AUTUMN | 2012

# frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

The James

Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

## A MUTUAL EXCHANGE

NCI CCC

A Comprehensive Cancer Center Designated by the National Cancer Institute

UPFRONT

*The Director's Perspective*

# Cancer Research at a Land Grant University

**On July 2, the United States celebrated the 150th anniversary of one of President Abraham Lincoln's most significant legacies: the Morrill Land-Grant College Act. It led to the founding in 1870 of The Ohio State University, Ohio's land-grant institution.**

**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

Like all land-grant institutions, Ohio State emphasized the agricultural and mechanical arts, while also including the sciences and classical studies. It has since embraced nearly every branch of study, and today it has 14 colleges, including a highly respected College of Medicine.

In 1976, Ohio State became a National Cancer Institute (NCI)-designated Comprehensive Cancer Center, and in 1990 it opened the Midwest's first free-standing cancer hospital. In 2010, the OSUCCC – James received an exceptional rating from the NCI, and in 2014 we will open a larger James Cancer Hospital and Solove Research Institute.

Its size, scope and the excellence of its programs have made Ohio State one of our nation's top research universities. This issue of *Frontiers* demonstrates how our breadth and depth provide extraordinary opportunity for diverse research collaborations.

"Campus Connections," for example, shows how OSUCCC – James researchers in computational drug design, organic synthesis and cancer biology came together to develop a targeted inhibitor of a key regulatory protein in cancer cells, while collaborators with expertise in cancer biology, food science and clinical trials testing are developing a soy bread to reduce the risk of prostate cancer.

"A Mutual Exchange" describes how the OSUCCC – James and Ohio State's College of Veterinary Medicine are collaborating in testing new anticancer agents. The Frontline commentary "Harnessing Ohio State's Innovation Engine" reviews how diverse elements at Ohio State are enabling the OSUCCC – James to systematically discover and develop new anticancer drugs.

As you peruse this issue, perhaps you will agree that, but for Ohio State, such innovative and promising efforts might never have occurred.



*Read Frontiers online or download an issue at http://cancer.osu.edu/Frontiers.*
*Underlining and f indicate more information online at http://cancer.osu.edu/Frontiers.*

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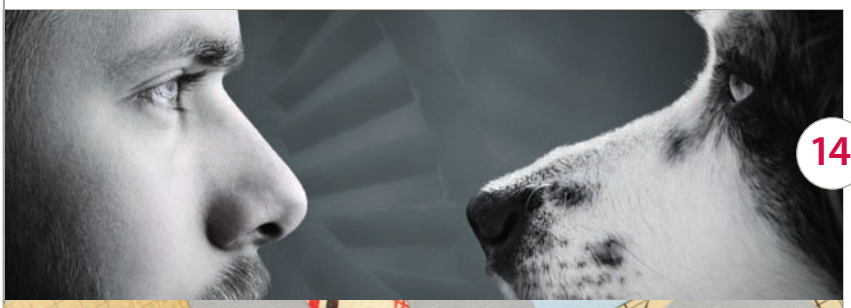


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ON THE COVER: CANCER RESEARCH IN HUMANS AND IN CANINES IS HELPING BOTH.

# Harnessing Ohio State's INNOVATIVE ENGINE

## The OSUCCC – James and the University are preparing an initiative to methodically develop cancer therapeutics

By **TIMOTHY WRIGHT**
*director, Drug Development Institute*

After a long career in the pharmaceutical industry, I recently joined Ohio State and the OSUCCC – James to help advance a drug-development initiative at the University and cancer center. After careful consideration, I concluded that the endeavor holds great potential to benefit cancer patients in Ohio and beyond. My role is to facilitate the work of the OSUCCC – James research community and to work with Ohio State's Technology Commercialization Office (TCO) to optimize the value from our research inventions.

It takes many people and diverse expertise to develop anticancer agents. Scientists and clinicians are essential, of course, but the needed know-how goes beyond that. It can include engineers to help solve solubility problems and experts who can navigate intellectual property laws, assess market opportunities and negotiate agreements. For chemopreventive agents, experts are needed in agriculture, food technology and nutrition. Systems are needed to manage product portfolios and to match developmental milestones with funding support.

As a broad-based, land-grant university, Ohio State possesses much of this expertise:

- The OSUCCC – James has nearly 300 investigators from 11 of Ohio State's 14 colleges. They include some 50 members in the Experimental Therapeutics Program from the colleges of Medicine, Pharmacy, Engineering, Veterinary Medicine and Business.
- The OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program and the University's Crops to Clinic program include members from the colleges of Food, Agricultural and Environmental Sciences; Arts and Sciences; Education and Human Ecology; Public Health; and Veterinary Medicine, as well as Medicine and Pharmacy.
- Ohio State is one of only seven centers funded by the National Cancer Institute (NCI) to conduct both phase I and phase II clinical trials on new anticancer agents sponsored by the NCI.

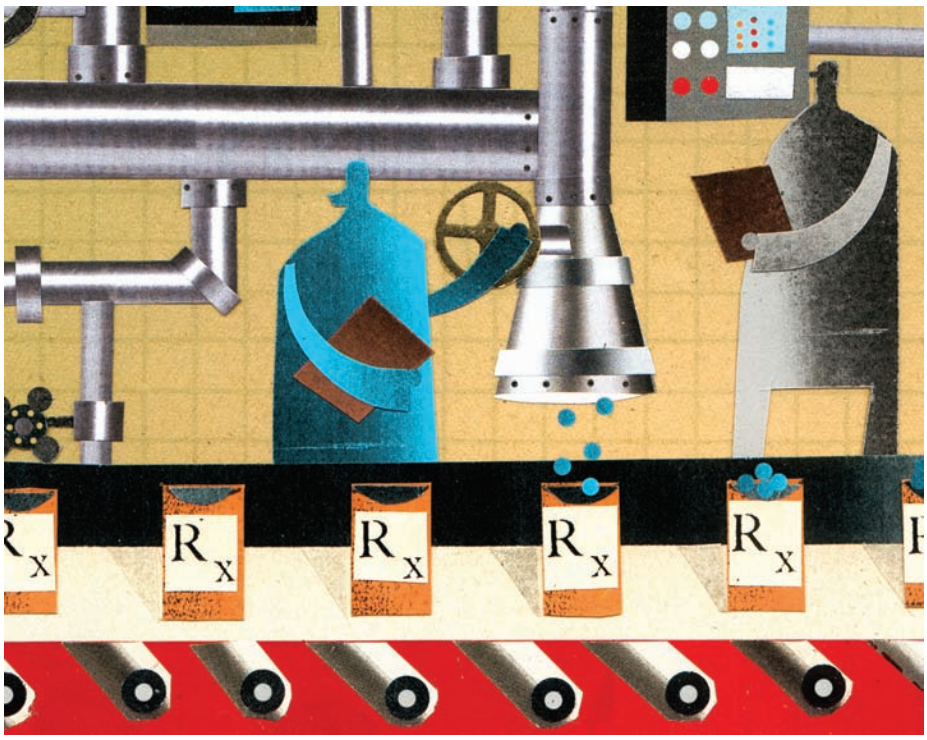
A nascent drug-development pipeline already exists, much of it in the discovery phase. There is huge potential for an early-stage pipeline to create value.

Two targeted agents invented by OSUCCC – James investigators are already in early-phase clinical trials: *AR-12*, for solid tumors, and *AR-42*, a histone deacetylase inhibitor for relapsed or treatment-resistant multiple myeloma, chronic lymphocytic leukemia or lymphoma. More agents – synthetic and natural-product based, therapeutic and chemopreventive – are in the pipeline.



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

## DRUG DEVELOPMENT




Furthermore, the timing is good to establish a drug-development initiative at Ohio State. Currently, the pharmaceutical and biotechnology industries are reducing their in-house research budgets and establishing external research and development partnerships. This is a long-term trend.

Our goal at Ohio State is to develop a model of collaboration that encourages pharmaceutical and biotech companies to partner with the OSUCCC – James to develop novel anticancer agents. These partnerships will help fund drug-development research at the OSUCCC – James, and products that are commercialized will produce royalties that can be invested in University research programs.

We are developing a methodology to advance a drug-development program systematically. The installation of project and portfolio management tools is under way. We are leveraging the capabilities of the University to advance these agents along a predetermined project plan that includes important milestones and "go/no-go" decision points.

Drug development is about science, but it's also about economics. To ensure a robust drug-development initiative, we will create a project plan for select drugs. This includes timing of experiments and determining who is accountable for what and when. A sound understanding of the time, costs and probability of technical success to develop a compound is essential in determining if investment should be pursued, as this forms the basis for key assumptions that ultimately drive financial valuation.

*At Ohio State, our goal is to develop a model of collaboration that encourages pharmaceutical and biotech companies to partner with the OSUCCC – James to develop novel anticancer agents.*

I am working with our researchers to generate data and with the TCO to facilitate appropriate patent filings to ensure that we can capture value down the road. The structure we are creating will mimic certain core processes of a pharmaceutical company while remaining academically sensitive. We must promote smart academic freedom to publish, and we must avoid conflicts of interest while also creating value for the inventions that are discovered and that mature here.

Few universities can match Ohio State's competitive scale and diverse capabilities, but bringing together the many colleges, departments and investigators into a single functioning system is a sensitive undertaking. We must be inclusive and good communicators as we build this initiative. Everyone involved must understand the many benefits it holds for the University, for cancer patients and their families, and for the efforts of the OSUCCC – James to achieve a cancer-free world.

ACUTE MYELOID LEUKEMIA

# AML INSIGHT

## microRNA Prognostic Marker Identified in Acute Leukemia

A study led by researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) has identified microRNA-3151 as an independent prognostic marker in certain patients with acute leukemia.

**CLARA D. BLOOMFIELD, MD,**
*Distinguished University Professor, the William Greenville Pace III Endowed Chair in Cancer Research, and cancer scholar/senior adviser to the OSUCCC – James*

The study involved patients with acute myeloid leukemia and normal-looking chromosomes (CN-AML). It found that when microRNA-3151 (miR-3151) is overexpressed in CN-AML, the disease responds poorly to treatment, and patients experience shorter remissions and survival periods.

This effect is independent of other gene mutations that may be present. Additionally, miR-3151 is encoded within a gene called *BAALC*, which itself is an independent marker of poor survival when overexpressed in CN-AML.

The findings provide insight into the nature of AML and might help determine the best therapy for individual patients, further personalizing AML therapy.

"Patients with high levels of both miR-3151 and *BAALC* had the poorest outcome compared with those showing high expression of either miR-3151 or *BAALC* alone, or those expressing low levels of both," says principal investigator Clara D. Bloomfield, MD, a Distinguished University Professor and cancer scholar/senior adviser to the OSUCCC – James. "This suggests that miR-3151 and *BAALC* may act through different mechanisms to enhance poor outcome of CN-AML patients."

The study involved 179 patients of age 60 or older with CN-AML who were treated on Cancer and Leukemia Group B (CALGB) clinical trials.

MicroRNAs are small molecules that cells use to help regulate the kind and amount of proteins they make. About a third of human microRNAs are encoded within host gene sectors called introns, short stretches of DNA that are not used when genetic information is translated to make a protein.

First author Ann-Kathrin Eisfeld, MD, a postdoctoral researcher in the laboratory of study co-author Albert de la Chapelle, MD, PhD, and Bloomfield, says this study provides "the first description of interplay of an oncogene and its intronic, and possibly oncogenic, microRNA."

*Published in the journal* Blood



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

BRAIN CANCER

# SYSTEM UPDATE

## Revised Classification Should Improve Patient Care

Radiation oncology researchers have revised the system used by doctors since the 1990s to determine the prognosis of people with glioblastoma, the most devastating of malignant brain tumors.

The outdated system, which was devised for glioblastoma and related brain tumors that were treated by radiation therapy only, relied on clinical signs and symptoms, and it divided patients into six prognostic groups. The new system accommodates advances in treatment, particularly the use of radiation therapy plus the chemotherapy drug temozolomide, and incorporates molecular biomarkers as well as clinical variables.

