WINTER | 2013

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frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

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OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER–JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

UPFRONT

The Director's Perspective

Understanding the Molecular Mechanisms of Malignancy is Key to Cancer Care

A tenet of Ohio State's cancer program is that there is no such thing as a routine cancer. Likewise, there is nothing routine about the science-based care we offer.

Research is teaching us that we cannot characterize cancer solely by its location in the body; we must also consider its biology. We now realize that cancer is hundreds of diseases, with disparate causes, that act, react and adapt differently to each person's biological makeup and that require individualized treatment.

To cure cancer, we must examine the molecular attributes of each patient's malignancy to see what mechanisms are at work and develop targeted therapies tailored to a tumor's genetics. That's how we are working to create a cancer-free world, and we chronicle several examples in this issue of *Frontiers*.

For instance, our cover story, "About-Face for Leukemia," focuses on an amazing new molecularly targeted drug, ibrutinib, that in clinical trials is proving to be highly effective and well tolerated among patients with chronic lymphocytic leukemia, producing durable remissions even among elderly patients and those who have relapsed and are resistant to other therapies.

In "Mechanisms of Resilience," we examine how our scientists are identifying biological mechanisms that enable certain cancer cells to survive radiation therapy so they can devise counteractive measures to improve treatment.

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

"A Singular Focus on Lung Cancer" features Dr. David Carbone, an expert in this disease who has joined our strong lung cancer team to organize and lead a thoracic oncology center that will integrate research with patient care to improve outcomes for patients with this malignancy, the top cancer killer in the United States. David specializes in the molecular biology of lung cancer and developing drugs to treat it.

I hope you will enjoy reading about some of our efforts to rise above the routine in fighting a foe that is anything but.

The OSUCCC – James invites you to be a member of our online community.

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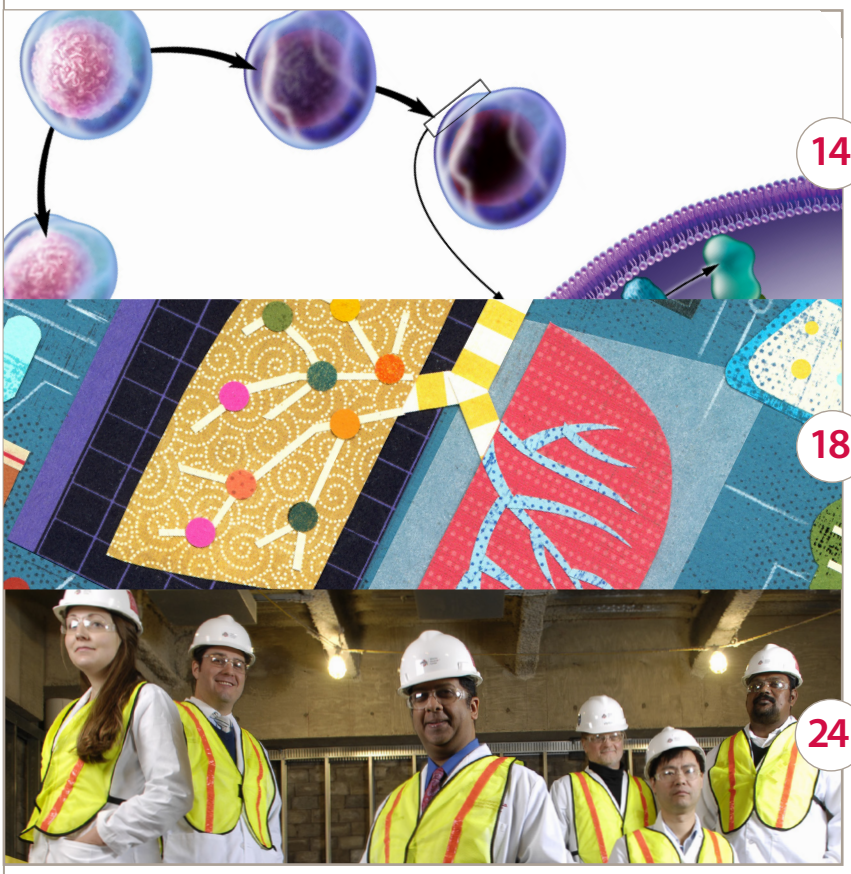
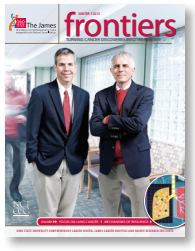


FEATURES



ON THE COVER: JOHN BYRD, MD (LEFT), AND IBRUTINIB CLINICAL-TRIAL PARTICIPANT DR. BRIAN KOFFMAN. STORY ON PAGE 14.

Recurrent Ovarian Cancer: WE MUST DO BETTER

Ovarian cancer is a relatively rare disease, but it is the most lethal of all gynecologic malignancies and the fifth most common cause of cancer death in women. About 22,300 women were expected to be diagnosed with the disease in the United States in 2012.

By **DAVID E. COHN, MD,** *director of the Division of Gynecologic Oncology, professor of Obstetrics and Gynecology and the Gertrude Parker Heer Chair in Cancer Research*

Lacking a reliable screening test, 60 percent of ovarian cancer cases have distant metastases and a five-year survival of 27 percent at diagnosis (see table).

Overall tumor response rates to standard therapy (paclitaxel and carboplatin) are relatively high at 70 to 80 percent, but 50 to 70 percent of responders relapse within about 18 months, and recurrent disease remains incurable.

Nonetheless, we have made progress against the disease over the last decade or so. More effective therapies for primary ovarian cancer have increased median survival to about five years after diagnosis, up from 12 to 18 months a decade ago.

In addition, more drugs are available to treat recurrent disease. Ten to 20 years ago, recurrent ovarian cancer was fatal within months because few therapies were available. Today, there are many more, including those the FDA has approved for treatment of the disease and others that are used "off label," enabling some patients to live for years with stable disease.

Given the options for treatment, ovarian cancer is considered by many to be a chronic disease that is treated somewhat like hypertension. Controlling refractory hypertension begins by prescribing a particular medication, and if that one doesn't work a second or third is tried. The goal is to hit on a drug that matches well with the patient's inherent response to blood pressure medication and might be used to maintain it until the drug ceases working. Similarly, ovarian cancer is typically treated with a number of drugs and regimens that produce a response for a few months, then lose effectiveness. Different agents are tried until, hopefully, one is found that matches well with the cancer's biology and provides therapy that allows the patient to be progression-free and feeling well for years.

Despite the successes in the treatment of ovarian cancer, patients who experience recurrence generally die of their disease after multiple treatment regimens. The OSUCCC – James Gynecologic Oncology program is engaged in clinical and translational research to improve the treatment and outcomes of women with recurrent ovarian cancer.

For example, we are conducting a national phase II study investigating a novel clinical agent called Reolysin. This is a non-genetically modified oncolytic (i.e., cancer-cell killing) virus that is prevalent in the community.

We completed a phase I study of the agent at Ohio State a few years ago, the first to use intravenous and

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OVARIAN CANCER

" It is our hope that identification of specific cancer-causing pathways and their potential treatments will lead to therapies that prolong survival, cause fewer side effects and improve outcomes – including quality of life – for women with ovarian cancer. "

intraperitoneal Reolysin in ovarian cancer. We showed that intravenous delivery led to viral replication in ovarian tumors present in the abdomen. This showed that it wasn't necessary to inject the virus directly into the tumor to achieve cancer-cell death, which was the previous strategy used in other types of cancers treated with Reolysin.

The outcome of that trial led to the current randomized, phase II Gynecologic Oncology Group trial, GOG 0186H (ClinicalTrials.gov identifier: NCT01199263), for which I am principal investigator. The trial will ultimately accrue 110 patients.

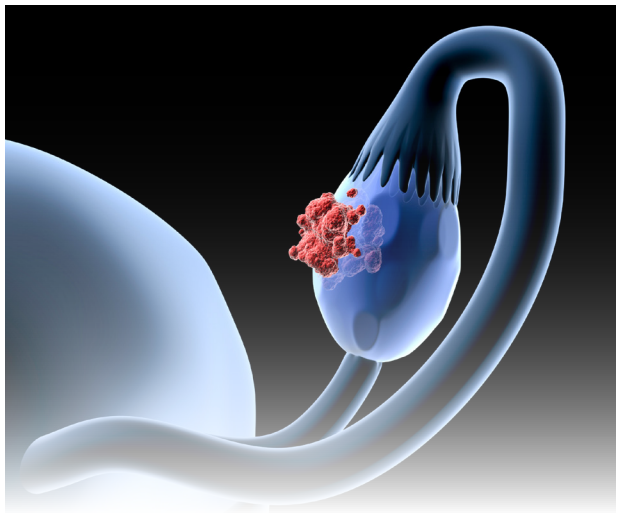
The study randomizes women with recurrent ovarian cancer to weekly paclitaxel or to paclitaxel plus intravenous Reolysin. The primary outcomes are response rate and survival.

We also have translational researchers investigating potential biomarkers and molecular pathways involved in ovarian cancer with the goal of developing targeted therapies to treat the disease. Selvendiran Karuppaiyah, PhD, in the Division of Gynecological Oncology, for example, is helping to design a drug that targets the STAT3 pathway, which is important in ovarian cancer. The drug is in laboratory and preclinical testing now, and it could begin phase I testing in the near future.

These studies are examples of the research needed to improve the treatment of ovarian cancer. While there have been substantial improvements in the outcomes of women with recurrent ovarian cancer, the fact that most women with the disease end up dying of their cancer highlights the importance of continued clinical, translational and basic research. It is our hope that identification of specific cancer-causing pathways and their potential treatments will lead to therapies that prolong survival, cause fewer side effects and improve outcomes – including quality of life – for women with ovarian cancer.

Ovarian cancer relative survival by stage at diagnosis, 2002-2008, all races (National Cancer Institute)

STAGE AT DIAGNOSIS	STAGE DISTRIBUTION (%)	5-YEAR RELATIVE SURVIVAL (%)
Localized (confined to the ovary)	15	91
Regional (spread to regional lymph nodes)	17	72
Distant (cancer has metastasized)	61	27
Unknown (unstaged)	7	22



The American Cancer Society estimated that 22,280 women in the United States would develop ovarian cancer in 2012 and that 15,500 of them would die of the malignancy.

BREAST CANCER

HEDGEHOG HUNTING

A Possible Therapy for Tamoxifen-Resistant Breast Cancer

BHUVANESWARI RAMASWAMY, MD,
a medical oncologist specializing in breast cancer at the OSUCCC – James

SARMILA MAJUMDER, PHD,
a research assistant professor in Molecular and Cellular Biochemistry at Ohio State and member of the OSUCCC – James

Researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) have discovered how tamoxifen-resistant breast cancer cells grow and proliferate. The study suggests an experimental agent might offer a targeted therapy for tamoxifen-resistant breast cancer.

Like a second door that opens after the first door closes, a signaling pathway called hedgehog (Hhg) can promote the growth of breast-cancer cells after tamoxifen shuts down the pathway activated by the hormone estrogen. A second signaling pathway, called PI3K/AKT, is also involved.

Activation of the Hhg pathway renders tamoxifen treatment ineffective and enables the tumor to resume its growth and progression. As part of the study, the researchers analyzed more than 300 human tumors and found that those with an activated Hhg pathway had a worse prognosis.

Finally, the researchers showed that an experimental drug called vismodegib, which blocks the Hhg pathway, inhibits the growth of tamoxifen-resistant human breast tumors in an animal model. The drug is in clinical trials testing for other types of cancer.

