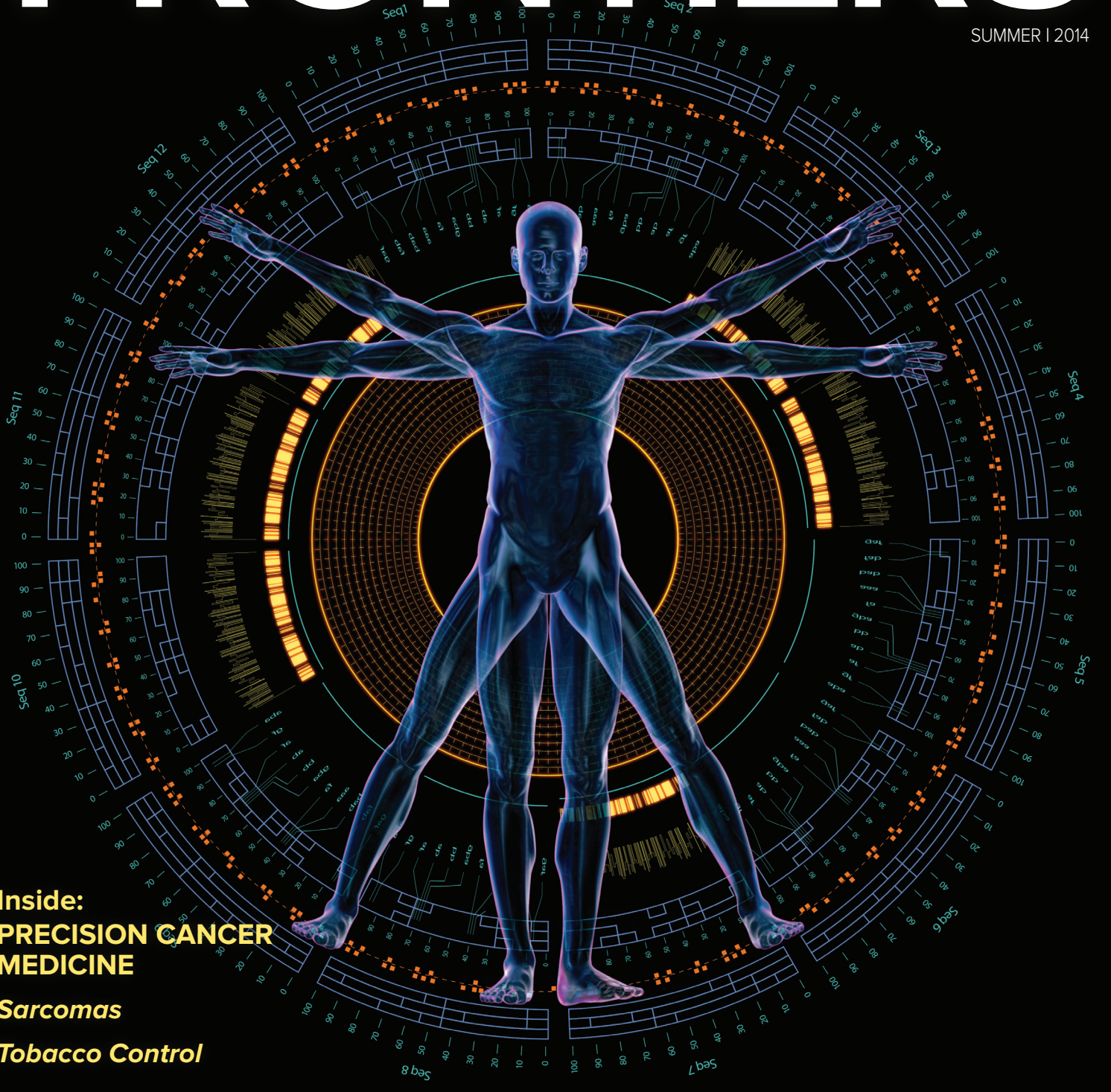
TURNING CANCER DISCOVERIES INTO TREATMENTS

FRONTIERS

SUMMER | 2014



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PRECISION CANCER MEDICINE

Sarcomas

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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

Making History

This is an especially exciting period at both The Ohio State University and the OSUCCC – James.

On July 1, Michael V. Drake, MD, became Ohio State's 15th president.

Dr. Drake is a tremendously accomplished and dynamic individual who came to Ohio State after serving nine years as chancellor at the University of California, Irvine. There, he also served as a Distinguished Professor of Ophthalmology and of Education and oversaw a significant expansion and development of the university, including new programs in public health, pharmaceutical sciences and nursing science.

We welcome Dr. Drake – the first medical doctor to serve as president of Ohio State – as we move forward with expansion of our cancer program.

That expansion will make Ohio State history with the opening of the new James Cancer Hospital and Solove Research Institute in December. The weekend of Dec. 13-14, we will transfer patients from the original James – the site of cutting-edge, compassionate care since 1990 – to the new James, which will be fully and officially open Dec. 15.

The new hospital features the nation's first fully integrated cancer emergency department, sub-specialty care by floor, translational research labs on all inpatient floors and much more.

For more about the new James, see pages 30-31.

Finally, I want to mention John Byrd, MD, and his team. The Clinical Research Forum selected them to receive one of its Top 10 Clinical Research Achievement Awards in the United States for 2014 for studies of the drug ibrutinib, a targeted agent for chronic lymphocytic leukemia (CLL).

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

John's team identified ibrutinib's mechanism of action, and John led the first early-phase trial of ibrutinib in CLL. The outcome of that trial prompted the U.S. Food and Drug Administration to designate the drug a Breakthrough Therapy. Other work by John and his lab has led to phase III trials that could make oral ibrutinib an initial therapy for CLL.

John is one of nearly 300 researchers and 200 cancer sub-specialists at the OSUCCC – James working to help patients and achieve our vision of a cancer-free world.

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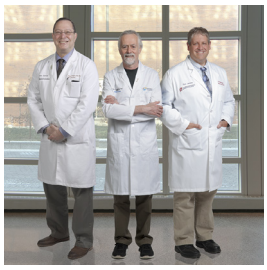
MATCH GAME

Precision cancer medicine is moving into the clinic to identify the right drug for the right patient based on tumor genomics



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Sarcomas are rare malignancies that historically have lacked research funding

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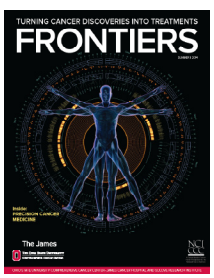
An Ohio State center provides rapid, robust science to support the FDA's new role in tobacco regulation



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

AN URGENT CHALLENGE: OLDER WOMEN WITH BREAST CANCER

By **EWA MROZEK, MD,** *Division of Medical Oncology, Stefanie Spielman Comprehensive Breast Center*

More than 232,000 women in the United States were diagnosed with breast cancer in 2013, and 43 percent of those cancers occurred in women age 65 and older. Breast cancer incidence increases with age. By 2030, almost 20 percent of the American population will be older than 65 years.

We therefore face significant growth in the number of older women with breast cancer, and this presents oncologists with an urgent challenge of determining appropriate treatments for this highly heterogeneous patient population. To help meet this growing need for cancer care, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) opened the Senior Adult Breast Cancer Clinic at the Stefanie Spielman Comprehensive Breast Center.

Many women reach old age free of severe medical conditions and with nearly complete functional capacity. Other aging women present with diminished functional reserves and social support, multiple comorbidities and common geriatric syndromes, including frailty, cognitive impairment, depression, failure to thrive and frequent falls.

They often have deficits in skills needed to live independently in the community (called "instrumental activities of daily living," or IADL) and in skills needed for independence at home (called "activities of daily living," or ADL). They are likely to take multiple medications, including inappropriate medications, which can lead to adverse drug events in cancer patients. The multiple medical problems of a frail breast cancer patient can have a greater longer-term impact on health than the cancer itself.

Typically, older patients have been under-represented in, or excluded from, chemotherapy trials. Thus, national guidelines for treating these patients generally lack a high level of evidence.

Studies have shown that older breast cancer patients are often under-treated. They have lower odds of receiving surgical therapy, adjuvant radiotherapy or chemotherapy, in spite of the evidence of significant survival benefit of standard chemotherapy regimens in healthy older patients who meet stringent eligibility criteria. On the other hand, older women may experience overtreatment and possible adverse events.

Consequently, older breast cancer patients have not fully benefited from improvements in outcomes achieved in the last two decades. A recent study reported that breast cancer mortality was 25 percent higher for women aged 65 to 74, and 63 percent higher for women 75 years or older, compared with women under age 65.

Tools are available that allow physicians and patients to estimate the benefits versus risks

Underlining and ▶ *indicate more information online at* **http://cancer.osu.edu/Frontiers**.

PRECISION CANCER TRIALS

of therapies. A comprehensive geriatric assessment (CGA) can objectively assess functional status; comorbidities; physical, cognitive and mental health; nutritional status; and social support of an older person.

Application of the CGA, supplementing a general oncologic examination, and categorizing patients as frail, vulnerable or fit, has been shown to improve prediction of survival, chemotherapy toxicity, and postoperative morbidity and mortality.

The guidelines of the National Comprehensive Cancer Network and the European Organization for Research and Treatment of Cancer recommend that all patients age 70 years and older with cancer should undergo some form of CGA. Since the care of older patients with breast cancer and multiple comorbidities is often provided by a fragmented group of clinicians, such care must be organized to ensure that it is well-coordinated and comprehensive.

Importantly, clinical research is needed to identify the benefits and harms of various treatment options for older breast cancer patients. This requires including older adults in the data collected on cancer interventions.

Patients referred to the Senior Adult Breast Cancer Clinic are evaluated by a medical oncologist, geriatric medicine nurse practitioner, pharmacist and social worker. Patients' functional status is assessed using ADL/IADL scales and "timed up and go" testing, which has been shown to predict the risk of falls in older patients with cancer.