"The new model is more relevant and contemporary, and it should do a better job of identifying patients who require the most aggressive therapy," says Arnab Chakravarti, MD, the study's chair for translational research.

Chakravarti, professor and chair of the Department of Radiation Oncology at Ohio State and co-director of the Brain Tumor Program at the OSUCCC – James, presented study findings at the 2012 annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago.


**ARNAB CHAKRAVARTI, MD,** *professor and chair of the Department of Radiation Oncology, co-director of the Brain Tumor Program at the OSUCCC – James and the Max Morehouse Chair in Cancer Research*

To devise the new system, Chakravarti and colleagues compared tumor and healthy tissue from 162 glioblastoma patients who were treated under the Radiation Oncology Group clinical trial 0525 (RTOG 0525). The investigators profiled protein, messenger RNA and epigenetic changes in patients' tumor cells while looking for alterations in key signaling molecules.

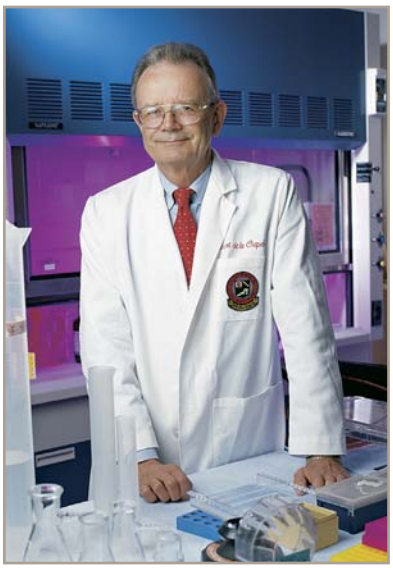
They showed that high expression of the proteins pAKT, c-met and MGMT was associated with poor prognosis, while methylation of the *MGMT* gene, which codes for a DNA repair protein, was associated with a better prognosis.

"We hope to begin further studies to validate our classification system soon," Chakravarti says.

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

# SMALL CHANGE

## Inherited DNA Alteration Explains Overactive Leukemia Gene



**ALBERT DE LA CHAPELLE, MD, PhD,**

*co-leader of the Molecular Biology and Cancer Genetics Program and the Leonard J. Immke, Jr. and Charlotte L. Immke Chair in Cancer Research Fund*

A new study shows that a small inherited change in DNA is largely responsible for overactivating a gene linked to poor treatment response in people with acute leukemia.

The study, led by researchers at the OSUCCC – James, focused on the *BAALC* gene, which is often overexpressed in acute myeloid or acute lymphoblastic leukemia. This work indicates that these diseases will likely respond poorly to standard therapy.

Researchers discovered that *BAALC* overexpression is caused by a small change called a single nucleotide polymorphism (SNP) in the gene's DNA. The SNP alters the gene's "on" switch, allowing a different molecule to keep it "running" when it shouldn't.

"This SNP doesn't raise risk of developing leukemia, but it predisposes to overexpression of the *BAALC* gene, which is associated with leukemia development and poor response to treatment," says principal investigator Albert de la Chapelle, MD, PhD, co-leader of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James.

The findings suggest this SNP could be a useful prognosis marker and help guide therapy in acute leukemia patients.

Researchers say the DNA change caused by the SNP creates a binding site for an activating molecule called RUNX1, which is also involved in forming normal and malignant blood cells. The scientists showed that patients with high levels of RUNX1 protein also had high *BAALC* expression, while those with low RUNX1 protein had low *BAALC* gene expression.

For this study, de la Chapelle and colleagues used DNA sequencing to examine the genomic region of *BAALC* in 253 patients with cytogentically normal AML treated in Cancer and Leukemia Group B clinical trials. The analysis revealed nine SNPs of interest, but the researchers focused only on one called rs62527607[T].

"We doubt that this SNP is entirely responsible for *BAALC* overexpression, but we believe it is a major contributor," de la Chapelle says.

*Published in* Proceedings of the National Academy of Sciences.

*Supported in part by NIH/National Cancer Institute grants CA098933, CA101140, CA114725, CA140158, CA31946, CA33601, CA16058, CA77658, and CA129657*



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

CHRONIC LYMPHOCYTIC LEUKEMIA

# TINY TIP-OFF

## Marker Distinguishes Aggressive Form of Chronic Leukemia

Researchers have identified a prognostic marker in the most common form of chronic leukemia that can help distinguish patients who should start treatment quickly from those who can safely delay treatment, perhaps for years.

The study, led by researchers at the OSUCCC – James, focused on chronic lymphocytic leukemia (CLL). Examining a gene called *ZAP-70* in CLL cells for a chemical change called methylation, they found that, when this gene in leukemia cells is methylated, patients are likely to have the slow-progressing form of CLL. When the *ZAP-70* gene is unmethylated, patients are likely to have aggressive disease and should consider immediate treatment.

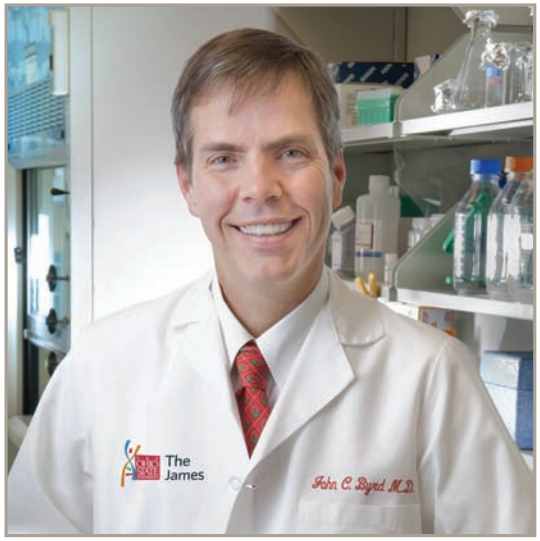
Currently, doctors must simply observe newly diagnosed patients to determine which type of CLL they have. This can delay the start of treatment in patients with aggressive disease, or it can lead to treating patients who don't yet require it.

"This study demonstrates that *ZAP-70* methylation status is a highly predictive, reproducible biomarker of poor prognosis in this disease, and a clinically useful prognostic test for CLL," says principal investigator John C. Byrd, MD, a CLL specialist who directs the Division of Hematology at Ohio State.

The presence of mutations in a gene called *IGVH* and the amount of protein produced by the *ZAP-70* gene in CLL cells are sometimes used to predict prognosis and response to treatment in people with this disease, "but these assays are expensive and difficult to perform," says study co-author and researcher David Lucas, PhD.

"In all cells, some areas of DNA undergo methylation, which controls how that DNA is used," Lucas says. "In cancer cells, the pattern of DNA methylation is often different from that of healthy cells, and this influences how much protein is produced by *ZAP-70* and other genes."

*Published in the* Journal of Clinical Oncology




**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*

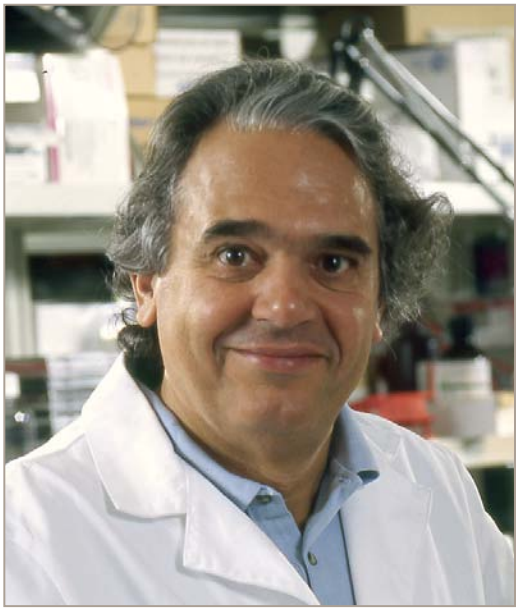
Visit the OSUCCC – James CLL Experimental Therapeutics Laboratory at http://cll.osu.edu.

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

# LEUKEMIC MECHANISM UNMASKED

## microRNA Loss May Power Malignant Transformation in CLL

Loss of a particular microRNA in chronic lymphocytic leukemia shuts down normal cell metabolism and turns up alternative mechanisms that enable cancer cells to produce the energy and build the molecules they need to proliferate and invade neighboring tissue.



**CARLO CROCE, MD,**
*director of Human Cancer Genetics and the John W. Wolfe Chair in Human Cancer Genetics*

The findings come from a study led by researchers at the OSUCCC – James, who showed that microRNA-125b (miR-125b) by itself regulates many enzymes and other molecules that allow cells to make building blocks for their growth and proliferation, such as DNA and lipids needed for cell membranes.

The study also showed that miR-125b is often lost in chronic lymphocytic leukemia (CLL), and that the loss is associated with higher rates of glucose metabolism. This is a characteristic of cancer cells called the Warburg effect, and it alters how cancer cells use glucose to generate energy. This finding suggests that loss of miR-125b is an early step in CLL development. The researchers say the study provides a more comprehensive understanding of how cancer develops and identifies potential targets for CLL drug development.

"Our findings indicate that miR-125b is downregulated in both aggressive and indolent forms of CLL, and that this downregulation is associated with metabolic adaptation to cancer transformation," says principal investigator and corresponding author Carlo Croce, MD, director of Human Cancer Genetics at Ohio State and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

"By identifying the metabolites that are changed, as we have here, we can propose to use drugs that target them and perhaps control the leukemia," Croce says.

Scientists have known for some time that, as normal cells become cancerous, different metabolic pathways are switched on and support the enhanced growth and energy needs of malignant cells. This study reveals one way that can happen.

*Published in the journal* Blood

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

BRAIN CANCER

# ALLERGEN ASSOCIATION

## People With Allergies May Have Lower Risk of Brain Tumors

An Ohio State University study adds to growing evidence that links allergies and reduced risk of a type of brain cancer. The study suggests the reduced risk is stronger among women than men, but men with certain allergy profiles also have a lower tumor risk.

Because these tumors, called gliomas, can suppress the immune system to allow themselves to grow, researchers have never been sure whether allergies reduce cancer risk or if, before diagnosis, these tumors interfere with the hypersensitive immune response to allergens.

In this study, scientists analyzed stored blood samples taken from patients decades before they were diagnosed with glioma. Men and women whose blood samples contained allergy-related antibodies had an almost 50-percent lower risk of developing glioma 20 years later compared with people without signs of allergies.

"This is our most important finding," says Judith Schwartzbaum, PhD, a member of the OSUCCC – James Cancer Control Program and the study's lead author. "The longer before glioma diagnosis that the effect of allergies is present, the less likely it is that the tumor is suppressing allergies."

The researchers analyzed stored blood samples from 594 people in Norway who were diagnosed with glioma (including 374 with glioblastoma) from 1974-2007, then compared them – for date of blood collection, age and sex – with 1,177 samples from people not diagnosed with glioma.

They next measured levels of two types of proteins called IgE, or immunoglobulin E – antibodies produced by white blood cells that mediate immune responses to allergens. In each sample, they determined whether the serum contained elevated levels of IgE specific to common allergens in Norway, as well as total IgE.

Among women, testing positive for elevated allergen-specific IgE was associated with a 54-percent decreased risk of glioblastoma compared with women who tested negative for allergen-specific IgE. The researchers did not see this association in men.

"There is definitely a difference in the effect of allergen-specific IgE between men and women," Schwartzbaum says.