Chemotherapy is currently used to treat hormone-resistant breast cancers, but it causes significant side effects. This study has identified targeted therapies that could be an alternative to chemotherapy for these resistant tumors.

"Our findings suggest we can target this pathway in patients with estrogen-receptor breast cancers who have failed tamoxifen therapy," says first author Bhuvaneswari Ramaswamy, MD, a medical oncologist specializing in breast cancer at the OSUCCC – James.

"We describe a link between the hedgehog signaling pathway, which promotes tamoxifen resistance, and the PI3K/AKT pathway," adds principal investigator Sarmila Majumder, PhD, a research assistant professor in Molecular and Cellular Biochemistry at Ohio State and member of the OSUCCC – James. "Targeting the hedgehog pathway alone or in combination with the PI3K/AKT pathway could be a novel therapeutic option for treating tamoxifen-resistant breast cancer."

Published in the journal Cancer Research

Funding from NIH/National Cancer Institute grants CA137567 and CA133250, and a Pelotonia Idea Grant supported this research.

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HEAD AND NECK CANCER

TRANSORAL TECHNIQUE

Robotic Surgery Through Mouth Safe for Removing Throat Tumors

Robotic surgery through the mouth is a safe and effective way to remove tumors of the throat and voice box, according to a study by head and neck cancer surgeons at the OSUCCC – James.

The researchers say this is the first report in the world literature to illustrate the safety and efficacy of transoral robotic surgery for supraglottic laryngectomy.

The preliminary study, which examined the outcomes of 13 head and neck cancer patients with tumors in the supraglottic region of the throat, found that robot-assisted surgery to remove these tumors through the mouth took about 25 minutes on average. The study also found that blood loss was minimal – a little more than three teaspoons, or 15.4 milliliters, on average, per patient. No surgical complications were encountered, and 11 of the 13 patients could accept an oral diet within 24 hours.

If, on the other hand, these tumors are removed via open surgery on the neck, the operation can take about four hours, require seven to 10 days of hospitalization and involve a tracheostomy tube and a stomach tube, the researchers say.

ENVER OZER, MD, *a head and neck surgeon who specializes in robot-assisted techniques*

"The transoral robotic technique means shorter surgery, less time under anesthesia, a lower risk of complications and shorter hospital stays for these patients," says first author Enver Ozer, MD, clinical associate professor of Otolaryngology at Ohio State.

"It also means no external surgical incisions for the patient and better 3-D visualization of the tumor for the surgeon," says Ozer, a head and neck surgeon who specializes in robot-assisted techniques.

The cases examined in this study were part of a larger prospective study of 126 patients undergoing transoral robotic surgery between 2008 and 2011.

Published in the journal Head and Neck

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

INIMICAL INFLAMMATION

Study Shows How Chronic Inflammation Can Cause Cancer

ANJALI MISHRA, PhD,
a postdoctoral researcher in Dr. Michael A. Caligiuri's laboratory

When present at high levels, a hormone-like substance produced by the body to promote inflammation can cause an aggressive form of leukemia, OSUCCC – James researchers have found.

Their study shows that high levels of interleukin-15 (IL-15) alone can cause large granular lymphocytic (LGL) leukemia, a rare and usually fatal disease, in an animal model. The researchers also developed a treatment for the leukemia that showed no discernible side effects in the animal model.

In addition, their findings show that IL-15 is overexpressed in patients with LGL leukemia and that it causes similar cellular changes, suggesting that the treatment should also benefit people with the malignancy.

"We know that inflammation can cause cancer, but we don't know the exact mechanism," says co-senior author Michael A. Caligiuri, MD, director of the OSUCCC and CEO of The James. "Here, we show one way it can happen, and we used that information to potentially cure the cancer."

The research was developed and carried out in collaboration with co-senior author Guido Marcucci, MD, associate director for translational research at the OSUCCC – James. "In this study, we show the joined role of genetic instability and microRNAs in leading directly to cancer," says Marcucci, who notes that this work is part of a long history of research at the OSUCCC – James that is revealing the role of microRNA in cancer and its potential as a therapeutic target.

"Once we understood how this inflammatory hormone causes this leukemia, we used that information to develop a treatment by interfering with the process," says first author Anjali Mishra, PhD, a postdoctoral researcher in Caligiuri's laboratory.

Caligiuri, Marcucci and Mishra were joined in this study by Robert Lee, PhD, professor of Pharmaceutics and Pharmaceutical Chemistry in Ohio State's College of Pharmacy, and a group of collaborators.

Published in the journal Cancer Cell

NIH/National Cancer Institute grants CA16058, CA95426, CA68458, CA09338, CA140158, CA102031 and CA149623, and National Science Foundation grant EEC-0914790 supported this research.

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CHRONIC LYMPHOCYTIC LEUKEMIA

AUSPICIOUS AGENT

Experimental Drug Ibrutinib Highly Active in CLL Patients

Updated results from a phase Ib/II clinical trial indicate that a novel therapeutic agent for chronic lymphocytic leukemia (CLL) is highly active and well tolerated in patients who have relapsed and are resistant to other therapy.

The agent, ibrutinib (PCI-32765), is the first drug designed to target Bruton's tyrosine kinase (BTK), a protein essential for CLL-cell survival and proliferation. CLL is the most common form of leukemia, with about 15,000 new cases annually in the United States. About 4,400 Americans die of the disease each year.

Study co-leader John C. Byrd, MD, who directs the Division of Hematology at Ohio State and is a member of the OSUCCC – James, presented the findings in December 2012 at the 54th Annual Meeting of the American Society of Hematology (ASH) Annual Meeting in Atlanta, Ga.

The study found that response to therapy was high across cohorts, with 71 percent of previously untreated older patients experiencing a complete or partial response at either treatment dose (420mg and 840mg). The same response was observed in 67 percent of the relapsed patients and half of the high-risk patient cohort. After 22 months of follow-up, the disease had not progressed in 96 percent of previously untreated patients and 76 percent of relapsed and high-risk patients.

JOHN C. BYRD, MD,
director of the Division of Hematology; professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences; and the D. Warren Brown Designated Chair in Leukemia Research

"These findings are exciting because they demonstrate ibrutinib's potential as a highly active, well-tolerated first-line therapy for CLL that produces a high rate of durable remissions – the remissions last months on end," Byrd says. "The drug is effective in part because patients are willing to stay on treatment since the side effects are very tolerable."

Only non-severe side effects such as diarrhea, fatigue, chest infection, rash, nausea, joint pain, and infrequent and transient low blood counts were observed. Investigators found no evidence of cumulative toxicity or long-term safety concerns with a median follow-up of 16 months for treated patients.

Visit the OSUCCC – James CLL Experimental Therapeutics Laboratory at http://cll.osu.edu.

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

LESS IS MORE

Reduced-Intensity Regimen Before BMT is Better for Older Leukemia Patients

STEVEN DEVINE, MD,
professor in the Division of Hematology at Ohio State and director of the Blood and Marrow Transplant Program

A study led by researchers at the OSUCCC – James shows that preparing older acute myeloid leukemia (AML) patients for bone marrow transplants (BMT) with a reduced-intensity conditioning regimen is associated with higher rates of disease-free survival relative to the more typical treatments these patients usually receive.

The study was presented at the December 2012 American Society of Hematology (ASH) Annual Meeting in Atlanta, Ga.

Typically, the prognosis for older AML patients is poor. Even among patients who achieve complete remission through chemotherapy, survival rates are low due to high risk of relapse. While blood or bone marrow transplants can be a viable option for younger patients, conventional preparative regimens for the procedure are often too toxic for patients over age 60.

"With a reduced-intensity regimen leading up to a transplant, the disease-free survival rate in older patients reached 39 percent," says Steven Devine, MD, professor in the Division of Hematology at Ohio State and director of the Blood and Marrow Transplant Program. "These outcomes are better than those achieved using more conventional treatments and warrant additional comparison research focused on preventing relapse in this patient population."

The objective of the phase II, prospective, multicenter trial was to determine the feasibility and effectiveness of a uniform reduced-intensity conditioning regimen prior to a blood cell transplant in older AML patients in clinical remission. The primary endpoint was two-year disease-free survival. Researchers hypothesized that disease-free survival at two years would exceed 20 percent.

The study involved 123 AML patients in first clinical remission following chemotherapy, ages 60-74, who were transplanted at 21 centers across the country. Rates of both acute and chronic graft-vs.-host disease and treatment-related mortality were relatively low. No unexpected toxicities were associated with the transplants. Relapse was the most common cause of death.

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

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CHRONIC LYMPHOCYTIC LEUKEMIA

AGE ANALYSIS

Older and Younger Chronic Leukemia Patients May Need Different Therapy

Doctors should use different therapies when treating older and younger patients with chronic lymphocytic leukemia (CLL), a new study at the OSUCCC – James suggests.

Age is usually not considered when determining treatment for people with CLL, but this study indicates that older people with the disease may not respond as well to the therapy used for most patients.

"Our analysis shows that optimal therapy for younger and older patients with chronic lymphocytic leukemia is likely to be different, at least when using current treatments," says first author Jennifer Woyach, MD, assistant professor in the Division of Hematology at Ohio State. "We hope this study will shape future research by highlighting the importance of enrolling older patients on clinical trials and of developing trials that specifically target older patients."

CLL most often occurs in people older than 65; the average age at diagnosis is 72. But most CLL clinical trial participants are in their early 60s.

"Our findings apply to both routine care of CLL patients 70 years and older and to future CLL trials," says principal investigator John C. Byrd, MD, who directs the Division of Hematology at Ohio State and is a member of the OSUCCC – James.

"The study suggests that chlorambucil is superior to fludarabine in older patients, and that CD20 antibody therapies such as rituximab are beneficial as front-line therapy for all CLL patients, regardless of age," Byrd says. "These data also show that future treatment trials for older adults with CLL should build on CD20 antibody therapies such as rituximab and ofatumumab, but not on fludarabine or alemtuzumab."

Byrd, Woyach and colleagues reviewed 663 CLL patients who were enrolled in four sequential CLL clinical trials evaluating front-line therapies. The researchers looked for differences in treatment outcomes between older and younger patients to identify the most effective therapy for older adults.

JENNIFER WOYACH, MD,
assistant professor in the Division of Hematology at Ohio State

Published in the Journal of Clinical Oncology

NIH/National Cancer Institute grants CA31946, CA33601 and CA140158, and funds from the Leukemia and Lymphoma Society, the Harry Mangurian Foundation and the D. Warren Brown Family Foundation supported this research.

