



THE  
OHIO  
STATE  
UNIVERSITY

The James

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

SPRING | 2012

# frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS



NCI  
CCC

A Comprehensive Cancer  
Center Designated by the  
National Cancer Institute

inside ►► DRUG DESIGN *IN SILICO* | THE POWER OF PREVENTION ►



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

# UPFRONT

*The Director's Perspective*

## Beating Cancer

The ultimate solution to beating cancer would be to avoid it altogether. We can do that to a large degree through lifestyle changes, by minimizing environmental risks and through research that enables us to devise evidence-based interventions.

At The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), we have a strong group of cancer prevention and control investigators who are developing innovative ways to help more people guard against primary and recurrent cancer.

“The Power of Prevention” in this issue of *Frontiers* highlights some of our efforts to halt the progression of precancerous lesions in the mouth, prevent or slow prostate-cancer recurrence, and reduce obesity and cancer risk through

diet and lifestyle changes.

Of course, people can still develop cancer even when they do all they can to reduce their risk, so we must keep searching for more effective therapies and surgical procedures to help patients overcome their illness and regain an acceptable quality of life – especially when cancer occurs in anatomic sites that are difficult to treat, such as bone.

This issue’s cover story, titled “Saving Life And Limb,” details complex surgeries performed at the OSUCCC – James by one of the most skilled sarcoma teams in the



**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

nation, a team that regularly accepts supremely difficult cases.

You can also read in this issue about our collaborative work with *in silico* drug design, a discipline that uses computers and computation to discover and optimize targeted anticancer agents, sometimes atom by atom.

As science and technology advance, so do our approaches to preventing and treating cancer. This new issue of *Frontiers* offers a glimpse of how progress against cancer is unfolding at Ohio State. I think you will find it interesting... and hopeful.

### THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER – ARTHUR G. JAMES CANCER HOSPITAL AND RICHARD J. SOLOVE RESEARCH INSTITUTE

Director, Comprehensive Cancer Center  
Chief Executive Officer, James Cancer  
Hospital and Solove Research Institute  
**MICHAEL A. CALIGIURI, MD**

Senior Executive Director for Administration  
**JEFF A. WALKER, MBA**

Deputy Director, OSUCCC – James  
**PETER SHIELDS, MD**

Physician-in-Chief  
**RICHARD GOLDBERG, MD**

Distinguished University Professor  
OSU Cancer Scholar and Senior Adviser  
**CLARA D. BLOOMFIELD, MD**

Director of Medical Affairs  
**WILLIAM FARRAR, MD**

Chief Financial Officer  
**JULIAN BELL**

Vice President, Medical Center  
Expansion and Outreach  
Medical Director, Expansion Campaign  
**DAVID E. SCHULLER, MD**

Chief Communications Officer  
**THERESA DINARDO BROWN**

Editor, *Frontiers*  
**DARRELL E. WARD**


### EDITORIAL BOARD

Susan Brown, PhD, RN, Stephen Chaykowski,  
Theresa DiNardo Brown, William Carson III, MD,  
Jennifer Carlson, Jeffrey Fowler, MD, Electra Paskett,  
PhD, MSPH, Patrick Ross, MD, PhD, Christine  
Scarcello, MBA, Nancy Single, PhD, Darrell E. Ward

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

[cancer.osu.edu](http://cancer.osu.edu)  
[facebook.com/thejamesosu](https://facebook.com/thejamesosu)  
[twitter.com/thejamesosu](https://twitter.com/thejamesosu)  
[youtube.com/osuthejames](https://youtube.com/osuthejames)

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

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



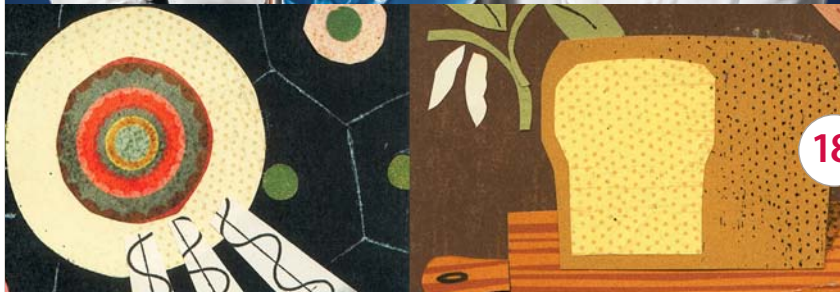
# frontiers

Spring | 2012



## 14 SAVING LIFE AND LIMB

Joel Mayerson, MD, leads a sarcoma team that tackles cases other hospitals turn away.