*Published in the* Journal of the National Cancer Institute

**JUDITH SCHWARTZBAUM, PhD,**
*a member of the OSUCCC – James Cancer Control Program and the study's lead author*

# OF NOTE

*Recent Recognitions of OSUCCC – James Physicians and Researchers*

## AWARDS AND HONORS

**CARLO CROCE, MD,** *chair of the Department of Molecular Virology, Immunology and Medical Genetics, holder of the John W. Wolfe Chair in Human Cancer Genetics and director of Human Cancer Genetics, has been recognized by Ohio State as a 2012 Distinguished University Professor. Croce's studies have transformed how cancers are diagnosed and treated, improving patient outcomes. He also discovered the role of microRNAs in the genesis of various cancers.*

**EWA MRÓZEK, MD,** *an assistant professor-clinical in the Division of Medical Oncology,* **received the Bertha A. Bouroncle Teaching Award, which is presented each year to a faculty member from either the Division of Hematology or the Division of Medical Oncology by the Hem-Onc Fellows at their annual awards banquet**. *Mrózek is a breast cancer specialist at the OSUCCC – James with research interests in clinical trials. The award is named for a professor emerita at Ohio State whose long and distinguished career as a physician, researcher and educator was highlighted by her identification and characterization of hairy cell leukemia, a rare chronic form of the disease for which she and colleagues also developed a drug that has become a standard of care.*

**QIANBEN WANG, PhD,** *assistant professor of Molecular and Cellular Biochemistry, and a member of the Molecular Carcinogenesis and Chemoprevention Program at the OSUCCC – James, has received a 2012 Endocrine Society Early Investigators Award supported by Amgen and Pfizer Inc. The award assists the development of early-career investigators and recognizes their accomplishments in endocrine research.*

## GRANTS

**JOHN C. BYRD, MD,** *director, Division of Hematology; professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences, and* **NATARAJAN MUTHUSAMY, DVM, PhD,** *associate professor of Medicine, Division of Hematology,* **have received a five-year, $1.6 million grant from the NIH/National Cancer Institute (grant CA159296) to study *"Novel Immunotherapies for Lymphoid Malignancies."***

**FEN XIA, MD,** *associate professor of Radiation Oncology,* **has received a five-year, $1.6 million grant from the NIH/National Cancer Institute (grant CA163838) for the study "GSK3B Mediates Radiation-Induced Cytotoxicity In Hippocampal Neurons."**

## LEADERSHIP ACTIVITIES AND APPOINTMENTS

**ARNAB CHAKRAVARTI, MD,** *chair of Radiation Oncology and co-director of the OSUCCC – James Brain Tumor Program,* **spoke at the plenary session for the 54th Annual Meeting of the American Society for Radiation Oncology (ASTRO).** *Chakravarti presented* "A Revised RTOG Recursive Partitioning Analysis Model for Glioblastoma Based Upon Multi-Platform Biomarker Profiles," *about the application of newly identified biomarkers to classify glioblastomas.*

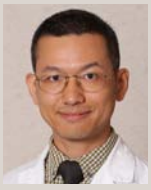


*Underlining and* f *indicate more information online at http://cancer.osu.edu/Frontiers.*

## FACULTY AND PROGRAMS

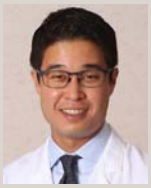
**TANIOS BEKAII-SAAB, MD,** *associate professor of Medicine and Pharmacology,* **has been named section chief of the Gastro-Intestinal Oncology Program.** *Bekaii-Saab is also the chair of the OSUCCC – James Gastrointestinal Cancer Disease-Specific Research Committee and a member of the Experimental Therapeutics Program.*

**LEI CAO, PhD, has joined the cancer program as an assistant professor of Medicine and of Molecular Virology, Immunology and Medical Genetics.** *Her research interests include understanding the impact of the external environment on brain function, metabolic regulation and tumor pathogenesis.*



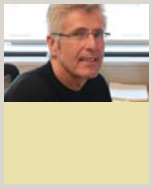
**BO H. CHAO, MD, has joined the cancer program as an assistant professor of Internal Medicine, Division of Medical Oncology.** *His clinical interests include lung cancer and head and neck cancer. His research interests include experimental and developmental therapeutics, and oncolytic virus therapy. Chao came to Ohio State from the University of Wisconsin.*

**DAVID CARBONE, MD, PhD, has joined the cancer program as a professor of Internal Medicine, Division of Medical Oncology and director of The James Thoracic Center.** *His clinical interest is lung cancer. He specializes in translational research in lung cancer, including development of genetic and proteomic biomarkers and identification of novel therapeutic targets. Carbone came to Ohio State from Vanderbilt University.*



**JAMES L. CHEN, MD, has joined the cancer program as an assistant professor of Biomedical Informatics and of Internal Medicine, Division of Medical Oncology.** *His clinical interests include personalizing the treatment of prostate, kidney and bladder cancers and sarcoma using non-invasive biomarkers. His research interests include gene signatures, translational bioinformatics (moving computer models of cancer into the clinic), and integrative genomics (merging gene data with traditional medical records). Chen came to Ohio State from the University of Chicago.*

**PAYAL DESAI, MD, has joined the cancer program as a clinical assistant professor of Internal Medicine, Division of Hematology.** *Her clinical interests include benign and classical hematology. Her research interests include complications, management and novel therapies for sickle cell disease. Desai came to Ohio State from the University of North Carolina.*



**PAUL GOODFELLOW, PhD, has joined the cancer program as a professor of Obsetrics and Gynecology.** *His research interests include the genetics of endometrial cancers. Goodfellow came to Ohio State from Washington University School of Medicine in St. Louis.*

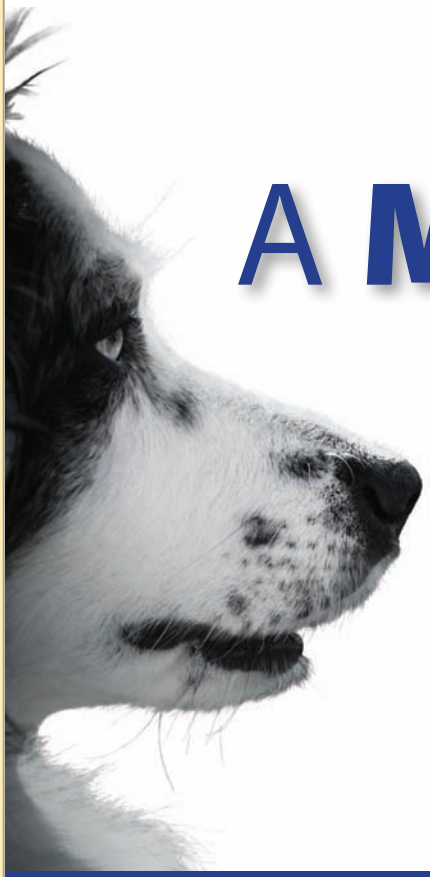
**JOHN HAYS, MD, PhD, has joined the cancer program as an assistant professor of Internal Medicine, Division of Medical Oncology.** *His clinical interests include new drug development for gynecologic cancers and rare gastrointestinal malignancies. His research interests include building a better understanding of protein-signaling networks and how these can guide rationally designed and personalized therapies for cancer patients. Hays came to Ohio State from the National Cancer Institute.*

**RAY HERSHBERGER, MD, is the new director of the Division of Human Genetics at Ohio State's Wexner Medical Center.** *He will be responsible for continuing to expand the clinical cancer genetics program for the OSUCCC – James. Hershberger came to Ohio State from the University of Miami's Miller School of Medicine.*

**J. HARRISON HOWARD, MD, has joined the cancer program as a clinical assistant professor of Surgery.** *His clinical interests include melanoma and metastatic melanoma, soft tissue sarcoma and GI malignancies. His research interests include melanoma clinical trials and clinical outcomes. Howard came to Ohio State from John Wayne Cancer Institute.*

**SAMEEK ROYCHOWDHURY, MD, PhD, has joined the cancer program as an assistant professor of Internal Medicine and of Pharmacology.** *His clinical interests include mutation-driven clinical trials for advanced cancer. His research interests include use of genetic profiles in treatment decisions. Roychowdhury came to Ohio State from the University of Michigan, Ann Arbor. He was awarded the 2012 Landon Foundation – AACR Innovator Award for Research in Personalized Medicine, which provides support for a physician-scientist who conducts meritorious studies that hold promise for near-patient benefit.*

**CHARLES SHAPIRO, MD,** *professor of internal medicine and director of breast medical oncology, has been named section chief of the Breast Cancer Program within the Division of Medical Oncology. Shapiro is also research director for the Breast Cancer Program at the OSUCCC – James and a member of the Cancer Control Program.*



# A MUTUAL EXCHANGE

*Ohio State researchers are integrating studies of anticancer drugs for canines into the development of drugs for humans for the benefit of both*

BY BOB HECKER

Hundreds of cancer patients are benefiting today from a novel drug called ganetespib that has roots in canine research at Ohio State.

Cheryl London, DVM, PhD, a canine cancer researcher in Ohio State's College of Veterinary Medicine and in the University's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), led a phase I clinical trial evaluating ganetespib in dogs brought to the clinic with spontaneous cancer.

Ganetespib (or STA-9090) is a potent inhibitor of heat shock protein 90, a molecule that promotes the maturation and stabilization of several proteins important to cancer development.

London's studies show that ganetespib is effective in treating a variety of canine cancers, including mast cell tumors, osteosarcomas and thyroid carcinoma. "Given that canine and human cancers share many similarities with respect to tumor biology and heat shock protein 90 activation, it's likely that ganetespib will demonstrate comparable anticancer activity in human patients," she says.

At the 102nd annual meeting of the American Association for Cancer Research in April 2011, Synta Pharmaceuticals Corp., which developed ganetespib, reported on human clinical trials that demonstrated the drug's strong activity in both preclinical models and patients, particularly as a single agent in patients with drug resistant non-small-cell lung cancer (NSCLC).

Synta Chief Medical Officer Vojo Vukovic, MD, PhD, credited the work of London and colleagues for bringing ganetespib into the clinic.

"The results from our collaborators at Ohio State have been instrumental in helping us think through clinical trial choices for ganetespib on dose, schedule and biomarker evaluation," he said. "The single-agent activity seen in dogs with cancer has been encouraging and consistent with single-agent activity seen in human clinical trials."

Ganetespib is now being evaluated in more than 20 human clinical trials nationwide for patients with various cancers. At Ohio State, Gregory Otterson, MD, a researcher with the OSUCCC – James, is principal investigator for a pending study that will be part of an ongoing Synta phase II trial of ganetespib in a subset of NSCLC patients who are positive for the anaplastic lymphoma kinase (ALK) fusion gene.

## CANINE CLOUT

Approximately 80 million dogs live in the United States, and about 1 million of them develop cancer each year. Many of these cancers are similar to their human counterparts in terms of the genetic changes that drive the malignancies.

With that in mind, researchers at the OSUCCC – James are increasingly collaborating with colleagues in Veterinary Medicine to integrate studies of anticancer drugs

*"Dogs represent an intermediate step in translating data from mouse models. If a therapeutic agent has biologic activity in dogs, chances are you'll see it in humans too."*

for canines into the development path of anticancer drugs for humans, for the benefit of both.

The National Cancer Institute (NCI) calls this integration of research on naturally occurring cancers in animals with the study of cancer biology and treatment in humans "comparative oncology." Ohio State – which is an NCI-designated Comprehensive Cancer Center and has a freestanding cancer hospital, an Experimental Therapeutics Program, and colleges of Medicine, of Veterinary Medicine and of Pharmacy – can support a strong program in this innovative area of oncology.

This integration will likely enhance translational outcomes for both species, says London, who is a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program. "Evidence suggests that 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," she explains.

Why are canine and human cancer studies so similar? It starts with physiology. London says humans have a much closer anatomic relationship with dogs than with rodents, the most commonly used animal models for cancer research. Humans and dogs also have similar genetic alterations in cancer, similar therapeutic targets, and similar angiogenic and natural cell death (apoptotic) pathways.

"One of the challenging aspects of human cancer therapy is translating data from animal models to people," London says. "There are big metabolic differences between mice and humans. Mouse models have been good for working out the biology of disease, but they pose a challenge in assessing treatment efficacy and side effects.

"Dogs represent an intermediate step in translating data from mouse models. If a therapeutic agent has biologic activity in dogs, chances are you'll see it in humans too."

Michael Grever, MD, who chairs the Department of Internal Medicine and co-leads the Experimental Therapeutics Program at the OSUCCC – James, agrees.

"Canines enable us to test new therapies in a model that is much more relevant to human cancers than xenograft studies, which usually involve injecting a cancer cell line into the subcutaneous flank of a rodent," Grever says. "Xenograft studies provide information of tumor response in an *in vivo* model, but they do not reflect the natural history of a spontaneous tumor as in a dog model. And large animals offer a more robust model for evaluating drug tolerance or toxicity."