Physical therapy and rehabilitation referrals are made for patients with the risk of falls and limitations in ADL/IADL. Cognitive impairment and depression are assessed by the Mini Mental State Examination and the Geriatric Depression Scale, respectively, and appropriate referrals for further cognitive testing, psychological evaluation or both are recommended.

A pharmacist completely reviews medications and assesses patients' adherence to and knowledge about their medications, along with inappropriate medication use as determined by Beer's criteria. The Mini Nutritional Assessment identifies patients at risk for malnutrition. We refer malnourished patients for nutrition counseling and education. A social worker evaluates social support, identifies barriers to treatment and assists with advanced-care planning.

At the end of each visit, the multidisciplinary team develops an individualized oncologic treatment plan based on CGA results and goals of care established by the patient and caregiver.

To refer patients to the Senior Adult Breast Cancer Clinic, please call The James Line New-Patient Referral Center toll free: 1-800-293-5066.

Exercising Control

Study Shows Yoga Can Help Breast Cancer Survivors

Practicing yoga for as little as three months can reduce fatigue and lower inflammation in breast cancer survivors, according to a study at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). The results were better the more the women practiced.

At the study's six-month point – three months after the formal yoga practice had ended – fatigue was 57 percent lower, on average, in women who had practiced yoga compared with the non-yoga group, and their inflammation was reduced by up to 20 percent.

JANICE KIECOLT-GLASER, PHD, *professor of Psychiatry and Psychology at the OSUCCC – James*

Though many studies suggest that yoga has many health benefits, this was the largest known randomized controlled trial that included biological measures, says first author Janice Kiecolt-Glaser, PhD.

Two hundred breast cancer survivors participated in the study. All had completed treatment before beginning the study and were yoga novices. Those in the yoga group met twice weekly for 12 weeks. Women in the control group were wait-listed to receive the same yoga sessions after the trial was over. During the study, they were instructed to go about their normal routines and not to do yoga.

"This showed that modest yoga practice over several months could have substantial benefits for breast cancer survivors," says Kiecolt-Glaser, a professor of Psychiatry and Psychology, and a Distinguished University Professor at Ohio State. She is also a member of the Institute for Behavioral Medicine Research and of the OSUCCC – James Cancer Control Program.

The researchers believe study results could generalize to other groups who have issues with fatigue and inflammation, but the team focused on breast cancer survivors because of the rigors of treatment.

"One of the problems they face is a reduction in cardiorespiratory fitness," Kiecolt-Glaser says. "The treatment is so debilitating and they are so tired, and the less you do physically, the less you're able to do. It's a downward spiral.

"That's one reason we think there are higher levels of inflammation in cancer survivors, meaning that an intervention that reduces inflammation could be beneficial."

Published in the Journal of Clinical Investigation

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

Watch online
www.youtube.com/watch?v=kL1Mr7J_kYY

CANCER GENETICS

Beneficial Findings

Genetic and Epigenetic Discoveries May Help Improve Cancer Therapies

Two genetic and epigenetic studies published in separate journals by OSUCCC – James researchers might improve the treatment of adult acute lymphocytic leukemia (AML) and other cancers.

In one study, researchers developed a scoring system for AML cells that is based on mutations in seven genes and an epigenetic change (DNA methylation) that altered the expression (activity) of the mutated genes. The findings suggest that a score based on both factors might guide treatment by identifying new subsets of AML patients.

The findings also indicate that patients with AML cells that score low – none or only one of the seven genes is overexpressed (too active) – had the best outcomes. Patients with high scores – six or seven of the genes in AML cells are overexpressed – had the poorest outcomes.

"Disease classification and prognostication for AML patients have been based largely on chromosomal and genetic markers; epigenetic changes that affect gene expression have not been considered," says principal investigator Clara D. Bloomfield, MD, a Distinguished University Professor at Ohio State who also serves as cancer scholar and senior adviser to the OSUCCC – James.

"Here we show that epigenetic changes in prognostically important mutated genes can identify novel patient subgroups, which might better guide therapy," she adds. Guido Marcucci, MD, professor of Hematology at Ohio State, and member of the Leukemia Research Program at the OSUCCC – James, was first author on the study.

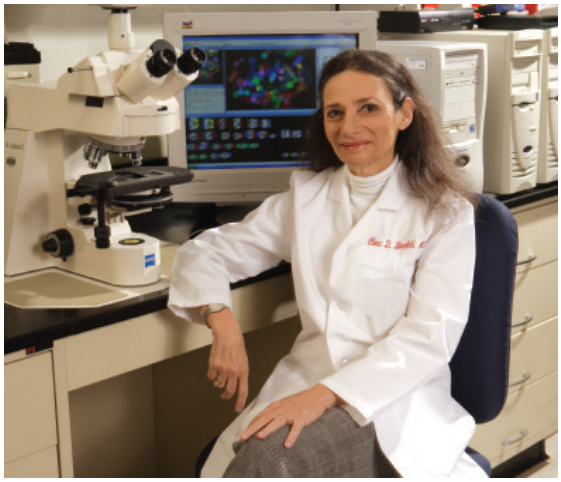
In a second study, researchers showed that the *NRAS* gene, which plays a role in cancer development, produces five variants, or isoforms, rather than just the original form. This discovery might improve drugs for cancers that stem from aberrant *NRAS* activation.

"The existence of these isoforms may be a reason why *NRAS* inhibitors have so far been unsuccessful," says corresponding author Albert de la Chapelle, MD, PhD, a Distinguished University Professor at Ohio State and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

Co-senior author Bloomfield notes that one of the newly discovered isoforms might play a greater role in cancer development than the known protein itself. First author Ann-Kathrin Eisfeld, MD, a postdoctoral fellow in the labs of de la Chapelle and Bloomfield, says the findings might lead to new drugs that improve cancer treatment.

The AML study was published in the Journal of Clinical Oncology

The NRAS study was published in Proceedings of the National Academy of Sciences of the USA



CLARA D. BLOOMFIELD, MD,
Distinguished University Professor at Ohio State who also serves as cancer scholar and senior adviser to the OSUCCC – James

Achilles Enzyme

A Possible New Target for Brain Cancer Drugs

ROBERT A. BAIOCCHI, MD, PHD
associate professor of Medicine and member of the Leukemia Research Program at the OSUCCC – James.

BALVEEN KAUR, PHD
professor and vice chair of Research, Department of Neurological Surgery and of Radiation Oncology at Ohio State, and associate director for Shared Resources at the OSUCCC – James.

A molecule in cells that shuts down the expression of genes might be a promising target for new drugs designed to treat the most frequent and lethal form of brain cancer, according to a new study by researchers at the OSUCCC – James.

The findings show that high levels of the enzyme PRMT5 are associated with aggressive growth of the brain cancer glioblastoma multiforme (GBM).

GBM is a highly invasive malignancy that strikes nearly 14,000 Americans annually. Average survival remains 15 months, even after surgery, chemotherapy and radiation.

In this study, inhibiting PRMT5 significantly improved survival in an animal model of GBM. "Our findings suggest that PRMT5 is a possible prognostic factor and therapeutic target for glioblastoma, and they provide a rationale for developing agents that target PRMT5 in this deadly disease," says co-corresponding author Robert A. Baiocchi, MD, PhD, a hematologist at the OSUCCC – James. Baiocchi is also collaborating on an Ohio State effort to develop a PMRT5 inhibitor.

"Our analyses also helped us identify PRMT5 as a master transcriptional repressor (gene silencer) in this disease, says co-corresponding author Balveen Kaur, PhD, professor and vice chair of research, Department of Neurological Surgery and of Radiation Oncology at Ohio State.

"We also learned that PRMT5 inhibition induced the death of glioblastoma cells whether the *P53* gene was mutated or not. This has important treatment implications because loss of *P53* is associated with a poor prognosis, so a PRMT5 inhibitor might be particularly important for these patients," Kaur says.

Published in the journal Cancer Research.

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

Underlining and ▶ *indicates more information online at* **http://cancer.osu.edu/Frontiers.**

Golden Arches

False Pedicle Surgery Allows for Advanced Spinal/Pelvic Reconstruction

A multidisciplinary team at the OSUCCC – James has pioneered a surgical technique that used false pedicles to reconstruct a load-bearing pelvic/spine structure to support and protect the spine following a complex cancer surgery.

Ehud Mendel, MD, FACS, and his colleagues built the false pedicles after en bloc resection to treat iliosacral chondrosarcoma with lumbar spine.

"Primary bone tumors such as chondrosarcomas must be removed completely intact; otherwise, the cancer is guaranteed to recur," says Mendel, the Justin Skestos Chair in Minimally Invasive Neurological Spinal Surgery and professor of Neurosurgery, Oncology and Orthopaedics at the Ohio State. "This technique allows fixation of the spine after the tumor is removed."

Removing these tumors intact (en bloc resection) is especially challenging, notes Mendel, who also directs Ohio State's Spine Oncology Program. "They often involve supporting bones in the pelvis and lower spine that are critical for maintaining mobility and bowel and urinary continence."

"Pedicle" refers to the short extensions of bone that help form the arches on each vertebra. The arches protect the spinal cord as it runs down the spinal column. Treating primary bone tumors often requires rebuilding structures needed to support the spine and pelvis. This surgical technique creates an artificial spinal support structure that incorporates narrow segments of living bone attached to the spinal column.