## 18 THE POWER OF PREVENTION

The adage that “an ounce of prevention equals a pound of cure” carries substantial weight in the realm of cancer control.



## 24 DRUG DESIGN *IN SILICO*

OSUCCC – James researchers have used computers and computation to develop a new class of drugs that targets a key enzyme they discovered 10 years earlier in cancer cells.

## 04 FRONTLINE



### JULIA WHITE, MD

Radiation therapy for breast cancer

## 06 BREAKTHROUGH

### CELLULAR COLLABORATION

Study Shows How Normal Cells Fuel Tumor Growth

### VIRAL ANALYSIS

Oral HPV Infection More Common in Men Than Women

### TRAVELING GENES

Mobile DNA Elements Can Disrupt Gene Expression

### SENSIBLE ANTISENSE

Finding Could Yield New Liver Cancer Therapy

### MENACING MARKER

Mutation Signals High Recurrence Risk in Older AML Patients

### BEYOND THE THYMUS

Tonsils Make T-Cells Too

## 12 OF NOTE

Recent grants, awards and honors, new faculty and program developments

## FEATURES

## 29 BENCH TO BEDSIDE



### SAMANTHA JAGLOWSKI, MD

An open-label, phase 1b/2, safety and efficacy study of the Bruton's tyrosine kinase inhibitor, PCI-32765, and ofatumumab in subjects with relapsed/refractory chronic lymphocytic leukemia.

## 30 NEED TO KNOW

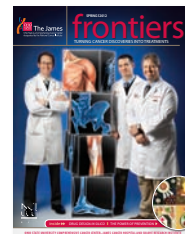
### SHARED RESOURCES

Behavioral Measurement Shared Resource

### EVENTS CALENDAR

### EXPANSION UPDATE

Experimental Therapeutics Program has space to call its own



ON THE COVER:  
James Boehmler, MD,  
Thomas Scharschmidt, MD,  
and Joel Mayerson, MD,  
of the OSUCCC – James  
sarcoma team

# Radiation Therapy for Breast Cancer

*Progress in clinical practice and personalizing treatment requires clinical trials*



By **JULIA WHITE, MD**, director of Breast Radiation Oncology and vice chair for Clinical Research, Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute; chair of the Radiation Therapy Oncology Group (RTOG) Breast Cancer Committee

By 2003, gene expression and profile studies were showing that breast cancer – previously regarded as a single disease – had four or five subtypes. In April 2012, the journal *Nature* published a study based on genome and transcriptome profiles from nearly 2,000 women that identified 10 breast-cancer subtypes.

As our understanding of breast cancer evolves, it's critical that the practice of radiation oncology, a principal treatment modality

for breast cancer, keep pace. We accomplish this, of course, through research. Our ultimate goal is to improve clinical practice so that we can better provide the right treatment for each woman's particular form of the disease. Changing the practice of medicine requires sufficient evidence, which is generally defined as the outcomes from at least two phase III randomized clinical trials.

But how do we determine which clinical trials to initiate? In radiation oncology, that typically happens in two ways. They can develop from intriguing preclinical and early-phase clinical studies that bubble up from single institutions, or they can arise when we bring together the best thinkers in radiation oncology to identify problems emerging from daily practice, and then design early-phase trials that begin to address them. I'm involved in two

ongoing trials that exemplify both approaches.

NSABP 239/RTOG 0413 is a 4,300-woman phase III trial that compares a six-week course of radiation following lumpectomy to a one-week course of radiation (10 treatments given twice daily over one week versus one treatment per day given for six to seven weeks). The trial includes correlative studies to discover what types of breast cancer are most amenable to a one-week partial-breast regimen. I am co-principal investigator on this study, which is accruing patients now.

This trial grew from evidence coming from Europe and within the United States indicating that therapy could be delivered over a shorter time by radiating just the lumpectomy site rather than the entire breast. That initial evidence led to early-phase trials such as RTOG 9517 in 2000, a phase I/II

## IDENTIFYING GENETIC PREDICTORS

*Our growing understanding of breast cancer will lead to improvements in radiation therapy for women with breast cancer that will increasingly individualize therapy over the next five to 10 years.*

trial evaluating brachytherapy as partial breast irradiation for stage I and II breast cancer, and [RTOG 0319](#), a phase I/II trial evaluating three-dimensional conformal radiation therapy of the region of the lumpectomy cavity for early-stage breast cancer in 2003.