Canine trials also face less stringent FDA oversight than human trials and can thus be completed more quickly and with less expense.

"While clinical trials in client-owned dogs are conducted with care and caution, the FDA has fewer restrictions for these studies compared with early trials in human cancer patients," Grever says. "Changes in doses, schedules and combinations are faster and more efficient in canine patients, and this information facilitates future human trials."

"From a drug-development standpoint, canine studies generally are more flexible and move faster than human trials," says Timothy Wright, director of Ohio State's emerging Drug Development Institute. "These advantages offer a more efficient way of collecting needed information about a drug's behavior and toxicity while hastening our ability to move novel therapies into human trials."

London says the average timeline for human drug development is 10 years. "A clinical trial in children with bone cancer can take five years to accrue enough patients, and then another five years for outcomes," she says. "So 10 years pass before you know something new, which is why the field moves so slowly.

"But in veterinary oncology, we can complete a study in dogs with bone cancer within one year and have outcomes in two to three years."

She says the low rate of FDA approval for novel drugs as standards of care in human cancer stems from both the volume of regulations and guidelines and from the fact that many cancer drugs ultimately fail during later phases of testing.

"Cancer drugs often get to phase III studies and fail. At least 50 percent of the time, drugs that have shown anticancer activity in earlier phases don't work anymore," London says. "Why? Is it because we

didn't get the dosing regimen right? Or that the mouse data simply didn't translate well?

"Mouse models that look promising often don't have the same level of therapeutic activity in larger animals. One of our goals with canine studies is to reduce the drug failure rate by providing enough reliable data for human studies to gain better results."

London says both humans and pets benefit from clinical trials in the veterinary setting. Pet owners who agree to enter their pets on a clinical trial gain access to advanced care at little or no cost, and critical information regarding the disease process and response to therapy is gained to advance the treatment of human disease.

"It's a win-win situation," she says. "And many owners feel good that their pets are in a clinical study that may also improve human health."

"From the human perspective," adds Lonnie King, DVM, MS, MPA, professor and dean of the College of Veterinary Medicine, "research involving novel agents in dogs with cancer can provide valuable information about side effects not identified earlier in the drug-development process, ways in which the drug can be given to enhance its activity, and biomarkers that can be used to predict which tumor is more likely to respond to therapy. From the veterinary perspective, our canine patients get cutting-edge treatments that can truly help treat their cancers."

## CAREFUL COLLABORATION

Despite fewer FDA regulations, canine studies in companion animals at Ohio State adhere to Good Clinical Practice guidelines and are under close and collaborative institutional control. Ohio State is one of 20 academic comparative oncology centers involved in a Comparative Oncology Trials Consortium (COTC), which is centrally managed by the NCI's Center for Cancer Research Comparative Oncology Program.

And in 2007, the College of Veterinary Medicine formed its own Clinical Trials Office (CTO), which is directed by London and functions in much the same manner as the CTO at the OSUCCC – James, facilitating studies by taking on more of the administrative and regulatory burdens so researchers can concentrate on science.

"Guidance provided by our Veterinary Medicine CTO has helped our researchers more effectively interface with biotech and pharmaceutical companies, assisted in grant preparation when clinical projects are involved, and provided a mechanism for interfacing with other researchers at Ohio State and Nationwide Children's Hospital (NCH in Columbus, Ohio)," King says.

Veterinary Medicine researchers have been working with Ohio State's medical community and NCH on several projects, King says, adding that the most advanced involves the application of a novel STAT3 protein inhibitor developed by Jiayuh Lin, PhD, at NCH, and Chenglong Li, PhD, of the College of Pharmacy, to canine bone cancer (see "Campus Connections"). Lin and Li are also members of the OSUCCC – James Experimental Therapeutics Program. King notes that this work "represents a combined effort among several researchers across multiple colleges and at NCH."

"We do 25 to 30 clinical trials per year, and 60 to 70 percent of them are cancer-related," London says, noting that she and some other researchers in Veterinary Medicine are also members of the OSUCCC – James. "Our college can assist researchers at Ohio State and NCH by facilitating the drug-development process and by compressing the timeline for transition into human clinical trials, particularly for drugs developed at OSU."

A plan is in the works, she adds, for the College of Veterinary Medicine CTO and Biospecimen Repository (CTO/BR) to become a Shared Resource with the OSUCCC – James. Jeff Walker, senior executive director for the OSUCCC – James, says the plan is far enough along for the CTO/BR to be considered a "developing" Shared Resource.

Patrick Green, PhD, professor and associate dean of Veterinary Medicine and leader of the Viral Oncology Program at the OSUCCC – James, believes this Shared Resource "will fully integrate the comparative and translational medicine efforts of the CTO/BR with those of Ohio State's Medical Center, Comprehensive Cancer Center and Nationwide Children's Hospital. This is likely to result in improved translational outcomes in both human and veterinary medicine through early evaluation of novel therapeutic approaches that can help guide the future use of such therapies to treat human and

animal disease."

Wright says the College of Veterinary Medicine "has created a sound strategic and financial business plan to execute successfully in comparative oncology. Ohio State is positioned to lead this on a national basis, and the OSUCCC – James is supporting this effort directly. Both our Comprehensive Cancer Center and Drug Development Institute are bullish on the promise of collaborative studies with Veterinary Medicine."

"The Veterinary Medicine resource adds to the enormous potential at Ohio State for drug development," Grever says. "Having multiple interactive bioscience medical colleges on one campus will place us at the forefront of therapeutic advancement."

## TRANSLATIONAL TRIUMPHS

London appreciates the support and believes it is justified. Besides the ganetespib studies, she can cite examples of other canine trials that have benefited human cancer research:

- OSUCCC – James researchers led by John C. Byrd, MD, are finding in a phase II human clinical trial that an agent called PCI-32765, also known as ibrutinib, is highly active and well-tolerated in patients with chronic lymphocytic leukemia (CLL) who were previously untreated or who have relapsed and are resistant to other therapy. This inhibitor is the first to target Bruton's tyrosine kinase (Btk), a molecule required for activating the B-cell receptor signaling pathway, which contributes to CLL and other B-cell malignancies. London notes that the initiation of Byrd's trial was supported by an earlier study that evaluated this agent in dogs with spontaneous B-cell non-Hodgkin's lymphoma. That study showed that ibrutinib effectively inhibited Btk in canine lymphoma patients and that this was associated with clinical responses, providing early support for the subsequent human clinical trials in B-cell malignancies.

**CHERYL LONDON, DVM, PhD,**
*associate professor of Veterinary Medicine and holder of the Thekla R. and Donald B. Shackelford Professorship in Canine Medicine*

- London led part of a national research effort to evaluate toceranib, a tyrosine kinase inhibitor that blocks several receptor tyrosine kinases involved in tumorigenesis and angiogenesis (VEGFR, PDGFR, Kit, Flt3). Biologic activity in dogs with several types of cancer (carcinomas, sarcomas, melanoma) was demonstrated, supporting the development of a similar drug, sunitinib, for humans with cancer. In 2009, toceranib became the first drug approved by the FDA specifically to treat cancer in dogs.
- London and colleagues are evaluating KPT-335, an inhibitor of the protein CRM1 that controls the shuttling of many key proteins in and out of the cell nucleus. Disrupting of CRM1 function results in failure of normal nuclear transport and death of tumor cells, making it a prime therapeutic target. London says work with KTP compounds in dogs in lymphoma, mast cell tumors, osteosarcoma and melanoma is guiding the development path of a similar drug, KPT-330, in humans.

Still other canine trials, including some with the COTC, are ongoing or pending at Ohio State. London projects even more will arise as the University's drug-development efforts escalate.

"It's phenomenally rewarding to contribute not only to veterinary medicine but to the human side as well; to see a new agent that has a beneficial effect on patients is what keeps me motivated," she says. "I hope referring physicians and their patients find it equally exciting that cancer studies involving pets can also help people.

"We're all in this together, and there's no reason that we can't all learn from everything we do."

*To learn if a pet could benefit from a College of Veterinary Medicine clinical trial, please contact the Clinical Trials Office at 614-688-5713 or via email at* **clinicaltrials@cvm.osu.edu**

# 80 is the new 50

## Research supports more aggressive treatment for colon cancer in older patients

BY KENDALL POWELL
ARTWORK BY RICHARD LILLASH

The patient was an 86-year-old woman, and surgeon Mark Bloomston, MD, carefully considered whether to remove half her liver to treat her metastatic colon cancer. "She looked younger than 86, but I knew her liver was 86 and that older people can have unpredictable outcomes after major liver operations," he recalls. He explained to her that there was a risk she might die as a result of surgery; she told him she wanted to "go down swinging."

"She survived the operation, went home four days later and never looked back," says Bloomston, a surgical oncologist and associate professor of surgery at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). "I had weighed surgery as a viable option because of her age, but she did fine."

Bloomston's decision to aggressively treat his older patient is consistent with a nationwide trend among physicians treating colorectal cancer (CRC) patients. Most of these patients are 70 and older, have multiple health conditions, take numerous medications and have mobility limitations, all of which makes treating them trickier. But new techniques and technologies are enabling oncologists to offer older patients better options for fighting advanced colon cancer, and research is showing that healthy older patients reap as much benefit from aggressive treatments as younger patients.

"Colon cancer is a disease of aging," explains Richard Goldberg, MD, medical oncologist and physician-in-chief at the OSUCCC – James. "Seventy-one is the average age of diagnosis in the U.S." But it is one of the slowest growing, and screening has made CRC one of the most preventable of cancers (see Colon Cancer – A Snapshot), he says.

Forty percent of all CRC cases arise in people age 75 or older, and these patients have an average of five other medical conditions at the time of diagnosis. Common comorbidities include anemia, hypertension, other gastrointestinal (GI) problems, and heart, liver and kidney disease, complications that can affect tolerance to chemotherapy and a patient's ability to withstand and recover from major surgery. Mobility limitations can affect treatment for patients who live alone or no longer drive.

"Managing older patients with colon cancer can be challenging," says Goldberg, who specializes in treating older people with colorectal cancer.

## ATTITUDE ADJUSTMENTS

Sometimes older patients with advanced disease will tell Goldberg: "Please don't knock me to my knees just to give me a few extra months to live." But others exemplify how attitudes are shifting among both patients and physicians about aggressive CRC treatments in the so-called elderly. Goldberg mentions a retired executive in his late 70s with advanced colon cancer that had metastasized to his liver and lungs. Shortness of breath brought him to the hospital.

"When I saw him in the clinic, he could barely speak," Goldberg remembers. On first examination, the patient's age and other indicators might have led Goldberg to advise the family to arrange hospice care. "But he had been fully functional just three months before," says Goldberg.

**RICHARD M. GOLDBERG, MD,**
*physician-in-chief at the OSUCCC – James and The Klotz Family Chair in Cancer Research*

***"If older patients are fit and robust, we can treat them aggressively and more than double their life expectancy."***

Instead, he sat down with the patient and family and suggested an aggressive treatment approach. It included a combination chemotherapy regimen, and it had a slightly higher rate of complications in older patients. But Goldberg and his colleagues had shown in a 2006 *Journal of Clinical Oncology* paper that the multi-drug approach benefited patients over 70 just as much as younger ones.

"He chose the aggressive therapy, and now he's out riding his tractor mowing his lawn," Goldberg reports. He notes that, except in cases where patients are critically ill with another ailment, older patients not only tolerate standard therapies well, but also do well on them. "We can tailor treatment to their other medical needs and their preferences."

Research has shown that older

stage IV colon-cancer patients treated with the chemotherapy agent 5-fluorouracil alone have a median survival of around 1 year. On the other hand, treating with combination therapy that includes two newer drugs, irinotecan and bevacizumab, the median survival time jumps to 28 months. "If older patients are fit and robust, we can treat them aggressively and more than double their life expectancy."

The same seems true for aggressive and potentially curative surgery. Advances in laparoscopic and robotic surgeries are making it easier to treat patients formerly perceived as too frail to recover from major surgery.