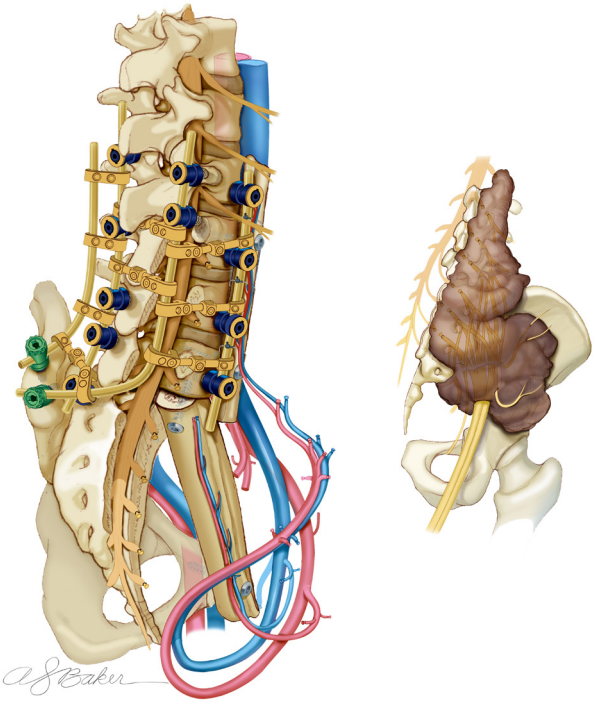
False pedicles were created using bone grafts from an amputated lower limb. These were attached to the patient's vertebrae, where they develop blood vessels that promote their growth and fusion. Surgery for primary bone tumors such as chondrosarcoma must be customized based on tumor characteristics and anatomical involvement.

Prior to surgery, Mendel's team builds a 3D model of the patient's spine to map the customized support system. "Creating false pedicles allows us to reconstruct a patient's spine and a functional load-bearing pelvic structure," Mendel says. "This gives patients the potential to walk with early mobilization."

Published in the Journal of Neurosurgery: Spine

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

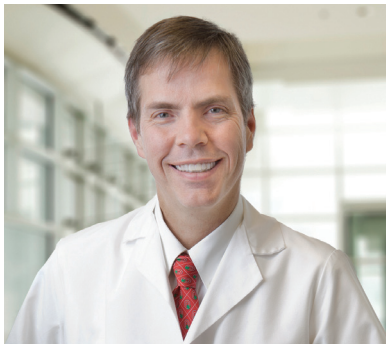
EHUD MENDEL, MD, FACS
professor of Neurosurgery, Oncology and Orthopaedics and director of director of Ohio State's Spine Oncology Program



Left figure: *Reconstructed lumbopelvic junction. Bilateral double-rod constructs with connectors and cross-links attached to the left ilium.*
Right: *The tumor resected en bloc.*

Relevant Research

Ohio State Research Played Significant Role in FDA Approval of New CLL Drug



JOHN C. BYRD, MD,
director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at Ohio State

In February, the U.S. Food and Drug Administration expanded the approved use of the drug ibrutinib (Imbruvica®) to chronic lymphocytic leukemia (CLL). Much of the clinical and basic-science research that led to the approval was performed at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute.

Much of the Ohio State work was led by John C. Byrd, MD, director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at the Ohio State. Byrd also directs the OSUCCC – James CLL Experimental Therapeutics Laboratory and co-leads the Leukemia Research Program at the OSUCCC – James.

Other key team members include Amy J. Johnson, PhD, Jason Dubovsky, PhD, Jeffrey Jones, MD, MPH, Joseph Flynn, DO, MPH, Jennifer Woyach, MD, Kami Maddocks, MD, and Kristie Blum, MD.

For more on Ohio State ibrutinib research, go to http://go.osu.edu/gQQ.

Study Reveals How Cancer Cells Thrive in Oxygen-Starved Tumors

How cancer cells thrive under conditions of low oxygen, or hypoxia, within tumors is poorly understood, but researchers at the OSUCCC – James have identified a mechanism that enables cancer cells to proliferate even in low oxygen.

NICHOLAS DENKO, PHD, MD,
associate professor of Radiation Oncology and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program

The findings might offer a new strategy for inhibiting tumor growth by reversing this hypoxia-triggered pathway.

The study found that cancer cells can alter how they use the amino acid glutamine.

Normally, cells use glutamine mainly to produce energy, diverting a small amount to make fatty acids and lipids. But in a growing tumor, low oxygen activates the gene *HIF1*, which shifts glutamine use heavily toward producing lipids needed for cell proliferation.

"We have blocked the growth of model tumors by redirecting hypoxic glutamine metabolism to make it follow the normal-oxygen pathway," says principal investigator Nicholas Denko, PhD, MD, associate professor of Radiation Oncology and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

"Such a therapeutic strategy should have few unwanted side effects because normal, oxygenated tissue is already using glutamine in the normal manner," Denko says.

Published in the journal Cell Metabolism.

Global Research

Investigating HPV-positive Cancers, Two Studies

Human papillomavirus (HPV) infection is responsible for a growing number of oropharyngeal cancers in the United States. OSUCCC – James researcher Maura Gillison, MD, PhD, led a study published in the *Journal of Clinical Oncology* to learn if the same might be true globally.

Gillison, an expert on HPV-associated oral cancer, and her collaborators investigated the potential effect of HPV infection versus smoking on oropharyngeal cancer incidence in 23 countries across four continents.

The researchers compared the incidence of oropharyngeal cancer, which is often associated with HPV, and oral cancer, which is associated with smoking, from 1982-2002. During the 19-year period:

- Oropharyngeal cancer incidence significantly increased in the United States, Australia, Canada, Japan and Slovakia, particularly among men.
- Oral cancer incidence in these countries remained unchanged or decreased.

"Our results suggest that the increase in oropharyngeal cancer was likely due to HPV infection," Gillison says, "and they underscore the potential importance of HPV as a cause of oropharyngeal cancer globally."

A second study coauthored by Gillison and published in the *Journal of Infectious Diseases* investigated concurrent oral-cervical HPV infections in the United States.

The study, led by researchers at the Centers for Disease Control and Prevention, analyzed HPV data collected from the oral cavity and the cervix by women participating in the U.S. National Health and Nutrition Survey (NHANES) in 2009 and 2010. Test results were available for 1,812 adult females. The study found:

- An HPV prevalence of 42.7 percent in the cervix and 3.8 percent in the oral cavity.
- The prevalence of oral HPV was five times higher among women with cervical HPV than among those without.
- Of the 3 percent of women with HPV infection at both sites, 7 percent had identical viral types at both sites, and 38 percent showed partial similarity.

"The high degree of dissimilarity in HPV at the two sites suggests that the infections might be acquired separately, or that the biology of the infections is different," Gillison says. "Either way, infection at one site could increase the risk of infection at the other site."

MAURA GILLISON, MD, PHD,
professor of Medicine, Epidemiology and Otolaryngology, the Jeg Coughlin Chair of Cancer Research at Ohio State, and a member of the OSUCCC – James Cancer Control Program

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

OF NOTE

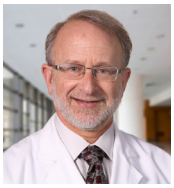
Recent Recognition of OSUCCC – James Physicians and Researchers

GRANTS

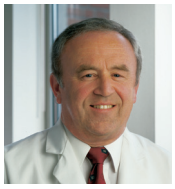
LEONA AYERS, MD, faculty emeritus, College of Medicine, received a five-year, $4.2 million competitive renewal National Cancer Institute (NCI) grant (CA183713) to form the Ohio Comprehensive Cancer Centers Biospecimen Consortium. The consortium will provide high-quality biological specimens, data and laboratory services to the general cancer research community.

MARTHA BELURY, PHD, RD, professor of Endocrinology, Diabetes and Metabolism in the College of Medicine, and of Environmental Health Sciences in the College of Public Health, has received a two-year, $414,956 NCI grant (CA185140) to study the possible role of the cytokine adiponectin in inhibiting the progression of cancer cachexia.

DAVID CARBONE, MD, PHD, professor of Medicine (shown)**,** and **MIKHAIL DIKOV, PHD, associate professor of Medicine, both in the Division of Medical Oncology,** have received a five-year, $1.5 million NCI grant (CA175370) to study notch ligands in regulation of anticancer immunity.



RICHARD GOLDBERG, MD, physician-in-chief at the OSUCCC – James, has received a five-year, $7.3 million NCI grant (CA180850) to support OSUCCC – James participation in the NCI's National Cooperative Clinical Trials Network.



MICHAEL GREVER, MD, professor and chair of the Department of Internal Medicine and principal investigator of the current NCI-sponsored Phase I program, has received a five-year, $4.19 million NCI grant (CA186712) for conducting phase I clinical trials on novel anticancer agents. The effort is part of a new consolidated NCI Experimental Therapeutics-Clinical Trials Network (ET-CTN). *Read more*

SAMSON JACOB, PhD, professor of Molecular and Cellular Biochemistry, and **KALPANA GHOSHAL, PHD, associate professor of Medicine,** have received a five-year, $1.5 million NCI grant (CA086978) to study the molecular mechanism of diet-induced non-alcoholic steatohepatitis (NASH) and liver cancer, and novel strategies to treat them.

JANICE KIECOLT-GLASER, PhD, professor of Psychiatry and of Psychology, has received a five-year, $4.3 million NCI grant (CA186720) to follow up on preliminary data suggesting that chemotherapy treatment and depression can enhance cardiovascular risk in breast cancer survivors.

A. DOUGLAS KINGHORN, PhD, DSc, professor and Jack L. Beal Chair of Pharmacognosy and Natural Products Chemistry in the College of Pharmacy, and an OSUCCC – James researcher, has received a five-year, $7.1 million NCI renewal award (CA125066) for the program project grant entitled "Discovery of Anticancer Agents of Diverse Natural Origin."

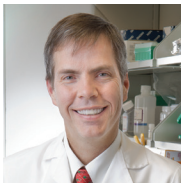
GUSTAVO LEONE, PhD, professor of Medicine and associate director of basic research at the OSUCCC – James, has received a five-year, $1.6 million NCI grant (CA121275) to study the tumor-suppressor roles of *E2F7* and *E2F8* in hepatocellular carcinoma.