OF NOTE

Recent Recognitions of OSUCCC – James Physicians and Researchers

AWARDS AND HONORS

JOHN C.BYRD, MD, *director, Division of Hematology; Professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences and the D. Warren Brown Designated Chair in Leukemia Research,* **was featured in Clinical Cancer Advances 2012: ASCO's Annual Report on Progress Against Cancer. Published by the American Society of Clinical Oncology**, *the annual report is an independent review of advances in clinical cancer research that are likely to improve patients' survival and quality of life.*

CHRISTOPHER PELLOSKI, MD, *associate professor of Radiation Oncology and director of the Pediatric Radiation Oncology Program,* **has been awarded a $180,000 grant from Roche for work titled "The Preclinical Investigation of Concurrent Radiotherapy and p53/MDM2 Inhibition in Pediatric Rhabdomyosarcoma (RMS)."** *His team also will harvest xenografts for dynamic molecular changes during therapy as a first-of-a-kind study in pediatric RMS. Pelloski is establishing a world-class preclinical testing program for radiotherapeutic studies at Ohio State that utilizes a high-throughput in vivo apparatus and approach.*

MARK FAILLA, PhD, *professor of Human Nutrition,* **has been elected a Fellow of the American Association for the Advancement of Science (AAAS)** *for distinguished contributions to the field of nutritional biochemistry for developing valuable models elucidating bioavailability, metabolism and efficacy of health-promoting dietary constituents.*

MAURA GILLISON, MD, PhD, *professor of Medical Oncology, of Epidemiology and of Otolaryngology,* **has been elected a Fellow of the AAAS for distinguished contributions to the fields of tumor virology, cancer biology and epidemiology, particularly in defining human papillomavirus as the etiologic agent for head and neck cancers.**

JULIA WHITE, MD, *director of breast radiation oncology at the OSUCCC – James and professor and vice chair of clinical research in the Department of Radiation Oncology,* **will be inducted as a Fellow into the American College of Radiology (FACR) for seminal contributions to the field.**

TRAINEE RECOGNITION

ANN-KATHRIN EISFELD, MD, *postdoctoral fellow in the Department of Molecular Virology, Immunology and Medical Genetics, and in the Division of Hematology,* **has been selected for the highly competitive 2013 Translational Research Training in Hematology Program created by the European Hematology Association and the American Society of Hematology.** *Eisfeld also was first author on a paper recognized as one of three "Best Published Manuscripts from 2011-2012" in a book produced by the clinical-cooperative group Alliance for Clinical Trials in Oncology. Her paper, published in the journal Blood, was highlighted for "Leadership by a Junior Investigator."*

TIMOTHY LAUTENSCHLAEGER, MD, *resident in Radiation Oncology,* **has been named a B. Leonard Holman Scholar by the American Board of Radiology.** *The national award recognizes residents who demonstrate potential as clinician-researchers in radiation oncology.*

LEADERSHIP ACTIVITIES AND APPOINTMENTS

GUIDO MARCUCCI, MD, *associate director for translational research at the OSUCCC – James, and professor in the Division of Hematology,* **served on an Institute of Medicine committee that guided the Department of Defense on the operation of the Joint Pathology Center, the world's largest collection of human pathologic specimens.** *The committee published its recommendations in a report titled "Future Uses of the Department of Defense Joint Pathology Center Biorepository."*

PATRICK ROSS JR., MD, PhD, *chief of the Division of Thoracic Surgery,* **has been named co-chair of Ohio's Cancer Liaison Physicians (CLPs). The American College of Surgeons' Commission on Cancer established CLPs as a network of physician volunteers who manage clinically related cancer activities locally and in surrounding communities.** *The program has nearly 65 state chairs who provide leadership to the CLPs in their state or region.*

GRANTS

NCI

NICHOLAS DENKO, MD, PhD, *associate professor of Radiation Oncology,* **has received a five-year, $1.6 million grant from the NIH/National Cancer Institute (CA163581-01A1) to study "Decreasing Oxygen Metabolism to Reduce Hypoxia and Radiosensitize Tumors."**

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

FACULTY AND PROGRAMS

CHRISTIN BURD, PhD, has joined the cancer program as an assistant professor of Molecular Genetics in the College of Arts and Sciences, and of Molecular and Cellular Biochemistry in the College of Medicine. *Her research interests include regulation of the INK4/ARF locus in cancer models, melanoma, senescence and aging.*

CRAIG BURD, PhD, *has joined the cancer program as an assistant professor of Molecular Genetics in the College of Arts and Sciences. His research focuses on the importance of hormone signaling in cancer development.*

NORMAN LEHMAN, MD, PhD, has joined the cancer program as an associate professor clinical in Pathology. *His clinical interests include histologic and molecular classification of gliomas. His research interests include cell-cycle regulation, radiation therapy and anti-neoplastic agents.*

STELLA LING, MD, has joined the cancer program as an associate professor clinical of Radiation Oncology. *Her clinical interests include optimizing patient outcome and satisfaction. Her research interests include pulmonary radiosurgery, proton beam radiotherapy, intraoperative radiation therapy, and head and neck intensity modulated radiation therapy.*

JAMES SPAIN, MD, PhD, has joined the cancer program as division chief of Interventional Radiology in the Department of Radiology. *His clinical interests include interventional radiology globally with focus on interventional oncology, especially concerning hepatic disease. His research interests include hepatic loco-regional therapies and IVC filters.*

JOYCE NANCARROW TULL, BSN, MSN, has joined the cancer program as director of the OSUCCC – James Clinical Trials Office. *Previously, Tull directed the Clinical Trials Office and the Beaumont Community Clinical Oncology Program at Beaumont Health System in Michigan.*

THE OHIO STATE UNIVERSITY has signed an agreement with the Sarawak Biodiversity Centre in Malaysia to collaborate on the further development and commercialization of the promising anticancer agent silvestrol, which is derived from the Aglaia tree that grows in the Malaysian state of Sarawak.

The OSUCCC – James awarded the 19th annual Herbert and Maxine Block Memorial Lectureship Award for Distinguished Achievement in Cancer to LEVI GARRAWAY, MD, PhD, *associate professor of Medicine at the Dana-Farber Cancer Institute, Harvard Medical School, and senior associate member of the Broad Institute. For his Block Lecture, Garraway presented "An Integrative Framework for 'Precision' Cancer Medicine."*

In December, **THE NEW JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE reached another construction milestone: The new building is now completely enclosed and most of the exterior work is complete. View a video of the hospital's progress.** *You can also access the video in our online version of* Frontiers *at* **http://cancer.osu.edu/Frontiers.**

ABOUT-FACE *for* Chronic Leukemia

Ibrutinib is a targeted drug that in early clinical testing has produced lasting remissions and few side effects in patients with chronic lymphocytic leukemia

BY KENDALL POWELL

A few days before Christmas 2011, physician assistant Margaret Lucas walked into her chronic lymphocytic leukemia clinic to see a dozen patients and for a moment wondered if she'd entered a flu vaccination clinic by mistake. The patients were smiling, looking well, all had their hair and no one was fighting an infection or required a blood transfusion. "Nobody needed anything from me," she recalls. "It was really overwhelming."

They did need one thing: refills of their once-daily dose of the pill that was keeping these relapsed leukemia patients healthy.

That day was in stark contrast to the usual clinic day. Chronic lymphocytic leukemia (CLL) is a highly heterogeneous malignancy that typically requires a mix of treatment options depending on the individual. Many newly diagnosed patients have an asymptomatic, indolent form of the disease that requires close monitoring only, sometimes for many years. Often, a routine blood test reveals the abnormally high lymphocyte count and leads to diagnosis. Median survival can exceed 10 years.

Other patients have an aggressive form of CLL that requires immediate treatment. Survival for these patients is about one or two years when untreated and two to five years when treated.

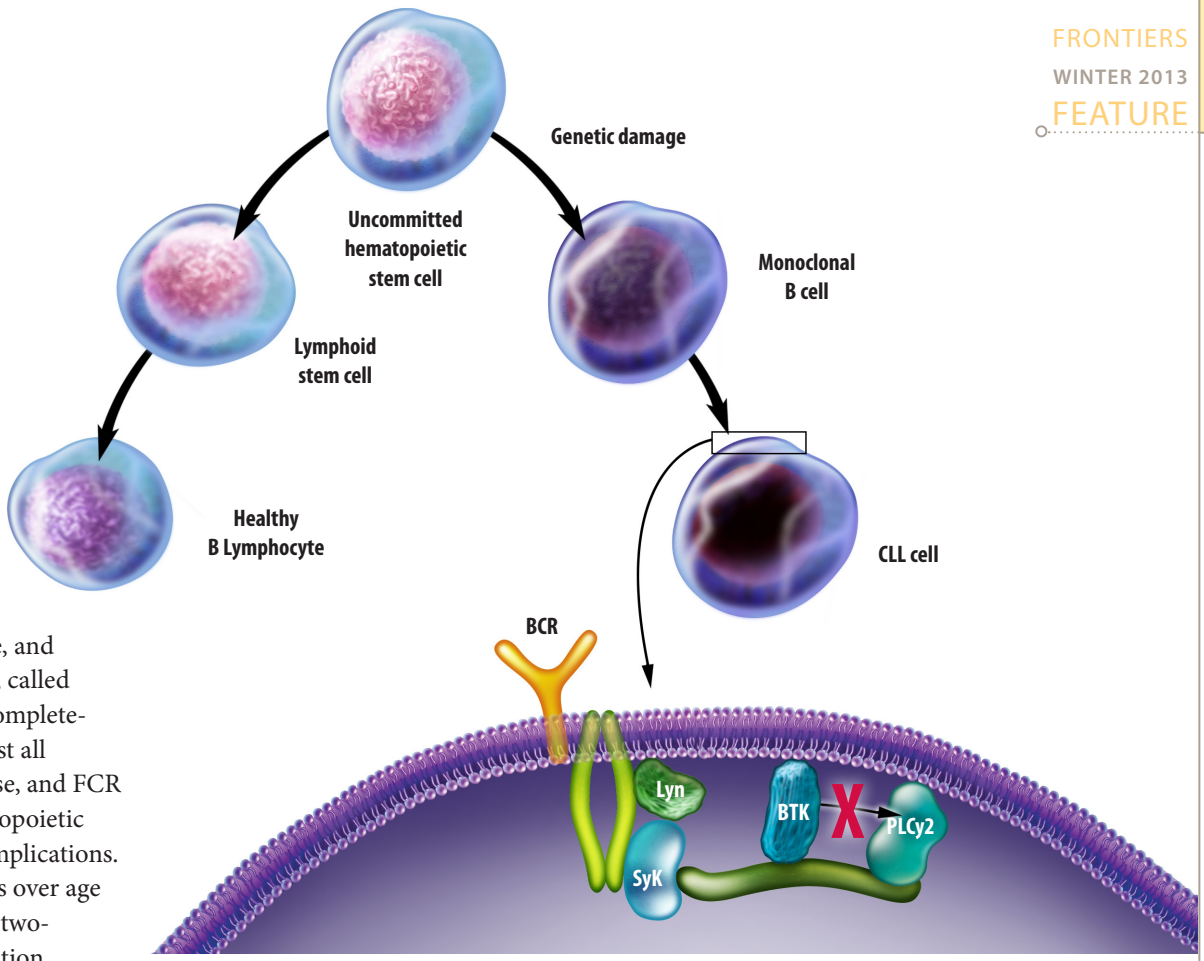
"CLL is the most common and prevalent adult leukemia in the Western Hemisphere," says John C. Byrd, MD, a CLL specialist and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

"More than 100,000 people in the U.S. are walking around with it, and it is not curable with current therapy. The median age at diagnosis is 72, and nearly 4,600 patients were likely to die from CLL in 2012," says Byrd, who co-leads the CLL Experimental Therapeutics Research Laboratory.

CLL is believed to begin as a premalignant disorder of B lymphocytes called monoclonal B cell lymphocytosis (MBL). Additional gene mutations in B cells or signals from the bone-marrow microenvironment probably drive progression of MBL to CLL and result in the proliferation of ineffective B lymphocytes that lead to abnormal immunoglobulin production and autoimmune disorders. With progression, CLL cells crowd into lymph nodes and the spleen and liver, painfully enlarging those organs. The disease disrupts red-blood-cell and platelet production, leading to anemia and bleeding.