RTOG 1014 is an example of a study initiated in response to a clinical question. The current standard of care for women with recurrent cancer following lumpectomy and radiation prescribes a mastectomy. The question was whether the entire breast should be removed in these women, or would a second lumpectomy and a partial breast reirradiation be less traumatic and equally effective?

In 2011, we organized RTOG investigators and initiated a phase I safety and feasibility study evaluating breast preservation therapy for recurrent disease as a first step toward replacing the current standard of care.

RTOG is developing other studies that are likewise based either on early data that might influence practice and require phase III clinical testing, or on a clinical need that requires early

data to help answer the question and suggest different treatment models.

The breast-cancer program here at Ohio State has the same objectives. With a strong team of scientists, and as one of only seven centers funded by the National Cancer Institute to conduct both phase I and phase II clinical trials, Ohio State is a leader in early-phase work. In addition, the OSUCCC – [James Stefanie Spielman Comprehensive Breast Center](#) brings together a range of clinical specialists and breast services under one roof, and the Ohio State breast cancer program bridges that comprehensive clinical-care component with its robust scientific program.

Our growing understanding of breast cancer will lead to improvements in radiation therapy for women with breast cancer that will increasingly individualize therapy over the next five to 10 years. These advances will require good patient participation in current and future clinical trials that will help us offer the right radiation therapy for the right woman and the right disease in the framework of breast cancer. [f](#)

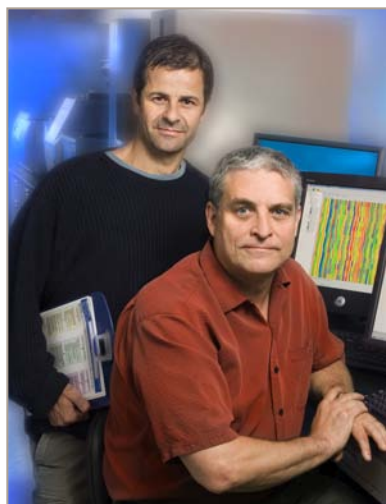




## » BREAST CANCER

## CELLULAR COLLABORATION

## Study Shows How Normal Cells Fuel Tumor Growth



**MICHAEL OSTROWSKI, PhD,**  
(right), OSUCCC – James  
Co-leader of the Molecular Biology  
and Cancer Genetics Program

**GUSTAVO LEONE, PhD,**  
OSUCCC – James  
Associate Director for  
Basic Research

Researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) have discovered how normal cells within tumors can fuel tumor growth.

Their study examined what happens when normal cells called fibroblasts in mouse mammary tumors lose the Pten tumor-suppressor gene. The findings:

- Suggest new strategies for controlling tumor growth by developing drugs that disrupt communication between tumor cells and normal cells;
- Provide insight into mechanisms that control the co-evolution of cancer cells and surrounding normal cells in tumors;
- Demonstrate how the Pten gene normally suppresses cancer development.

“Our study is the first to define a specific pathway in tumor fibroblasts that reprograms gene activity and the behavior of multiple cell types in the tumor microenvironment, including tumor cells themselves,” says co-principal investigator Michael Ostrowski, PhD, co-leader of the Molecular Biology and Cancer

Genetics Program at the OSUCCC – James.

The findings increase basic knowledge about how tumors grow and spread, and they have translational implications for the treatment of breast-cancer patients, Ostrowski says.

The researchers found that Pten regulates a molecule called microRNA-320 (miR-320), and that loss of Pten leads to a dramatic drop in levels of that molecule in a tumor fibroblast. With little miR-320 around, levels of a protein called ETS2 rise in the fibroblast, activating genes that cause the fibroblast to secrete more than 50 factors that stimulate proliferation and invasiveness of nearby cancer cells.

“The cancer field has long focused solely on targeting tumor cells for therapy,” says co-principal investigator Gustavo Leone, PhD, associate director for basic research at the OSUCCC – James. “Our work suggests that modulation of a few key molecules such as miR-320 in noncancer cells in the tumor microenvironment might be sufficient to impede the most malignant properties of tumor cells.”



Published in the journal *Nature Cell Biology*

## ▶ ORAL CANCER

# VIRAL ANALYSIS

## Oral HPV Infection More Common in Men Than Women

Research at the OSUCCC – James shows that men are three times more likely to have an oral [human papillomavirus](#) (HPV) infection than women – findings that help explain why HPV-related oral cancers are three times more common in men than women.

