TURNING CANCER DISCOVERIES INTO TREATMENTS

FRONTIERS

WINTER | 2017

CANCER SUSCEPTIBILITY GENES:

Multigene testing of early-onset colorectal cancers can reveal unexpected mutations

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UPFRONT

The Director's Perspective

Offering Research-Based Compassionate Care

Year three begins for the new James Cancer Hospital and Solove Research Institute

It's hard to believe that two years have passed since we opened our transformational James Cancer Hospital and Solove Research Institute as the adult patient-care component of The Ohio State University Comprehensive Cancer Center (OSUCCC – James).

Easier to believe is how much this facility has helped us extend our global impact in research and compassionate care. The OSUCCC – James has become an international destination for cancer treatment; we have now served patients from all 88 Ohio counties, all 50 American states and 36 other countries.

More people from around the world are turning to us for help because of our groundbreaking research, which we translate into innovative cancer care and prevention strategies, some of which are featured in this new *Frontiers*.

Our cover story examines a statewide project that we launched a few years ago called the Ohio Colorectal Cancer Prevention Initiative, which established a 50-hospital network for screening colorectal cancer (CRC) patients and their at-risk relatives for Lynch syndrome, an inherited genetic condition that predisposes to CRC and other cancers. One outcome of the project is a study published in *JAMA Oncology* that used multigene sequencing to learn the prevalence of mutations linked to hereditary cancer syndromes in a large group of CRC patients diagnosed under age 50. The prevalence proved to be amazingly high—16 percent—and not always Lynch syndrome.

Another story describes the work of four OSUCCC – James research groups that are studying how cancer cells derive the energy they need for rapid growth and proliferation.

MICHAEL A. CALIGIURI, MD
DIRECTOR, COMPREHENSIVE CANCER CENTER; CHIEF EXECUTIVE OFFICER, JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE, THE OHIO STATE UNIVERSITY; JOHN L. MARAKAS NATIONWIDE INSURANCE ENTERPRISE FOUNDATION CHAIR IN CANCER RESEARCH

Their work is identifying promising prognostic and predictive biomarkers and new therapeutic targets to enhance cancer therapy.

You can also read about new microsurgical techniques to prevent or relieve lymphedema, about the support services needed for the ever-growing population of cancer survivors and about a clinical trial for uveal melanoma. I hope you'll find this issue interesting and informative.

FRONTIERS

WINTER | 2017

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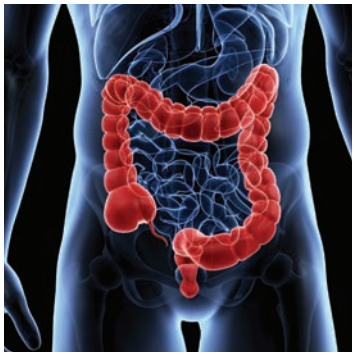

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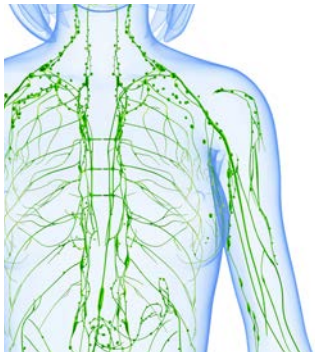

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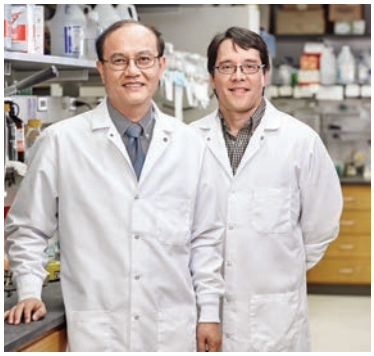

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Read Frontiers online or download an issue at **http://cancer.osu.edu/Frontiers.**

CANCER SURVIVORSHIP

We need a unified system of psychosocial, spiritual and emotional care

BY JANET SNAPP, MSN, RN, FPCN, AND DORI KLEMANSKI, DNP, CNP

The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James)

JANET SNAPP, MSN, RN, FPCN

DORI KLEMANSKI, DNP, CNP

Cancer survival rates in the United States have dramatically increased during the past 40 years as a result of improved prevention, detection and treatment. The newest treatments keep cancer growth in check and train the immune system to hunt tumor cells. In addition, policies such as the 2016 federal Cancer Moonshot initiative are bridging research efforts into a unified assault.

But cancer treatment is just the first challenge that faces survivors. Many Americans emerge from treatment only to confront difficulties that go far beyond their illness. Common challenges that cancer survivors can experience include:

- Disability that can range from mild to complete;
- Fatigue, pain and changes in appearance or memory;
- Emotional distress such as depression or fear of recurrence;
- Financial, employment and legal problems.

Some of cancer's most devastating effects can grow from the care demands placed on spouses and caregivers; from the post-traumatic stress experienced by parents of pediatric cancer survivors; and from the loss of fertility that leaves some young cancer survivors unable to start a family before they've had time to consider one. There is no medical reimbursement for the banking of eggs or sperm.

The American healthcare system is woefully unprepared and underfunded to provide such supportive services to cancer survivors and caregivers. Furthermore, many cancer survivors cannot access the treatments and resources that are available to improve their quality of life because the care is simply not available where they live, and, if it is, they lack health insurance or the financial ability to pay for it.

Cancer treatment must be patient-centric and holistic, and it must encompass supportive symptom-management needs as well as comprehensive psychosocial support for both patients and caregivers. All cancer survivors should have access to mental health providers, support groups, career and legal advice, as well as the opportunity to participate in rehabilitative care focused on maximizing their functional ability.

Today, every cancer patient should be screened for distress early in

"Evidence demonstrates that this support can reduce morbidity and sometimes extend life. OSUCCC – James researchers have found that practicing yoga for as little as three months twice a week reduced both fatigue and inflammation in breast cancer survivors."

the course of their illness and at strategic intervals. Institutions should ensure that resources are available and funded to respond to the distress needs of survivors. These can be either internal resources or verified external resources.

When appropriate, and as mandated by the American College of Surgeons, survivors should be given a Treatment Summary and Survivorship Care Plan following treatment. In addition, oncology institutions should develop and promote programs along the cancer continuum that prepare survivors for life after cancer. This support should start at the time of diagnosis.

Last, academic medical centers and other educational entities should offer educational initiatives for healthcare science students, staff and faculty to address specialty concerns related to survivorship care. Primary care providers especially should be aware of the impact of cancer therapies across a survivor's lifetime.

In the long term, we need a comprehensive, unified, reimbursable system of psychosocial, spiritual and emotional care that promotes healthy living and wellness to encourage healthy behaviors and healthy coping. Support for every cancer survivor should include oncologists, primary care providers, and survivorship and palliative-care providers. These experts should provide coordinated guidance as well as monitoring for recurrence and for late and long-term effects of cancer treatment.

The United States could be a world leader in cancer survivorship, as well as treatment. By bringing together experts from a range of disciplines, we can help patients overcome the most devastating effects of their disease.

Evidence demonstrates that this support can reduce morbidity and sometimes extend life. OSUCCC – James researchers have found that practicing yoga twice a week for as little as three months reduced both fatigue and inflammation in breast cancer survivors. The reduction in inflammation is significant. Chronic inflammation is linked to the frailty and functional decline that often accompany aging. It is also linked to numerous chronic health conditions such as type 2 diabetes, heart disease, arthritis and Alzheimer's.

Another OSUCCC – James study showed that stress reduction for caregivers extended life by four to eight years. Stress reduction also has been shown to reduce the size of cancerous tumors.

Additional research shows that lung cancer patients who have early palliative care along with standard-of-care treatment live longer than patients who do not have palliative care.

We are winning the war on cancer one patient at a time, and it has been one of the greatest triumphs of modern medicine. Cancer treatment has evolved, and it is time for the U.S. healthcare system to evolve with it. Cancer care cannot end when cancer survivors return home. We must also provide the support they need to thrive.

INTRAOCULAR MELANOMA |

Insightful Data

Genetic markers of pigmentation identify genomic sites of possible uveal melanoma risk

MOHAMED ABDEL-RAHMAN, MD, PHD,
OSUCCC — James researcher

"This important paper will help focus future UM research efforts on the interactions of certain pigmentary genes with other genetic and environmental risk factors."

Roughly 2,500 people in the United States are diagnosed annually with uveal melanoma (UM), a rare form of melanoma that arises in the iris, ciliary body or choroid layer of the eye. Clinical data suggest that uveal melanoma is more common in Caucasians and individuals with light eye coloration, but the genetic mechanisms underlying the development of the malignancy are largely unknown.

A recent study co-led by an OSUCCC – James researcher provides insight into the cause of UM. The study found the first evidence of a link between genes associated with eye color and development of the malignancy. Leading the study were ophthalmologic pathologist and cancer geneticist Mohamed Abdel-Rahman, MD, PhD, of the OSUCCC – James, and cancer geneticist Tomas Kirchhoff, PhD, of the Perlmutter Cancer Center of NYU School of Medicine.

"This important paper will help focus future UM research efforts on the interactions of certain pigmentary genes with other genetic and environmental risk factors," Abdel-Rahman says.

"This could provide a paradigm shift in the field. Our study suggests that in eye melanoma a difference in pigmentation may play a direct cancer-driving role, unrelated to sunlight protection," he adds.

Progress in understanding the genetic risk factors in the development of uveal melanoma has been limited, the researchers say, because this cancer is rare and large sample populations are unavailable.

To overcome that limitation, Abdel-Rahman, Kirchhoff and their colleagues focused on 28 single-nucleotide polymorphisms (SNPs) that are associated with increased risk of cutaneous melanoma and looked for links to uveal melanoma.

The researchers analyzed samples from 272 UM patients and 1,782 controls, most of whom were treated at Ohio State. They identified five variants that were significantly associated with UM. The three most important of these mapped to a region on chromosome 15 that determines eye color.

The researchers believe the findings provide a deeper understanding of both ocular and cutaneous melanoma.

Published in the journal Scientific Reports.

METASTATIC CANCER

Immune Turn-Down

Oxygen-sensing proteins may facilitate tumor metastasis to the lungs

An immune mechanism that permits the lungs to tolerate exposure to harmless antigens also helps metastatic cancer cells colonize the organ.

Nearly 90 percent of cancer deaths are caused by tumors metastasizing to distant organs. The lungs are a common site of metastasis for primary bladder, breast, colon, kidney, ovary, pancreas, bone, rectal, stomach, thyroid and uterine cancers, as well as melanoma.

The researchers found that the highly oxygenated lung microenvironment enables cancer cells to spread to the lung more easily.