Treatment with traditional chemotherapy drugs could keep the disease in remission for a while but does not improve overall survival. In the late 1990s, drugs with greater activity against CLL were developed. They included rituximab, a monoclonal antibody designed to target leukemia cells, and fludarabine, a purine analogue that destroys both B and T cells. These agents produced more frequent and longer remissions, but the disease eventually recurs and usually resists further treatment.

Currently, there is no curative therapy for CLL, other than possibly a high-risk hematopoietic stem-cell transplant. Moreover, CLL is associated with a wide range of potentially fatal hematopoietic and immune-system complications. A common first-line treatment combines fludarabine, the alkylating



Origin of CLL and the Molecular Mechanism of Ibrutinib

Multipotent hematopoietic stem cells (HSC) give rise to healthy B lymphocytes. Recent evidence suggests that genetic changes at the HSC level lead to monoclonal B cells that then give rise to CLL cells. Enlargement: The experimental oral agent ibrutinib blocks B-cell receptor (BCR) signaling, thereby preventing B-cell activation and proliferation. Ibrutinib binds irreversibly with Bruton's tyrosine kinase (BTK), a protein that is overexpressed in CLL and other B-cell malignancies. This blocks signals from the B-cell receptor that are essential for CLL-cell survival and proliferation and triggers cell death.

agent cyclophosphamide, and rituximab. This regimen, called FCR, has a 70-percent complete-remission rate, but almost all patients eventually relapse, and FCR often worsens the hematopoietic and immune-system complications.

Unfortunately, patients over age 65, who represent about two-thirds of the CLL population, generally cannot tolerate FCR treatment because it puts patients at high risk of respiratory and other infections. Instead, older patients may be treated with drugs such as chlorambucil and rituximab, though these agents are less effective at producing lasting remissions.

"We need newer therapies for older patients – therapies that keep patients in remission longer and don't have the immunosuppressive side effects of chemotherapy," Byrd says. "Our quest is to identify targeted therapies that selectively kill leukemia cells."

PRECLINICAL FINDINGS

Ibrutinib (or PCI-32765) has the potential to fulfill all of Byrd's requirements. Pharmacyclics, based in Sunnyvale, Calif., licensed the drug from Celera Genomics in 2006. Recognizing the OSUCCC – James group as a leader in preclinical research and early-phase trials of new drugs for CLL, Pharmacyclics approached Byrd and the OSUCCC – James CLL Experimental Therapeutics Laboratory about testing ibrutinib.

Ibrutinib belongs to a class of drugs called B-cell receptor (BCR) antagonists. The B-cell receptor is overexpressed in CLL, and BCR signaling is essential for B-cell maturation and growth. Having already tested another B-cell agonist, CAL101/GS1101, that was proving to be effective in early clinical testing, the team agreed to put ibrutinib through the same preclinical paces.

Ibrutinib binds to and inhibits a molecule called Bruton's tyrosine kinase (BTK), a protein that is essential for BCR signaling and is overexpressed by CLL cells. By inhibiting BTK, ibrutinib prevents BCR signaling and B-cell activation, says Amy Johnson, PhD, a research assistant professor in the Division of Hematology and a molecular pharmacologist.

"But when we expose CLL cells to ibrutinib in lab dishes, they don't instantly die. When we first saw this

in the lab, we were kind of worried because ibrutinib is not highly cytotoxic," she says. "We learned there is more to it than that."

The team pushed ahead with experiments to test ibrutinib in CLL cells and mouse models. In a 2011 paper published in the journal *Blood*, the group showed that CLL cells overexpress BTK, that ibrutinib makes CLL cells more susceptible to apoptosis compared with normal B cells, and that the agent had no toxic effect on T cells.

Ibrutinib also quashed the proliferation of BCR-activated B cells and shut down their survival pathways. Finally, their laboratory studies showed that the drug blocked survival signals that CLL cells receive from the microenvironment, including IL-6, IL-4, TNF-α and stromal-cell contact.

In subsequent research, Johnson tested ibrutinib on a mouse strain that spontaneously develops a CLL-like leukemia at about nine months of age. (The mice carry B cells that overexpress a human oncogene called *TCL1*.) "If we provide continuous treatment with ibrutinib starting when they are really young, we can prevent the leukemia from developing," says Johnson.

In another experiment, the team transplanted the leukemic cells from the *TCL1* mouse model into 100 mice without leukemia. Then, at the time of leukemia diagnosis (by flow cytometry), they gave the mice ibrutinib daily in their drinking water. The treated animals had a significantly longer overall survival than control animals at 46 days versus 24 days, respectively.

Using mouse genetic models, the team has also shown that BTK is indeed a critical target in the development of CLL. In both mice and humans, a mutation that knocks out the function of BTK causes the immune deficiency hypogammaglobulinemia. Johnson and her team crossed the mouse with the mutated *BTK* gene with the *TCL1* mouse. The resulting offspring, which in essence are predisposed to develop CLL but have BTK permanently disabled, do not develop the leukemia at nine months as usually happens, and most were behaving normally and appeared free of side effects after more than 12 months.

"So we've shown that inhibiting BTK – both pharmacologically and genetically – prevents leukemia from developing in mice," says Johnson.

TRIALS WITHOUT TRIBULATIONS

In the meantime, clinical testing of ibrutinib was moving forward. In 2010, trials began in patients whose CLL had relapsed and was refractory to other treatments. In phase I and II trials, cohorts of CLL patients experienced a 90-percent response rate in terms of shrinking lymph nodes, spleens and white blood cell counts, and improving anemia. In 70 percent of patients with relapsed disease, ibrutinib removed detectable CLL cells from the blood, with a partial response or better, Byrd says.

"Ibrutinib has really opened up a door of hope for people," says Lucas. Turnarounds like those of her Christmastime-clinic patients were characteristic of most patients put on ibrutinib. "It's dramatic," she says.

One such patient is Brian Koffman, a family physician who lives in Newport Beach, Calif. The 61-year-old has been living with an aggressive variant of CLL for seven years. He underwent a stem-cell transplant and rituximab therapy, both of which failed. A complication called autoimmune thrombocytopenia made pursuing the harsher therapies, such as FCR, a high-risk choice.

At one point, he grew a "Santa-beard" to hide his massively swollen lymph nodes from his own patients. After participating in the phase II ibrutinib-plus-ofatumumab trial for eight months, his lymph nodes are no longer palpable and his blood work is "boringly normal," he says.

"What's most notable about ibrutinib is that, with more than two years of follow-up, the median time to relapse has not yet been reached. The drug – a pill taken daily – is holding people in remission," Byrd explains. And the side-effect profile of ibrutinib? "Compared to most new chemotherapy drugs, it's apples to oranges," Byrd says.

Koffman had some mild diarrhea, heartburn and a couple of rashes. All typical, he says.

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

"People are using the word revolutionary to describe ibrutinib – we have never had a medication that worked so well with so few side effects." – Margaret Lucas, PA

"Overall, taking the medication is a non-event." Fatigue and bruising are also common. Even though the trial requires him to fly to Columbus frequently, Koffman calls his participation "one of the best decisions I've ever made."

Because the trial in relapsed patients has gone so well, and because the drug does not appear to increase infection risk further in CLL, Byrd wanted to move ibrutinib into a trial for first-line treatment of patients over 65, giving it as monotherapy.

The results in this previously untreated, over-65 patient group are "similarly spectacular," Lucas says. At 27 months, 96 percent of this group of 31 patients was progression-free. "With chemotherapy, we would expect this to be about 50 percent.

"People are using the word revolutionary to describe ibrutinib – we have never had a medication that worked so well with so few side effects."

Byrd, who typically speaks in measured, reserved tones, also cannot hide his enthusiasm: "It's beating the socks off other treatment options. This class of drug is going to transform CLL just as Gleevec did for CML," he says, referring to the molecularly targeted drug for chronic myelogenous leukemia.

Byrd doesn't use "transform" lightly – he and Lucas have seen patients' lymph nodes and spleens shrink within the first week of treatment; patients who thought they were headed for hospice care instead head out on cruises and trips to Europe. Simply put, says Byrd, "It's an amazing drug."

NEXT STEPS

Ibrutinib could be game-changing for the treatment of end-stage CLL, which too often is a frustrating act of moving patients from one therapy to the next and hoping for the best. "With ibrutinib, we have some patients on their second and third years of treatment with no relapses," Lucas notes.

Byrd cautions that resistance could occur in the future. And even though the numbers of patients who have relapsed on ibrutinib or who cannot tolerate the drug are very small, doctors need a next-drug in the arsenal to offer those patients. This might be an improved, second-generation BTK inhibitor (akin to dasatinib and nilotinib for Gleevec), he explains.

Lab researchers will investigate the question of resistance and what happens when mice stop taking the drug. Clinicians want to know if ibrutinib, which also kills healthy B cells, will cause long-term immune suppression and whether the drug has benefit for treating early-stage CLL.

Currently, ibrutinib is entering phase III testing for both previously untreated CLL and for relapsed patients. In the RESONATE trial taking place in 44 centers around the world, 350 relapsed or refractory CLL patients will be randomized to receive either ibrutinib or the monoclonal antibody drug ofatumumab. In the RESONATE-2 trial, 272 patients 65 or older with previously untreated CLL will be randomized to receive either ibrutinib or chlorambucil.

Byrd has conducted translational studies of CLL for 15 years, moving from laboratory bench to patient bedside and back to the bench, working to improve CLL treatment. Lucas has worked with him that entire time and says ibrutinib is unlike anything they have seen before.

"I've seen Campath, rituximab and fludarabine as they were introduced. They can make patients incredibly sick and vulnerable to fatal infections," she says. "The more specifically targeted agents that we can find for malignancies, the better."

A Singular Focus

on Lung Cancer

David Carbone joins Ohio State's lung cancer team to organize a thoracic oncology center

BY BOB HECKER

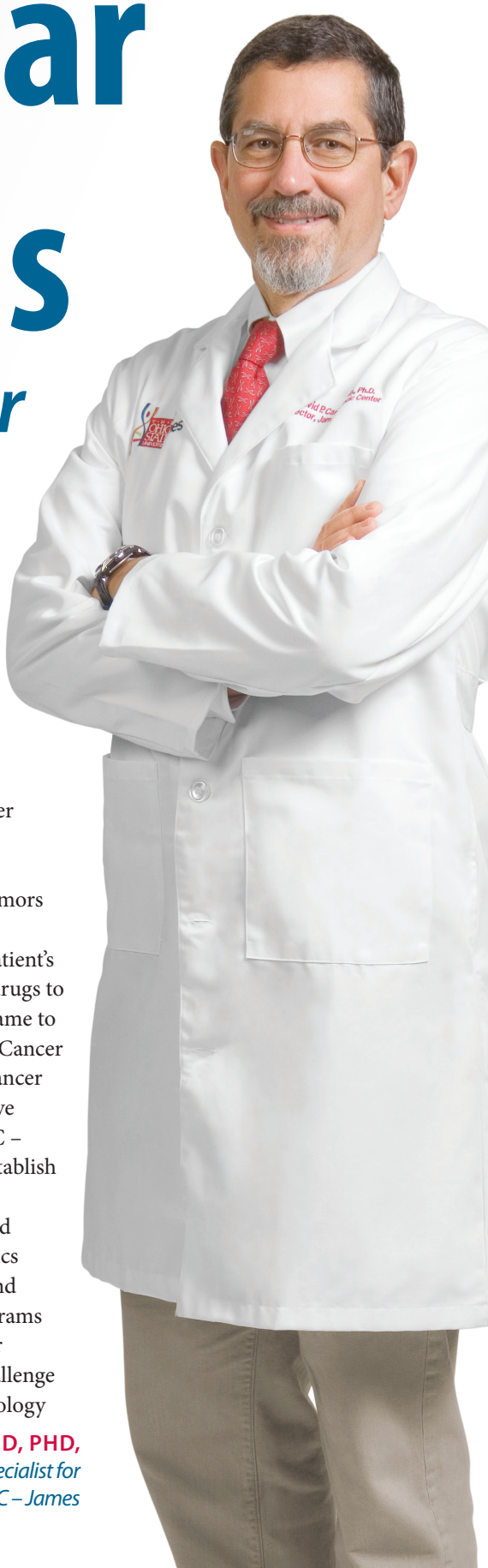
David Carbone, MD, PhD, a renowned lung cancer specialist recently recruited to The Ohio State University, believes that integrating basic and clinical research with patient care is essential for improving patient outcomes and the dismal statistics associated with this malignancy.