Maura Gillison, MD, PhD, a medical oncologist who is a head and neck cancer specialist and member of the OSUCCC – James [Viral Oncology](#) and [Cancer Control](#) programs, led the study, which sought to determine the prevalence of oral HPV infection in the United States and to understand factors associated with infection and oropharyngeal cancer. Her team analyzed mouth-rinse samples for HPV DNA and examined data collected from 5,579 men and women who participated in the 2009-2010 National Health and Nutrition Examination Survey.

“This study of oral HPV infection is the first step toward developing potential oropharyngeal cancer-prevention strategies,” Gillison says. “This is important because HPV-positive oropharyngeal cancer is poised to overtake cervical cancer as the leading type of HPV-caused cancer in the United States, and we have no means to prevent or detect these cancers early.”

The researchers estimate that 7 percent of Americans between

ages 14 and 69 have an oral HPV infection, with 10.1 percent of men infected versus 3.6 percent of women.

Other key findings include:

- About 1 percent of the U.S. population is infected with HPV 16 – the type of HPV most often responsible for cervical cancer – and HPV 16 infection is five times more common in men than in women.
- Oral HPV infection is uncommon among those with no history

of sexual contact compared with those with a history of sexual contact of any type (0.9 percent versus 7.5 percent, respectively).

- Oral HPV infection was independently associated with age, gender, number of sexual partners and current number of cigarettes smoked per day.

Maura Gillison, MD, PhD, describes her findings. (Requires RealPlayer.)

*Published in the Journal of the American Medical Association*



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



**MAURA GILLISON, MD, PhD,**  
medical oncologist and head and  
neck cancer specialist

# TRAVELING GENES

## Mobile DNA Elements Can Disrupt Gene Expression



**DAVID SYMER, MD, PhD,**  
*a member of the Viral Oncology  
Program at the OSUCCC – James*

The many short pieces of mobile DNA that exist in the genome can contribute to significant biological differences between lineages of mice, a study at the OSUCCC – James has shown.

These movable pieces are called transposons or “jumping genes” because they can migrate from one chromosomal location to another. Unlike viruses, they are not infectious and do not move from cell to cell. They have accumulated over time in the genomes of mice and humans and now constitute about half of genomic DNA in both.

For this study, researchers mapped the genomic locations of transposons called endogenous retroviruses (ERVs) in diverse mouse strains and compared those strains to learn how ERVs might influence gene expression. They found that ERVs can significantly disrupt expression by prematurely halting gene transcription, even when the ERV is more than 12,000 base pairs away in the same chromosome. They also found that the disruptive influence is affected by the gender of the parent who supplied the ERV.

“These findings add an interesting new angle to our understanding of fundamental mechanisms of natural variation and human biology, and possibly cancer and other diseases,” says principal investigator David Symer, MD, PhD, a member of the Viral Oncology Program at the OSUCCC – James.

A mouse gene containing an ERV inherited from the father often produced only an incomplete, truncated form of messenger RNA (mRNA); if the ERV came from the mother, not only the truncated transcript but also nearly normal levels of the full-length mRNA were produced from the gene.

“We believe this is an unusual, interesting example of a well-known phenomenon called DNA imprinting,” Symer says. “We are now conducting experiments to understand how premature termination of gene expression can be triggered by the transposons, and also how the parent-of-origin effect occurs.”



*Published in the journal Genome Research*



# SENSIBLE ANTISENSE

## Finding Could Yield New Liver Cancer Therapy

Hepatocellular carcinoma, or liver cancer, kills an estimated 549,000 people annually worldwide. Recent findings by researchers at the OSUCCC – James and the Mayo Clinic show that it is possible to target and block a microRNA that is important in the disease, perhaps offering a new therapy for the malignancy.

The animal study focused on microRNA-221 (miR-221), a molecule that is consistently present at abnormally high levels in liver cancer.

To control the problem molecule, researchers designed a second molecule as a mirror image of the first. The mirror molecule, called an antisense oligonucleotide, selectively bound to and blocked the action of miR-221 in human liver cancer that was transplanted in mice. The treatment significantly prolonged the animals' lives and promoted the activity of important tumor-suppressor genes.

“Liver cancer generally has a poor prognosis, so we badly need new treatment strategies,” says principal investigator Thomas Schmittgen, PhD, a member of the OSUCCC – James Experimental Therapeutics Program.