"Every time we inhale, we bring things into our lungs that could produce a pretty dramatic and potentially harmful immune response—but they usually don't because in a normal, healthy state our immune systems are set up to accommodate for this," explains David Clever, PhD, first author of the manuscript and a current medical student at Ohio State. Clever completed this research under the mentorship of Nicholas Restifo, MD, of the National Cancer Institute (NCI) during the doctoral portion of his Medical Scientist Training Program.

Specifically, the team discovered that certain oxygen-sensing prolyl-hydroxylase (PHD) proteins limit inflammatory responses by T cells in the lung microenvironment. At the same time, those proteins also limit immune responses against cancer cells, facilitating metastasis.

Blocking the PHD proteins pharmacologically or by using mice that lack the proteins in T cells enhanced T-cell responses against cancer and limited metastasis to the lungs.

The results contribute a new immunological basis for the predisposition of many cancers to metastasize to the lungs that could help scientists develop new therapies to prevent this.

"Although our finding is in mice," Restifo says, "we are eager to test whether disrupting the oxygen-sensing machinery in T cells with drugs, genetics, or regulation of environmental oxygen—will enhance the efficacy of T-cell-mediated immune therapies for cancer in humans."

Published in the journal Cell

DAVID CLEVER, PHD,
first author of the manuscript and a current medical student at Ohio State

Triple Treatment

Innovative therapy might improve glioblastoma outcomes

BALVEEN KAUR, PHD,
professor and vice chair of research, departments of Neurological Surgery and Radiation Oncology, and a member of the OSUCCC – James Translational Therapeutics Program

"Our findings provide a rationale for testing the three therapies in combination in a clinical trial."

A study by researchers at the OSUCCC – James suggests that an innovative triple combination therapy might be particularly effective for glioblastoma (GBM) and should be evaluated in a clinical trial.

The therapy consists of the targeted-drug bortezomib, an oncolytic virus plus natural killer (NK) cell immunotherapy.

"Bortezomib, oncolytic viruses and NK cell immunotherapy are each being investigated separately in clinical trials for glioblastoma," says principal investigator Balveen Kaur, PhD, professor and vice chair of research, departments of Neurological Surgery and Radiation Oncology, and a member of the OSUCCC – James Translational Therapeutics Program. "Our findings provide a rationale for testing the three therapies in combination in a clinical trial."

In this study, bortezomib and an oncolytic herpes simplex virus (oHSV) caused glioblastoma cells to die by a process called necroptosis. This form of cell death is different from the type of cell death caused by either agent alone. In addition, it triggers the release of hormone-like factors—proinflammatory cytokines—that attract natural killer (NK) cells, which are cancer-cell killing immune cells.

Furthermore, the bortezomib and oHSV treatment significantly improved the ability of NK cells to identify and kill GBM cells.

More than 11,880 new cases of GBM were estimated to occur in 2015, with overall survival averaging 12 to 15 months after diagnosis. New strategies for treating the disease are critically needed.

"Because proteasome inhibitors, oHSV and NK-cell immunotherapy are currently being investigated individually in GBM patients, this study may help guide the future clinical development of novel combination therapies for glioblastoma," Kaur says.

Published in the journal Clinical Cancer Research

To refer a patient, please call The James Line New-Patient Referral Center toll free: 1-800-293-5066

Return Reduction

Psychosocial Factors Associated With High Readmission Rates, Longer Hospital Stays

A study by OSUCCC – James researchers shows that psychosocial risk factors that affect a person's ability to cope with chronic stress are associated with significantly higher readmission rates and longer hospital stays among blood cancer patients undergoing hematopoietic stem cell transplantation (HSCT).

The researchers say that this demonstrates a critical need that should be addressed in a systematic way by the oncology community.

"Stem cell transplant can be a curative treatment for certain cancers, but it is a long process that can place severe strains on patients," says senior author Ashley Rosko, MD, an OSUCCC – James hematologist.

"Just like we assess potential impact and risks of a patient's co-morbidities before pursuing a stem cell transplant, we saw a need to evaluate psychosocial vulnerabilities to identify those patients at the highest risk for complications and to develop interventions to ensure the smoothest recovery possible."

The observational study examined 395 patients undergoing stem-cell transplantation for acute leukemia, multiple myeloma, lymphoma and other cancers at the OSUCCC – James.

Prior to treatment, all patients were screened to identify factors affecting their ability to cope, including history of anxiety, depression, substance abuse, health behaviors, family social support, emotional tone and mental status. Patients deemed at-risk were subcategorized into mild and moderate risk.

The researchers found 48 percent of the patients to be at risk. The most common identified risk factors were psychiatric conditions (24 percent), poor health behaviors (16 percent) and poor coping history (13 percent).

"Hospital readmission in stem cell transplant patients is associated with poor overall survival, increased cost and worse quality of life," says Rosko. "It is important that we do all we can to identify these patients in advance to help them successfully navigate the treatment process."

Presented at the 2016 American Society of Hematology meeting

To refer a patient, please call The James Line New-Patient Referral Center toll free: 1-800-293-5066

ASHLEY ROSKO, MD,
OSUCCC – James hematologist

"Stem cell transplant can be a curative treatment for certain cancers, but it is a long process that can place severe strains on patients."

Second hits

Two genetic mutations discovered in subset of acute myeloid leukemia

ANN-KATHRIN EISFELD, MD,
Internal Medicine resident in the Medical Scientist Training Program at Ohio State and a researcher with the OSUCCC – James Leukemia Research Program

"The hematology community has long sought to determine what other factors in addition to the fusion genes occur in this special type of leukemia."

Mutations in two genes that play a role in many solid tumors might help explain why some people develop acute myeloid leukemia (AML), according to a study led by OSUCCC – James researchers.

The *CCND1* and *CCND2* genes have been implicated in solid tumors, but this recent study provides some of the first data to describe their role in core binding factor acute myeloid leukemia (CBF-AML).

CBF-AML has two subtypes, called t(8;21) and inv(16). Both are caused by chromosomal damage that merges two different genes. But the resulting fusion genes alone are incapable of causing leukemia; a second mutation is necessary.

"The hematology community has long sought to determine what other factors in addition to the fusion genes occur in this special type of leukemia," says first author Ann-Kathrin Eisfeld, MD, Internal Medicine resident in Ohio State's Medical Scientist Training Program and a researcher with the OSUCCC – James Leukemia Research Program. Eisfeld works in the laboratories of OSUCCC – James researchers Clara D. Bloomfield, MD, and Albert de la Chapelle, MD, PhD, who led the study.

"We are the first to describe that mutations in *CCND1*, and among the first to describe that mutations in the sister gene *CCND2,* are unique features of CBF-AML with t(8;21)," Eisfeld says.

The researchers also found that mutations in *CCND2* lead to more aggressive growth of leukemia cell lines. "Based on those results, we are seeking to learn if they actually provide a transformative 'second hit' that propels the cells carrying the fusion gene to progress into cancer," Eisfeld adds.

The team analyzed pretreatment bone marrow and peripheral blood samples from 177 adult CBF-AML patients who received similar medical treatment through a national clinical trial conducted at multiple centers across the United States.

The findings could help explain the clinical differences between patients with t(8;21) and those with inv(16), and could also lead to the identification of new potential therapeutic targets.

Published in the journal Leukemia

SURVIVORSHIP

Psychosocial Trajectories

Study tracks 5-year trajectories of stress, depression and immunity in cancer survivors

The disease course that cancer follows during the five years after diagnosis is well known for every cancer site. But similar five-year trajectories are not known for psychological, behavioral and immune responses to cancer.

A study led by researchers at the OSUCCC – James has addressed this gap. The researchers evaluated 113 women who were surgically treated for breast cancer. The study followed the women for five years, beginning just after surgery. The women self-reported measures of stress and depression, and they provided blood for immune assays (natural killer cell cytotoxicity [NKCC] and T-cell blastogenesis). The assays were repeated every four to six months for five years.

The study was led by OSUCCC – James researchers Barbara L. Andersen, PhD, professor of Psychology, and William E. Carson III, MD, professor of Surgical Oncology and associate director for clinical research at the OSUCCC – James.

The results showed that, for the average individual, psychological and innate immunity markers generally follow a pattern of recovery for the first 18 months, with depression and NKCC remaining stable, and stress showing continued improvement through year five. No reliable trajectory was found for T-cell blastogenesis.

"This study is the first to track trajectories of change in biobehaviors and immune markers for breast cancer survivors for a five-year period.

"We believe our findings have clinical relevance for guiding the timing and substance of survivorship care," Andersen says. "They also underscore the importance of screening patients at the time of diagnosis for symptoms of anxiety and depression."

To refer a patient, please call The James Line New-Patient Referral Center toll free: 1-800-293-5066

BARBARA L. ANDERSEN, PHD,
professor of Psychology

WILLIAM E. CARSON III, MD,
professor of Surgical Oncology and associate director for clinical research

"We believe our findings have clinical relevance for guiding the timing and substance of survivorship care."

—Barbara L. Andersen, PhD

OF NOTE

Recent Recognition of OSUCCC – James Physicians and Researchers

GRANTS

SUJIT BASU, MD, PhD, professor of Pathology, has received a five-year, $1.5 million grant (HL131405) from the National Heart, Lung and Blood Institute titled "Role of Chebulinic Acid in Angiogenesis."

WILLIAM CARSON III, MD, professor in the Division of Surgical Oncology at Ohio State and associate director for clinical research at the OSUCCC – James, is overseeing a $2.5 million, five-year, National Cancer Institute (NCI) grant (CA186712) titled "UM1 Supplement for Early Therapeutic Trials With Phase 2 Intent."

THE DEPARTMENT OF DEFENSE awarded a $1.5 million, three-year Breast Cancer Research Program Breakthrough Award to **Ramesh Ganju, PhD, professor and vice chair of Pathology,** and **Xue-Feng Bai, MD, PhD, associate professor of Pathology,** for a project titled "CNR2: A Novel Therapeutic Target Against Aggressive and Metastatic Breast Cancer."

CRAIG HOFMEISTER, MD, MPH, associate professor in the Division of Hematology, has received a five-year, $2.3 million NCI grant (CA201382) titled "Overcoming Imid Resistance in Myeloma." Also, Hofmeister is co-principal investigator for a $2.74 million, five-year NCI grant for a project titled "Reolysin-Based Combination Therapy in Relapsed Multiple Myeloma."

BALVEEN KAUR, PhD, professor of Neurological Surgery and associate director for shared resources at the OSUCCC – James, has received a five-year, $2 million NCI grant (CA150153) titled "Enhancing Viral Oncolysis with Vasculostatin Gene Delivery."