GUIDO MARCUCCI, MD, professor of Medicine, and **CLARA D. BLOOMFIELD, MD, Distinguished University Professor and Ohio State University Cancer Scholar,** have received a five-year, $3.5 million NCI grant (CA180861) to form an Integrated Translational Science Center for Leukemia to support new ideas from outstanding investigators with the goal of revolutionizing the treatment of leukemia.

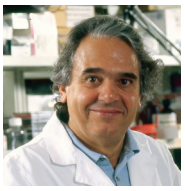
LISA YEE, MD, associate professor of Surgical Oncology, has received a four-year, $1.28 million NCI grant (CA164019) to test the ability of a fish-oil supplement rich in omega-3 polyunsaturated fatty acid to reduce the risk of recurrence in women with highly aggressive breast cancer. *Read more*

JENNIFER WOYACH, MD, assistant professor of Medicine in the Division of Hematology; AMY JOHNSON, PHD, associate professor of Medicine in the Division of Hematology; and **JOHN C. BYRD, MD, director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences,** have received a five-year, $2.59 million NCI grant (CA183444) for "Molecular Evaluation of Targeted Therapies in Lymphoid Malignancies." *Read more*

AWARDS AND HONORS

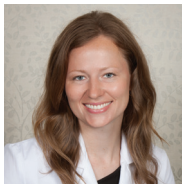


JOHN C. BYRD, MD, director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences, and his team have received one of the Top 10 Clinical Research Achievement Awards in the United States for 2014 by the Clinical Research Forum (*CRF*) for their study "Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia." *Read more*



CARLO CROCE, MD, professor and chair of the Department of Molecular Virology, Immunology and Medical Genetics, and director of Human Cancer Genetics, has been elected a Fellow in the National Academy of Inventors.

DAVID LIEBNER, MD, assistant professor of Medicine and of Biomedical Informatics, and **JAMES L. CHEN, MD, assistant professor of Biomedical Informatics and of Medicine,** have received two of three Career Development Awards issued annually by the Sarcoma Alliance for Research through Collaboration (SARC) to support sarcoma research by new investigators.



ERIN MACRAE, MD, assistant professor of Medicine, Division of Medical Oncology, has received a 2014 Career Development Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology for $200,000 over three years for a study titled "Targeting Molecular Pathways in Metastatic Triple Negative Breast Cancer."

TERENCE WILLIAMS, MD, PHD, assistant professor of Radiation Oncology, has received a three-year KL2 Scholar Award for $564,300 from Ohio State's Center for Clinical and Translational Science and the National Center for Advancing Translational Science. His study is titled "Unraveling KRAS Mechanisms of Radioresistance and Developing Novel Radiosensitizers for KRAS Mutant Carcinomas by Targeting Downstream Pathways."

TRAINEE RECOGNITION

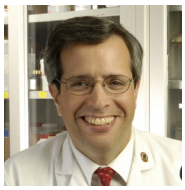
TIM LAUTENSCHLAEGER, MD, and **STEVE WALSTON, MD, both residents in Radiation Oncology,** received Resident Awards from the American College of Radiation Oncology (ACRO) for best research papers by residents at the ACRO annual meeting. The association grants just two of these awards per year.

FACULTY AND PROGRAMS

THE OSUCCC – JAMES has partnered with Moffitt Cancer Center in Tampa, Fla., to accelerate discoveries in cancer research. The Oncology Research Information Exchange Network (*ORIEN*) will hasten the development and delivery of more precise cancer treatments, diagnostic tools and prevention strategies through secure research sharing among the nation's top cancer centers and institutions. *Read more*

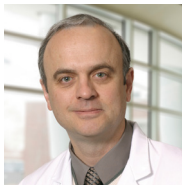
LEADERSHIP ACTIVITIES AND APPOINTMENTS

JOHN C. BYRD, MD, director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Bioscience, has been named associate editor of the journal *Blood*, one of the premier publications in the field of hematology and the official publication of the American Society of Hematology.



MICHAEL A. CALIGIURI, MD, director of The Ohio State University Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute, is the new chair of the National Institute of Medicine's National Cancer Policy Forum.

JEFFREY FOWLER, MD, professor of Obstetrics and Gynecology, has been voted President Elect II of the Board of the Society of Gynecologic Oncology (SGO), and **DAVID COHN, MD, professor of Obstetrics and Gynecology,** has been voted SGO Secretary-Treasuer Elect.



MICHAEL MILLER, MD, professor and chair of the Department of Plastic Surgery, has been elected to a six-year term as a director of the American Board of Plastic Surgery (ABPS). Miller is nationally recognized for breast reconstruction using microsurgical techniques following mastectomy.

JULIA WHITE, MD, director of Breast Radiation Oncology and vice chair for Clinical Research, Department of Radiation Oncology, has been elected general director of the National Clinical Trials Network Foundation Board of Directors and will help oversee NRG Oncology's academic, clinical and financial activities.

MATCH GAME

Precision cancer medicine is moving into the clinic to identify the right drug for the right patient based on tumor genomics

BY DARRELL E. WARD

"Precision cancer medicine" refers to a new standard of cancer care based on genomics that is making its way into the clinic.

"'Precision' refers to the use of genomic technologies that provide additional information to aid cancer diagnosis and treatment," says Sameek Roychowdhury, MD, PhD, assistant professor of Medicine and of Pharmacology at The Ohio State University and member of the Translational Therapeutics Program at Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

"Precision cancer medicine is already having a profound influence on clinical cancer care and clinical trial design, and it likely will move us away from the current organ-based classification of cancer to a molecular-based taxonomy," says Roychowdhury, a specialist in clinical genomics for prostate cancer and other solid tumors. The OSUCCC – James is both incorporating PCM in the clinic and advancing it through research.

The story of the epidermal growth factor receptor (*EGFR*) as a target of cancer therapy illustrates the development and advantages of PCM. By the late 1990s, clinical trials were under way to evaluate whether the drug gefitinib, designed to block EGFR signaling, was effective for non-small-cell lung cancer (NSCLC).

Gefitinib was the first of the *EGFR* inhibitors (erlotinib soon followed).

"The original gefitinib trials tested all patients with non-small-cell lung cancer, and the results were mildly encouraging," Roychowdhury says. "About 10 percent of American patients with NSCLC responded quickly with stabilized disease and other partial responses, while other patients showed little or no response." In Japan, a gefitinib trial showed 27 percent of patients experienced partial responses.

The drug seemed moderately promising. Afterward, two separate research groups sequenced *EGFR* genes from patients in the two trials to investigate why some patients responded better than others. The two groups reported their results simultaneously in 2004, one group in the *New England Journal of Medicine*, the other in the journal *Science*.

The findings were identical: Patients who responded to gefitinib had specific mutations in the *EGFR* gene. The results suggested that screening patients for *EGFR* mutations might identify which patients had gefitinib-sensitive tumors.

"The hypothesis that *EGFR* mutations played a role in gefitinib activity was there at the time, but those original trials were done before we could test patients in advance," Roychowdhury says.

"In 2000, we lacked the understanding of new genetic alterations that are important for cancer and for drug development, and we lacked the technology to test large numbers of genes in individual patients," he says. "Today, we can sequence hundreds of genes for under $5,000, which enables us to look at the scope of all the genes we currently think are clinically important in cancer. Testing patients for *EGFR* mutations is now standard in the OSUCCC – James lung-cancer clinic."

GLOSSARY

Advances in high-throughput gene sequencing— also called next-generation sequencing—make precision cancer medicine possible.

- **WHOLE-GENOME SEQUENCING –** sequencing the entire genome.
- **CANCER GENOME SEQUENCING –** sequencing the genes that are altered in cancer cells to identify gene changes that drive the malignancy—point mutations, copy-number changes and structural rearrangements such as translocations and gene fusions—from tumor cells versus healthy cells.

Underlining and ▶ *indicate more information online at http://cancer.osu.edu/Frontiers.*

GREGORY OTTERSON, MD
medical oncologist and lung cancer specialist at the OSUCCC – James

"Genomics and next-generation sequencing have been the most important advance in lung cancer in the last 10 years... It's been revolutionary."

—Gregory Otterson, MD

PCM AT THE OSUCCC – JAMES

The OSUCCC – James uses genomic testing to help determine therapy for patients with lung cancer, certain gastrointestinal cancers, melanoma, leukemia and lymphoma, often in conjunction with clinical trials, Roychowdhury says.

"This enables us to include patients in the trial who are more likely to benefit from the therapy and to avoid treating patients who are less likely to benefit," he says. "It also enriches studies with patients who are more likely to benefit from the therapy. That should enable us to conduct trials more efficiently and complete them faster with fewer patients and at lower cost. Hopefully, this will lead to earlier drug approval for those diseases."

"Genomics and next-generation sequencing have been *the* most important advance in lung cancer in the last 10 years," says Gregory Otterson, MD, professor of Medical Oncology at Ohio State and member of the Translational Therapeutics Program at the OSUCCC – James. "It's been revolutionary."

He says that, currently, the James Lung Cancer Clinic routinely tests for *EGFR*, *RAS* and 10 other genes to help make treatment decisions.

In 2013 the clinic began using a panel consisting of 50 genes and more than 250 mutations. The panel includes both the clinically important lung cancer mutations and mutations of research interest. The OSUCCC – James is a member of the Lung Cancer Mutation Consortium, and it shares mutation data it collects, plus clinical outcome data, with the national project. "In part, through the consortium, we've opened clinical trials for inhibitors that target *MET*, *HER2* and *BRAF*," Otterson says.

"We want as much as possible to match the right drug with the right person based on the molecular characteristics of the patient's tumor," he says.