Schmittgen and colleagues injected liver cancer cells labeled with the luminescent lightning-bug protein known as luciferase into the livers of mice, then used bioluminescence imaging to monitor tumor growth. When the tumors reached an appropriate size, one group of animals received the

anti-miR molecule while the other group received a control molecule.

After treatment with the antisense oligonucleotide, half of the treated animals were alive at 10 weeks versus none of the controls. Also, the antisense oligonucleotide significantly reduced levels of miR-221 in both tumor and normal liver samples. And treatment with the antisense oligonucleotide caused a three-fold increase in the activity

of three tumor-suppressor genes that are blocked by miR-221 in liver cancer.

“Overall, this study provides proof-of-principle for further development of microRNA-targeted therapies for hepatocellular carcinomas,” Schmittgen says.



*Published in the journal Cancer Research*



**THOMAS SCHMITTGEN, PhD,**

*a member of the OSUCCC – James  
Experimental Therapeutics Program*

# MENACING MARKER

## Mutation Signals High Recurrence Risk in Older AML Patients



**CLARA D. BLOOMFIELD, MD,**  
*Distinguished University Professor and  
OSUCCC – James cancer scholar and  
senior adviser*

Older patients with acute myeloid leukemia (AML) and normal-looking chromosomes in their cancer cells have a higher risk of recurrence if they have mutations in the *ASXL1* gene, according to a study by OSUCCC – James researchers.

The study is the first to investigate the influence of these mutations on prognosis in patients with cytogenetically normal AML (CN-AML) and in conjunction with other prognostic gene mutations. It also reports the first gene-expression signature for CN-AML with mutated *ASXL1*.

“Our findings could lead to more effective targeted therapies and improved cure rates for these patients,” says principal investigator Clara D. Bloomfield, MD, a Distinguished University Professor who also serves as cancer scholar and senior adviser to the OSUCCC – James.

Bloomfield and colleagues found that patients age 60 and older with CN-AML and *ASXL1* mutations had significantly shorter survival than patients with the normal gene – only 5 percent of patients with the mutation were alive after three years, compared with 23 percent of patients without the mutation. Complete remission rates were also significantly lower, at 53 percent for

patients with versus 71 percent for patients without the mutation.

The findings were presented at the 53rd Annual Meeting of the American Society of Hematology. The study’s first author, Klaus Metzeler, MD, a research fellow at the OSUCCC – James, received an “Abstract Achievement Award” for this novel and clinically relevant work.

“Mutations in the *ASXL1* gene appear to be an important marker of poor prognosis in older AML patients,” says Bloomfield, Metzeler’s mentor. “Importantly, their negative impact was greatest in patients who, based on established genetic markers, would be expected to have favorable outcomes.

“*ASXL1* mutations therefore identify a previously unknown high-risk subgroup in older AML patients,” she adds. “These patients don’t do well with current standard therapy and may be candidates for treatment with novel drugs in a clinical trial.”



*Published in the journal Blood*

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

## ▶ T-CELL CANCERS

# BEYOND THE THYMUS

## Tonsils Make T-Cells Too

T lymphocytes (T cells) have been thought to develop only in the thymus, but a study led by OSUCCC – James researchers suggests they can also develop in human tonsils. This finding could improve the understanding of T-cell cancers and autoimmune diseases, as well as how stem-cell transplantation is done.

The study identified T cells at five stages of development in the tonsils. These stages, revealed by molecular signposts on the cells, were very similar to the stages of T-cell development in the thymus, although some differences were found. The study also discovered that the cells develop in areas near the fibrous scaffold of the tonsil.

“We’ve known for a long time that a functional thymus is necessary to develop a complete repertoire of T cells, but whether a T-cell factory existed outside the thymus was controversial,” says principal investigator Michael A. Caligiuri, MD, director of the OSUCCC and CEO of The James. “I believe our study answers that question. It is the first to describe a comprehensive, stepwise model for T-cell development outside the thymus.”

It also raises other questions. Caligiuri says it is still unclear whether T cells that develop in the tonsils also mature there or leave to mature elsewhere.



**MICHAEL A. CALIGIURI, MD,**  
director of the  
OSUCCC and CEO  
of The James

“The complete implications of this phenomenon for human health and disease are not entirely known,” adds first author Susan McClory, a graduate fellow in Caligiuri’s laboratory. “It could be important in the development of T-cell cancers and autoimmune diseases, or it might suggest a location for T-cell development when thymus function is poor. We hope to explore these possibilities.”