MICHAEL TWEEDLE, PhD, (left) **and MICHAEL KNOPP, MD, PhD,** (center) **professors in the Department of Radiology,** along with **THOMAS ROSOL, DVM, PhD, professor of Veterinary Biosciences,** have received a four-year, $2.33 million grant from the National Institute of Biomedical Imaging and Bioengineering to study an image-guided transcatheter peptide receptor radiotherapy for prostate cancer.

Emeritus professor **ALTAF WANI, PhD,** (left) and research assistant professor **QIANZHENG ZHU, PhD, both of the Department of Radiology,** have received a five-year, $2.26 million grant from the National Institute of Environmental Health Sciences to study cross-talk between DNA damage responses.

TERENCE WILLIAMS, MD, PhD, assistant professor of Radiation Oncology, was awarded a five-year, $2 million NCI grant (CA198128) titled "Exploiting Caveolae-Dependent Albumin Endocytosis to Optimize Therapy in Pancreatic Cancer."

THE HARRY T. MANGURIAN JR. FOUNDATION is donating $5 million to fund the Drug Development Institute and strategic cancer research initiatives at the OSUCCC – James, and to establish the Human Performance Innovation Initiative.

AWARDS AND HONORS

MICHAEL A. CALIGIURI, MD, (left), **director of the OSUCCC and CEO of The James, SHELDON RETCHIN, MD, MSPH,** (center), **CEO of The Ohio State University Wexner Medical Center,** and **STEVEN ALLEN, MD, CEO of Nationwide Children's Hospital,** were recognized in the 2016 list of 110 physician leaders to know by Becker's Hospital Review.

ARNAB CHAKRAVARTI, MD, professor and chair of Radiation Oncology, received the 2016 Lifetime Achievement Award from the Society of Asian-American Scientists in Cancer Research for seminal research that has advanced the treatment of brain tumors.

LANCHUN LU, PhD, assistant professor of Radiation Oncology, received the 2016 ASTRO Basic/Translational Senior Investigator Award from the American Society for Radiation Oncology for innovative work on Endoscopic 3-D OCT-Guided Brachytherapy for Early Stage Pancreatic Cancers.

THE JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE is among **14 institutions worldwide that were named as Designated Centres of Integrated Oncology and Palliative Care by the European Society for Medical Oncology.** The James also earned a **2016 Press Ganey Guardian of Excellence Award for Patient Experience in Inpatient Care and HCAHPS** (Hospital Consumer Assessment of Healthcare Providers and Systems).

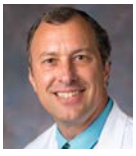
THE AMERICAN NURSES CREDENTIALING CENTER'S COMMISSION ON ACCREDITATION awarded "Accreditation with Distinction" status to The James Oncology and Critical Care Advanced Practice Fellowship. Only organizations that demonstrate no deficiencies requiring a progress report achieve this status.

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER received the 2016 Grace Award from the American Health Information Management Association. The award honors healthcare-delivery organizations that demonstrate outstanding, innovative approaches to using health information management as a way to deliver high-quality care to patients. Also, for the fourth consecutive year, the OSUWMC was among 13 academic medical centers nationwide to win Vizient's 2016 Bernard A. Birnbaum, MD, Quality Leadership Award for demonstrating superior performance.

FACULTY AND PROGRAMS

PEIXUAN GUO, PhD, a top nanobiotechnology expert, was recruited from the University of Kentucky to the Ohio State College of Pharmacy. He is a member of the OSUCCC – James Translational Therapeutics Program.

K. CRAIG KENT, MD, an internationally recognized vascular surgeon, is the new dean of The Ohio State University College of Medicine. He came to Ohio State from the University of Wisconsin School of Medicine and Public Health.



DEAN LEE, MD, PhD, is the new director of the Cellular Therapy and Cancer Immunotherapy Program at Nationwide Children's Hospital. Lee, recruited to Ohio State from The University of Texas MD Anderson Cancer Center, **is also director of cellular therapy at the OSUCCC – James.**

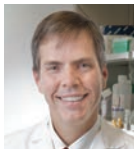
STEPHEN LESSNICK, MD, PhD, has joined **The Ohio State University College of Medicine and Nationwide Children's Hospital as director of the Center for Childhood Cancer and Blood Disorders. He is a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.**

ELAINE MARDIS, PhD, and RICK WILSON, PhD, who formerly directed the McDonnell Genome Institute at Washington University in St. Louis, have joined The Ohio State University College of Medicine and Nationwide Children's Hospital to lead a new genomics institute. Mardis is also a member of the OSUCCC – James Translational Therapeutics Program.

TIMOTHY PAWLIK, MD, MPH, PhD, a renowned surgeon and liver cancer expert, is the new chair of the Department of Surgery. Pawlik came to Ohio State from Johns Hopkins Hospital Department of Surgery.

CHERYL TAYLORE LEE, MD, a prominent expert in bladder cancer, is the new chair of the Department of Urology. Lee came to Ohio State from the University of Michigan.

LEADERSHIP ACTIVITIES AND APPOINTMENTS



JOHN C. BYRD, MD, Distinguished University Professor, director of the Division of Hematology at Ohio State, and co-leader of the OSUCCC – James Leukemia Research Program, was elected a councilor for the American Society of Hematology (ASH).

MAURA L. GILLISON, MD, PhD, professor in the Division of Medical Oncology, the Jeg Coughlin Chair in Cancer Research, and a member of the OSUCCC – James Cancer Control Program, has been elected to the National Academy of Medicine for her contributions to the fields of cancer biology, tumor virology and epidemiology.

MARYAM LUSTBERG, MD, MPH, assistant professor in the Division of Medical Oncology and a member of the OSUCCC – James Cancer Control Program, has been appointed vice chair of the Neurological Complications Study Group within the Multinational Association of Supportive Care in Cancer.

DOUGLAS MARTIN, MD, associate professor of Radiation Oncology, has been appointed as physician chair of the American Society for Therapeutic Radiology and Oncology's APEX Accreditation Committee.

ELECTRA PASKETT, PhD, MSPH, associate director for population sciences and leader of the OSUCCC – James Cancer Control Program was appointed by President Barack Obama to the National Cancer Advisory Board. Paskett also holds the Marion N. Rowley Chair in Cancer Research at Ohio State and directs the Division of Cancer Prevention and Control.

Early-Onset Colorectal Cancer

OSUCCC – James researchers recommend screening all early-onset cases for hereditary cancer syndromes

BY AMANDA HARPER

HEATHER HAMPEL, MS, LGC,
associate director for the Division of Human Genetics and for Biospecimen Research

"People with LS need intensive surveillance, with annual colonoscopies beginning at age 20-25, . . .This increased monitoring can save lives by catching precancerous polyps early, before cancer develops. "
— Heather Hampel

Lynch syndrome is the most common cause of hereditary colorectal cancer (CRC) in the United States, accounting for about 8 percent of CRC patients under age 50 and 3-4 percent of all CRC patients. The syndrome arises from mutations in one of four genes, called *MLH1, MSH2* (including *EPCAM* deletions), *MSH6* and *PMS2*. All are involved in DNA mismatch repair.

People with Lynch syndrome (LS) mutations are at high risk for developing cancer. The risk is greatest for CRC, followed by endometrial, stomach, ovarian and other cancers.

"People with LS need intensive surveillance, with annual colonoscopies beginning at age 20-25," says Heather Hampel, MS, LGC, associate director for the Division of Human Genetics and for Biospecimen Research at The Ohio State University. "This increased monitoring can save lives by catching precancerous polyps early, before cancer develops."

What hasn't been known is the prevalence of other hereditary cancer syndromes among early-onset CRC patients. "That hasn't been possible because next-generation gene sequencing, which allows us to test multiple genes at the same time for a lower cost, was not available until recently," Hampel says.

Hampel helped lead a study by researchers at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) that used next-generation sequencing to determine the prevalence and spectrum of germline mutations in 25 genes associated with LS and other hereditary cancer syndromes.

The prevalence study (ClinicalTrials.gov identifier NCT01850654) was part of the Ohio Colorectal Cancer Prevention Initiative (OCCPI), an ambitious, statewide CRC screening and prevention effort that began in 2013. Fifty Ohio hospitals worked together with the common goal of screening all newly diagnosed CRC patients in the state for LS. Funding for the OCCPI was provided by Pelotonia, an annual bicycling event held in Columbus, Ohio, to raise money for cancer research at the OSUCCC – James.

The prevelance-study findings were published in the journal *JAMA Oncology* in December 2016. Germline DNA was tested using next-generation sequencing; tumors were also studied for characteristics of LS using microsatellite instability, immunohistochemistry or both.

The new analysis involved 450 early-onset CRC patients under age 50. It is the first detailed report of the prevalence and spectrum of mutations in 25 genes associated with hereditary cancer syndromes in early-onset CRC patients, says Hampel, who also serves as associate director for biospecimen research at the OSUCCC – James. Overall, 75 mutations in cancer susceptibility genes were identified in 72 patients, or 16 percent. Also:

- 36 patients (8 percent) had LS only;
- Two patients (0.4 percent) had LS plus another hereditary cancer syndrome;
- One patient had two hereditary cancer syndromes, neither of which was LS;
- 34 patients (7.6 percent) had a different hereditary cancer syndrome.

Surprisingly, a third of patients (24 of 72) who had one or more pathogenic mutations did not meet National Comprehensive Cancer Network guidelines for at least one of their mutated genes and would have remained undetected by single-gene testing. Many of these mutations occurred in genes that have known links to CRC, but 13 patients had mutations in genes not usually associated with CRC, including *ATM, PALB2, BRCA1* and *BRCA2* (see table on page 17).

One Family's Story

Dale S. and his family, of Lima, Ohio, provide a powerful example of how knowledge about inherited genetic risk factors can affect a person's life.

After learning a family member had enrolled in the OCCPI and then tested positive for an LS mutation, Dale scheduled genetic counseling and testing for himself. He learned that he also had LS. A colonoscopy found stage 1 colon cancer, and he is expected to do very well.

"I had my first screening colonoscopy at age 45 due to my family history – just one year before learning I also had Lynch syndrome and an early tumor," says Dale. "The aggressiveness of this form of colon cancer is scary, but I think it is better to know. Now I know I have to stay vigilant for the rest of my life."

More than 126 members of this family have been tested for Lynch syndrome through the OCCPI. Forty of them learned they have Lynch syndrome. Dale, a father of six, hopes that his children also will choose to get tested once they are of age.

RACHEL PEARLMAN, MS, LGC (LEFT),
research genetic counselor, Clinical Cancer Genetics Program
HEATHER HAMPEL, MS, LGC (RIGHT), AND ALBERT DE LA CHAPELLE, MD, PHD,
Distinguished University Professor, Department of Cancer Biology and Genetics. He played key roles in the discovery of Lynch syndrome (LS) genes, in development of the LS screening test and in studies on universal tumor screening for LS. He also has provided leadership on the OCCPI Steering Committee.