"We are learning that older people aren't frail based solely upon their age. A healthy 80-year-old can be as able as a healthy 50-year-old," says Bloomston. Indeed, physicians who treat elderly CRC patients turn to performance-status measurements such as the Charlson co-morbidity index or Karnofsky performance scale to estimate frailness. Health status and performance-status – measures of daily activity and stamina – are more telling than a person's biological age.

## TAILORING TREATMENTS

Currently, oncologists generally use six drugs to treat colorectal cancer: three chemotherapeutics (5-fluorouracil, or its oral form capecitibine; oxaliplatin; and irinotecan) and three targeted therapies (the VEGF inhibitor bevacizumab; and two EGFR inhibitors, cetuximab and panitumumab).

Goldberg mostly sees patients with advanced cancers commonly treated with combination chemotherapy. However, as drugs are combined in patients who may be on multiple agents already, the potential for side effects increases. Goldberg chooses to start with either a single drug and add more as the patient tolerates it, or to start a three-drug regimen with a reduced dose that can be escalated. "It's not one size fits all," he says; rather, chemotherapy should be tailored to the individual patient's medical and lifestyle needs.

For example, bevacizumab can aggravate high blood pressure and necessitate upping a patient's anti-hypertensive drug dosage. Oxaliplatin can cause sensory neuropathy, a numbness in the fingers and toes, which can increase the risk of an injury due to a fall for older patients. This is where the new specialty of geriatric oncology comes into play, using assessment tools like the Charlson Index to determine "who is robust and who might worry you," says Goldberg.

These assessment tools help physicians determine whether a factor like "walks with a cane" is a true sign of frailty. Such assessments identify patients at high risk of serious chemotherapy side effects or those not able to withstand surgery.

## Colon Cancer – *A Snapshot*

Screening colonoscopies can prevent colon cancer by detecting precancerous polyps.

- The U.S. Preventive Services Task Force recommends that people of non-African descent and no family history of colon cancer get a screening colonoscopy at age 50, repeated every 10 years generally until age 75.
- African-Americans, who tend to develop colon cancer earlier, should get their first screening colonoscopy at age 45.
- The cure rate for stage I colon cancer is 95 percent, dropping to 5 percent for stage IV metastatic disease.
- Of the 150,000 new cases of colon cancer in the United States each year, about half develop metastatic disease.

## SURGICAL SHIFTS

Bloomston notes that it's the recovery, rather than the surgery, that concerns him when treating older patients. "Older patients can often handle an operation; what they don't handle well are complications," he says.

Developments such as post-operative pneumonia, infections or confusion, along with a higher risk of falling, can initiate a downward spiral for older patients. "By minimizing even small complications, we can potentially prevent the domino effect of complication upon complication," Bloomston says. Along these lines, minimally invasive laparoscopic surgery techniques to remove colon tumors have been shown to be as effective as traditional surgery and also reduce complication rates, particularly in older patients. "Today, surgical oncologists and colorectal surgeons have so much experience with laparoscopy that any part of the colon could potentially be removed with minimally invasive techniques," says Bloomston, although these techniques are more complicated the further downstream in the colon or rectum the tumor is located.

After such surgery, the smaller incisions mean less pain and a faster return to mobility with several potential benefits. Less pain means less need for narcotic pain relievers, and this in turn can lower the risk of respiratory complications.

**MARK BLOOMSTON, MD,** *surgical oncologist and associate professor of Surgery at the OSUCCC – James*

***"We can trick the liver into starting the regeneration process before we operate," Bloomston says. The outpatient procedure involves closing off the liver's right portal vein, which forces the liver's blood supply to the left side. This releases a hormone signal that tells the liver to begin regenerating the left side.***

Reduced narcotic use also lowers the risk of confusion, which is often exacerbated in older patients and can lead them to pull out intravenous fluid lines, oxygen tubes and monitoring lines or to attempt to get out of bed prematurely.

For CRC patients who develop metastatic disease, surgery can prolong their lives. "And a handful we can actually cure with surgery – pretty extensive surgeries, that is," Bloomston notes.

# LYNCH SYNDROME

## *Universal screening finds hereditary colon cancer in older patients*


While the vast majority of colon cancers arise from spontaneous mutations, about 3 percent of cases result from inherited mutations in one of four genes for DNA-mismatch-repair protiens. Called Lynch Syndrome (LS), these inherited forms of colon cancer were thought until recently to show up at an earlier age.

But two studies led by OSUCCC – James researchers revealed several surprises, says genetic counselor Heather Hampel, associate director of the Division of Human Genetics at the OSUCCC – James.

Hampel and her colleagues tested more than 1,500 colorectal cancer patients for the inherited mutations, regardless of age or family history.

Although the average age for diagnosis of LS was thought to be around 45, the Ohio State-led team revealed it to be 54. "In addition, half the people diagnosed with LS in our study were age 50 or older," notes Hampel. In other words, if hospitals screened only patients younger than 50, they would miss half of the cases with LS.

The finding has critical implications, Hampel says. Identifying LS patients early can save both their lives and the lives of relatives: An LS patient's siblings and children have a 50-percent risk of carrying the same mutation. LS patients themselves are at high risk for multiple cancers – most commonly colorectal, uterine, ovarian and gastric cancers – and they are more likely to develop a second primary colon cancer after successful treatment of the first.

Since 2006 the OSUCCC – James has screened all CRC patients for LS. Hampel's study showed that every patient with LS has three family members on average who are also affected. Relatives who learn they also carry a mutation can undergo earlier and more frequent cancer screenings.

"If you find people with LS before they get cancer, you have the potential to really save lives," Hampel says. LS patients can prevent colon cancer by having colonoscopies earlier, starting at age 20 to 25 every one to two years for life. To prevent uterine and ovarian cancers, women with LS may choose to have a hysterectomy and oophorectomy once they are done having children.

Hampel's team estimates that LS affects one of every 370 people in the United States, making it a bit more frequent than hereditary breast cancer. "There were some patients with colon cancer in their 80s that I never would have guessed in a million years had LS, but they did," says Hampel, underscoring how universal screening finds surprising cases without a previous family history and saves lives.



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

*Williams notes that the older patients he treats, mainly for rectal cancer, are benefiting from advances in how radiation therapy is delivered.*

Fortunately, the liver – the organ most affected by metastatic CRC – has an exceptional ability to regenerate. In younger patients, up to 80 percent of the organ can be safely removed and will re-grow after removal, Bloomston explains. "But that's not the case even in a very healthy 80-year-old. Aged livers do not regenerate as quickly or as robustly," he says.

Surgical oncologists, however, have liver-sparing, minimally invasive options that enable them to treat even advanced cases of metastatic CRC in older patients.

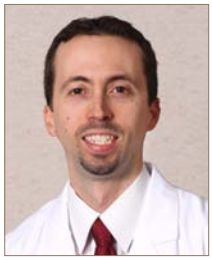
For patients who may not tolerate surgery at all, a surgeon can use a technique called microwave ablation, in which a needle placed into a liver tumor carries an electrical current that literally cooks the tumor from the inside out. Heating the tissue to above 100 degrees Celsius kills the tumor cells and can work effectively for tumors three centimeters in diameter or smaller. A surgeon can also use a combined approach, removing some tumors and ablating others.

Another technique enables a surgeon to estimate the liver's ability to regenerate prior to an extensive resection. "We can trick the liver into starting the regeneration process before we operate," Bloomston says. The outpatient procedure involves closing off the liver's right portal vein, which forces the liver's blood supply to the left side. This releases a hormone signal that tells the liver to begin regenerating the left side.

"This litmus test can tell us if an older patient's liver is capable of regeneration at all," says Bloomston. If the answer is yes, the liver will have begun the process of regeneration before the major resection begins.

Certain comorbid conditions such as fatty liver disease, diabetes and cirrhosis can rule out major surgery. Liver metastases in these patients can be treated using stereotactic ablative radiation therapy, a non-invasive, nonsurgical procedure that delivers high-dose radiation to liver tumors. Terence Williams, MD, assistant professor of Radiation Oncology at the OSUCCC – James who specializes in treating GI and thoracic malignancies, notes that this method can achieve a local control rate of 70-90 percent for one to two years. "Especially for patients with liver-limited disease, this can afford better control of the growth of these tumors," Williams says.

Williams notes that the older patients he treats, mainly for rectal cancer, are benefitting from advances in how radiation therapy is delivered. Intensity-modulated radiation therapy (IMRT) divides radiation up into "beamlets" that



**TERRENCE WILLIAMS, MD,**
*assistant professor of Radiation Oncology at the OSUCCC – James*

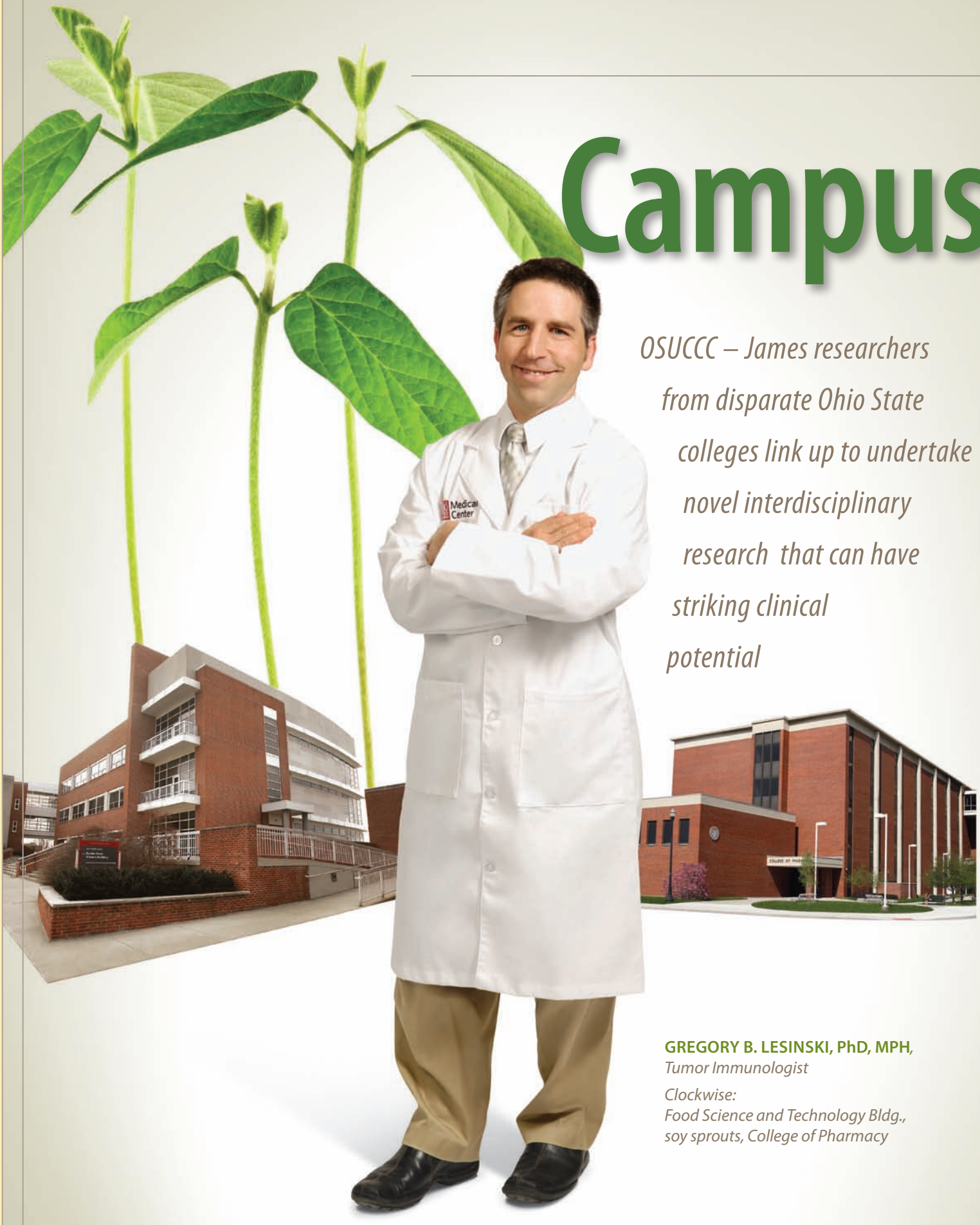
allow for more degrees of freedom in designing the radiation fields. A computer algorithm controls the intensities of the beamlets to deliver a well-controlled dose and to protect nearby structures such as the bladder, small bowel and hip joints. Chronic side effects in these areas, such as fracture of the hips, diarrhea, bowel obstruction and urinary frequency or incontinence, can be especially difficult to manage for elderly patients with limited mobility.