Lung cancer is the leading cancer killer of both men and women in the United States. In 2012, the disease was expected to kill 160,300 Americans, more people than breast, prostate and colorectal cancer combined. Only 16 percent of lung cancer patients are alive five years after diagnosis.

"I've focused my whole career on lung cancer," Carbone says. "I'm determined to make a difference in the field through research, caring for patients and training other physicians."

Carbone specializes in the molecular biology of lung tumors – the genetic, proteomic and metabolic features of each patient's cancer – and in developing drugs to better treat the disease. He came to Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) in autumn 2012 to establish a thoracic oncology center.

Formerly, Carbone directed the Experimental Therapeutics Program and the Thoracic and Head and Neck Cancer programs at Vanderbilt-Ingram Cancer Center. He welcomes the challenge of developing a thoracic oncology



DAVID CARBONE, MD, PHD,
lung cancer specialist for the OSUCCC – James

"All the structural elements here, from committed leadership to an outstanding clinical team, are aligned to build a major and effective lung cancer program . . . The institution has an almost unparalleled financial and philanthropic base. We are in a growth mode, and I believe we have tremendous potential." *– David Carbone, MD, PhD*

center at the OSUCCC – James.

"All the structural elements here, from committed leadership to an outstanding clinical team, are aligned to build a major and effective lung cancer program," Carbone says. "The institution has an almost unparalleled financial and philanthropic base. We are in a growth mode, and I believe we have tremendous potential."

Longtime members of Ohio State's lung cancer team are working closely with Carbone to develop the center that ultimately would provide multidisciplinary care in one location, similar to Ohio State's Stefanie Spielman Comprehensive Breast Center.

"An integrated center that provides the full spectrum of care, from screening to survivorship, and that leverages translational research, will help us change outcomes for patients," says Patrick Ross Jr., MD, PhD, a surgical oncologist and researcher who directs Ohio State's Division of Thoracic Surgery.

Gregory Otterson, MD, a lung cancer specialist and researcher at the OSUCCC – James, notes that the multidisciplinary center would bring together the range of specialties required to care for lung cancer patients, which includes medical oncology, radiation oncology, pulmonary medicine, thoracic surgery, pathology, diagnostic radiation and interventional radiation.

"The center would also bolster clinical and translational research," Otterson says. "Seeing patients at a single locale will enhance the process of obtaining biopsies on-site and the collection of tissue for biomarker analyses."

"Ohio and surrounding states have a relatively higher proportion of lung cancer cases than other parts of the country," adds Miguel Villalona, MD, a lung cancer specialist and OSUCCC – James researcher who directs Ohio State's Division of Medical Oncology. "Having a center that provides comprehensive care at the epicenter of this epidemic will be a dream come true. To alter the catchy phrase, 'Build it, and they will come,' I say, 'Build it, they are already here.'"

TARGETED RESEARCH

Translational research at the proposed center is expected to lead to innovations in screening, molecular-based diagnosis, stereotactic radiation, robotic-assisted surgery, photodynamic therapy and early-phase drug design.

Carbone's research focuses on gene sequencing/proteomics, the *NOTCH* gene signaling pathway, immunosuppression and discovery of biomarkers for predicting clinical outcome.

Protein-expression patterns in lung cancer cells are of key interest. He believes the genetic mutations that cause cancer are important only by virtue of their impact on cellular proteins.

"Trying to understand the causes and behavior of cancer by studying single genes is worse than the 'blind men and the elephant' parable – you get a different impression depending on where you look," he says. "We're taking a more comprehensive look at lung cancer by studying proteome and protein expression patterns in addition to RNA expression and mutations in the genome.

"We now have tools to inventory all the genetic alterations, RNA expression changes and protein alterations found in tumor cells as distinct from normal cells," he continues. "I'm interested in studying all this information in cancer cells with particular clinical characteristics so we can determine why the cancer developed or behaved a certain way, and then come up with candidate targets for therapy."

One such target is the *NOTCH3* gene. A dozen years ago, Carbone's lab team discovered a chromosome rearrangement in a lung cancer that activated this gene, which they have since determined is overexpressed in a majority of cases. "We are characterizing its potential as a direct therapeutic target and other elements of this pathway as a modulator of the immune response," he says.

Equally important, his lab is studying biomarkers – molecular

"Having a center that provides comprehensive care at the epicenter of this epidemic will be a dream come true. To alter the catchy phrase, 'Build it, and they will come,' I say, 'Build it, they are already here.'"

MIGUEL VILLALONA, MD,
director of the Division of Medical Oncology and a lung cancer specialist

features of lung cancer cells – that will help identify optimal therapy for each patient. "We have studied many candidate biomarkers in peripheral blood using proteomic technologies," Carbone says.

He notes that his research complements that of several OSUCCC – James investigators, such as Villalona, who specializes in drug development.

"We are at the dawn of a new era in lung cancer. Many molecular changes that can be pharmacologically targeted have been discovered, and others will follow," Villalona says. "The new center will help my efforts to develop the right drug for the right group of patients in the right clinical trial."

One molecular target Villalona is studying is the *KRAS* gene. Mutations in this gene occur at high frequency in lung cancer. No drugs exist yet that target it, but Villalona and his colleagues are working with a naturally occurring virus combined with chemotherapy as a promising strategy for treating these patients.

Otterson's research team has joined the Lung Cancer Mutation Consortium (LCMC), a group of 18 thoracic oncology centers that performs extensive molecular characterization of patients with lung adenocarcinoma (the most common form of lung cancer).

"The LCMC is predicated on obtaining adequate tissue specimens followed by extensive molecular characterization," Otterson says.

Ross says his work, too, will benefit from collaborating with Carbone.

"We provide cutting-edge therapy for lung cancer with minimally invasive approaches such as robotic-assisted surgery and photodynamic therapy (PDT)," Ross says. His team will present its innovative robotic cases at the next meeting of the Society for Surgical Oncology, and Ohio State's PDT program was featured in the October 2012 *Journal of the National Comprehensive Cancer Network*.

"Our collaborations with Dr. Carbone focus on earlier detection and multidisciplinary therapy to shrink tumors," he says. "In this way, more patients will benefit from the less invasive surgical techniques that we perform."

INNOVATIVE EARLY SCREENING

As with all cancers, Carbone says, the importance of early detection in lung cancer cannot be overemphasized.

"Until recently, there was no early-detection test for lung cancer that was proven to reduce deaths from this disease," he says. "Without screening, most cases are diagnosed when they are metastatic – through the pain of bone metastases or seizures from brain metastases, for example – and at that point they are typically

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

incurable."

But, he notes, the National Lung Screening Trial (NLST) – a National Cancer Institute-sponsored study of more than 53,000 current or former heavy smokers – compared computed tomography (CT) scans with standard chest X-rays and showed that lung CT scans lowered the risk of dying from lung cancer by 20 percent by catching the disease earlier, when it is more treatable.

"CT scanning has the potential for a much greater impact on saving lives than multiple regimens of chemotherapy performed later when the cancer is more advanced," Carbone says.

Based on the NLST findings, the OSUCCC – James began providing lung cancer CT scans in the spring of 2012 for high-risk patients (see sidebar, page 23), but Carbone says that more research is needed to optimize the way screening is done, and there are risks to screening outside of academic centers.

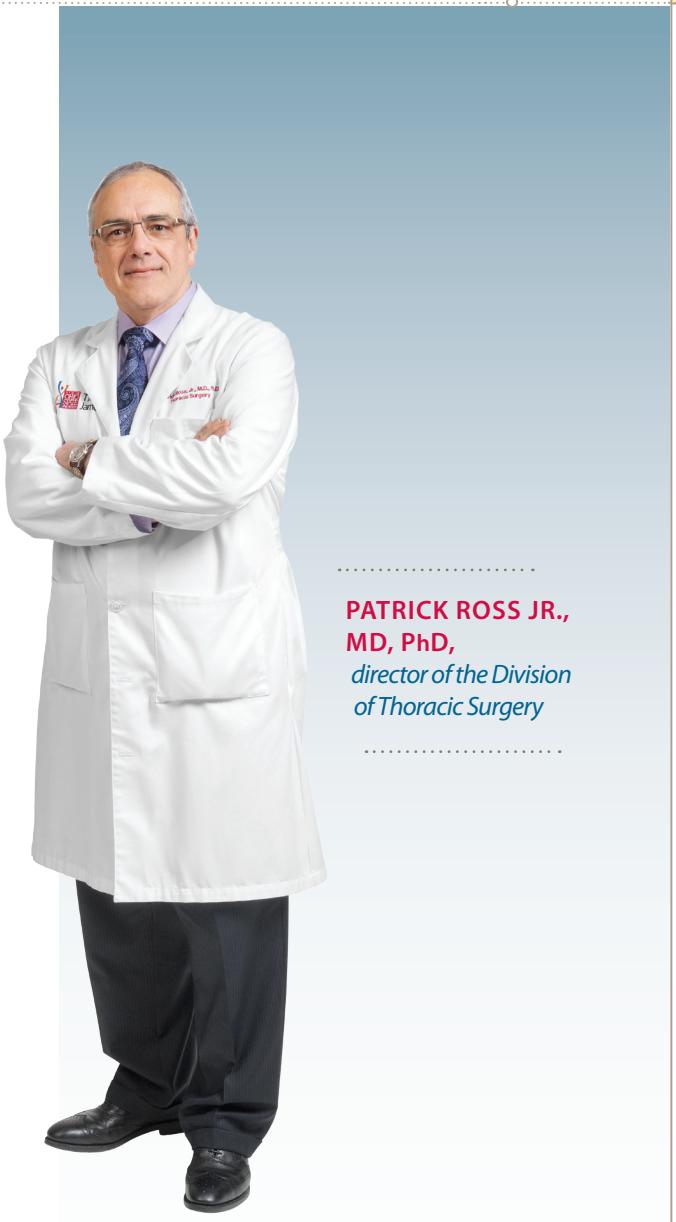
"Medicare doesn't cover these scans, and most insurance companies don't pay for them," he explains. "Plus, not everyone is qualified to perform or interpret them."

He points out that 95 percent of positive findings on test results are not cancer, "so it takes a well-trained team of multidisciplinary experts to examine the results and determine whether a patient has cancer or something else. At the OSUCCC – James, our scans are backed by an expert team that can analyze and best manage what is found."

Carbone notes that studies of CT screening are blending with another promising area of research: identifying patterns of abnormal microRNA (miRNA) molecules in the blood of lung cancer patients. In 2011, an OSUCCC – James team led by Carlo Croce, MD, *reported in the Proceedings of the National Academy of Sciences* that they had identified miRNA patterns in plasma that might reveal the presence and aggressiveness of lung cancer, and perhaps who is at risk for developing it. The study compared miRNA expression profiles of lung tumors, normal lung tissues and plasma samples from lung cancer cases identified in a CT screening trial.