Statewide to nationwide

As of Dec. 30, 2016, the OCCPI screening effort had enrolled 3,343 newly diagnosed CRC patients. As of November 2016, 96 CRC patients and 116 of their relatives had tested positive for LS; 69 additional CRC patients were found to have a hereditary cancer syndrome other than Lynch syndrome.

"The OCCPI and our work over the past four years demonstrate that it is possible to screen all newly diagnosed colon cancer patients for genetic risk factors through a statewide hospital collaboration," Hampel says. "And the findings of our research study demonstrate the need and value of screening early-onset CRC patients."

Hampel and her colleagues estimate that the OCCPI will save 1,000 years of life and provide $32 million in benefit to the community because of the lives it saved in the state of Ohio through the early diagnosis of LS and the reduced need of cancer treatment.

"We are now working to launch this approach nationally and to promote the screening of the 136,000 colorectal cancer patients expected to be diagnosed in 2017," Hampel says. "We believe the OCCPI can serve as a roadmap for other states to implement Lynch syndrome screening for their newly diagnosed colon cancer patients at the time of diagnosis."

Based on their new data, the OSUCCC – James research team recommends genetic counseling and a broad, multi-gene panel test of cancer susceptibility genes for all early-onset colorectal cancer patients, regardless of family history or the results of tumor screening for LS.

This differs from current professional guidelines, which recommend all colorectal cancer patients be screened for LS, with referral for genetic counseling and LS-specific genetic testing if the tumor screening test is abnormal.

"We expected to find a high rate of Lynch syndrome among early-onset colon cancer patients," says Rachel Pearlman, MS, LGC, first author of the paper and statewide

"Until multi-gene panel testing, we typically would not have tested patients with colorectal cancer for mutations in those genes unless they met criteria based on their family history."

— Rachel Pearlman

study coordinator. "What was surprising were some of the other gene mutations found, including mutations in genes traditionally linked to breast cancer risk, even in patients whose family history was not suggestive of those mutations.

"Until multi-gene panel testing, we typically would not have tested patients with colorectal cancer for mutations in those genes unless they met criteria based on their family history.

"We know that the spectrum of mutations in early-onset colorectal cancer is much broader than we originally thought—both in the number of different gene mutations causing this disease and the rates at which they occur," Pearlman says. "We believe this data offers additional support for complete genetic testing for all early-onset colorectal patients. This information can save lives by identifying at-risk family members who can then benefit from intensive cancer surveillance and prevention options."

RACHEL PEARLMAN, MS, LGC,
first author of the paper and statewide study coordinator.

GERMLINE MUTATIONS AND THEIR ASSOCIATED CANCER SYNDROMES IDENTIFIED IN THE OCCPI PREVALENCE STUDY

GENE	ASSOCIATED SYNDROME OR CANCER(S)	Overall penetrance
Genes associated with colon cancer		
MLH1	Lynch syndrome	High
MSH2	Lynch syndrome	High
MSH6	Lynch syndrome	Moderate
PMS2	Lynch syndrome	Moderate
APC	Familial adenomatous polyposis (FAP)	High
SMAD4	Juvenile polyposis syndrome	High
MUTYH	Colon Cancer	Low
Genes not traditionally associated with colon cancer		
BRCA1	Hereditary breast-ovarian cancer syndrome	High
BRCA2	Hereditary breast-ovarian cancer syndrome	High
CDKN2A	Melanoma, pancreatic cancer	High
ATM	Breast cancer, pancreatic cancer	Moderate
PALB2	Breast cancer, pancreatic cancer	Moderate

Relieving Lymphedema

New techniques and technologies are easing the pain and debilitation of lymphedema

BY BOB HECKER

An estimated 40 percent or more of patients who undergo lymph node dissection for cancer treatment will develop secondary lymphedema, but two innovative microvascular surgeries are helping patients control or even prevent this permanent and often debilitating condition.

These specialized procedures reroute lymphatic channels to allow proper fluid drainage after cancer surgery, and they are available only at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and a few other institutions in the United States.

The procedures are called lymphatic venous anastomosis (LVA), or lymphatic bypass, and vascularized lymph node transfer (VLNT), and some of these were pioneered by surgeons at the OSUCCC – James.

"Cancer surgery often involves the removal of lymph nodes that are used to help determine whether the cancer has spread," says Roman Skoracki, MD, professor and director of the Division of Reconstructive Oncological Plastic Surgery at Ohio State. He is also a member of the OSUCCC – James Cancer Control Program.

In the developed world, secondary lymphedema usually stems from oncologic therapy and is the most common type of lymphedema. Less common is primary or congenital lymphedema, which is caused by genetic defects and

The Lymphatic System and Lymphedema

The lymphatic system returns fluid and protein molecules from the tissues to the circulatory system via the lymph nodes and plays an important role in the body's immune defenses. It is composed of a network of thin-walled vessels, the lymph nodes, spleen, tonsils, adenoids and diffuse lymphoid tissue in the digestive and respiratory systems.

Removal of lymph nodes during cancer surgery can impair fluid drainage from the affected area, resulting in lymphedema. The condition is characterized by chronic and painful swelling (usually in the extremities), tightness and heaviness in the affected area, a heightened risk of infection, limited range of motion, and impaired ability to engage in activities of daily living and to wear normal clothes.

can occur at different times of life. "Worldwide," Skoracki says, "the most common reason for lymphedema is a parasitic infection called filariasis that is transmitted by mosquitoes, but we very rarely see it in the developed world."

Morbid obesity, he adds, is another etiological factor in lymphedema. "Patients with a body mass index greater than 40 or even 50 can develop significant dysfunction of their lymphatic system."

In the United States, Skoracki says, most lymphedema stems from lymph node dissection in the treatment of cancer, particularly cancers that frequently metastasize to lymph nodes, such as breast cancer, gynecologic and urologic cancers, melanomas and other skin cancers. Lymph node removal in the head and neck region can also cause swelling, but to a much lesser degree.

Skoracki says the risk of lymphedema is significantly higher among patients whose treatment requires full lymph node removal—or removal of an entire lymphatic basin—rather than just sentinel node removal for a biopsy sampling. Full lymph-node removal carries varying degrees of risk.

"For example," he says, "if all lymph nodes are removed from the axilla during surgery for breast cancer, there is a 40-percent risk of lymphedema in the arm near the affected breast. In the lower extremities, removing the superficial and deep inguinal lymph nodes probably presents a 60 percent chance of developing lymphedema."

Until recently, most patients could hope to control their swelling only by using compression garments, massage and physical therapy, but that is changing thanks to the gradually expanding availability of LVA and VLNT surgeries.

"With their expertise as microvascular plastic surgeons, Dr. Skoracki and his colleagues offer hope and relief for patients suffering from lymphedema," says Michael Miller, MD, professor and chair of the Department of Plastic Surgery at Ohio State. "They're among only a few surgeons nationwide performing these microvascular procedures, which relieve lymphedema's painful symptoms."

Besides Skoracki, surgeons who perform LVA and VLNT at the OSUCCC – James include David Cabiling, MD, and Albert Chao, MD. Both worked with Skoracki at The University of Texas MD Anderson Cancer Center before coming to Ohio State.

LVA AND VLNT

Skoracki notes that the LVA and VLNT procedures are very different.

"LVA attempts to recreate connections that naturally exist between the lymphatic system and the bloodstream in areas where they have been disrupted by lymph node removal," he says. "We utilize a super-microsurgical technique to create tiny shunts between lymphatic channels and blood vessels that carry fluid around the blocked areas. The rerouted fluid is then dumped into the bloodstream, which has the capacity to take on a significantly greater amount of fluid than it usually carries."

Skoracki was part of a 2013 study published in the journal *Plastic and Reconstructive Surgery* that involved 100 patients who underwent LVA. "We saw symptom improvement in 96 percent of patients," he says. "This technique proved especially effective for those who had already developed early-stage lymphedema in their arms and hands."

Importantly, he adds, "We now offer this same approach prophylactically to high-risk breast cancer patients to minimize their risk of developing lymphedema. By performing this procedure at the time of a lumpectomy or mastectomy, we can lower a woman's risk of developing lymphedema by 90 percent.

ROMAN SKORACKI, MD,
professor and director of the Division of Reconstructive Oncological Plastic Surgery at Ohio State

"We may offer something similar prophylactically for lower extremity patients as well, including those with urologic and gynecologic cancers, but that's still in its infancy."

LVA is not an option for patients who, according to fluorescent imaging techniques, have no functioning lymphatic channels to connect to in the affected region. Those patients may be candidates for the newer VLNT procedure, which reintroduces lymph nodes into an area where they have been removed.

"We transplant lymph nodes from an unaffected area of the body and attach them to a blood supply in the affected area," the microsurgeon says. "Then the lymph nodes themselves sprout connections and release vascular endothelial growth factor C (VEGF-C), which attracts the growth of lymphatic channels toward them as well. So this procedure essentially recreates a functioning lymphatic system by replacing what's been lost."

In one approach to VLNT, Skoracki says, the OSUCCC – James surgeons are true pioneers. They were the first team to harvest and transplant lymph nodes from the body's mesentery, a fan-shaped tissue that tethers the blood vessels that come to the bowel.

"The mesentery also has a great number of lymph nodes embedded in it," he says, "and we can harvest small clusters of nodes from it without causing lymphedema at the site from which we take them.

"Most of the lymph nodes that surgeons traditionally transfer put the harvest site at risk for lymphedema. This is why we remove them from the mesentery and also the omentum (another fold of the peritoneum). We think it's a great option for patients that minimizes potential complications."

Skoracki says the OSUCCC – James microsurgeons "essentially invented" the mesentery approach and adds that, as of now, it is available nowhere else in the nation.

Technology Boost

Skoracki attributes the emergence of LVA and VNLT in part to the evolution of technology. In a September 2016 review article that he coauthored in the journal *Plastic & Reconstructive Surgery*, Skoracki and his colleagues explain that improvements in microsurgical equipment allowed the development of these super-microsurgery techniques.

"LVAs are indicated when the patient still has functionality of the lymphatic system," they write, "which may be assessed and documented using ICG lymphography as defined as linear channels propelling dye from the distal extremity toward the trunk…

"ICG lymphangiography and MRL (a specialized magnetic resonance imaging technique of the lymphatic system) enable the surgeons to locate the most functional lymphatic channels, which they then join to small blood vessels after marking the channels on the patient's skin before surgery."

Other critical advances include improvements in operating microscopes that enable surgeons to perform bypasses that were impossible to do earlier because the magnification didn't exist. New

"We still have no 'gold standard of care for lymphedema,' but research will provide more insight and better options for patients as we learn more about the pathophysiology and progression of this condition."

