment of the Children's Advocacy Center. An adjunct professor of psychology at UT, he was named professor emeritus at his 1990 retirement, and was honored in 2002 when a treatment facility for traumatized children, adolescents and families was named the Cullen Center.

John H. Hageman MD, Toledo, who played an integral role in the practice, education and advancement of vascular surgery for more than 40 years, March 30 at 76. He joined the MCO faculty in 1984 as an associate professor in the Department of Surgery and was promoted to professor in 1994. While there, he served as chief of peripheral vascular surgery and medical
director of the surgical intensive care unit. After retiring in 1998, Hageman took a volunteer faculty position as clinical professor in the Department of Surgery; he held the position until 2006.

John M. Howard MD, Toledo, professor emeritus of surgery, March 16 at 91. He joined the MCO faculty in 1974 as professor of surgery. During the Korean War, Howard directed the U.S. Army's Surgical Research Team, which pioneered the MASH unit; he received the Legion of Merit from President Eisenhower for his efforts. Working with national trauma organizations, he also spearheaded the early development of a coordinated program for emergency care of the acutely ill and injured in northwest Ohio. When he retired in 1990, Howard was named professor emeritus. Ten years later, he established a fund, the John M. Howard Endowed Professorship of Surgery. He was a member of the Heritage Oaks Society.

Lloyd R. Kavanagh MD, Toledo, clinical associate professor in MCO Department of Obstetrics and Gynecology from 1971 until 1993, July 4 at 81. In January 2010, the Academy of Medicine of Toledo and Lucas County recognized his 50 years as a physician.

Donald F. Loeffler MD, Catawba Island, Ohio, longtime volunteer MCO faculty, Jan. 11 at 86. He was a clinical assistant professor in the Department of Radiology from 1982 until he retired from practice in 2004.

Stephen A. Lutz MD (MED ’77), Wolcottville, Ind., June 15 at 60. Longtime medical missionary in Papua New Guinea.

Marian Rejent MD, Toledo, clinical professor of pediatrics who helped establish programs for children with disabilities, Feb. 27 at 90. She was director of pediatrics at Maumee Valley Hospital in 1968 when she joined the MCO Department of Pediatrics, becoming a faculty member and acting as chair of pediatrics until 1974. She also was an adjunct professor of public health at UT and established a medical student award fund in her name.

Stuart K. Remley MD, Toledo, an endocrinologist who was an MCO volunteer faculty member, March 17 at 86. He was appointed a clinical associate in the Department of Medicine in 1970, and was a clinical instructor when his appointment ended in 1985.


Gene E. Wright MD, Lima, family medicine practitioner for 43 years, Oct. 3 at 85. He was involved in education for many years as a clinical instructor for medical students, first at OSU, then as a preceptor for family practice residents at the then-MCO, which in 1992 honored him with its Distinguished Citizen Award.
It's not that we broke the mold, we just didn't use one.
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