A PILOT STUDY

A clinical trial designed and led by Roychowdhury opened at The James in November 2013 to evaluate a mechanism that uses precision cancer medicine to refer patients to novel clinical trials that have molecular eligibility criteria. The study (OSU-13053, NCT02090530) integrates next-generation sequencing and other molecular testing for patients, a multidisciplinary precision tumor board to interpret the test results, and precision cancer trials that are based on molecular eligibility. All cancer types are eligible, including advanced, refractory and metastatic diseases, that are appropriate for early-phase trials. Key steps in the Ohio State precision cancer medicine trial include:

- Genetic counseling to help patients understand the trial's goals;
- Obtaining a tumor biopsy and a buccal swab or blood sample (for germline analysis);
- Sequencing and data analysis;
- Presenting sequence data to a precision tumor board to identify actionable mutations;
- Disclosing clinically important results to the patient through a genetic counselor, and to his or her physician.

"Patients with particular mutations might receive a certain therapy regardless of the type of solid tumor it is," he says. (Roychowdhury's trial is also highlighted in more detail on page 29.)

RESEARCH

OSUCCC – James clinical and basic researchers routinely use high-throughput technology for studies that advance precision cancer medicine. Here are three examples.

EXCEPTIONAL RESPONDERS

As the story of anti-*EGFR* therapy for NSCLC shows, identifying mutations that drive cancer development is critical for developing effective targeted cancer therapies and for identifying the patients most likely to benefit from those therapies.

Underlining and ▶ *indicates more information online at* **http://cancer.osu.edu/Frontiers.**

But driver mutations have yet to be identified in over 50 percent of lung adenocarcinomas, says specialist David P. Carbone, MD, PhD, director of the OSUCCC-James Thoracic Oncology Program, and co-leader of the OSUCCC – James Translational Therapeutics Program,

Carbone seeks clues to new driver mutations through genomic studies of clinical-trial "super responders," people who show exceptional drug responses.

A recent multi-institutional study co-led by Carbone and reported in the *Journal of Clinical Investigation* describes a clinical-trial patient with advanced lung cancer who was treated with the targeted drug sorafenib. Within two months, she experienced a near complete response, and she remained progression-free and asymptomatic for five years while continuing sorafenib orally.

The patient was one of nine who responded to the treatment during the 306-patient trial. "She had by far the best and longest-lasting response to the drug," Carbone says. Using whole-genome sequencing, Carbone and his colleagues identified more than 100 alterations in the patient's cancer genome. The top dozen included a plausible target of sorafenib.

The gene was both mutated and highly overexpressed. The researchers found the same mutation in 1 percent of an independent group of lung cancer cases. They also showed that cells with this mutation formed tumors, and that the tumors were inhibited by sorafenib.

"Our study suggests that we can discover important new gene mutations that drive cancer development and progression by analyzing genes in cancer cells from patients who fare far better or far worse than others in a particular clinical trial," Carbone says.

DRUG RESISTANCE

A study published in the *New England Journal of Medicine* and co-led by OSUCCC – James researchers is an example of how Ohio State researchers use next-generation sequencing to understand how cancers become drug resistant.

The work was led by John C. Byrd, MD, director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at Ohio State, and by Amy Johnson, PhD, an associate professor in the Division of Hematology.

The findings described two mechanisms of resistance for the new drug ibrutinib, which received accelerated approval from the Food and Drug Administration for chronic lymphocytic leukemia (CLL) and for mantle-cell lymphoma. The agent irreversibly binds with Bruton's tyrosine kinase (BTK), blocking a growth signal that kills the malignant cells.

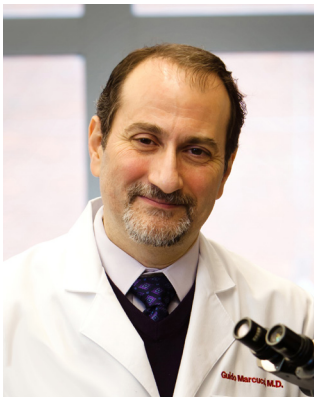
JOHN C. BYRD, MD
director, Division of Hematology, and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at Ohio State

AMY JOHNSON, PHD,
associate professor in the Division of Hematology.

Using whole-exome sequencing on cell samples from CLL patients who relapsed while taking ibrutinib, the researchers identified two mechanisms of resistance *(download an illustration)*. One involved an amino acid substitution in the BTK binding site; the other involved mutations in a protein downstream of BTK that enable growth signals to circumvent BTK.

CLARA D. BLOOMFIELD, MD, *Distinguished University Professor and holder of the William Greenville Pace III Endowed Chair in Cancer Research*

GUIDO MARCUCCI, MD, *professor of Hematology*



(*Read more* about ibrutinib research by the Byrd lab.)

EPIGENETICS

High-throughput sequencing technology can also detect epigenetic changes in genes that contribute to cancer. Epigenetic changes influence gene expression without affecting DNA structure.

Clara D. Bloomfield, MD, Distinguished University Professor and holder of the William Greenville Pace III Endowed Chair in Cancer Research, and Guido Marcucci, MD, professor of Hematology, led a study that used next-generation sequencing to detect an epigenetic change called DNA methylation.

Cells use DNA methylation – they add methyl groups to DNA – to reduce or silence gene expression. Abnormal DNA methylation in cancer cells can silence tumor-suppressor genes.

Published in the *Journal of Clinical Oncology*, the 2014 study looked at patients with cytogenetically normal acute myeloid leukemia (CN-AML). The researchers identified abnormal methylation in prognostically important mutations in 134 patients aged 60 years and older.

Bloomfield, Marcucci and their colleagues used the data to formulate a seven-gene score that encompassed both epigenetic and genetic prognostic information.

Low scores – in which one or none of the seven genes is overexpressed in AML cells – were associated with the best outcomes; high scores – in which six or seven genes were highly expressed – were associated with the poorest outcomes.

The researchers believe the seven-gene score could identify novel AML subsets that might help guide treatment.

Roychowdhury notes that genome-based cancer medicine currently does not address important aspects of cancer biology, including:

- Biopsy sampling error due to tumor heterogeneity;
- Epigenetic changes;
- microRNA dysregulation;
- Cancer stem cells;
- Tumor microenvironment influences;
- Nongenomic-based treatment options such as immunotherapy.

"Precision cancer medicine is the right direction to go, but it's in its infancy," he says. "We will no doubt see future advances, and as we factor those in, we will further improve precision cancer medicine and patient outcomes."

Underlining and *indicate more information online at http://cancer.osu.edu/Frontiers.*

AN ORPHAN PROGRAM

From Left:

RAPHAEL POLLOCK, MD, PHD, *director of Ohio State's Division of Surgical Oncology and chief of surgical services at the OSUCCC – James*

PETER HOUGHTON, *director of the Center for Childhood Cancer and Blood Diseases at The Research Institute at Nationwide Children's Hospital and member of the OSUCCC – James Translational Therapeutics Program*

JOEL MAYERSON, MD, *director of the Division of Musculoskeletal Oncology in Ohio State's Department of Orthopaedics*

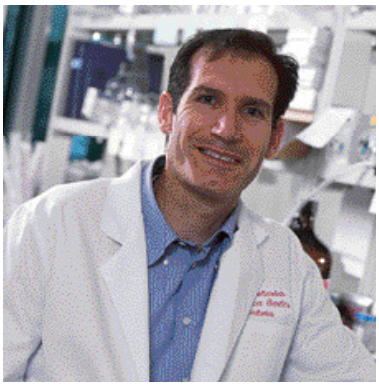
Sarcomas are rare malignancies that historically have lacked research funding

BY BOB HECKER

Like orphan malignancies generally, sarcomas are uncommon, and research into their causes and treatment are underfunded. They are a broad and heterogeneous group of cancers that make up less than 1 percent of adult malignancies and about 10 percent of childhood cancers.

Sarcomas arise from cells that resemble those that compose bone and a variety of soft tissues. Skeletal sarcomas include osteosarcoma, chondrosarcoma and Ewing sarcoma. Soft-tissue sarcomas (STS) occur in striated and smooth muscle, fibrous and adipose tissue, blood vessels, nerve tissue, tendons and the lining of joints.

Because sarcomas are rare, grant support to study them is limited, but sarcoma expert Raphael Pollock, MD, PhD, director of Ohio State's Division of Surgical Oncology and chief of surgical services at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove



"Over 70 percent of children with sarcoma are considered cured, but the five-year survival rate is 30 percent or less for those with advanced disease. . . Because these cancers are rare, few cancer centers research them and translate findings to the clinic."

—Denis Guttridge, PhD

DENIS GUTTRIDGE, PHD, *co-leader of the OSUCCC – James Translational Therapeutics Program*

Research Institute (OSUCCC – James), leads a federally funded multi-institutional research program, including investigators at the OSUCCC – James, that should help scientists better understand and treat these diseases.

Prior to his recruitment to Ohio State in 2013, Pollock worked 31 years at The University of Texas MD Anderson Cancer Center. In October 2012, he became principal investigator for a five-year, $11.5 million Specialized Programs of Research Excellence (SPORE) grant from the National Cancer Institute (NCI). The grant itself was awarded to the Sarcoma Alliance for Research through Collaboration (SARC), a nonprofit consortium of physicians and scientists dedicated to the development of new treatments for sarcoma.

"Our SPORE is an innovative approach to integrating translational and clinical study of an orphan malignancy that historically has been understudied," Pollock says.

The NCI expects about 12,000 new cases of STS and 3,000 new cases of primary bone sarcoma in the United States in 2014, as well as 4,740 deaths from STS and 1,460 deaths from bone sarcoma. Incidence rates have risen slightly over the past 35 years.