Importantly, the researchers had evidence that these patterns might be detectable up to two years before the tumor is found by CT scans. They also showed that it might be possible to use the miRNA patterns to detect lung cancer in a blood sample – findings that could lead to a blood test for lung cancer.

"We are working with several groups to study the development of blood tests for CT screening, and we want to take advantage of the microRNA expertise at Ohio State for that purpose," Carbone says.



PATRICK ROSS JR., MD, PhD,
director of the Division of Thoracic Surgery

"Our collaborations with Dr. Carbone focus on earlier detection and multidisciplinary therapy to shrink tumors. In this way, more patients will benefit from the less invasive surgical techniques that we perform."

"Patients will benefit from the expansion of our molecular pathology resource, which will enable us to open more clinical studies directed toward those with various subsets of lung cancer."

GREGORY OTTERSON, MD,
co-director of Thoracic Oncology and a lung cancer specialist

HOPEFUL HORIZON

Ultimately, everything at the new thoracic oncology center will be geared toward improving outcomes for patients, with whom Carbone can empathize from his own experience with cancer. In 1999 he was diagnosed with mediastinal large B-cell lymphoma, a rare and aggressive form of non-Hodgkin's lymphoma. His therapy involved removing part of his left lung and receiving chemotherapy and chest radiation – similar to treatments he often recommends for his lung cancer patients.

"The experience gave me a better understanding of the psychological impact of receiving a life-threatening diagnosis, both on me as a patient and on my family," he says. "It also gave me an appreciation of how hard chemotherapy can be in both acute and chronic toxicities, how inefficient our medical system is in many ways, the effects of 'scan anxiety' and the chronic consequences of cancer and its treatment."

In addition, it gave him insights that could be of value to all healthcare professionals working with lung cancer patients, no matter how bleak the prognosis.

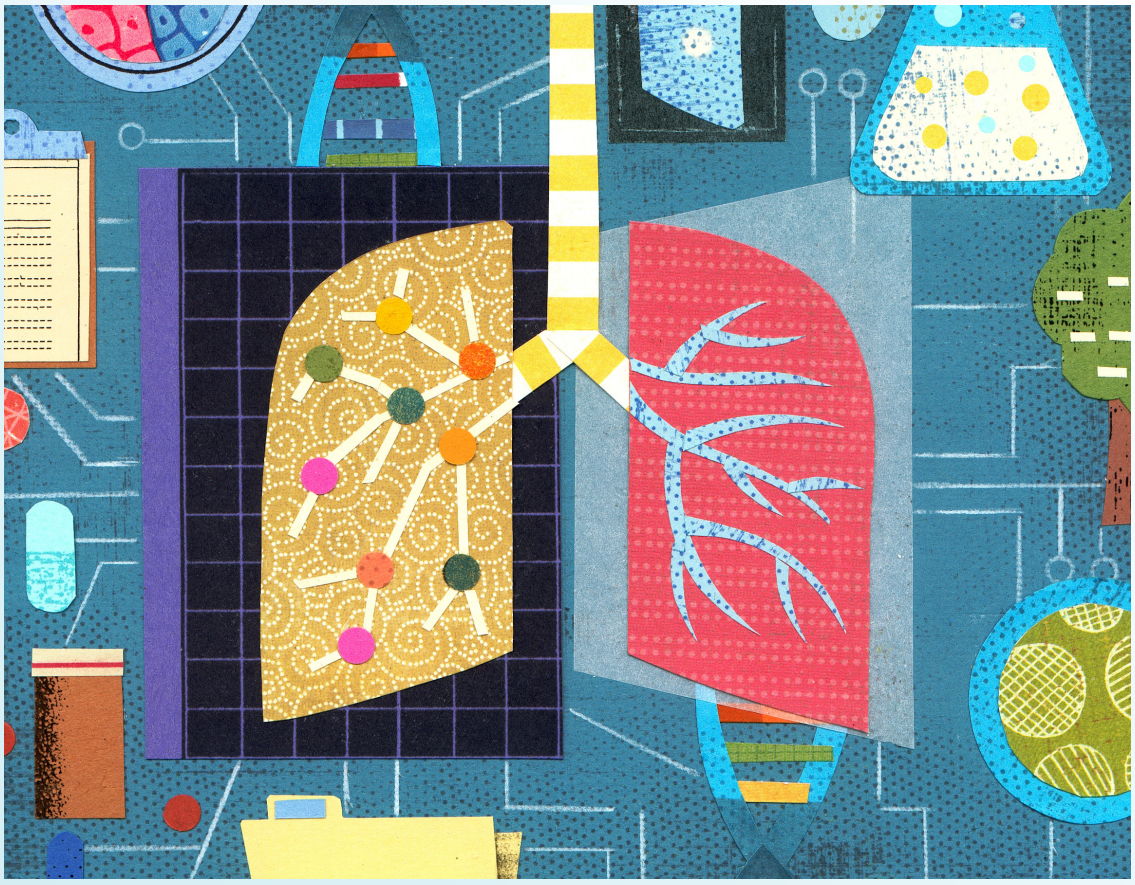
"Be very cautious about taking away hope," Carbone says. "Statistics apply to populations and not individuals. I have seen patients literally on death's door come back to a normal lifestyle, for a while at least. And I've seen patients with metastatic lung cancer who have lived only a few weeks and those who have lived 20 years with the disease. Nobody can predict the future with certainty."

Progress is being made against lung cancer, Carbone says, and that progress will continue through research.

"The management of lung cancer and the expectations for outcomes are changing," Ross says. "The OSUCCC – James is influencing how these patients will be managed."

Otterson says patients will benefit from "the expansion of our molecular pathology resource, which will enable us to open more clinical studies directed toward those with various subsets of lung cancer."

"We provide expertise in genomics, access to new agents and a multimodality approach to diagnosis and treatment," Villalona says, noting that patients can fare better from this comprehensive approach. "To all who are afflicted with lung cancer or who know someone who is, there is hope".



CT Scans Offer Earlier Detection of Lung Cancer

After the National Lung Screening Trial (NLST) showed that lung computed tomography (CT) scans lowered the risk of dying of lung cancer by 20 percent compared with standard chest X-rays, the OSUCCC – James began offering CT scans to those at high risk for developing the disease.

The screenings involve one low-dose CT scan annually for three consecutive years. To qualify, participants must be 55-74 years old, be a current smoker with a history of smoking two packs per day for 15 years or one pack per day for 30 years, or be an ex-smoker who has quit within the past 15 years.

"Our lung cancer screening program provides results to the patient within a few minutes," says Director Patrick Nana-Sinkam, MD, a pulmonologist who is part of the multidisciplinary lung cancer team at the OSUCCC – James. "The goal is to look for asymptomatic spots on the lung. About 85 percent of lung cancers are smoking-related, which is why this group is targeted to have these early screenings, before the cancer is advanced."

"Even better than early detection is preventing lung cancer altogether, so smoking cessation is also an integral part of our screening program," says David Carbone, MD, PhD, a lung cancer specialist who is working to establish a thoracic oncology center at the OSUCCC – James.

Carbone notes that CT scanning is not the entire answer. Many people develop lung cancer who have never smoked, are not considered high risk and therefore do not qualify for screening. "We need methods for early detection for the 15 percent of lung cancer patients who never smoked, and we are working on this as well."

The CT scans cost $99 and are offered every other Monday from 4-6 p.m. at Ohio State's Martha Morehouse Medical Pavilion, Second Floor Clinic, 2050 Kenny Road, Columbus. To schedule, call The James Line at (614) 293-5066.

Shown in one of the seven "vaults" that will house linear accelerators on the second floor of the new James Cancer Hospital and Solove Research Institute *(from left)*: Erica Hlavin Bell, PhD, research assistant professor of Radiation Oncology; resident Timothy Lautenschlaeger, MD; American Board of Radiology B. Leonard Holman Scholar; Arnab Chakravarti, MD, chair of Radiation Oncology, co-director of the Brain Tumor Program, and Max Morehouse Chair in Cancer Research; Nicholas Denko, MD, PhD, associate professor of Radiation Oncology; Deliang Guo, PhD, assistant professor of Radiation Oncology; and Kamalakannan Palanichamy, PhD, research assistant professor of Radiation Oncology.

MECHANISMS *of* RESILIENCE

Understanding how malignant cells survive our attempts to kill them is critical for improving cancer therapy

BY DARRELL E. WARD

More than 1.6 million Americans were expected to develop cancer in 2012, and more than half of them were likely treated with radiation therapy. "Glioblastoma and certain other cancers are highly radiation resistant, while others such as neuroblastoma and certain lymphomas are inherently sensitive to radiation," says Timothy Lautenschlaeger, MD, an American Board of Radiology B. Leonard Holman Scholar in Radiation Oncology at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

"Cells that cannot repair double-strand breaks die by apoptosis, whereas tumors adept at repairing double-strand breaks tend to be radiation resistant."

"At this point, we don't really know why some types of cancer are so sensitive and others so resistant," Lautenschlaeger says. "It isn't simply a mutation or change in a particular gene that determines radiosensitivity in general; these differences are cancer-specific and dramatic."

The failure of radiation therapy – which uses high-energy X-rays to kill tumor cells – is a significant cause of the 577,000 deaths from cancer that were expected in 2012. "Overcoming the mechanisms of therapeutic resistance is key to improving cancer treatment," says Arnab Chakravarti, MD, chair of Radiation Oncology and co-director of the Brain Tumor Program at the OSUCCC – James.

Radiation resistance has multiple components that involve DNA repair, hypoxia, activation of pro-survival pathways, cancer stem cells, and changes that lead to invasion and metastasis, he says. Chakravarti has recruited Lautenschlaeger and other leaders in the field to the OSUCCC – James in an effort to understand and overcome radiation resistance.

DNA REPAIR

Radiation kills cancer cells mainly by causing breaks in both strands of the DNA helix. "Failure to repair double-strand breaks triggers cell-death processes, including apoptosis, whereas tumors adept at repairing double-strand breaks tend to be radiation resistant," says Fen Xia, MD, PhD, associate professor of Radiation Oncology and an OSUCCC – James researcher who specializes in DNA damage response and repair in radiation resistance.

Xia wants to understand how cells sense DNA damage and initiate the repair response, and how these actions differ between tumor and normal cells. "We want to interrupt this process and kill tumor cells while preserving normal cells," she says.

To overcome radiation resistance, Xia is exploring two strategies: protecting normal cells from the lethal effects of radiation while concurrently enhancing radiation-induced tumor cell death.

BRCA1 AND PARP1 INHIBITION

An example of the second strategy is Xia's work to make cancer cells with functional BRCA1 protein susceptible to PARP1 inhibition. PARP1 – or poly ADP-ribose polymerase – is a molecular complex that quickly repairs breaks in one of DNA's two strands.

DNA single-strand breaks can lead to double-strand breaks during replication. Unrepaired double-strand breaks are lethal to proliferating cancer cells. Dysfunction in the repair of both single-strand breaks and double-strand breaks will be synthetically lethal.

BRCA1 – infamous, along with BRCA2, for raising breast-cancer risk when mutated – is a DNA-repair protein that corrects double-strand breaks. Xia, in a 2012 study published in the journal *Cancer Research*, and others have shown that the PARP1 inhibitor olaparib is highly selective in killing BRCA1-mutated familial breast tumors.