—Roman Skoracki, MD

infrared cameras allow surgeons to visualize lymphatic channels and obstructions through the skin before making an incision.

This equipment is available in the clinic, as well as in the operating room, Skoracki says, so physicians can preoperatively determine the stage of a patient's lymphedema and optimal surgical options.

Not All Qualify

LVA and VLNT cannot be applied to all lymphedema patients.

"For patients who are morbidly obese, the primary intervention is weight loss, and unfortunately there is no proven method of weight loss for this population other than bariatric surgery," Skoracki says. "If residual lymphedema is a problem after they lose weight, then we can offer our surgical procedures."

Others who may not qualify are patients with late-stage lymphedema. Late-stage disease is characterized by little remaining fluid and much fibrosis. Most of the swelling is due to fat overgrowth, a side effect of lymphedema.

"Sometimes we can offer liposuction to remove the fatty layer and reduce the limb size, but that doesn't address the fluid component of the problem, which we need to address first," Skoracki says.

Patients with end-stage lymphedema can present with elephantiasis and verrucous (wart-like) skin changes, he says. "Affected limbs are extremely large and very disfigured. They are difficult to wrap or compress, and they sometimes contain skin breakdown and wounds.

"We offer an excisional procedure to these patients in which we remove the affected tissue and place skin grafts on the muscle underneath. It's not the most esthetically appealing outcome, but it can improve their quality of life because these patients tend to be extremely debilitated.

"Beyond these exceptions," he says, "we have microsurgical interventions to offer most patients with lymphedema."

Expanding Availability

Skoracki and his colleagues are pleased that LVA and VLNT are becoming more widely available.

"Younger microsurgery clinicians are being trained and starting programs elsewhere," Skoracki says. "Lymphedema is a condition that calls for a multidisciplinary, individualized approach. You need to look at it from several angles, including surgical, medical, imaging and certified lymphedema therapy."

The OSUCCC – James team includes all of those components, Skoracki says. The team includes vascular internists such as Steven Dean, DO; certified lymphedema therapists such as Karen Hock, MS, who leads an oncology rehab team of physical therapists; and Daniel Eiferman, MD, a general surgeon "who has significant experience and expertise in lymphedema."

In addition, "We're seeing a huge uptick in lymphedema research around the country, including some exciting clinical trials that we are participating in here at Ohio State. One is a pharmaceutical trial for an anti-inflammatory agent that's showing effectiveness in the body's intrinsic repair mechanism for injuries to the lymphatic system," he says, pointing out that the medication is not yet available in the United States outside of a study protocol.

"We still have no 'gold standard of care for lymphedema,'" he says, "but research will provide more insight and better options for patients as we learn more about the pathophysiology and progression of this condition."

Skoracki believes this should be encouraging for physicians and their patients.

"We're seeing a blooming of treatment options, and the immediate translation from research into the clinic of things that we didn't know about five or 10 years ago, at least not to the extent that we do now," he says. "And patient access to lymphedema teams is becoming more widespread. Rather than just two or three pockets where these options are available, patients have more choices of getting help nearby."

The Six-Carbon Target

Unlocking how cancer cells derive energy from glucose is leading to novel cancer biomarkers and therapies

BY DARRELL E. WARD

Human beings are fundamentally solar powered. The energy that drives the human body—and nearly all life on Earth—originates in the sun and arrives in the diet. Much of that energy is stored in the chemical bonds of glucose, a simple six-carbon sugar. Cells extract the energy using a series of biochemical reactions to generate ATP, an energy-storage molecule that drives most of the myriad chemical reactions that keep cells and the body running.

In fact, a typical human cell contains an estimated 1billion molecules of ATP at any moment, and these molecules are consumed and replaced every minute or two. Cells draw energy from glucose and transfer it to ATP using a sequence of chemical pathways: the glycolytic pathway, the tricarboxylic acid pathway (TCA) and the electron transport chain. Cancer cells derive ATP from glucose, too, but somewhat differently from healthy cells. Researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) are studying those differences for ways to improve cancer diagnosis and treatment.

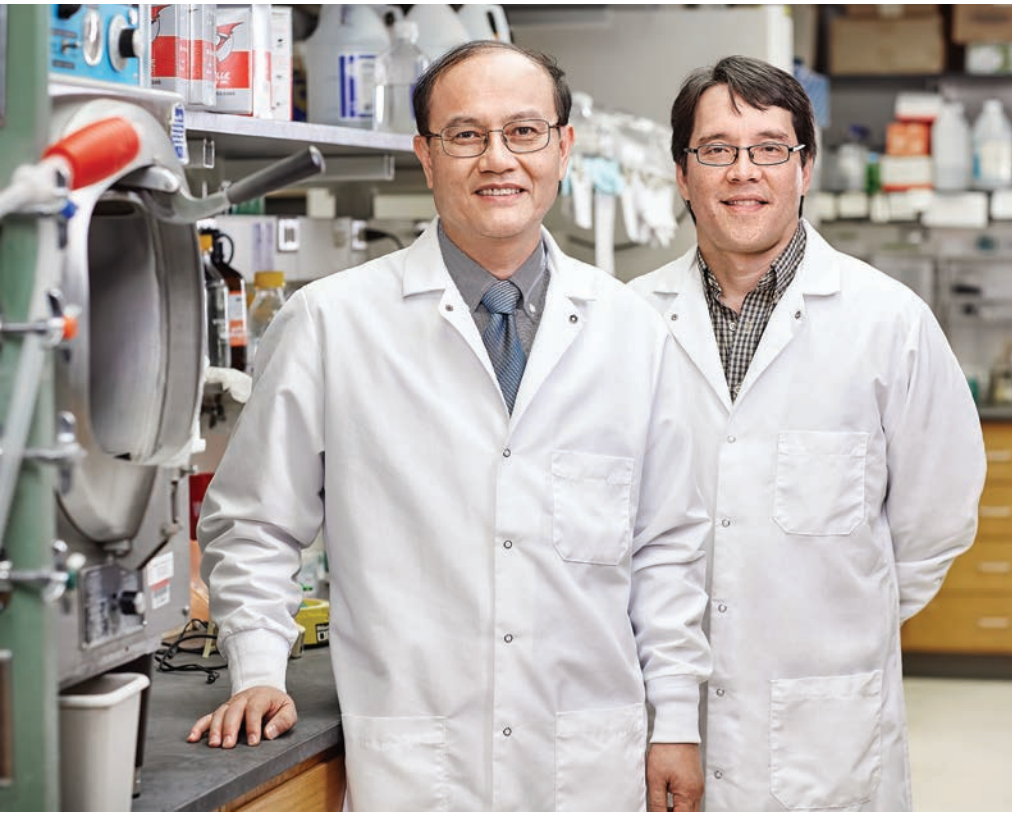
After a brief overview of glucose metabolism in healthy and cancer cells, this article provides four examples of that research, each focusing on different parts of cancer-cell energy metabolism (identified by color in the diagram on page 25). Their work has led to promising new prognostic and predictive biomarkers to improve diagnosis, and to new therapeutic targets and agents to improve cancer therapy.

FROM GLUCOSE TO ATP

In healthy human cells, glucose metabolism is carefully controlled. It begins in the cytoplasm (blue boxes) and ends in the mitochondria (orange boxes). Transporter proteins in the cell membrane take up the six-carbon sugar from the extracellular space and then undergo a conformational change that pops the molecule into the cytoplasm. There, the sugar enters the glycolysis pathway. This 10-step gauntlet of enzymes tears the molecule in two, generating two net molecules of ATP and two molecules of pyruvate.

The pyruvate enters the mitochondria, where it is converted into acetyl-CoA. The molecule spins through the tricarboxylic acid (TCA) cycle, then shoots through the electron transport chain. That process requires molecular oxygen (O_2) and generates ATP through oxidative phosphorylation. All told, this energy pathway generates about 36 molecules of ATP per molecule of glucose, plus a molecule of carbon dioxide and water.

Cancer cells require abundant ATP to drive their growth and proliferation, but genetic instability, erratic conditions in the tumor microenvironment and natural selection make each mitosis an experiment in survival for each daughter cell. Glucose metabolism becomes reprogrammed, leaving the cells less reliant on oxygen and

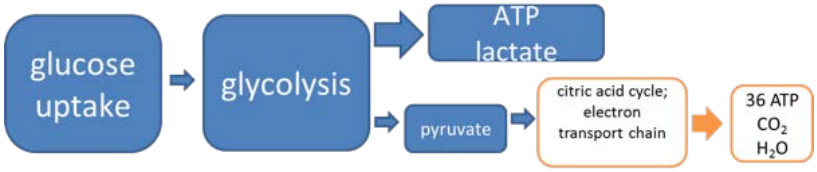


CHING-SHIH CHEN, PHD
(left) professor of Medicinal Chemistry, of Pharmacognosy, of Internal Medicine and of Urology
SAMUEL KULP, DVM, PHD,
research scientist in Medicinal Chemistry and Pharmacognosy. Both are in The Ohio State University College of Pharmacy.

better able to survive conditions of low oxygen.

As a result, while healthy cells generate about 10 percent of their ATP from the glycolysis-lactate pathway, glycolysis rates in cancer cells can be 200 times greater than those of matched healthy cells. This metabolic shift by cancer cells is sometimes called the Warburg effect, named after Otto Warburg, who first discovered it in 1924, or "aerobic glycolysis."

Consequently, cancer cells generate much more ATP in the cytoplasm (blue boxes above) while continuing to rely on aerobic respiration in the mitochondria (orange boxes).