As many as 100 STS subtypes have been described according to site of origin, genetic alterations, behavior, metastatic mechanisms and response to therapy, Pollock notes. "Since the early 1970s, overall five-year survival rates for sarcoma have remained static at about 50 percent," he adds. "Our SPORE has the potential to provide major therapeutic advances."

HDAC INHIBITOR TRIAL

In addition to serving as principal investigator (PI) for the entire SARC SPORE, Pollock is co-PI for one of its four projects (see sidebar), along with Shreyaskumar Patel, MD, of MD Anderson Cancer Center, and Edwin Choy, MD, PhD, of Massachusetts General Hospital. The project is entitled "Histone Deacetylase Inhibitor (HDACi)-Based Therapeutic Strategies for the Treatment of Genetically Complex Soft Tissue Sarcoma" and evaluates a novel systemic therapy possibility for genetically complex STS.

Preclinical studies suggest that a class of drugs called histone deacetylase (HDAC) inhibitors might improve outcomes for these patients. HDACs help regulate gene expression and are also involved in cancer progression. The Pollock/Patel/Choy trial evaluates an HDAC inhibitor called mocetinostat plus the chemotherapy drug gemcitabine in adults with advanced STS.

Mocetinostat is designed to selectively inhibit specific HDACs. Patient accrual is under way. "We hope to enroll 20 to 25 patients per year, or about 100 patients overall, for this multi-institutional trial, which includes Ohio State," Pollock says.

The researchers want to learn whether the combination of the HDAC inhibitor and gemcitabine is more effective than either agent alone. "HDAC inhibitors have shown activity in a variety of STSs," Pollock says. "But to date, these agents have typically been administered alone instead of in combination with standard chemotherapy."

The project also includes laboratory and animal studies to learn whether blocking a particular HDAC (there are 18 isoforms) can produce the same therapeutic efficacy but with less toxicity.

"If our novel approach works," Pollock says, "it may form a new approach for future STS clinical trials involving other sarcoma subtypes and ultimately improve sarcoma patient management."

STRONG COLLABORATION

The OSUCCC – James, in conjunction with Nationwide Children's Hospital (NCH) in Columbus, has a history of research in adult and pediatric sarcoma, with a mix of veteran and younger investigators.

Peter Houghton, PhD

Houghton directs the Center for Childhood Cancer and Blood Diseases at The Research Institute

at NCH. He is a member of the OSUCCC – James Translational Therapeutics Program, and he develops sarcoma models for the SPORE's Tissue and Pathology core. "We have grown 20 tumors that are now being molecularly characterized," Houghton says.

In addition, Houghton is PI for a five-year, $7.8 million NCI Program Project Grant (PPG, CA165995) awarded in 2013 for studying childhood sarcomas. Through three projects, Houghton and his colleagues explore three separate but integrated signaling pathways active in these malignancies.

They are characterizing the interrelationship of these pathways and identifying potential agents to inhibit them.

"Whereas the SPORE focuses on adult sarcoma, our PPG focuses on pediatric sarcoma," says Houghton. "That said, there is reason to consider Ewing sarcoma in adults and osteosarcoma in adults as similar diseases to those occurring in children at the molecular level. Thus, our research on childhood sarcoma may have direct application to certain adult sarcomas."

Houghton serves on the SARC Developmental Therapeutics Committee along with Pollock, who notes that Ohio State is the only academic institution in the nation to have principal investigators for both a SPORE grant and a PPG for sarcoma research.

Denis Guttridge, PhD

Guttridge co-leads the OSUCCC – James Translational Therapeutics Program and leads one of the three PPG projects. His sarcoma-related research also includes a recent study published in the journal *Science Signaling* describing a molecular mechanism responsible for the loss of a critical tumor-suppressor gene in rhabdomyosarcoma – the most common pediatric sarcoma – and other STSs.

"Over 70 percent of children with sarcoma are considered cured, but the five-year survival rate is 30 percent or less for those with advanced disease," Guttridge says. "Because these cancers are rare, few cancer centers research them and translate findings to the clinic."

At the OSUCCC – James, Guttridge says, basic and clinical scientists' interactions include weekly sarcoma tumor-board meetings directed by Joel Mayerson, MD, and extend to research laboratories across the university and at NCH.

Joel Mayerson, MD

Mayerson, an orthopaedic surgeon, directs the Division of Musculoskeletal Oncology in the Department of Orthopaedics. He also is medical director of the sarcoma service for The James. His research and clinical specialties include adult and pediatric bone and soft tissue sarcomas, adjuvant chemotherapy for STSs, the use of positron emission tomography in managing bone and soft tissue sarcomas, metastatic carcinoma to bone, and complex limb reconstruction in adults and children.

Mayerson came to Ohio State in 2001 and helped build the sarcoma program from one person "to a program that our institution uses as a model for multidisciplinary care," he says. He adds that the SPORE and PPG are helping Ohio State become a leader in developmental therapeutics for STS.

"The sarcoma program now encompasses one of the most, if not the most, complete continuums of clinical and research faculty in the United States, involving the OSUCCC – James, NCH and Ohio State's College of Veterinary Medicine," Mayerson says. "As the only sarcoma program in the country to have both a SPORE grant and a pediatric Program Project Grant simultaneously, we can use molecular advances in medicine to change the paradigm of sarcoma care throughout the world."

Cheryl London, DVM, PhD

The College of Veterinary Medicine link to sarcoma research at Ohio State stems primarily from London, a researcher who studies canine cancers and is a member of the OSUCCC – James, and her many colleagues. London is a co-leader for one of the three PPG projects and leads the PPG's Comparative Animal Core. Comparative oncology integrates research on naturally occurring cancers in animals with the study of cancer biology and treatment in humans, for the benefit of both.

"Data from clinical trials in dogs with spontaneous cancer can be used to identify disease-related genes and to explore the safety and bioactivity of new therapeutic approaches to human cancers."
Cheryl London, DVM, PhD, who directs the College of Veterinary Medicine's Clinical Trials Office. Sixty to seventy percent of the CTO trials are cancer-related.

Guttridge says that, through London and her canine clinic, "We plan to test one of the drugs we are developing in our PPG in her patients with osteosarcoma."

"Data from clinical trials in dogs with spontaneous cancer can be used to identify disease-related genes and to explore the safety and bioactivity of new therapeutic approaches to human cancers," says London, who directs the College of Veterinary Medicine's Clinical Trials Office (CTO). She notes that 60-70 percent of trials performed through the CTO are cancer-related. Guttridge says this collaboration with the College of Veterinary Medicine "is another example of why our sarcoma team is so complete."

O. Hans Iwenofu, MD

Iwenofu is an assistant professor of Pathology at Ohio State and one of only a few fellowship-trained soft tissue and bone pathologists in the nation. His research focuses on discovery of novel biomarkers and characterization of the molecular underpinnings for these orphan tumors. Iwenofu also presents and discusses the adult sarcoma cases at a weekly sarcoma tumor-board meeting.

He believes that the rare and complex nature of sarcomas needs a comprehensive and multidisciplinary approach "to advance frontiers that will change the entire landscape of treatment and outcome.

"Our integrated sarcoma program is a unique resource that will doubtless get significant traction from Dr. Pollock's SARC SPORE grant," Iwenofu says. "This is an exciting time for sarcoma research at Ohio State."

YOUNG OHIO STATE RESEARCHERS RECEIVE SARC AWARDS

Each year SARC issues three Career Development Awards to promising young investigators in sarcoma. Two of the 2014 awards went to Ohio State researchers James L. Chen, MD, and David Liebner, MD.

Liebner is an assistant professor of Medicine (Division of Medical Oncology) and of Biomedical Informatics. Chen is an assistant professor of Biomedical Informatics and of Medicine (Division of Medical Oncology).

Liebner combines clinical expertise in sarcoma and melanoma with a research focus in cancer bioinformatics. His vision is to develop and leverage computational tools that integrate with the Electronic Health Record (EHR) to improve prognostic and predictive models in sarcoma and melanoma. Chen specializes in genomics and complex computational modeling. He is interested in identifying molecular biomarkers using automated genomic techniques.

"Our integrated sarcoma program is a unique resource that will doubtless get significant traction from Dr. Pollock's SARC SPORE grant... This is an exciting time for sarcoma research at Ohio State."

—O. Hans Iwenofu, MD

These biomarkers may help clinicians personalize treatment for sarcoma and other cancers.

"Our growing sarcoma program benefits from the perspectives of talented junior investigators such as Drs. Liebner and Chen," Pollock says. "It's gratifying to know that we have young scientists at Ohio State who are interested in this disease."

The young investigators are part of the highly collaborative sarcoma program that brings together basic, translational and clinical researchers at the OSUCCC – James and Nationwide Children's Hospital. Backed by the SARC SPORE and an NCI program project grant, the program holds great potential to improve sarcoma care, Houghton says.

"Having the sarcoma SPORE at Ohio State strengthens our laboratory and clinical research in this disease, potentially cross-feeding therapeutic ideas between the adult and pediatric fields," he says.

Pollock agrees. "We have a real sense of teamwork, and a strong desire to expand our efforts to help sarcoma patients. Ohio State is super that way."

Components of the SARC SPORE

The sarcoma SPORE (CA168512) is led by principal investigator (PI) **Raphael Pollock, MD, PhD,** and has four research projects. It also includes administrative, tissue and pathology, clinical trials and biostatistics cores, and a Career Developmental Program and a Developmental Research Program.

Here are the four projects:

Project I

"Histone Deacetylase Inhibitor (HDACi)-Based Therapeutic Strategies for the Treatment of Genetically Complex Soft Tissue Sarcoma." Co-PIs: **Raphael Pollock, MD, PhD**, the OSUCCC – James; **Shreyaskumar Patel, MD**, MD Anderson Cancer Center; **Edwin Choy, MD, PhD**, Massachusetts General Hospital. (Pollock also leads the administrative core.)