“Our work suggests that the tonsils serve as a T-cell factory, along with the thymus,” Caligiuri

says. “Next we need to learn what proportion of T cells is derived from the tonsils compared with the thymus.”



Published in the Journal of  
Clinical Investigation



Watch online



## AWARDS AND RECOGNITIONS



**CLARA D. BLOOMFIELD, MD**, Distinguished University Professor, cancer scholar and senior adviser to the OSUCCC – James, was awarded the 2012 Richard L. Schilsky Cancer and Leukemia Group B Achievement Award at the Alliance for Clinical Trials in Oncology Group Meeting. The award acknowledges the significant contributions of an individual to cooperative group research.



**ARNAB CHAKRAVARTI, MD**, professor and chair of Radiation Oncology and co-director of the Brain Tumor Program, has been inducted as a fellow of the American College of Radiation Oncology in recognition of his contributions to the field of Radiation Oncology.



**CARLO M. CROCE, MD**, director of Human Cancer Genetics and chair of the Department of Molecular Virology, Immunology and Medical Genetics, received the Association for Molecular Pathology Award for Excellence in Molecular Diagnostics. The award recognizes extraordinary achievement in the fields of molecular biology, molecular pathology, pathology, genetics, microbiology and basic medical sciences. Croce will also receive the 2012 Anthony Dipple Carcinogenesis Award at the 2012 Biennial Congress of the European Association for Cancer Research in Barcelona, Spain in July. The award goes to individuals who have made major contributions to research in carcinogenesis.



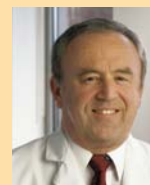
**JOANNE LESTER, PhD, CRNP, ANP-BC, AOCN**, a member of the Cancer Control Program at the OSUCCC – James, is a co-recipient of the 2012 Oncology Nursing Society Excellence in Survivor Advocacy Award.



**GAIL DAVIDSON, RN, BSN, OCN**, disease management coordinator in Surgical Oncology, has won the Oncology Nursing Society's 2012 Excellence in Surgical Oncology Nursing Award. The award recognizes excellence of nursing contributions to surgical oncology.



**RICHARD GOLDBERG, MD**, physician-in-chief at the OSUCCC – James, was selected to deliver the first Charles G. Moertel Lecture to be presented through the newly formed Alliance for Clinical Trials in Oncology during the plenary session of the Alliance's June meeting. The Alliance was created from the merger of the North Central Cancer Treatment Group (NCCTG), Cancer and Leukemia Group B (CALGB) and the American College of Surgeons Oncology Group. Goldberg's lecture was titled "Meaningful Outcomes: Lives Saved Due To Clinical Trials In Early-Stage Colon Cancer."



**MICHAEL GREVER, MD**, professor and chair of the Department of Internal Medicine and co-leader of the OSUCCC – James Experimental Therapeutics Program, has received the Philip S. Hench Distinguished Alumnus Award from the University of Pittsburgh School of Medicine's Medical Alumni Association. The award is presented annually to a graduate of the School of Medicine and is the highest honor the alumni association confers upon one of its members.



**NINA A. MAYR, MD**, professor of Radiation Oncology, has been inducted as a Fellow of the American Society for Radiation Oncology. The ASTRO Fellows program recognizes service to ASTRO and outstanding contributions to the field of radiation oncology.



**ELECTRA PASKETT, PhD, MSPH**, Marion N. Rowley Professor of Cancer Research, director of the Division of Cancer Prevention and Control and associate director for population sciences at the OSUCCC – James, delivered the Jimmie Holland Lecture at the Alliance for Clinical Trials in Oncology Group Meeting. Her lecture was entitled *Interventions to Address Cancer Health Disparities: The Case of Cervical Cancer in Appalachia*.

## FACULTY AND PROGRAMS



**THOMAS LUDWIG, PhD**, has joined the cancer program as a visiting associate professor of Molecular and

**Cellular Biochemistry**. His research interests include the functional analysis and consequences of loss of the breast-cancer genes BRCA 1 and BRCA 2 in animal models.