BARRING THE DOORS (PURPLE)

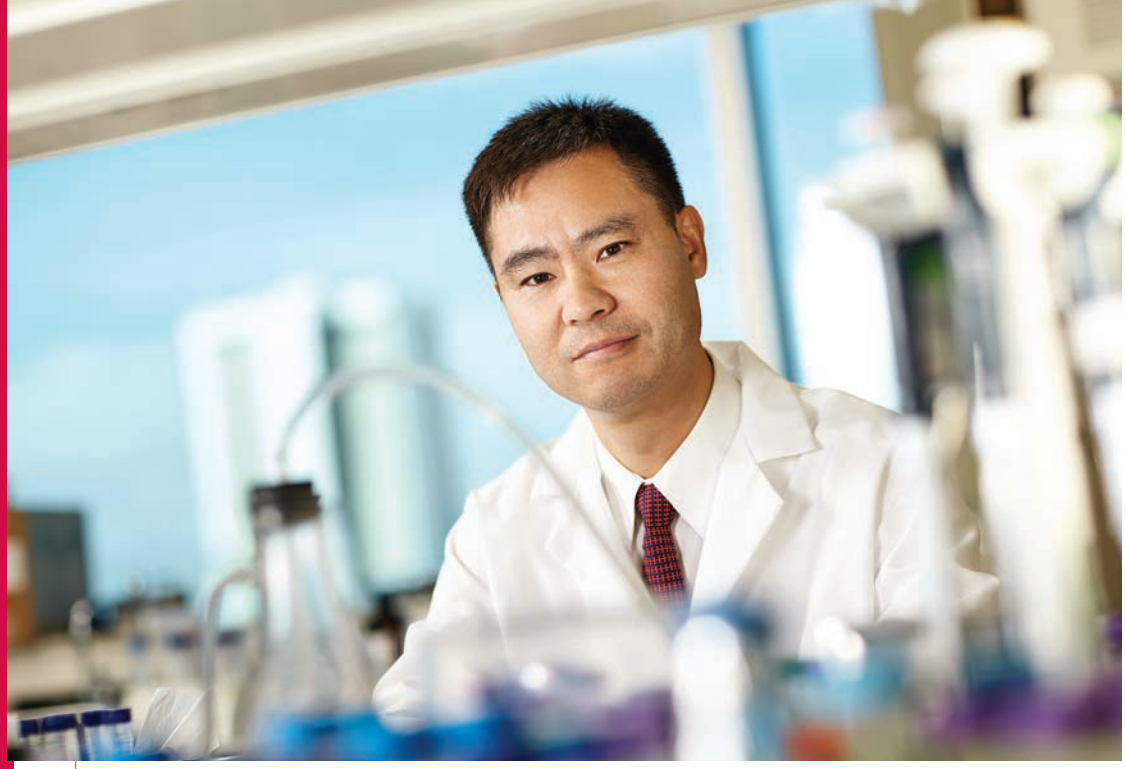
An early event in the reprogramming of glucose metabolism is the overexpression of glucose transporter proteins, and it enables cancer cells to stoke their increased use of glucose.

OSUCCC – James researcher Ching-Shih Chen, PhD, professor of Medicinal Chemistry, of Pharmacognosy, of Internal Medicine and of Urology in The Ohio State University College of Pharmacy, is leading a research team in the design of an agent, called CG-5, that inhibits glucose uptake in cancer cells. If all goes well, CG-5 will belong to a new class of anticancer drugs called energy-restriction mimetic agents.

Chen's work is part of a five-year grant awarded to him by the National Cancer Institute titled "Novel Energy Restriction-Mimetic Agents for Prostate Cancer Prevention" (grant CA112250).

"Energy restriction could be a powerful new strategy for treating cancer because it targets a survival mechanism used by many types of cancer," Chen says.

Like a cork in a bottle, CG-5 blocks glucose transport proteins, preventing the energy molecule



DELIANG GUO, PHD,
assistant professor of Radiation Oncology

from entering the cell. Chen and his lab team have found that blocking the transporter suppresses a series of signaling pathways and results in tumor suppression.

"We have learned that restricting glucose uptake can trigger a starvation-associated cell response that leads to the degradation of a series of oncogenic proteins and is often tumor suppressive," says Samuel Kulp, DVM, PhD, a research scientist in Medicinal Chemistry and Pharmacognosy in the College of Pharmacy, who helps lead the study.

Their studies in pancreatic cells and an animal model suggest that CG-5 might be effective in pancreatic cancer and might even prevent or reverse resistance to the chemotherapy drug gemcitabine, a mainstay in pancreatic cancer treatment.

Working with Christina Wu, MD, of Emory University, the researchers have evidence that the agent blocks an important signaling pathway in colon cancer called the WNT pathway and two downstream molecules in that pathway called cyclin B1 and TCF4. "This strongly suggests that CG-5 could potentially have application in preventing colon-cancer recurrence," Chen says.

THE LIPID CONNECTION (ORANGE)

Along with ATP, glycolysis and the TCA cycle produce intermediates that cancer cells need to synthesize the amino acids, nucleic acids, carbohydrates and lipids required for cell growth and mitosis. Studies led by OSUCCC – James researcher Deliang Guo, PhD, assistant professor of Radiation Oncology, have teased out the links between glycolysis and lipid synthesis in glioblastoma (GBM) cells. The findings suggest new strategies for treating cancer.

In a 2011 paper published in the journal *Cancer Discovery*, Guo and his collaborators show that GBM cells with mutations in the epidermal growth factor receptor (EGFR), which are common in GBM, upregulate the low-density lipoprotein receptor. The findings suggested that GBM tumors require external cholesterol for tumor growth, and that an EGFR inhibitor might be useful for the treatment of GBM with mutated EGFR.

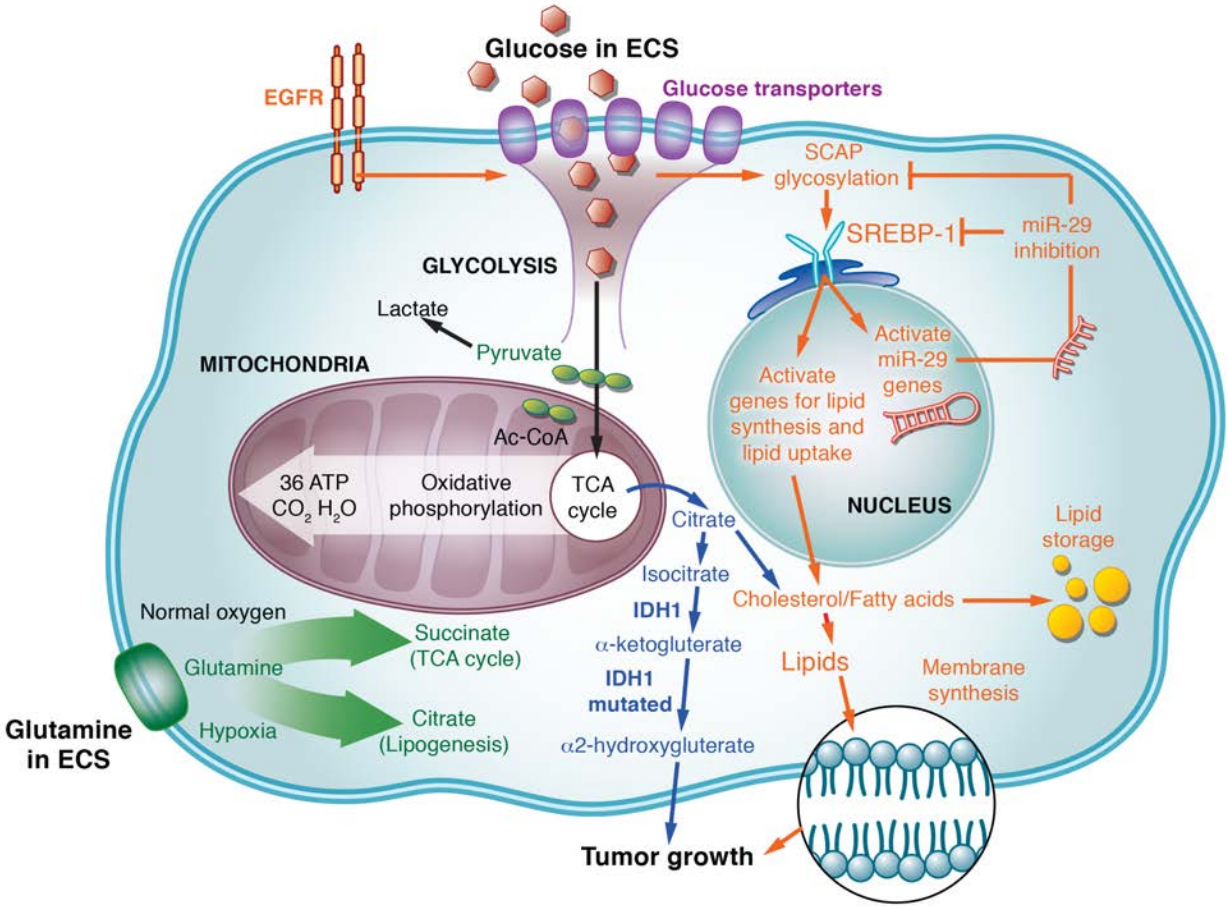
In 2015, Guo and his colleagues published a study in the journal *Cancer Cell* showing how glucose levels activate lipid synthesis during tumor growth. "Our findings reveal a previously unrecognized, critical role of glucose in controlling lipid synthesis during tumor development," Guo says.

The metabolic pathway integrates glucose metabolism, lipid synthesis and oncogenic signaling. It includes a switch that deactivates the cell's large and energetically expensive lipogenesis systems when glucose fuel levels are low.

The study shows how high glucose levels lead to the glycosylation of a protein called SCAP. The glycosylation of SCAP activates a transcription factor called SREBP-1, which travels to the nucleus and activates genes that regulate lipid biogenesis.

When glucose levels are low, SCAP glycosylation doesn't happen: The switch is off, and lipogenesis goes dark. Use of an animal model showed that inhibiting SCAP glycosylation significantly blocks GB tumor growth. The findings provide a novel approach to blocking lipid synthesis. "This pathway for synthesis of membrane lipids is required for cell growth,"

(continued on page 26)



OSUCCC – James glucose metabolism research
The four examples of OSUCCC – James research described here focus on different areas of the cell's energy metabolic pathways. (ECS – extracellular space)

Inhibiting the glucose receptor (purple)
Ching-Shih Chen, PhD, and Samuel Kulp, DVM, PhD, lead the design of the glucose uptake inhibitor called CG-5.

Glucose and lipid synthesis (orange)
Deliang Guo, PhD, led a series of studies that identified a glucose-responsive pathway that regulates lipid synthesis in glioblastoma (GBM). High intracellular glucose levels trigger glycosylation of a protein called SCAP. That activates the transcription factor SREBP-1, which activates genes that initiate lipid synthesis. Low glucose levels leave SCAP unglycosylated, and lipogenesis ceases. Other studies showed that SREBP-1 activation also upregulates microRNA-29, which, in turn, inhibits SCAP and SREBP-1 activation. Guo has also shown that activation of a gene called *SOAT1* (not shown) leads to storage of cholesterol in cytoplasmic fat droplets. Presence of the droplets correlated with poorer patient survival. Guo has also found that mutated epidermal growth factor receptor (EGFR), common in GBM, upregulates the low-density lipoprotein receptor (LDLR), suggesting that an LDLR inhibitor might be useful for the treatment of GBM with mutated EGFR.

IDH1 (blue)
Arnab Chakravarti, MD, investigated the value of mutated *IDH1* gene as a prognostic and predictive biomarker for GBM.

Glutamine metabolism (green)
Nicholas Denko, PhD, MD, led research that identified how hypoxic conditions shift glutamine use in cancer cells from energy production to lipid synthesis, which helps cancer cells survive hypoxic conditions, and how hypoxic conditions inhibit glucose-derived pyruvate from entering the TCA cycle.