THIS RESEARCH BY
FEN XIA, MD, PhD
is funded by NCI grant CA163838-01A1.

"Unfortunately, over 90 percent of patients who develop sporadic breast cancer carry functional BRCA1 and BRCA2 proteins and are proficient in repair of double-strand breaks, precluding them from this potent therapy," Xia says. "An important goal of our work is to make PARP inhibitors available to the majority of patients, those with working BRCA1 genes."

In earlier work, Xia demonstrated that BRCA1's repair function occurs in the nucleus, but that the BRCA1 protein shuttles between the nucleus and cytoplasm. In the cytoplasm, it loses its DNA-repair function and instead facilitates apoptosis. "We show that if the BRCA1 protein moves to the cytoplasm, cells die much more quickly and efficiently," Xia says.

Xia and her collaborators believe that if they can force BRCA1 out of the nucleus, it could make tumors that have functional DNA repair susceptible to PARP-inhibition therapy. The same strategy could be used to sensitize tumors to radiation-induced DNA damage, she says.

THIS RESEARCH BY
NICHOLAS DENKO, MD, PHD,
is supported by NCI program project grant CA067166-15 and NCI grants CA156950-02 and CA163581-01A1.

"People have understood the oxygen enhancement ratio for 50 years, but no one has figured out how to use it clinically."

HYPOXIA

When tumors outgrow their blood supply, they develop new blood vessels that are abnormal and leaky. These poorly perfused tumors have pockets of low oxygen and necrosis; that is, they are hypoxic.

Hypoxia within tumors reduces the effectiveness of radiation therapy. When therapeutic ionizing radiation strikes cellular molecules, it generates ions, free electrons and hydroxyl radicals. Some of these reactive elements are captured by the cell's natural buffering system, but many strike its DNA and cause double-strand breaks that overwhelm the repair system and kill the cell.

"The presence of oxygen enhances the fixation of this DNA damage and the lack of oxygen inhibits it," says Nicholas Denko, MD, PhD, associate professor of Radiation Oncology at the OSUCCC – James and an authority on hypoxia and radiation therapy.

The absence of oxygen in tissue can decrease the effective radiation dose by a factor of three – defined as the oxygen enhancement ratio. That is, it can take three times the radiation dose to kill seriously hypoxic cells versus well-oxygenated cells, he says.

But there is little latitude for raising a patient's radiation dose, which is chosen primarily to kill tumor cells and is about the maximum possible without causing complications.

"Most tumor types have areas of hypoxia," Denko says. Studies have been done in patients with head and neck cancer, cervical cancer or soft-tissue sarcomas. "We calculate that in these tumors even a small fraction of hypoxic tumor cells can have a big effect on patient outcome," he says.

"People have understood the oxygen enhancement ratio for 50 years, but no one has figured out how to use it clinically," he explains. Investigators have tried to deliver more oxygen to the tumor. They've transfused patients with red blood cells, given patients erythropoietin to grow more red blood cells and had patients breathe pure oxygen to get more oxygen to the tumor. "These have all had disappointing clinical effectiveness," he says.

Denko and his colleagues are approaching the problem differently. "Rather than trying to increase the tumor's oxygen supply, we want to reduce the tumor's oxygen demand," he says.

The researchers are evaluating drugs that reduce oxygen consumption by mitochondria, the main oxygen sink in cells. "Mitochondria produce ATP, which powers everything we do," Denko says. "There are drugs that inhibit mitochondria as a side effect. If we can use them in tumors to reduce oxygen demand by mitochondria, we might improve the tumor's response to radiation therapy."

PRO-SURVIVAL PATHWAYS

Research by Ohio State's Arnab Chakravarti shows that radiation therapy can activate critical pro-survival signal-transduction pathways and shut down cell-death pathways, enhancing cancer-cell survival and radiation resistance.

In a *Journal of Clinical Oncology* study, Chakravarti reported that activation of the PI3 kinase/AKT pathway is associated with adverse outcomes in malignant glioma patients. These pro-survival molecules were activated far more often in higher-grade gliomas. "Glioblastomas had the highest activation of PI3 kinase family members compared with grade III tumors or grade II tumors, and the degree of activation was strongly associated with adverse clinical outcome and radiation resistance," Chakravarti says. As such, the degree of pathway activation in glioblastoma is an independent prognostic marker over and beyond tumor grade.

In a 2011 *New England Journal of Medicine* paper, Chakravarti collaborated with Marcus Bredel, MD, an associate professor at the University of Alabama Birmingham and an adjunct associate professor of Radiation Oncology at the OSUCCC – James, and showed that loss of a gene called *NF-kBIA* promotes the growth of glioblastoma multiforme, the most common and deadly form of brain cancer. The findings suggested that therapies that stabilize this gene

might improve survival for certain glioblastoma patients.

"The NF-kB pathway is thought to be related to the PI3 kinase/AKT pathway, so it's interesting that an NF-kBIA deletion is also strongly associated with therapeutic resistance," Chakravarti says. "Overall, this shows that these pro-survival pathways play a major role in mediating radiation resistance."

LOW-GRADE GLIOMAS

Erica Hlavin Bell, PhD, research assistant professor of Radiation Oncology at the OSUCCC – James, works closely with Chakravarti to identify biomarkers of radiation resistance in low-grade gliomas and prostate cancer.

"We want to learn whether grade 2 and grade 3 gliomas respond differently to treatment compared with grade 4 tumors (i.e., glioblastoma multiforme)," Bell says.

"Most studies of brain tumors have been completed with varying grades, and patients with different grades are often treated in a very similar fashion," she adds. "We are asking whether lower grade tumors need the same treatment as glioblastoma. We've learned that, at the molecular level, lower-grade brain tumors are very different from grade 4 tumors. Because of this, we believe that their treatment response is probably also different. We want to understand that in detail."

Bell's investigations use tumor samples obtained through two Radiation Therapy Oncology Group (RTOG) trials: RTOG-9813 (ClinicalTrials.gov identifier NCT00004259) and RTOG-9802 (ClinicalTrials.gov identifier NCT00003375). She is looking at low-grade glioma tissue for new and known biomarkers and comparing them with patient outcomes.

"This tissue is precious," she says, "and we want to acquire as much information as possible from each specimen."

GLIOBLASTOMA AND MELANOMA

People with grade-4 melanoma of the skin or with grade-4 glioma (glioblastoma) in the brain survive about one year after diagnosis. Both malignancies are highly resistant to chemotherapy and radiation. "We are trying to identify the cause of that resistance," says Kamalakannan Palanichamy, PhD, research assistant professor of Radiation Oncology at the OSUCCC – James.

In both malignancies, Palanichamy and his lab are combining genomic, transcriptomic, epigenomic, proteomic and metabolomic analyses to identify subsets of patients who will better benefit from a particular treatment.

In addition, Palanichamy is investigating the role of self-renewing populations of cancer cells, also called cancer stem cells (CSCs), in radiation resistance. They isolate CSCs from glioblastoma tumors, culture them and expose them to chemotherapy, small-molecule inhibitors and radiation alone and in combination.

RECURRENT BLADDER CANCER

Some 73,500 Americans were expected to develop bladder cancer in 2012, and an estimated 14,900 people died from the disease. Three quarters of newly diagnosed bladder-cancer cases present with superficial, noninvasive tumors. These are treated by minimally invasive surgery through the urethra, sometimes with chemotherapy. There is a high rate

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THIS RESEARCH BY

ARNAB CHAKRAVARTI, MD

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of prolonged survival.

For invasive bladder cancer, the bladder is frequently removed. In many cases, however, it is possible to preserve the bladder with transurethral surgery, radiation and chemotherapy, says Lautenschlaeger, who is studying radiation therapy for bladder cancer.

"Bladder removal versus bladder preservation is also important when superficial bladder cancer recurs as muscle-invasive cancer," Lautenschlaeger says.

Lautenschlaeger is working to identify biomarkers of recurrence that will enable urologists to identify patients who are better candidates for surgery or for bladder-preservation therapy in collaboration with a team led by William U. Shipley, MD, at the Massachusetts General Hospital (MGH)/Harvard Medical School. Together with MGH investigators who originally pioneered the concept of bladder-preservation therapy, Lautenschlaeger leads a correlative study for markers of treatment resistance that is part of a phase II randomized study for patients with muscle-invasive bladder cancer evaluating transurethral surgery and concomitant chemoradiation (Clinical trials.gov identifier NCT00777491).

"Ideally, we will one day be able to tell patients whether or not they are good candidates for bladder preservation," he says. "Patients with markers indicating bladder preservation can avoid the quality-of-life changes associated with bladder loss, and patients with markers indicating a high risk of recurrence can avoid the side effects of chemotherapy and radiation."

FUELING RESISTANCE

Deliang Guo, PhD, assistant professor of Radiation Oncology, is investigating links between tumor-cell metabolism cells and radiation and chemotherapy resistance.

"Cancer cells have altered and enhanced metabolism, and oncogenes are involved in that metabolic reprogramming," Guo says. "We want to unravel the links between oncogenic signaling pathways and cancer metabolism."

Additionally, Guo hypothesizes that radiation therapy can alter glucose metabolism in cancer cells in ways that contribute to radiation resistance. He reasons that radiation can boost the production of ATP and of nucleic acids, lipids and amino acids, which cancer cells need for growth and proliferation.

"We are now investigating whether the irradiation of cancer cells directly increases glucose uptake and ATP production in cancer cells," he says.

Guo, whose specialty is oncogene signaling and metabolic pathways, is collaborating on this work with Chakravarti, a specialist in radiation therapy. "We've combined our expertise to learn whether radiation causes this metabolic change, and whether we can interrupt this interaction and reduce radiation resistance," Guo says.

THE FUTURE

Research is improving radiation therapy, Lautenschlaeger says. "We're learning, for example, that changing the fractionation schedule might improve treatment outcomes in certain tumors. The traditional schedule of low daily doses works well and is safe, but some cancers might be more sensitive to one or just a few high doses of radiation.

"There are now protocols for lung cancer that use only a few fractions of very high doses of radiation," he says. "This was first tried in patients with advanced, inoperable disease. Now, trials using radiation without surgery are available to patients who are operable.

"The day is coming when we will do molecular profiling of tumors and understand that the tumor has a particular array of gene changes, and that information will enable us to determine the optimal treatment regimen," he says. "Radiation therapy for cancer will become much more personalized and even more effective."

Read this story online for more details about the research described here.

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

Phase II study of lenalidomide to repair immune synapse response and humoral immunity in early-stage, asymptomatic chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with high-risk genomic features

HYPOTHESES: Low-dose lenalidomide will enhance the efficacy of vaccination for infectious diseases among patients with CLL as measured by antibody response to pneumonia vaccination with conjugated 13-valent pneumococcal vaccine. Low-dose lenalidomide can also induce complete remissions in asymptomatic patients with high genomic risk CLL, delaying the time to first conventional therapy.

STUDY DESIGN: Patients are randomized to one of two treatment arms. Oral low-dose lenalidomide is administered daily on a continuous basis for at least 24 28-day courses in the absence of disease progression or unacceptable toxicity. Patients also receive two doses of 13-valent protein-conjugated pneumococcal vaccine (PCV13) intramuscularly concurrent with or sequential to lenalidomide, depending upon treatment arm.

RATIONALE: OSU-10156 investigates the use of lenalidomide and vaccine therapy for treating early-stage, asymptomatic CLL or SLL. Survival of CLL patients ranges from months to more than 20 years, but infectious complications account for 30-50 percent of deaths. Unfortunately, many of the most common therapies for CLL (e.g., fludarabine, alkylating agents) can increase the risk for infection.