**JULIA WHITE, MD**, has joined the cancer program as a professor of Radiation Oncology and director of

**Breast Radiation Oncology** at the Stefanie Spielman Comprehensive Breast Center.



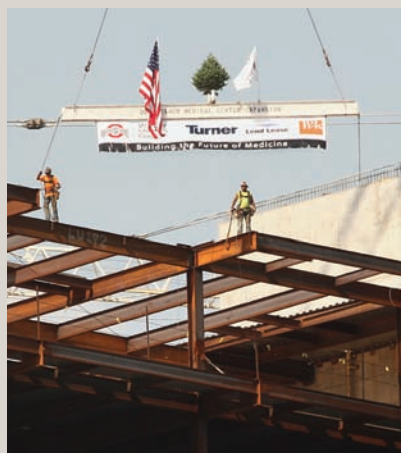
**TIMOTHY WRIGHT** has joined The Ohio State University to lead the drug discovery institute that is being

initially developed within the cancer program.

**THE OHIO STATE UNIVERSITY'S MEDICAL CENTER** has been renamed by the Board of Trustees as The Ohio State University Wexner Medical Center.

**THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER** has opened the Center for Regenerative Medicine and Cell-Based Therapies. The Center is a collaboration of the colleges of Medicine, Engineering, Dentistry, Nursing, Veterinary Medicine, Arts and Sciences, and Pharmacy.

**THE FINAL BEAM FOR THE NEW JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE** was riveted into place May 21.



**A NEW CLINICAL TRIALS SEARCH TOOL** is available to anyone wanting to learn about active clinical trials at the OSUCCC – James. Or visit <http://cancer.osu.edu> and click on the red “search clinical trials” link.

## GRANTS

**DANILO PERROTTI, MD, PhD**, associate professor in the Department of Molecular Virology, Immunology and Medical Genetics, and a member of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James, has received a five-year, \$1.52 million grant from the NCI to study the “Role of microRNAs in the Regulation of CML Stem Cell Survival and Self-Renewal.”

## LEADERSHIP ACTIVITIES AND APPOINTMENTS



**TANIOS BEKAII-SAAB, MD**, assistant professor of Medicine and of Pharmacology, and medical director of Gastrointestinal Oncology, has been accepted to the American Society of Clinical Oncology's (ASCO) Leadership Development Program, which prepares mid-career oncologists for leadership positions within ASCO.

# SAVING LIFE AND LIMB



*Joel Mayerson, MD, leads a sarcoma team that tackles cases other hospitals turn away.*

BY KENDALL POWELL

When orthopaedic oncologist Joel Mayerson, MD, and a team of surgeons resected the softball-sized chondrosarcoma – a tumor of cartilage that does not respond to any known cancer treatment other than surgical removal “en bloc” – it left a gaping hole where the patient’s lower spine and left leg connected to his pelvis.

The team now focused on repairing the damage with the nation’s first live-bone pelvic reconstruction surgery. During the risky 36-hour, two-day operation, the patient, a 51-year-old mail carrier named Mike Prindle, lost 70

liters of blood – 14 times the amount that normally circulates in the body.

“These are some of the largest surgeries you can do on the human body. They are life-threatening at any point in time in the OR,” explains Mayerson, director of Musculoskeletal Oncology at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James.)

“We’ve spent a decade building a surgical and anesthesia team to care for these patients. If you are missing just one part of the surgical team, you cannot do these operations,” says Mayerson.

Orthopaedic oncology presents significant challenges. It often

requires removal of bone sections that are critical for walking, weight-bearing and limb function. Osteosarcomas in children require excision of bone from a still-growing skeleton. Removing a soft-tissue sarcoma can leave a void that must be filled through creative plastic surgery. Involvement of the spine and bowels can require additional specialist surgeons.

Mayerson’s sarcoma team executes difficult, innovative surgeries to give patients the best chance for restoring mobility or even an active lifestyle. The team, which includes six surgical specialties, has a willingness to tackle first-of-their-kind and rare procedures, cases other hospitals would turn away.

Such operations need a high degree of coordination and



*“Orthopaedic surgery normally deals with returning a patient to normal function. Orthopaedic oncology is about saving a life and returning the patient to as close to normal function as possible.”*

communication among high-powered surgeons who normally would operate solo. The rare mix of personalities and skills on the OSUCCC – James sarcoma team ensures patients get back to their lives and passions.

## A ‘SURGICAL DISEASE’

Mayerson’s interest in orthopaedics began at age 15 when he injured his knee playing high school football in Lima, Ohio. Fascinated by his surgeon’s ability to fix the injured joint, he thought he’d work in sports medicine. But on the first day of his senior medical school rotation in orthopaedic surgery at Johns Hopkins University in 1993, he watched orthopaedic oncologists perform limb-salvage surgery for a patient with an osteosarcoma of the femur.