Guo says. "So these transcription factors and their regulator, *SCAP*, are promising targets for anticancer therapy."

Guo and his colleagues showed that the *SCAP/SREBP-1* pathway is also regulated by a microRNA called miR-29. The study was published in the journal *Cell Reports*. They showed that SCAP glycosylation activates both *SREBP-1* and miR-29. The microRNA operates through a negative feedback loop to inhibit *SREBP1* and *SCAP.*

The researchers used an animal model to show that transfection of the tumor with miR-29 significantly reduced *SCAP/SREBP-1* expression in tumor tissue and prolonged the overall survival of mice with human GBM tumors. Adding fatty acids or active SREBP-1 protein reversed this effect, showing that miR-29-mediated suppression of GBM growth is due to decreased lipogenesis.

In addition, the prolonged survival of mice implanted with GBM cells and transfected with miR-29 suggests that miR-29 suppression of *SCAP* and *SREBP-1* might offer an effective treatment for other malignancies and for metabolic syndromes. "Further analysis of miR-29 distribution in normal brain tissues versus tumor tissues will be important for improving the treatment of glioblastoma," Guo says.

Last, in a 2016 study published in the journal *Clinical Cancer Research,* Guo and his colleagues discovered that GBM cells store large amounts of lipid as droplets in the cytoplasm, an abnormal behavior. They also found that elevated lipid storage in GBM correlated with aggressive tumor behavior and lower patient survival.

"Normally, cells do not store lipids in the cytoplasm," Guo says. "When the body has too much glucose, the excess is stored as lipids in adipocytes."

The researchers also showed that inhibiting a key gene involved in lipid-droplet formation, *SOAT1*, suppresses lipid synthesis that is regulated by *SREPB-1*. This also led to GBM-cell death.

"Our findings suggest that this approach might be most effective against GBM tumors that contain large amounts of lipid droplets," Guo says. "*SOAT1* is a more viable therapeutic target than *SREPB-1*, and a *SOAT1* inhibitor has already been studied in cardiovascular clinical trials. So the strategy of inhibiting *SOAT1* as treatment for glioblastoma could be quickly tested in cancer patients.

"Our data explain some of the underlying molecular mechanisms that enable cancer cells to survive the harsh nutritional variability of the tumor microenvironment," he says.

IDH-REGULATED METABOLISM (BLUE)

Grade II gliomas are uncommon tumors that often progress to much more lethal grade III and IV tumors (also known as glioblastoma), "but how best to treat them has been an open question," says OSUCCC – James researcher Arnab Chakravarti, MD, chair and professor of Radiation Oncology and director of the Brain Tumor Program. "Treatment for these tumors in different countries ranges from surgery alone to surgery and radiation or combined surgery, radiation and chemotherapy." Chakravarti was the translational-research national study chair for an international trial designed to determine optimal treatment for low-grade glioma (ClinicalTrials.gov number NCT00003375).

The trial involved 251 patients with grade II astrocytoma, oligoastrocytoma and oligodendroglioma. The study had three arms: radiation (RT) only; RT plus procarbazine, lomustine (also called CCNU) and vincristine; and observation only.

The findings, published in the *New England Journal of Medicine* in April 2016, showed that overall survival was significantly greater in patients receiving RT plus chemotherapy; median overall survival was 13.3 years versus 7.8 years for those who received RT alone.

"We are now trying to learn how IDH1 mutation increases sensitivity for radiation-chemotherapy."

ARNAB CHAKRAVARTI, MD,
chair and professor of Radiation Oncology and director of the Brain Tumor Program

Furthermore, those who benefited most from the RT-chemotherapy combination were patients with tumors that had a particular mutation in a gene called *IDH1*. That mutation (IDH1 R132H) signaled improved survival in GBM patients. The analysis was done using preserved tissue that was available for 57 patients in the RT-only group and 56 patients in the RT-plus-chemotherapy group.

The analysis showed that, regardless of treatment, median overall survival was significantly longer among patients with the *IDH1* mutation than those without it (13.1 years vs. 5.1 years, respectively). And patients with the mutation who were treated with RT plus chemotherapy had longer overall survival than those who received RT alone.

"The numbers were relatively small but quite significant, suggesting that this mutation could be a good prognostic marker in low-grade glioma," Chakravarti says. His lab was instrumental in validating *IDH1* as a prognostic biomarker during the trial. "We are actively investigating whether *IDH1* could be a useful predictive biomarker, as well, to identify glioma patients who would benefit from chemotherapy plus radiation therapy."

IDH1, or isocitrate dehydrogenase 1, is an enzyme in the TCA cycle that normally catalyzes the conversion of isocitrate to a-ketogluterate and NADP to NADPH. The product of mutated *IDH1*, on the other hand, is 2-hydroxygluterate (2HG). *IDH1* mutations are found in about 75-80 percent of grade II tumors, about 60 percent of grade III tumors and in 5-8 percent of grade IV tumors.

"Tumors with a normal (wild type) *IDH1* gene are extremely aggressive," Chakravarti says. "Even if they look like a grade II tumor under the microscope, they behave like grade IVs.

"We are now trying to learn how *IDH1* mutation increases sensitivity for radiation-chemotherapy," Chakravarti says.

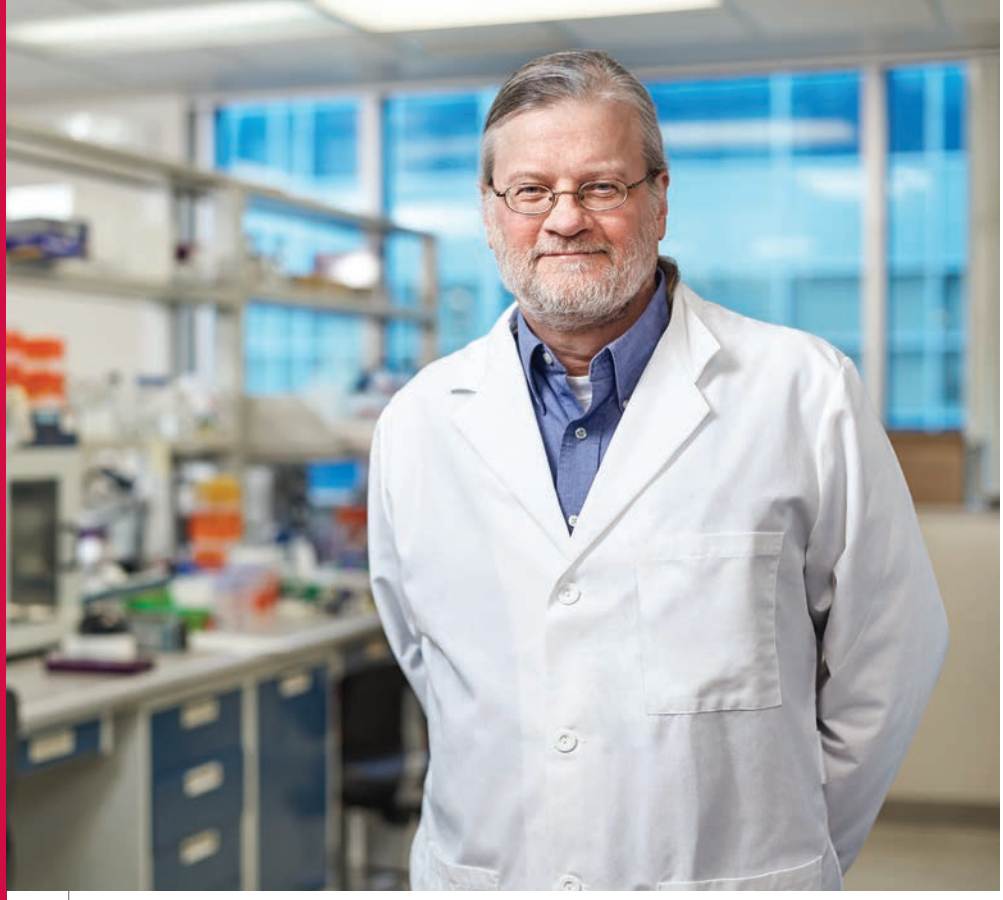
"In the cell," he adds, "mutated *IDH1* results in lower NADPH production, which increases oxidative stress, and in high 2HG levels. One idea is that the mutation leaves the cell less stable and more prone to oxidative stress, and the cell dies more easily."

GLUTAMINE DIVERSION (GREEN)

OSUCCC – James researcher Nicholas Denko, PhD, MD, associate professor of Radiation Oncology, led a 2014 study published in the journal *Cell Metabolism* (grant number CA067166) that identified how hypoxic conditions shift glutamine use in cancer cells from energy production to lipid synthesis. The change helps cancer cells survive hypoxic conditions.

"Our results are particularly exciting because glutamine metabolism is a potential target for anticancer therapy," Denko says.

The findings might offer a new strategy for inhibiting tumor growth by developing agents that reverse the hypoxia-activate pathway, making the cells again vulnerable to hypoxia, he explains. "Tumor cells require glutamine for growth, but drugs that completely block glutamine metabolism will have unwanted side effects because glutamine is also an important neurotransmitter.



"Tumor cells require glutamine for growth, but drugs that completely block glutamine metabolism will have unwanted side effects because glutamine is also an important neurotransmitter."

NICHOLAS DENKO, PHD, MD,
associate professor of Radiation Oncology

"We show that we can block the growth of model tumors by making hypoxic glutamine metabolism follow the normal-oxygen pathway," Denko adds. He notes that such a therapy should have few-if-any unwanted side effects because normal tissue is oxygenated and already using glutamine in the normal manner.

Denko and his colleagues found that hypoxic conditions activate a gene called *HIF1*. This led to the breakdown of an enzyme called OGDH2, which is necessary for glutamine to produce energy via the TCA cycle. Loss of the enzyme shifted glutamine use into its conversion to citrate and lipid synthesis.

But malignant cells that were forced to express a hypoxia-resistant form of OGDH2 grew significantly slower in an animal model than tumors with normal OGDH2. "This suggests that reversing this hypoxia pathway might be an effective strategy for inhibiting tumor growth," Denko says.

In 2016, Denko led a study that provides insights into how hypoxic conditions inhibit glucose-derived pyruvate from entering the TCA cycle. Hypoxia decreases mitochondrial function by diverting pyruvate into increased lactate production. Published in the journal *Scientific Reports*, the study investigated the mechanism that inactivates pyruvate dehydrogenase (PDH), a large mitochondrial enzyme complex that converts pyruvate to acetyl-CoA for entry into the TCA cycle.