Standard care for CLL involves treating only symptomatic disease. Routine treatment of early-stage CLL is generally not considered beneficial. However, a subgroup of patients is at high-risk for early progression and death. For example, patients with CLL cells showing unmutated immunoglobulin heavy-chain genes (IgVH), a complex karyotype and deletions of chromosomes 11q22.3 and 17p13.1 demonstrate a shorter treatment-free interval and impaired survival.

Lenalidomide is a potent immunomodulatory analogue of thalidomide. Its immunomodulatory effects include stimulating T-cell proliferation and production of IL-2, IL-10 and IFN-γ. The agent has shown promising activity in both untreated and relapsed/refractory CLL, including patients with high-risk genomic features.

Evidence suggests that lenalidomide can promote both cellular and innate immune activation, and the drug has effected both remissions and improvement of immune-system parameters when given to patients with symptomatic CLL/SLL.

Lenalidomide might further benefit patients if administered earlier in the disease course, when humoral and cellular immune mechanisms are more intact.

The Prevnar 13 (PCV13) vaccine is a conjugate vaccine for prevention of disease caused by the 13 pneumococcal serotypes. Research has shown that such vaccines are not only safe but also potentially more effective in several immunocompromised adult populations. Additionally, preliminary findings from a study of protein-conjugated pneumococcal vaccine and lenalidomide in multiple myeloma patients suggest that the vaccine and lenalidomide interact to boost immune responses.

OSU-10156 will help determine whether early treatment of early-stage, high-risk CLL patients with the PCV13 vaccine and either concurrent or sequential lenalidomide will help prevent immune deterioration in early-stage disease. Key objectives include determining the complete response rate after two years of lenalidomide therapy and determining the incidence of infection, particularly invasive pneumococcal infections.

AT A GLANCE

Trial no.: OSU-10156 (ClinicalTrial.gov identifier NCT01351896

PI: **JEFFREY A. JONES, MD, MPH**

Phone: 614-293-3507

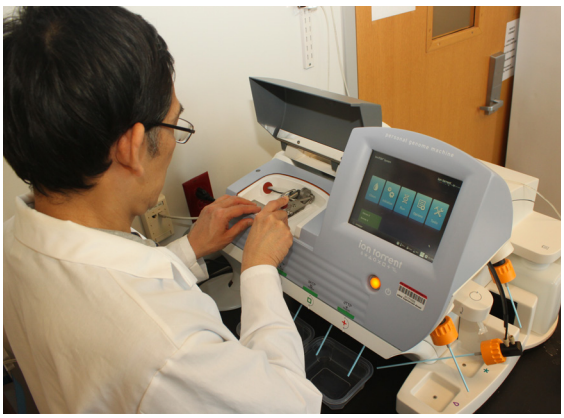
Email: *jeffrey.jones@osumc.edu*

Eligibility: Histologically confirmed, asymptomatic CLL/SLL with at least one high-risk genomic feature; age ≥18 years; ECOG performance status ≤ 2; non-pregnant and/or using adequate birth control; no previous treatment for CLL/SLL; no history of AIHA/ITP; no VTE events within 6 months; estimated life expectancy ≥24 months

SHARED RESOURCES

NUCLEIC ACID SHARED RESOURCE ADDS NEW TECHNOLOGIES AND APPLICATIONS

The OSUCCC – James Nucleic Acid Shared Resource (NASR) provides genomic support for biomedical research, including Sanger sequencing, next-generation sequencing, genotyping, methylation and gene-expression analysis. Recently, the facility extended its next-generation sequencing by adding an Ion PGM Sequencer (Life Technologies) and its gene expression analytical capabilities with a QuantStudio™ 12K Flex system. New applications were added to the nCounter System (NanoString Technologies).



ION PGM SEQUENCER

The NASR introduced the Ion PGM Sequencer in early 2012. Life Technologies' Ion Torrent is based on electrical detection (i.e., pH change) of base extension.

The Ion PGM sequencer is ideal for sequencing genes, small genomes and panels of genes, or for performing gene expression profiling. Total workflow, from DNA to sequence, takes about eight hours for 200 base-reads on an Ion 314 Chip. Three Ion semiconductor chips are available: The Ion 314, the Ion 316 and the Ion 318 (stated output, 10 megabases, 100 megabases and 1 gigabase of sequence data, respectively).

GENE EXPRESSION ANALYSIS

The QuantStudio™ 12K Flex system A new QuantStudio™ 12K Flex system adds extra capacity to the NASR's three Applied Biosystems 7900HT Fast Real-Time PCR Systems and its two Applied Biosystems StepOnePlus Real-Time PCR Systems. Extra capacity will be reflected in the OpenArray format for effortless scaling from 1 to 12,000 data points in a single run and the simple OpenArray workflow, including the Accufill System.

NEW COUNTER APPLICATIONS

NanoString's nCounter technology detects target molecules using color-coded molecular barcodes, providing a digital count of target molecules. The NASR has added two new applications to its nCounter system:

- miRGE analysis: Permits profiling of 100-200 mRNA targets and 5-30 miRNA targets in a single reaction.
- nCounter single-cell expression assay: Provides ultra-sensitive, reproducible and highly multiplexed gene-expression profiling from single cells or with as little as 10pg of total RNA. The assay linearly amplifies up to 800 target transcripts from a single cell in a single tube without bias.

Please visit the NASR for more information or send an email to *Hansjuerg.Alder@osumc.edu.*

Events Calendar

UPDATE IN ROBOTIC SURGERY ACROSS DISCIPLINES

March 22, 2013, THE OHIO STATE UNIVERSITY BIOMEDICAL RESEARCH TOWER

This all-day CME-certified workshop will enable participants to:

- Identify applications for robotic surgery across surgical specialties
- Review emerging issues related to new robotics techniques
- Define patient populations that can benefit from robotic surgery
- Describe the potential benefits of robotic surgery over open surgery

Pre-registration is required for this free workshop.
Visit **https://ccme.osu.edu/ConferenceDetail.aspx?ID=1231**

PELOTONIA 13

August 9-11

Pelotonia is an annual bicycling event that takes riders through bucolic Ohio countryside on routes of varying length. The event attracts thousands of cyclists from across the nation, and 100 percent of the funds raised supports cancer research at the OSUCCC – James.

For information or to register as a rider or volunteer, visit **http://www.pelotonia.org.**

EXPANSION UPDATE

SECOND FLOOR: RADIATION ONCOLOGY

The OSUCCC – James Department of Radiation Oncology will occupy the second floor of the new James Cancer Hospital and Solove Research Institute when construction is complete.

On page 24 of this issue of *Frontiers*, Arnab Chakravarti, MD, chair of Radiation Oncology, and a group of OSUCCC – James investigators were photographed in the unfinished second-floor space, in one of seven "vaults" that will house linear accelerators (linacs).

A second-floor perch is unusual for a radiation therapy department – most such facilities are located below ground – but when it opens in 2014, its windows will allow natural daylight to enter from the north and south, providing a more cheerful treatment environment. Twenty-four patient exam rooms are designed to make visits as comfortable and convenient as possible for patients.

Adding the Radiation Oncology department to the new hospital was made possible by a $100 million competitive grant awarded to Ohio State by the federal Health Resources Services Administration.

The Radiation Oncology area is also equipped with computerized tomography (CT), positron emission tomography/CT and magnetic resonance imaging. Each imaging modality has particular advantages and is used to simulate and customize radiation treatment for each patient. Integrating these imaging modalities with treatment delivery by the most technologically advanced linear accelerators will result in the best care possible for patients treated at the OSUCCC – James.

FACTS ABOUT THE SECOND FLOOR AND THE LINAC VAULTS

At 27 million pounds, the second floor is the heaviest component of the building. It required redesigning the building's foundation and structure and adding 263 concrete piles to support the weight, and additional and heavier-gauge columns had to be incorporated into the structural support.

- The department's **seven linacs** each weigh **65,000 pounds**;
- The vaults that contain the linacs are built of **specialized concrete, steel and lead to contain the radiation**.
- The vaults' floors and ceilings are about five feet thick and constructed of concrete that includes **8.2 million** pounds of a special high-density aggregate made of hematite mined in South Africa and supplemented by lead shot.
- The walls are about two feet thick and made of a proprietary high-density brick (visible in the photograph on page 24). About **139,000 of the bricks, totaling 5.1 million pounds**, were used to shield the walls of the seven linacs, a brachytherapy suite (a specialized operating room for delivering localized high-dose radiation), and an operating room on the fourth floor that offers intraoperative radiation therapy.

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FUNDRAISING

Pelotonia Total Tops $42 Million in Just Four Years

Riders and donors in Pelotonia 12, the annual grassroots bicycle tour that generates money for cancer research at the OSUCCC – James, raised a record $16,871,403, a 28-percent increase over the Pelotonia 11 total of $13.1 million.

This year's tally brings the four-year fundraising total for Pelotonia, which began in 2009, to more than $42 million. Pelotonia 12, which took place Aug. 10-12 on routes between Columbus and Kenyon College in Gambier, Ohio, drew a record 6,212 riders from 43 states and three countries, as well as 3,141 virtual riders and more than 2,000 volunteers. Measured by riders, Pelotonia this year became the largest single-event biking fundraiser in the nation.

Participants included a record 1,635 members of Team Buckeye, the official superpeloton (riding group) for The Ohio State University. The team included 1,198 riders, 336 virtual riders and 101 volunteers. Team Buckeye comprised 84 pelotons and collectively raised more than $2.1 million.

"Everyone associated with Pelotonia should be proud of what we are accomplishing," says OSUCCC Director and James CEO Michael A. Caligiuri, MD. "At a time when government funding for cancer research is hard to obtain, we have stepped forward to raise money ourselves. And not just a little money: more than $42 million in four years is the kind of financial firepower that enables us to confidently proclaim that we will one day conquer this disease in its many forms."

Thanks to generous sponsors – Huntington Bank, Limited Brands Foundation, Richard and Peggy Santulli, American Electric Power Foundation, Nationwide Insurance, Cardinal Health Foundation, JP Morgan Chase and The Scotts Miracle-Gro Company – 100 percent of every dollar raised by Pelotonia goes to support cancer research at the OSUCCC – James.

Pelotonia 13 is scheduled for Aug. 9-11. Register at **www.pelotonia.org.**

NATIONAL RECOGNITION

The James Earns 'Top Hospital' Status for Fifth Time in Six Years

For the fourth consecutive year, and the fifth time in six years, the OSUCCC – James has been named one of the safest and most effective hospitals in the country by The Leapfrog Group, a national consortium of Fortune 500 companies that pay for healthcare needs for an estimated 37 million Americans.

Only one other cancer hospital has earned this honor four years in a row.

The James is among 92 hospitals from a field of almost 1,200 to be named 2012 Leapfrog Top Hospitals based upon a rating system that provides an up-to-the-minute assessment of a hospital's quality and safety. A complete list of 2012 Leapfrog Top Hospitals can be viewed at www.leapfroggroup.org.

IN THE NEXT ISSUE OF **frontiers**…

MELANOMA RESEARCH AND CARE

Under the leadership of medical oncologist Kari Kendra, MD, PhD, the expanding OSUCCC – James melanoma program is using a multidisciplinary, science-based approach to innovative patient care that involves targeted therapies, immunotherapeutic techniques and agents with novel mechanisms of action. The program has seen increases in patient volume, in clinical trials and in the number of patients enrolled in these studies.