Project II

"Identification of Therapeutic Windows for NFI-Related Malignant Peripheral Nerve Sheath Tumor." Co-PIs: **Yuan Zhu, PhD**, Children's National Medical Center, Washington, D.C.; **Laurence Baker, DO,** University of Michigan.

Project III

"Investigating G-Protein Coupled Receptors (GPCRS) as Biomarkers of Aggressive Disease and Novel Therapeutic Targets in Ewing Sarcoma." Co-PIs: **Elizabeth Lawlor, MD, PhD; Rashmi Chugh, MD,** both of the University of Michigan.

Project IV

"Development of Quantitative Imaging Biomarkers for Assessing Response to Sarcoma Therapy." Co-PI's: **Jeffrey Yap, PhD**, University of Utah; **Lawrence Schwartz, MD,** Columbia University.

Other collaborators in the SPORE are at Harvard University, Stanford University, the Albert Einstein College of Medicine in New York City, Cancer Research and Biostatistics (CRAB®) in Seattle, Wash., and the NCI.

TOBACCO CONTROL

An Ohio State center provides rapid, robust science to support the FDA's new role in tobacco regulation

MARY ELLEN WEWERS, PHD, MPH, *professor of Health Behavior and Health Promotion in the College of Public Health and co-principal investigator for CERTS*

PETER SHIELDS, MD, *deputy director of the OSUCCC – James and co-principal investigator for CERTS*

BY KENDALL POWELL

In September 2013, a joint program between the Food and Drug Administration (FDA), the National Institutes of Health and the National Cancer Institute awarded The Ohio State University a five-year, $18.7 million grant (CA180908) to establish the Center of Excellence in Regulatory Tobacco Science (CERTS). The center investigates the diverse and changing types of tobacco products on the market and how adolescents and adults choose to use those products. The researchers will study use of the full spectrum of tobacco products, including cigarettes, smokeless tobacco, cigars and electronic cigarettes.

Ohio State's CERTS is one of 14 national centers funded by the Tobacco Centers of Regulatory Science. The FDA will provide more than $273 million for research over five years, with the National Institutes of Health providing administrative oversight and support. CERTS will include 18 researchers from Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). The researchers represent six of Ohio State's colleges.

"The FDA has an unprecedented opportunity to regulate tobacco products in the United States, and they want to make those decisions based on science—not hunches, social beliefs or politics," says Peter Shields, MD, deputy director of the OSUCCC – James and co-principal investigator for CERTS. "There are few opportunities where scientists can so directly and quickly influence national policies and government decision making."

Passage of the 2009 Family Smoking Prevention and Tobacco Control Act gave the FDA new authority to regulate the manufacture, marketing and distribution of tobacco products to protect public health. However, for the FDA to set policies that are scientifically sound and defensible in court, it needs solid data. "The research that CERTS is doing will set a foundation for policy that significantly affects how Americans use tobacco," Shields says, noting that the center adds to many ongoing tobacco research efforts at Ohio State, including clinical trials that also target regulatory science.

Currently, about 20 percent of the United States population smokes, and tobacco use is the leading cause of preventable death, killing more than 440,000 people yearly, according to the Centers for Disease Control and Prevention. The tobacco-related causes of death include lung cancer, kidney cancer, bladder cancer, heart disease, atherosclerosis, stroke, pneumonia, bronchitis and emphysema.

"Our goal is to reduce the significant morbidity and mortality associated with tobacco use," says Cathy Backinger, MPH, PhD, deputy director for Research in the Office of Science at the FDA's Center for Tobacco Products. "The law mandates that we use a public-health standard when we make a decision, looking not at the individual level but at the impact on the population as a whole."

CAMPUS-WIDE COLLABORATORS

Investigating tobacco use at the population level requires a range of expertise. The center will conduct regulatory science—research directed at particular problems the FDA needs and requests.

Why and how people use particular tobacco products, and how products foster tobacco use and hinder cessation are complex problems. "They include questions of toxicity, product design and risk perception," Shields says. "It's work that requires transdisciplinary research." The fields involved can include epidemiology, chemistry, genetics, marketing, toxicology, policy, biostatistics, and addiction and behavior research.

Consequently, the Ohio State center includes OSUCCC – James researchers for Ohio State's colleges of medicine, nursing, public health, business, law, and arts and sciences.

The FDA is particularly interested in learning how dual- and poly-use of tobacco products affects

ARTWORK BY RICHARD LILLASH

public health, an overarching theme for three of the four CERTS projects. "The tobacco industry has creatively introduced a number of different types of products," says CERTS co-principal investigator Mary Ellen Wewers, PhD, MPH, professor of Health Behavior and Health Promotion in the College of Public Health at Ohio State. "We're interested in understanding who might be attracted to them and how these products are introduced and marketed to adolescents and adults."

CERTS studies will address questions about people who combine the use of combustible products such as cigarettes, cigars and cigarillos with the use of smokeless tobacco products, including e-cigarettes, chewing tobacco, snuff and snus, a relatively new spitless tobacco product in the American market.

Backinger says the FDA wants to learn whether people who use two or more tobacco products are cutting their health risks because they replace some cigarette smoking with smokeless tobacco, which has fewer carcinogens. Or, does the nicotine in smokeless products actually drive up addiction and cigarette smoking? Does using smokeless tobacco make it easier or harder for smokers to quit cigarettes? "Right now, we just don't know," she says.

CERTS research will help answer such questions. Shields and Amy Ferketich, PhD, an epidemiologist in the College of Public Health and a researcher in the OSUCCC – James Cancer Control Program, are conducting studies comparing two cohorts of young males, aged 11 to 14. One group lives in the city of Columbus, which has been used in the past for test marketing new tobacco products. The other group is in rural Appalachian Ohio, where some counties have a smoking rate as high as 40 percent, and kids routinely start smoking at age 11.

The team will spend three years monitoring tobacco marketing strategies in the two areas and tobacco use among the two groups.

Shields will track how long it takes for youth who begin using tobacco to become addicted and whether the time to addiction depends on the type of products used—smokeless tobacco, cigarettes or both. He hypothesizes that dual-use will speed addiction. If he is correct, that data could help the FDA restrict the marketing of smokeless tobacco and develop regulations to lower the amount of nicotine in products.

Shields will also collect saliva samples from the teens and family members to identify genes that might contribute to addiction and perhaps product preferences. At the same time, Ferketich will assess the initiation rate of smokeless-tobacco use and dual-use among the rural and urban youth. She will examine how tobacco advertising and marketing, and the boys' attitudes about and awareness of that marketing, predict their use of smokeless tobacco and dual-use.

The other investigators on her team include Christopher Browning, PhD, professor of Sociology; Karol Krotki, PhD, a statistician at RTI International; Bo Lu, an associate professor in Public Health; Annie-Laurie McRee, an assistant professor in Public Health; Brady Reynolds, an association professor from the University of Kentucky; and Michael Slater, a professor of Communications at Ohio State.

"We want to learn if there is a connection between product pricing and what products people buy... If the study finds that pricing directly influences buying patterns, then the FDA can use that information to regulate pricing."

—Micah Berman, JD

Ferketich hypothesizes that kids most likely to start tobacco include "kids who have more exposure to tobacco marketing, who go to fast food restaurants more often, who view more TV programs, movies, and websites that portray smoking, and who have less awareness of marketing's aims to change their behavior." A smaller set of each cohort will carry a smartphone device for 10 days to chart real-time exposures to tobacco advertising.

Ellen Peters, PhD, professor of Psychology in the College of Arts and Sciences, and a researcher in the OSUCCC – James Cancer Control Program, is studying a question that addresses a regulatory conundrum that has already landed in the courts: how best to design the graphic warning labels on tobacco product packaging (see sidebar).

The Tobacco Control Act states that the FDA must design images to match nine simple health warnings such as "Cigarettes cause cancer," and "Tobacco smoke can harm your children."

"These labels are part of the FDA's mandate to help the public better understand the health risks of tobacco," says Peters, who also directs Ohio State's Behavioral Decision Making Initiative. "But the court disagreed with how the FDA first went about it." Now, the FDA needs strong evidence that will hold up in court and prove that its labels effectively get the message across.

For CERTS, Peters and her team will randomly assign smokers and nonsmokers to view different levels of warning labels, ranging from text-only to graphic photos. Afterward, the participants will be quizzed about their reactions to the labels. The study will pay particular attention to adolescents, young people who have experimented with smoking but have not smoked for very long.

To learn how use of e-cigarettes and other smokeless tobacco influences smoking habits, Wewer's team is surveying 800 adults from three groups: those who only smoke, those who use only smokeless tobacco, and those who use both products. "Does dual-use in fact help smokers quit cigarettes, or does it keep them addicted and using multiple products?" she asks. The FDA needs hard data to answer the questions, Wewers says.

She is also leading a project to catalog the advertising, marketing and price promotions that tobacco users are exposed to at the point-of-sale retail environments. The team, which includes Micah Berman, JD, assistant professor at the College of Public Health and at the Moritz College of Law; Christopher Browning, PhD, professor of Sociology; and consumer preference expert H. Rao Unnava, PhD, professor of Marketing at the Fisher College of Business, will compare price deals and discounts found in convenience stores, tobacco outlets and grocery stores in both rural and urban settings.

"We want to learn if there is a connection between product pricing and what products people

MICAH BERMAN, JD, *assistant professor at the College of Public Health and at the Moritz College of Law*

H. RAO UNNAVA, PHD, *professor of Marketing at the Fisher College of Business*

ELECTRA PASKETT, PHD, MSPH, *a professor in the College of Medicine and the College of Public Health*

ARTWORK BY RICHARD LILLASH

A CASE FOR STRONGER SCIENCE

Studies by Ohio State's Center for Excellence in Tobacco Regulatory Science (CERTS) will help the Food and Drug Administration (FDA) design regulations that will stand up against litigation by the tobacco industry.