The researchers show that an enzyme called PDHK1 phosphorylates one of three locations on the PDH enzyme complex, and this inactivates the enzyme. The metabolic reprogramming that shifts glucose away from TCA activity to lactate production was necessary for tumor growth in an animal model. In addition, an examination of tumor tissue from head and neck cancer patients showed that high PDHK1 levels or PDH phosphorylation correlated with poorer clinical outcomes.

"This study suggests that inhibiting PDHK1 might prevent the metabolic reprogramming that stimulates tumor growth," Denko says.

Overall, the work led by these OSUCCC – James researchers demonstrates how an understanding of cells at the molecular level helps improve cancer diagnosis and treatment. And, it reveals the remarkable mechanisms living cells use to extract energy that originates in a star.

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU-14129 Adjuvant crizotinib's effect on relapse-free survival in patients with uveal melanoma who are at high risk of recurrence following definitive therapy with surgery or radiotherapy

HYPOTHESIS: That cMET inhibition with crizotinib will prevent the development of metastases in patients with high-risk primary uveal melanoma (UM, also called ocular melanoma). The addition of adjuvant crizotinib will increase relapse-free survival by 25 percent in UM patients at high risk of recurrence.

STUDY DESIGN: This phase II, single-arm trial is designed to assess the 32-month rate of distant relapse in UM patients at high risk of recurrence following definitive therapy with surgery or radiation who receive adjuvant crizotinib. The study will also evaluate safety of the drug and determine overall survival and disease-specific survival.

RATIONALE: UM develops from melanocytes within the inner layers of the eye (choroid, ciliary body or iris). It represents about 5 percent of all melanomas and affects an estimated 2,000 people in the United States annually, mainly Caucasians. Approximately 85 percent of ocular melanomas are uveal in origin. No systemic therapy has been shown to improve survival in these patients, and about half of UM patients develop metastatic disease within 15 years of diagnosis. Median survival of distant metastatic disease is six to 12 months.

About 60-86 percent of UM cases overexpress c-MET, or the hepatocyte growth factor (HGF) receptor. Research has shown that crizotinib (already FDA approved for lung cancer) inhibits migration of UM cell lines through cMET inhibition.

This UM adjuvant trial was proposed based on the biological relevance of the HGF/cMET axis in UM, as it pertains to the preclinical data supporting the antimigratory and antitumor activity in this disease.

This is a multicenter trial in the United States. It is history-making in that is entirely funded by patient donations. Regardless of outcome, significant baseline data will be established for this tumor, giving physicians a good baseline for the development of future trials.

AT A GLANCE

Trial no.: ClinicalTrial **OSU-14129**
gov identifier: **NCT02223819**

PI: THOMAS OLENCKI, DO
Professor-clinical of Medical Oncology
Phone: 614-293-9868
Email: *Thomas.Olencki@osumc.edu*

Eligibility: All of the following: (1) Primary diagnosis of uveal melanoma with largest basal diameter greater than 12 mm, as clinically determined by the treating investigator; (2) Definitive therapy of the primary UM by surgery or radiotherapy within 120 days of initiating protocol therapy; (3) high-risk (Castle class 2) UM as determined by gene expression profiling; (4) no evidence of metastatic disease.

Three new instruments boost metabolomics analyses at the OSUCCC – James

Metabolomics is a relatively new area of analysis that identifies and monitors the metabolites present in biological samples such as cells, tissues or serum. In cancer research, it can provide important insights into how the metabolism of cancer cells differs from healthy cells, and how individuals differ in the way they respond to therapeutic or preventive treatments.

For example, a group of OSUCCC – James researchers investigated the ability of two soy bread formulations to prevent recurrent prostate cancer. In a study published in the journal *Cancer Prevention Research*, the group showed that men with asymptomatic prostate cancer who consumed the soy bread clustered into four groups according to the levels of certain soy isoflavone metabolites in their urine and blood that derive from the gut microbiome.

Such clustering might help identify individuals who are more or less responsive to soy intervention, which has important implications for designing future cancer prevention trials.

Metabolomic analyses are available to OSUCCC – James investigators through the Nutrient and Phytochemical Analytics Shared Resource (NPASR). The NPASR specializes in the development and implementation of liquid chromatography-mass spectrometry (LC-MS)-based analytical methods for the qualitative and quantitative determination of small molecules.

Ken Riedl, PhD, associate director of the OSUCCC – James Nutrient and Phytochemical Analytics Shared Resource, and research scientist Morgan Cichon, PhD, with the Agilent 6550 QTOF-MS

The NPASR recently acquired three new instruments for high-throughput untargeted metabolomics, targeted metabolomics and lipidomics, respectively:

- The Agilent 6550 QTOF separates and detects thousands of small molecule metabolites in a single biological sample (biofluids, tissues, cells). The information can often differentiate individuals or treatment groups by metabolic phenotype. The data can be combined with other omics data to better understand mechanisms underlying cancer progression, treatment and prevention.
- The Agilent 6495 triple quadrupole MS is used for targeted metabolomics experiments and biomarker validation and complements the 6550 QTOF. For example, small molecule biomarkers identified in untargeted metabolomics experiments can be quantitated and validated with this platform.
- The Sciex Lipidyzer quantitatively captures over 1,100 biological lipids spanning 13 lipid classes in blood. The instrument can profile the most abundant lipid species in biological samples and assess the effects of various treatments or disease states on these profiles.

For more information about the NPASR, visit http://cancer.osu.edu/npasr.

Free Online Cancer Course Available

"Introduction to the Science of Cancer" is a free, noncredit, online course being offered through iTunes U by The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) in conjunction with Ohio State's Office of Distance Education and eLearning.

More than 30 OSUCCC – James oncologists and researchers explain key cancer-related concepts in accessible, user-friendly terms. In 35 videos within the course's five modules, these cancer experts explain the nature of cancer; the diagnosis, treatment and prevention of cancer; and cancer research. Course content includes downloadable slides and readings, along with supplemental information.

"Introduction to the Science of Cancer" is designed for people who have limited knowledge of science but who want a better understanding of cancer. It could also be useful to those with interest in cancer in under-resourced countries, including nursing and medical students, hospital staff, reporters/editors, secondary-school teachers, social workers and community-health personnel.

"The OSUCCC – James offers this free course to encourage a greater commitment to cancer prevention globally," says OSUCCC Director and James CEO Michael A. Caligiuri, MD.

Caligiuri introduces each module and presents an overview of cancer research.

In 2012, an estimated 14.1 million people developed cancer worldwide, and 8 million people died of it. The number of cancer cases is expected to rise to 22 million in the next 20 years due to growth and aging of the world population. Sixty percent of cancer cases and 70 percent of cancer deaths occur in Africa, Asia and Central and South America, which have few resources for cancer treatment.

"We believe that a sound understanding of cancer by people everywhere will encourage a stronger commitment to cancer prevention by individuals, communities and nations, and lead to better cancer care," Caligiuri says. "For that reason, the OSUCCC – James is making this course available."

To view the course and course materials, visit http://go.osu.edu/scienceofcancer. Full access to the course and course materials requires an Apple ID and the iTunes U app. Both are free.

The OSUCCC – James also makes the Introduction to the Science of Cancer course available to teachers and other educators on a password-protected website specifically designed for them. For more information and to request access to the site, send an email to Darrell.Ward@osumc.edu.

UPCOMING EVENTS

14TH ANNUAL OHIO MASS SPECTROMETRY SYMPOSIUM AND JOINT CONFERENCE ON FOOD AND NUTRITIONAL METABOLOMICS

May 17 and 18

This two-day event provides an opportunity for academic and industrial researchers to present findings, share information, discuss research challenges and develop new collaborations.

Visit **http://go.osu.edu/conference2017**

PELOTONIA 17

August 4-6

Pelotonia is an annual bicycling event that takes riders through bucolic Ohio countryside on routes of varying lengths. Thousands of cyclists participate and 100 percent of the funds raised supports cancer research at the OSUCCC – James. Registration opens Feb. 8. For information visit **http://www.pelotonia.org**

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COMPREHENSIVE CANCER CENTER–
ARTHUR G. JAMES CANCER HOSPITAL AND
RICHARD J. SOLOVE RESEARCH INSTITUTE

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PELOTONIA 16 RAISES OVER $24 MILLION FOR CANCER RESEARCH AT OHIO STATE

Riders, virtual riders and volunteers who participated in the Pelotonia 16 bicycling event in August raised a record $24,104,432, all of which will support cancer research at the OSUCCC – James. The amount brings the event's eight-year total to $130,159,438.

Donors from all 50 states and more than 60 countries contributed to the funds raised by the 275 pelotons (riding groups) in the 2016 event. Pelotonia began in 2009 and is held in Columbus each August. Pelotonia 16 drew 7,749 riders and 2,790 volunteers from 40 states and eight countries. Riders participated in six routes that ranged from 25 to 180 miles.

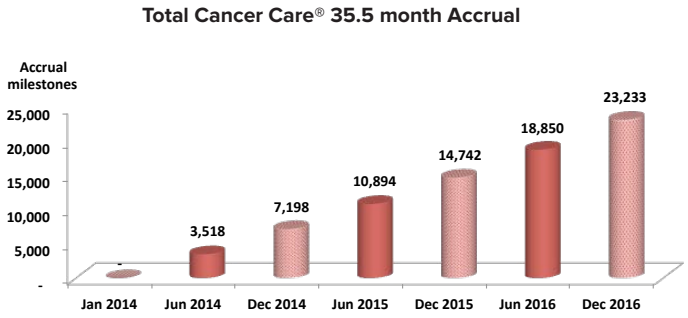
Pelotonia 17 is scheduled for Aug. 4-6. Rider registration opens Feb. 8 at pelotonia.org.

PATIENT PARTICIPATION TOPS 23,000 IN TOTAL CANCER CARE® PROTOCOL

More than 23,000 patients at the OSUCCC – James are voluntarily participating in the Total Cancer Care® (TCC) protocol for sharing biospecimens and clinical data that help move cancer research forward and personalize cancer care.

The TCC protocol has been adopted by 15 medical institutions across the nation that constitute the Oncology Research Information Exchange Network (ORIEN), a research collaboration that was co-founded and is co-anchored by the OSUCCC – James and Moffitt Cancer Center in Tampa, Fla. ORIEN members implement a common protocol (TCC) and share de-identified data to support research and help match patients to clinical trials.

Ninty-six percent of patients at the OSUCCC – James who have been approached about joining the TCC protocol have agreed to participate.



INSIDE THE NEXT FRONTIERS

RAS WORKS

The *RAS* oncogene was discovered more than 30 years ago. *RAS* mutations drive more than 30 percent of all cancers, including 95 percent of pancreatic cancers and 45 percent of colorectal cancers. Research has yet to produce an effective way to block the mutant *RAS* proteins. OSUCCC – James researchers are working to solve the problem.