"For certain rectal cancer patients, IMRT allows us to carefully sculpt the radiation dose around sensitive structures that we want to avoid receiving high doses of radiation," Williams explains.

The number of robust older CRC patients will only increase as the baby-boomer generation ages, Goldberg notes. "It's important to have risk-benefit discussions with older patients and their families at every stage of CRC screening and treatment. It's important to talk to each patient to establish what their goals are and to work within those goals. Then you adjust your approach so that patients get what they want out of treatment. The options available to older colorectal cancer patients today are much greater than they were in the past."

# Campus

*OSUCCC – James researchers from disparate Ohio State colleges link up to undertake novel interdisciplinary research that can have striking clinical potential*



**GREGORY B. LESINSKI, PhD, MPH,**
*Tumor Immunologist*

*Clockwise:*
*Food Science and Technology Bldg., soy sprouts, College of Pharmacy*

# Connections

BY DARRELL E. WARD

During the 1990s, details began emerging showing how the immune system defends the body against cancer. People with weak immunity due to organ transplants or HIV infection showed a higher risk for certain cancers; animal models and autopsy studies provided further evidence.

Yet, the body's anticancer immune mechanisms often fail – some 1.6 million Americans will likely develop cancer in 2012, and more than 577,000 are expected to die from one of its many forms. The great majority of these deaths will be due to progressive disease as the cancer evolves specific mechanisms to evade the host's immune system and resist immune-based therapy. New strategies are needed to prevent or treat these malignancies, and tumor immunologist Gregory B. Lesinski, PhD, MPH, at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), believes that boosting the body's anticancer immune response is one of them.

Lesinski, who is a member of the Molecular Carcinogenesis and Chemoprevention Program, runs a basic-science laboratory that teases apart how tumors evade the immune system, or fall prey to it. Together with collaborators in a range of colleges across Ohio State's land-grant campus, he and his laboratory are working to develop a targeted therapeutic and a whole-food prevention intervention, both designed to enhance the immune response to cancer.

"There's an immune-tumor interaction in all types of cancer, and we see a tremendous opportunity to use the immune system as a therapy against cancer," says Lesinski, an assistant professor of Internal Medicine. "Our goal is to improve patient care, perhaps through a dietary intervention with a whole food, or by developing a small-molecule inhibitor based on a natural product."

Lesinski is working on one hand with OSUCCC – James colleagues in the colleges of Pharmacy and Veterinary Medicine to develop small-molecule inhibitors based on the natural product curcumin, which is derived from the spice turmeric, used in many southern Asian recipes. In addition, he is collaborating with colleagues in the colleges of Medicine and of Food, Agricultural and Environmental Sciences to develop a soy bread intervention to reduce inflammation and the risk of cancer recurrence.

The small-molecule inhibitor targets the STAT3 protein, a key regulator of both cancer cell proliferation and dysfunctional immunity in cancer patients. A second-generation version of the agent is currently in preclinical testing. The fortified soy bread was designed, developed and refined by OSUCCC – James investigators in Ohio State's Department of Food Science and Technology to reduce the risk of prostate cancer recurrence; the bread has been evaluated in a phase II clinical trial.

"It's pretty hard for people at other institutions to do multidisciplinary studies of the quality and level we can do them here because few universities have a National Cancer Institute-designated Comprehensive Cancer Center, a College of Medicine, and such a strong presence in agricultural science through our College of Food, Agricultural and Environmental Sciences," Lesinski says.

## ANTITUMOR IMMUNITY

Lesinski is a biologist. His lab works with cells and animal models, and analyzes blood samples from patients on clinical trials for various markers of immune response. They use incubators to culture cells, microscopes to examine them, and gel electrophoresis, a method to separate and identify proteins in cell lysates and serum samples.

Lesinski's lab is particularly interested in the immune cells that attack tumors – cytotoxic T cells and natural killer (NK) cells – and in the hormone-like

chemicals called cytokines and chemokines that tumor cells release to inhibit the antitumor immune response. In 2011, Lesinski and his colleagues showed that the release of interleukin-6 (IL-6) and IL-10 by cancer cells promotes inflammation, stimulates the proliferation of suppressor cells that inhibit the anti-tumor response and probably limit immune-based therapies.

Lesinski and others have shown that when the proinflammatory cytokine IL-6 binds with its receptor on cancer cells, it ultimately activates STAT3, a potent transcription factor that regulates a range of genes. "When STAT3 is hyperactivated in cancer cells, it promotes cell survival and growth, immune evasion, angiogenesis and metastasis," Lesinski explains.

In immune cells, STAT3 activation triggers a phenomenon called cancer-associated immunosuppression. "When STAT3 is activated in immature immune cells, it inhibits their differentiation and leaves them in a more primordial but immune-suppressive state," he says.

The inhibitor that blocked STAT3 activation in both tumor and immune cells should therefore both knock out the suppressive response while enhancing the antitumor response.

## CURCUMIN COLLABORATION

In 2008, Lesinski met with *in-silico* drug designer Chenglong Li, PhD, a member of the OSUCCC – James Experimental Therapeutics Program, and with James Fuchs, PhD, assistant professor of Medicinal Chemistry and Pharmacognosy, both in Ohio State's College of Pharmacy. The two were developing a small-molecule STAT3 inhibitor derived from curcumin.

The molecule showed much potential, but it also presented serious challenges: It inhibited cytokines important for anticancer immune therapies; it had poor solubility and bioavailability; it was rapidly eliminated from the body; and it was nonspecific – it interacted with many different proteins throughout the body.

On the plus side, curcumin inhibited not only STAT3, but also JAK2, a signaling molecule located upstream in the STAT3 pathway, suggesting a derivative molecule might provide double-barreled inhibition. Curcumin was also commonly available and had a relatively simple molecular structure. In 2009, Lesinski led research showing that curcumin induced cell death (apoptosis) in melanoma cells.

Li, an associate professor in Medicinal Chemistry and Biophysics, runs a computational drug-design lab furnished with eight desktop computers. The Ohio Supercomputer Center is nearby when he needs it, and he has a wet lab where he can synthesize molecules. His six graduate students and a postdoctoral researcher are split between the computer and wet labs.

Lesinski joined the collaboration, and Li believed that, working together, they could develop a curcumin-derived inhibitor that was both potent and highly specific for STAT3.

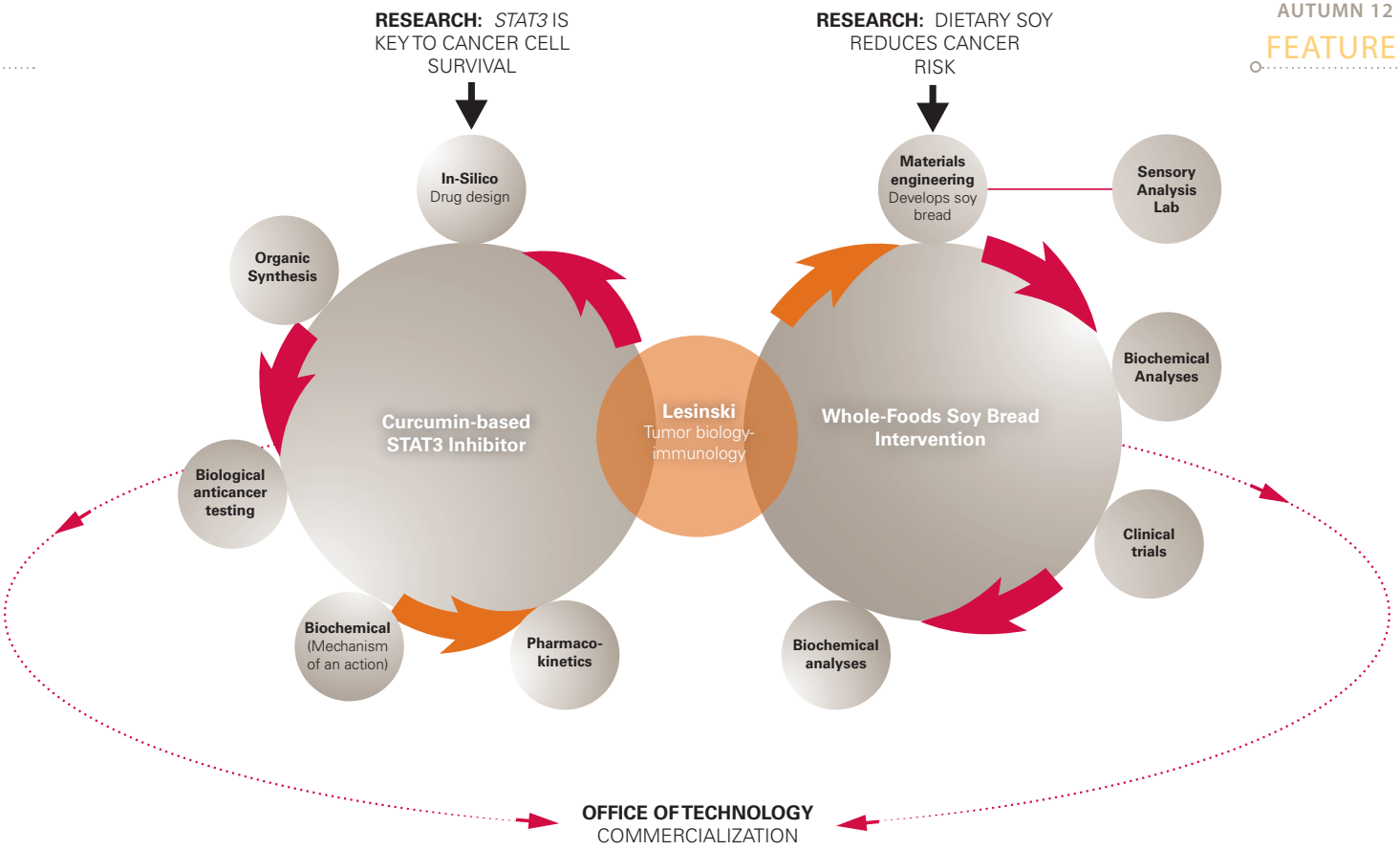
Using *in silico* drug design methods, Li computationally pulled apart the curcumin molecule and eventually constructed a lead molecule called FLLL-32. Fuchs and his lab then used the techniques of synthetic organic chemistry to make the agent, an orange powder.

"As medicinal chemists," Fuchs says, "we not only have to know how to synthesize a molecule, we must synthesize a bioactive molecule, one that does a job. We blend state-of-the-art organic synthesis with a medicinal approach. We can tackle simple molecules or more challenging structures."

## A CYCLE OF DEVELOPMENT

Fuchs and his lab synthesized up to 50 grams of FLLL-32 and distributed it to collaborating labs to evaluate its potency against several cancer types, its toxicity and STAT3 specificity, and its mechanism of action:

- Lesinski's lab tested it in melanoma and renal cell carcinoma, and pancreatic cancer; and in an animal model for its physiological effects, and its effects on cancer and immune biomarkers and on STAT3.
- The lab of Jiayuh Lin, PhD, associate professor of Pediatrics at




Nationwide Children's Hospital, and a member of the OSUCCC – James Experimental Therapeutics, tested the agent against pancreatic cancer.

- The lab of Cheryl London, DVM, associate professor of Veterinary Biosciences in the College of Veterinary Medicine and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program, tested it against canine osteosarcoma.
- Pui-Kai "Tom" Li, PhD, associate professor and chair of Medicinal Chemistry and Pharmacognosy, and his lab showed that the agent blocked STAT3 by preventing two subunits from coming together to form a complete STAT3 molecule.
- Mitch Phelps, PhD, who directs the OSUCCC – James Pharmacoanalytical Shared Resource, and his lab evaluated the agent's pharmacokinetics (i.e., how the body metabolizes the drug).