For example, the 2009 Tobacco Control Act gave the FDA authority to design color images to match nine health warnings to be printed on tobacco product packaging. The messages will replace the current "Surgeon General's Warning" used since the 1970s.

The graphic images were to depict the negative consequences of tobacco use. In June 2011, the FDA released nine pictures to go with the warnings, such as diseased lungs. The tobacco industry sued, arguing that the graphic warnings restricted the companies' right to free speech.

In August 2012, a U.S. appeals court ruled in favor of the tobacco companies, citing that the FDA offered no significant evidence showing that graphic warnings would reduce smoking rates by a "material degree."

"It was a mismatch between the research and the question the court ended up asking," says Ohio State assistant professor of Public Health and of Law Micah Berman, JD, who is guiding CERTS research on how best to build a scientific case that will withstand a court test.

For the revised images, the FDA will have CERTS research to back its case.

buy," says Berman, an expert in tobacco control policy. If the study finds that pricing directly influences buying patterns, then the FDA can use that information to regulate pricing.

In addition, Berman co-leads a project under the CERTS grant that trains the next generation of tobacco regulatory scientists. He is developing a course that covers the FDA's authority, how regulations are developed and approved, and the role of science in that process. Electra Paskett, PhD, MSPH, a professor in the College of Medicine and in the College of Public Health, directs the Training Core.

As the Ohio State tobacco regulatory scientists pursue studies about new tobacco products hitting the market, they are particularly concerned about the appeal these products might hold for adolescents.

Marketing tactics that were banned long ago for cigarettes because of their appeal to youth—celebrity endorsements, fruit and candy flavors, and cartoon mascots—are being used with these new products. Researchers are also concerned that e-cigarettes might be a gateway product that leads young people first to nicotine addiction, then to smoking.

"The OSUCCC – James is working to help Americans better understand the negative effects of tobacco," Shields says. "And through the Center of Excellence in Regulatory Tobacco Science, we're helping the FDA fulfill its mandate to protect public health."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU-13053: Precision Cancer Medicine for Advanced Cancer Through High-throughput Sequencing

HYPOTHESIS: Genomics-based, personalized medicine in cancer is rapidly moving into the clinic due to advances in cost-efficient, high-throughput sequencing technology. We hypothesize that the ability to sequence individual cancers in real time will facilitate the design and implementation of clinical trials based on personalized cancer genomics; e.g., a clinical trial for a fibroblast growth factor receptor (FGFR) inhibitor that includes *FGFR* gene mutations as a molecular eligibility requirement. Clinically significant results will be disclosed to patients and their clinicians.

RATIONALE: This protocol evaluates a mechanism for the timely sequencing of tumor samples and the return of potentially clinically useful sequence results in patients with advanced or refractory cancer. This mechanism involves:

- Biospecimen collection– Patients will undergo a research tumor biopsy (most common) or contribute a tissue sample from a standard-of-care procedure or surgery (less common). Or, a previously collected tumor block can be contributed to the study. Research biopsies are done to evaluate a patient's current disease that has become resistant to previous therapies. Patients will also provide blood, buccal smear and serum samples.
- Tumor sequencing – Next-generation genome sequencing will be used to obtain a molecular profile of individual cancer specimens.
- Precision Tumor Board – A multidisciplinary Precision Tumor Board with expertise in clinical oncology, clinical genetics, pathology, genomics, bioinformatics, genetic counseling, psychology and bioethics will assess sequencing results and provide study oversight.

NOTE: Only results obtained in a CLIA-certified laboratory can be disclosed to patients and utilized for clinical decision making. In some instances, additional testing might be required and carried out by the study.

- Follow-up – Study patients will be tracked at 4 months, 8 months, 12 months, 18 months (generally by chart review, not clinic visits) to collect clinical data for individuals with respect to disease recurrence, clinical responses and overall survival.

Along with verifying a mechanism for the use of sequencing to make clinical decisions, this study will provide data for basic, translational and clinical research studies designed to teach surgeons to perform this new procedure.

AT A GLANCE

Trial no.: OSU-13053 (NCT02090530)

PI: SAMEEK ROYCHOWDHURY, MD, PHD

Phone: 614-293-6529

Email: *Sameek.Roychowdhury@osumc.edu*

Eligibility: Patients 18 years and older with a confirmed diagnosis of advanced or refractory cancer, any malignancy or tissue of origin; tumor must be suitable for research tumor biopsy; patients must be medically fit to undergo a tissue biopsy or surgical procedure to obtain tumor tissue; patients with multiple malignancies and patients with an inherited cancer syndrome or a medical history that suggests an inherited cancer syndrome.

NEED TO KNOW

At the OSUCCC—James

KEY STATS

- Third largest cancer hospital in the nation
- **21** stories
- **1.1 M** square feet
- **306** Inpatient beds, including 24-bed BMT unit
- **14** Operating Rooms
- **6** Interventional Radiology Suites
- **7** Linear accelerators for radiation therapy
- Dedicated Early-Phase Clinical Trials Unit
- *Opens December 2014*

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

INNOVATIVE DESIGN THAT PROVIDES A STATE-OF-THE-ART, HEALING ENVIRONMENT

- **Inpatient floors that specialize in specific cancer subtypes** to facilitate care by subspecialist multidisciplinary teams of physicians, nurses and pharmacists.
- **Translational research labs on each inpatient floo**r that bring physicians together with researchers to develop and deliver the most effective targeted treatments for patients.
- **A Cancer Clinical Trials Unit** offers a comforting patient environment with a staff highly experienced in safely conducting innovative, early-phase trials.
- **A State-Of-The-Art, GMP Cellular Processing Laboratory** for blood and marrow supports the hospital's 24-bed Blood and Marrow Transplant Unit.
- **Precision Cancer Medicine** using advanced genomic technologies to identify both the molecular changes causing a patient's cancer and the right drugs to treat it.
- **A Fully Integrated Cancer Emergency Department**, opening March 2015, that will treat cancer-related medical emergencies. Emergency medicine physicians and nurses will work with oncologists and oncology nurses to care for patients and ease their transition to further care at The James or at home.
- **The Oncologic Surgery Suite** has 14 operating rooms supported with the most advanced technology, including minimally invasive robotic surgery, to enable teams of surgeons to perform complex procedures.
- **Intra-Operative Radiation Therapy and Intra-Operative MRI technologies** that can be used for patients in the operating room for greater safety and efficiency.
- **The Radiation Oncology Department** that is equipped with seven Varian TruBeam linear accelerators, as well as a brachytherapy unit, bringing the newest technologies for delivering radiation therapy.

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OHIO STATE JOINS EUROPEAN LEUKEMIANET

The Ohio State University is now an official member of the European LeukemiaNet (ELN), a European Union-funded organization of physicians, scientists and patients who focus on leukemia. The organization has 194 participating centers in 39 countries, and 1,000 researchers and associates. Along with the United States, other non-European member countries include Israel, Lebanon and Russia.

The ELN integrates more than 100 chronic- and acute-leukemia trial groups and more than 100 academic and industry partners across Europe involved in diagnostics (cytogenetics and genomics), treatment research, tumor registry and guidelines development, to form a cooperative network for progress in leukemia-related research and health care.

OSUCCC – James researcher Clara D. Bloomfield, MD, Distinguished University Professor, Ohio State University Cancer Scholar and Senior Adviser, and William Greenville Pace III Endowed Chair in Cancer Research, played a key advisory role beginning in 2000 to help organize the network. She worked with European colleagues to help unify a number of independent leukemia cooperative groups into an interacting, collaborative system, first in Germany, then more generally in Europe, with funding provided by the European Union.

ELN membership offers OSUCCC – James leukemia researchers broad, international opportunities for collaborative studies, the exchange of information and ideas, and the development of widely applied treatment guidelines.

ELN European LeukemiaNet

OPENING DECEMBER 15, 2014

Ohio State's new James Cancer Hospital and Solove Research Institute will open its doors in December. The 21-story facility will be the third-largest cancer hospital in the United States and the first to have its own fully integrated Emergency Department (ED) for specialized emergency oncology care.

The hospital's design unites the Ohio State cancer program's missions of research, education and patient care, including bringing patients and researchers together. Each patient floor has a translational research laboratory with a glass front. These labs will facilitate collaboration between physicians and bench scientists. At the same time, patients can look in and researchers can look out – instilling greater hope in patients and reminding researchers of their work's vital importance.

Such innovations should expedite the development of new, genetically personalized treatments and of new strategies for preventing cancer.

Inpatients will be moved to the new James Cancer Hospital and Solove Research Institute the weekend of Dec. 13-14, and the hospital will officially open Dec. 15.

For more features of the new James Cancer Hospital and Solove Research Institute, see pages 30-31.

UPCOMING EVENTS

2ND CANCER CACHEXIA CONFERENCE: EVOLVING MECHANISMS AND THERAPIES

Sept. 26-28, Montreal Marriott Chateau Champlain, Montreal, Canada

FOCUS: The clinical manifestations of cancer cachexia, molecular mechanisms leading to weight loss and fatigue, common and distinct pathways between cancer and other atrophy conditions, potential biomarkers, therapeutic targets and current status of clinical trials.

For information or to register, visit
http://cancercachexia2014.com/html/registration.html

FROM CANCER TO HEALTH TRAINING INSTITUTE: A STRESS MANAGEMENT AND COPING INTERVENTION

May 14-16, 2015, The Ohio State University Department of Psychology

FOCUS: This three-day training institute equips healthcare professionals to teach an empirically supported, biobehavioral stress-management intervention to newly diagnosed cancer patients. The intervention can improve patients' coping skills and ability to adjust emotionally to the challenges of cancer from diagnosis to survivorship.

For eligibility requirements and information, visit
http://cancertohealth.osu.edu