This schematic indicates the specialties and flow of information involved in the process of designing, producing, testing and refining a targeted anticancer drug (left sphere); and a cancer-preventive soy bread to prevent cancer recurrence (right sphere).

OSUCCC – James tumor immunologist Gregory Lesinski is a collaborator on both projects, which involve diverse specialties, all located on The Ohio State University campus.

The STAT3-inhibitor collaboration includes labs in Ohio State's colleges of Pharmacy and Medicine that focus on computational drug design, drug synthesis and biological testing (including Lesinski's lab). The OSUCCC – James Pharmacoanalytic Shared Resource (SR) provided pharmacokinetic analyses.

The soy bread collaboration includes OSUCCC – James researchers in the Department of Food Science and Technology and in the College of Medicine. The bread was developed, taste-tested and evaluated in a clinical trial of men with prostate cancer. The trial included correlative studies of metabolites and immune effects. The OSUCCC – James Nutrient and Phytochemical Analytics SR provided metabolite and pharmacokinetic analyses.

Ohio State's Office of Technology Commercialization works with researchers to license and help bring agents such as these to market.

*For a slide show of laboratories and facilities involved in these interdisciplinary projects, go to Frontiers online, navigate to this illustration and click in the center of each large sphere.*

Phelps, an assistant professor of Pharmacy with the College of Pharmacy and a member of the OSUCCC – James Experimental Therapeutics Program, showed that FLLL-32, though better than curcumin itself, still had poor solubility and was rapidly metabolized. "This stalled further development at the *in vitro/in vivo* transition phase for a time," Phelps says.

Fuchs suggested a solution: Produce a phosphate derivative of the agent. Li and Fuchs altered the molecular structure and produced the second-generation agent, called FLLL-100P. "This 'simple' structural modification ended up taking about a year for us to solve – there were a number of unforeseen difficulties in reactivity that my graduate student, Eric Schwartz, needed to overcome," Fuchs says.

As before, samples went to Lesinski and other collaborators for biological and chemical testing in a cycle of refinement that would continue until the agent is potentially ready for clinical-trials testing. The change improved the agent's pharmacokinetic profile and produced a 10-fold increase in serum concentration in an animal model.

**JAMES FUCHS, PhD,** *assistant professor of Medicinal Chemistry and Pharmacognosy*

*Tumeric, the plant and the spice*

*"As medicinal chemists," Fuchs says, "we not only have to know how to synthesize a molecule, we must synthesize a bioactive molecule, one that does a job."*

**CHENGLONG LI, PhD,** *a member of the OSUCCC – James Experimental Therapeutics Program*

"Studies in patients can prove whether an intervention truly has an effect," Lesinski says. "If so, we've achieved our main goal; if not, we might tweak the molecule further to improve it…or we might have to start over."

Either way, he says, "Ohio State is one of the few universities that can do this efficiently, almost like a pharmaceutical company. The College of Pharmacy is just down the street. We can walk there in minutes, discuss a problem and make changes. It doesn't take conference calls and plane flights; everything is under the cancer center's umbrella."

## A WHOLE-FOODS INTERVENTION

Carcinogenesis is often characterized by chronic inflammation, and Lesinski notes that there is great interest in harnessing the anti-inflammatory properties of many natural products to reduce cancer risk. In 2010, OSUCCC – James prostate cancer medical oncologist Steven Clinton, MD, PhD, leader of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program, invited Lesinski to join a team focusing on the impact of soy on prostate cancer.

Epidemiologic studies show that in Asian countries where soy is regularly eaten, prostate cancer rates are 10-fold lower than in the United States. In addition, clinical, animal and cell-culture studies have demonstrated soy's anti-inflammatory effects.

Research, including findings by Lesinski, suggests that phytochemicals in soy called isoflavones have anti-inflammatory properties and may influence specific aspects of the immune response. "We believe that soy might have a role in preventing or reducing inflammation before cancer develops," Lesinski says.

## A SOY BREAD CHALLENGE

In 2000, food scientist Yael Vodovotz, PhD, arrived at Ohio State from NASA's Johnson Space Flight Center in Houston, where she developed novel foods for a mission to Mars, including a soy-bread formulation.

Soon after her arrival in the Department of Food Science and Technology and College of Food, Agricultural and Environmental Sciences, a colleague there, Steven Schwartz, PhD, introduced her to Clinton.

Both Clinton and Schwartz were founders of Ohio State's Center for Advanced Functional Foods Research and Entrepreneurship (CAFFRE), and they approached Vodovotz about collaborating on soy bread chemoprevention studies. This conversation led to preliminary studies and a National Institutes of Health-funded pilot study in men with prostate cancer to test their compliance with a soy-bread product and to study the metabolism of soy phytochemicals.

"We wanted to provide a dose of soy into the diet of American men that would be similar to what someone in China would consume," Clinton says. "We felt that bread would be an ideal vehicle for this because bread can be incorporated into any meal. And if we could make a tasty, high-quality bread product, it would be one of the most efficient ways to ensure high compliance for long-term clinical studies."

Like Fuchs' medicinal chemist who must not only synthesize a molecule but synthesize a molecule that does a job, Vodovotz had to develop a soy bread that not only tastes good but delivers a specific dose of isoflavones.

Ultimately, the bread would be provided to men with prostate cancer during a four-month clinical trial. The validity of the trial would rely heavily on the sound and uniform formulation of the bread.

Vodovotz, who is also a member of CAFFRE, specializes in the physical, chemical and functional properties of foods and food components. She characterizes the physical and chemical composition of food products; measures mechanical properties that affect food storage, stability and texture; and develops functional foods that target health outcomes.

Her lab is equipped to measure the caloric content of foods and their components; moisture content of foods at nanogram levels; and the compression of foods, an indicator of texture and firmness. "Such measurements enabled us to quantify and maintain the soy bread's texture, palatability and moisture content as we refined the

*"We have a team of experienced investigators who know how to efficiently recruit and rapidly complete dietary studies at The James. Of course, it would not be possible without our wonderful prostate cancer patients who regularly volunteer for clinical studies."*

**ELIZABETH GRAINGER, PhD, RD,**
*a registered dietitian and clinical research specialist in the laboratory of Nutrition and Chemoprevention*

formulation," says Jennifer Ahn-Jarvis, RN, a graduate research associate and Pelotonia graduate in Vodovotz's lab.

Vodovotz developed the bread and baked loaves using Ohio State's Food Science and Technology pilot processing plant. She conducted taste tests at the department's food sensory lab, which is equipped with 10 cubicles (see the online slide show).

"We tested the soy bread frequently to be sure it was palatable and had flavor and was good to eat," Ahn-Jarvis says. "Texture affects palatability, and how well subjects will comply with the protocol, which affects the dose of anticancer nutrients we think a participant is getting."

The bread's development took several years. Studies were done on isoflavone content and activity, digestive stability and bioaccessibility, and changes in their distribution during soy bread proofing and baking. Other studies looked at water distribution and molecular changes, and physical properties and water state changes in bread with and without almonds.

The soy isoflavone composition was determined by the OSUCCC – James Nutrient and Phytochemical Analytic Shared Resource, headed by director Schwartz and associate director Ken Riedl, PhD.

To boost the absorption of isoflavones from the bread, Vodovotz and her lab developed a formulation that included a small amount of almond powder. Normally, 70-90 percent of soy isoflavones have an attached sugar group. The human digestive system, however, more quickly absorbs isoflavones that lack that sugar group. Almonds contain an enzyme called beta-glucosidase that removes the sugar groups and converts 75 percent of the "sugared" isoflavones in the bread to the "sugarless," aglycone, form.

"All this work had to be done just to reach the point of clinical testing," Vodovotz says. "The analyses at the end of the trial will tell us which bread formation we should choose, with or without the almond powder, and provide other ideas for improving the product.

"If all goes well, the final step will be to commercialize the bread," she says. "The University's office of Technology Commercialization and Knowledge Transfer would help us with that."

## THE CLINICAL TRIAL

To evaluate soy bread intervention in patients, Clinton designed a phase II clinical trial for men with progressing metastatic prostate cancer. The study tested the soy bread against the soy-almond bread in 40 men who were to eat three slices of soy bread per day for eight weeks. This was followed by a "wash out" period, then the men consumed the other formulation for eight weeks.

Elizabeth Grainger, PhD, RD, a clinical research specialist trained as a registered dietitian and translational scientist, coordinated the participants' clinic visits, educated them about the intervention and any required diet modifications, served as contact person and ensured that all biological samples were obtain.

Ahn-Jarvis, who is a trained registered nurse and is now working on her doctoral degree in Vodovotz' lab, helped with some of these functions. She also helped direct the production of the four-month supply of soy bread, completed all the quality control analyses for the bread and processed and stored blood and urine samples as they were collected.

"That study, like many that we have done recently with various collaborators, was like a well-oiled machine," Grainger says. "We have a team of experienced investigators who know how to efficiently recruit and rapidly complete dietary studies at The James. Of course, it would not be possible without our

wonderful prostate cancer patients who regularly volunteer for clinical studies."

About 1,200 loaves of soy bread were needed for the study. "They needed to be made in a single batch to reduce variability," Ahn-Jarvis says. "A Columbus-area commercial baker, who was intrigued by the project, greatly supported our efforts and provided that service."

The researchers monitored participants' blood and urine samples to study the metabolism of soy phytochemicals, and they examined prostate specific antigen (PSA), an indicator of prostate cancer progression, as well as an array of biomarkers related to the regulation of the immune system and inflammation.

Schwartz and Riedl are food scientists and analytical chemists with expertise in the analysis and metabolism of diverse phytochemicals that may influence cancer risk such as carotenoids, isothiocyanates and isoflavones. Riedl applies high pressure liquid chromatograph-mass spectrometry (HPLC-MS) to analyze food components and metabolites in plants and foods, as well as blood and urine samples.

**STEVEN SCHWARTZ, PHD**

**YAEL VODOVOTZ, PHD,** *food scientist*

**STEVEN CLINTON, MD, PHD,** *leader of the OSUCCC – James Molecular Carcinogenesis and Chemo-prevention Program*

cancer.osu.edu

## CHARACTERISTICS MEASURED DURING SOY BREAD DEVELOPMENT

- Loaf volume; crust and crumb color;
- Protein and ash content;
- Water mobility; "freezable" water and "unfreezable" water; stiffness at 25 C.

*"It's part of the beauty of being in a place like Ohio State, where we can interact with faculty in fields totally disparate from our own and find common ground for novel research pursuits in our war on cancer."*

"Foods are complicated," Riedl says. "For example, soy contains dozens of interesting compounds, and how foods are processed can alter their patterns and even their structure, which may influence absorption and biological impact." Lesinski and his lab measured markers of immune response in the white-cell (buffy coat) fraction of the blood samples, work that was funded by a pilot grant from Ohio State's Food Innovation Center, The Ohio Soybean Council, and the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program. Some of the findings have been presented at national meetings. For example, they found statistically significant declines in the levels of four proinflammatory proteins and seven proteins related to suppression of the cellular immune response, and a reduction in the number of certain immune suppressive cells.

"Overall, our studies suggest that soy isoflavones and their metabolites can influence immune function and potentially immunotherapy," Lesinski says. "Some of these might deserve further investigation as lead compounds for clinical use."

Some of the analyses are still under way. "We are doing thorough and comprehensive immunology to assess how isoflavones in soy and other foods affect markers of inflammation," Lesinski says.

In addition to measuring cytokines and chemokines in plasma, they're investigating how isoflavones affect specific aspects of the cells' biology, including differentiation, response to proinflammatory stimuli, how they respond *in vivo* in a cancer model, and whether dietary enrichment alters the levels of proinflammatory immune cells.

Finally, they are examining individual proteins and signaling pathways inside immune-cell subsets that might be targeted by the whole food, by a crude extract of the food or by individual bioactive fractions or components from within these various foods. "We want to learn what signaling pathways within the immune cells are being targeted by foods or food components to limit the inflammatory processes," he says.

"If we discover which fractions or compounds in soy or other whole foods are active antitumor agents, we can work with our Ohio State collaborators to develop a small-molecule inhibitor that is fine-tuned to hit an appropriate target."

The Crops to Clinic Program, which is a collaboration between the OSUCCC – James and Ohio State's College of Food, Agricultural and Environmental Sciences, is designed to develop novel food products for cancer prevention. Clinton notes that Lesinski's work expands this effort into the exciting and dynamic realm of cancer immunology.

"This opens a whole new avenue for looking at how foods affect the cancer process," Clinton says.

"Our whole-food approach, illustrated by the soy-almond bread research, brings together a high-quality and well-trained immunologist with investigators having expertise in food chemistry, food technology, nutrition, and translational clinical research. The joint effort provides state-of-the-art research in an area where these fields overlap. It really gets down to the great value of team science when you have folks who can interface, communicate and work together so seamlessly," Clinton continues.

"It's part of the beauty of being in a place like Ohio State, where we can interact with faculty in fields totally disparate from our own and find common ground for novel research pursuits in our war on cancer."

# BENCH TO BEDSIDE

*From the Laboratory to the Pharmacy*

## A phase I dose-escalation study of ABT-888 (veliparib) in combination with carboplatin in HER2-negative metastatic breast cancer

HYPOTHESIS: Combining a DNA-damaging agent such as carboplatin with the PARP inhibitor veliparib will improve outcomes in patients with triple-negative breast cancer and patients with ER/PR-positive breast cancer that has defects in Fanconi Anemia DNA-repair pathway. Also that higher doses of veliparib will be tolerated when combined with single agent carboplatin alone, and that FLT-PET uptake will reliably predict antitumor responses, and that higher induction of γH2AX in CTCs will be observed with higher doses of veliparib.

RATIONALE: More than 1 million new breast-cancer cases occur annually worldwide. In general, 70 percent of early and about 50 percent of metastatic breast-cancer patients respond to initial therapies. However, the disease recurs in a significant number of patients, either because tumor cells have acquired drug resistance, or possibly because cancer-initiating stem cells that are inherently therapy resistant lead to eventual disease progression. Targeted therapies such as tamoxifen and trastuzumab have been highly successful as adjuvant therapies, yet a considerable number of patients still develop metastatic disease.

This protocol primarily focuses on pathways that could result in treatment resistance. The trial investigates the use of the PARP inhibitor veliparib to enhance the sensitivity of cancer cells to chemotherapies to gain maximum benefit and improve outcomes for breast-cancer patients. If our hypothesis is confirmed, it could have a significant impact on clinical outcomes.

Veliparib is an oral small-molecule inhibitor of poly (ADP-ribose) polymerase (PARP). PARP is an essential nuclear enzyme that recognizes DNA damage and facilitates DNA repair. Expression of PARP is higher in tumor cells compared with normal cells. This overexpression has been linked to drug resistance and the ability of tumor cells to withstand nontoxic stress. We therefore anticipate that inhibiting PARP will enhance the effects of DNA damage and will function as sensitizing agents for chemotherapy and radiation therapy that are designed to cause DNA damage, in this case by carboplatin.

This multi-center, open-label, multi-dose single-arm, phase I, dose-escalation study targets two groups of patients with HER2-negative metastatic breast cancer: 1. ER/PR negative (triple negative) and 2. ER and/or PR positive with defect in Fanconi Anemia repair pathway as tested by the FATSI immunofluorescence screening test.

The study has three key objectives:

1. Determine the recommended phase II dose, toxicity and preliminary efficacy of veliparib in combination with carboplatin.

2. Evaluate pharmacodynamic markers possibly associated with PARP inhibition in tumor cells. These include changes measurable by positron emission tomography (specifically, FLT-PET) and the induction of the histone variant gamma H2AX in circulating tumor cells.

3. Evaluate biomarkers in primary tumor that could predict antitumor response following PARP inhibitor treatment such as *BRCA-1* and *2*, FANCD2 nuclear foci formation and expression of miR-155.

### AT A GLANCE

OSU-10080: A phase I dose-escalation study of ABT-888 (veliparib) in combination with carboplatin in HER2-negative metastatic breast cancer

PI: **BHUVANESWARI RAMASWAMY, MD, MRCP**

Phone: 614-293-6401

Email: *Bhuvaneswari.Ramaswamy@osumc.edu*

Eligibility: Patients with triple negative metastatic breast cancer or ER/PR-positive HER2 negative metastatic breast cancer with defects in Fanconi anemia pathway. Patients with known *BRCA1/2* germline mutations will also be eligible irrespective of their ER/PR status. Study allows up to three prior lines of chemotherapy for metastatic breast cancer, which could include carboplatin and will allow any number of prior hormonal agents.

FOOD-BASED RESEARCH

# GROWING A CURE


Five Ohio- and Indiana-based farm cooperatives have joined together to support food-based cancer research at the OSUCCC – James and at Ohio State's College of Food, Agricultural and Environmental Sciences. The five organizations of growers have formed Cooperatives for the Cure, an endowment fund at the OSUCCC – James, in collaboration with the College of Food, Agricultural and Environmental Sciences.

The cooperatives kicked off the endowment with a check for more than $103,000 presented to the OSUCCC – James in September during the *2012 Farm Science Review,* Ohio State's annual showcase of advances in agriculture.

At Ohio State, faculty members, graduate students and researchers in cancer biology work with researchers in plant genetics, horticulture, crop science, food technology and marketing to develop food products that are optimized for clinical trials of cancer prevention or an adjunct to therapy.

For example, the researchers are using scientific breeding methods to develop crop strains that are high in natural anticancer compounds, such as specific carotenoids in tomatoes, followed by the application of modern food technology to preserve the anticancer activity in novel and tasty foods.

At the OSUCCC – James, many patients and members of the community have opportunities to participate in several Crops to the Clinic™ clinical research studies of novel food products and nutritional strategies to prevent cancer or enhance cancer therapy as well as survivorship.

"We believe that this collective effort will produce discoveries that bring novel food products and nutritional strategies into the mainstream of the war on cancer and reduce one's risk of specific cancers or perhaps improve the safety and efficacy of therapy," says Steven Clinton, MD, PhD, director of the OSUCCC – James Prostate and Genitourinary Oncology Clinic and leader of the Molecular Carcinogenesis and Chemoprevention Program. "Our ultimate goal for this collaboration is to contribute to a world free of cancer."

For more information or to make a tax-deductible contribution, go to http://growingthecure.org/. All funds raised go toward food-based cancer-prevention research.

# Events Calendar

## STATE-OF-THE-ART ENDOSCOPIC SKULL BASE SURGERY: A HANDS-ON COURSE

**Oct. 25-28, 2012 GREATER COLUMBUS CONVENTION CENTER**

**FOCUS:** This course for neurosurgeons, head-and-neck surgeons and other skull-base surgeons covers current indications, limitations and surgical techniques for endoscopic endonasal surgery of the skull base, pituitary fossa, orbit and craniocervical junction, and for the supraorbital keyhole craniotomy approach.

## OHIO STATE'S 2012 SCARLET AND GRAY RECEPTION DURING THE 54TH AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING

**Saturday, Dec. 8**

While attending the 2012 ASH Annual Meeting in Atlanta, please join your Ohio State colleagues at our reception on Saturday at the Omni Hotel at CNN Center (the official headquarters hotel for the 2012 ASH Annual Meeting), International Ballroom, from 7:30-9:30 p.m.

Please RSVP at **go.osu.edu/ASHReception2012**. For questions, contact Katie Jones at **Katie.Jones@osumc.edu** or 614-366-5183.

EXPANSION UPDATE

# SURGERY IN THE NEW JAMES

## The fourth floor of the new James Cancer Hospital and Solove Research Institute will house surgery and interventional radiology.

The floors advanced design includes operating rooms, an interventional radiology suite and perioperative support space all on one floor. The floor includes a family-reception and waiting area, a 40-bed preoperative care unit and a 28-bed postanesthesia care unit (PACU). The heart of the floor occupies its northwest quadrant – a suite of 14 operating rooms (OR), including several designed for specialized uses:

- Two are equipped for robotic surgery using the daVinci® surgical system;
- Two are equipped to deliver radiation treatment intraoperatively (intraoperative radiation therapy), one of which can handle high-dose radiation;
- Two are equipped with intraoperative real time magnetic resonance imaging guidance, which can be updated mid-procedure without leaving the OR suite;
- Eight are general purpose cancer ORs;
- All ORs will have the ability to capture video from multiple cameras for live viewing as a procedure progresses or for later teaching or research needs;
- All ORs have LED-based state-of-the-art surgical lights, with integrated flat panel displays;
- Medical gases, power, video and network connections are delivered through ceiling-mounted booms that serve both the anesthesia and surgery locations, leaving the area around the OR table uncluttered with hoses, wires and ancillary equipment.

Also on the fourth floor, the interventional radiology suite has three rooms of digital imaging for minimally invasive cancer interventions. Plans are under way to use adjacent shell space to complement those with CT- and ultrasound-based "body" interventions.

*Visit Frontiers online to view a simulation of the new ORs with their lights, equipment booms and flat panel displays.*


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

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NEW REGULATIONS

# New Law Requires Licensing of Genetic Counselors in Ohio

In June 2012, Ohio Gov. John Kasich signed into law a bill initiated by the OSUCCC – James and sponsored by Rep. Anne Gonzales (R-Westerville) that requires the licensing of genetic counselors in the state of Ohio.

The bill ensures that genetic counseling is provided by qualified individuals. Formerly, Ohio had no state regulations that prevented unqualified individuals from providing genetic counseling and calling themselves genetic counselors.

Harm caused by unregulated genetic counseling in the state has included inappropriate use of genetic testing; incorrect assessment of a patient's disease risk; and erroneous interpretation of genetic tests resulting in unnecessary medical treatment, failure to provide potentially life-saving prevention strategies or treatment, and irreversible decisions regarding childbearing and pregnancy.

The new law requires that genetic counselors in Ohio have a minimum of a master's degree, are board certified and obtain continuing education to remain current with the rapid advances in the field.

Licensure will increase access to genetic counseling services by opening paths to credentialing and improved reimbursement.

NATIONAL RECOGNITION

# OSUCCC – James Adopts Relationship-Based Care Model

It's easy to talk about providing a caring, patient-centered environment, but it takes a sincere commitment by staff and leadership for a major cancer hospital to make it happen.

**JAMIE EZEKIELIAN, RN, OCN,** *the RBC implementation leader*

A few years ago, the nursing staff at the James Cancer Hospital and Solove Research Institute began a grassroots effort to systemically establish an exemplary patient-centered care environment at the hospital. Their efforts culminated in May 2012 when the cancer program adopted a Professional Practice Model that incorporates Relationship-Based Care (RBC), a theory of care that James oncology nurses felt defined the standards they work to provide and the teamwork they promote.

RBC places the patient and family at the center of patient care, while stressing that to have a truly caring and healing environment also requires caring for oneself and nurturing collaborative relationships with coworkers. The James model also stresses healthy, positive relationships with the community.

"RBC represents our beliefs as a community of nurses regarding the care of oncology patients," says Jamie Ezekielian, RN, OCN, the RBC implementation leader. "Our rollout of RBC continues and we are grateful for the support of the cancer program, which fully embraces RBC and supports our effort to live it every day."

IN THE NEXT ISSUE OF **frontiers**…

## DRUG RESISTANCE

Of the more than 570,000 Americans expected to die from some form of cancer this year, the great majority will succumb to disease that is resistant or unresponsive to treatment. Scientists at the OSUCCC – James are identifying the mechanisms that enable certain cancer cells to survive chemotherapy and radiation therapy. Their goal is to improve treatment for advanced disease.

## LUNG CANCER RESEARCH

The OSUCCC - James has bolstered its efforts against lung cancer, the leading cause of cancer death in the United States, by recruiting David Carbone, MD, PhD, an expert in the molecular genetics of solid tumors and in translating these findings to therapy. His studies on lung cancer genetics, immunotherapy, tumor-associated immunosuppression mechanisms and gene therapy complement an already strong Ohio State team that is working to personalize lung cancer care.