“When I came home, I couldn’t stop talking about it. My wife predicted that’s what I would do,” Mayerson recalls. Currently, he and his partner, Thomas Scharschmidt, MD, are two of only about 150 orthopaedic oncology surgeons in the United States. “Orthopaedic surgery normally deals with returning a patient to normal function. Orthopaedic oncology is about saving a life and returning the patient to as close to normal function as possible.”

All sarcomas are different, as is the damage done by their removal, he says. “One thing I love about this field is that people can come in with a similar tumor, and you can solve the problem in different ways based on the tumor’s location and the patient’s needs and age,” says Mayerson.

About 2,500 cases of bone sarcoma are diagnosed annually in the United States, with about 800 of those being osteosarcoma in children. There are also just under 10,000 new soft-tissue sarcoma cases, which include about 50 subtypes that occur in muscle, fat, skin, cartilage and other tissues of mesenchymal origin. The team treats between 400 and 500 sarcoma patients yearly. Only a handful of those cases need mega-surgery like Prindle’s.

“A major challenge for us is the rarity of these tumors, which means there is little funding for research to improve their treatment,” explains Scharschmidt, assistant professor of Orthopaedics at the OSUCCC – James.

James Boehmler, MD, a plastic and reconstructive microsurgeon on the team, notes that adult bone sarcomas and most soft-tissue sarcomas rarely respond to chemotherapy or radiation. “They also usually go unrecognized until they are very large tumors,” he says. “And they tend to occur around major blood vessels and nerves in the inner thigh or pelvis, like the femoral artery and sciatic nerve and other areas of high-value real estate.”

That leaves surgery to remove these tumors, followed by reconstruction, with Mayerson, Scharschmidt, Boehmler and the other surgeons on the team often working in tandem. In a surgery as complex as the pelvic reconstruction, the surgeons include an orthopaedic oncologist, a general oncologist, a neurosurgeon, a urologist, a plastic surgeon and an anesthesiologist (see sidebar).

## DRASTIC MEASURES


When Prindle arrived at The James in January 2009, he was limping from progressively worsening pain in his left hip and buttock. MRI and CT scans showed a tumor in his left pelvis. A needle biopsy confirmed chondrosarcoma, a cancer known to be immune to current therapies.

To save his life, the team would have to remove the tumor and a large section of surrounding tissue and bone. This would include the left half of his pelvis, the bottom of his spine, his left hip joint, and – with nothing left to connect it – his healthy left leg.


Fortunately, the tumor had not metastasized (nearly all metastatic and one-third to one-half of primary sarcomas are fatal).

Normally, loss of the left half of the pelvis would leave Prindle without an intact pelvic ring, which connects and stabilizes his remaining spine and leg. Without it, he would be unable to bear weight and walk, even with a prosthetic left leg. But, for a man who formerly walked eight-mile neighborhood routes and who was an avid golfer, the sarcoma team thought it could try something that had never been done before.

“We reasoned that we could reconstruct the pelvic ring using the healthy femur and the fibula that we had to remove,” Mayerson recalls. The idea came up during the sarcoma tumor board meeting, a weekly discussion among surgeons, medical oncologists, radiation oncologists, pathologists and other team members about each case.


The team knew that pelvic reconstructions had been done using metal parts or donated cadaver bone, but neither of those options can support live bone in a weight-bearing area. They figured the living bones would heal into a more stable ring, suitable for supporting a prosthetic leg. The two-day surgery would require a dozen metal screws in Prindle's spine, a team of two dozen in the operating room, and close to 500 medical personnel for pre- and  postoperative care. When the idea was presented to Prindle, remembers Mayerson, "He thought about it for a time, then said, 'If that's what it takes, that's what I'll do. I want to live, get better, and I want to walk.'" The innovative pelvic reconstruction won "Reconstructive Surgery of the Year" honors from the [American Society of Reconstructive Microsurgeons](http://www.asms.org/) in 2010 and was published in the [Journal of Neurosurgery: Spine](http://www.jneurology.com/).

Frank conversations with patients are essential, says Boehmler. Although limb salvage has become standard whenever possible, the surgeons do not know exactly what structures are affected until they perform surgery. If a tumor encases nerves or critical blood vessels, the limb may not be functional.

Mayerson recalls the conversation with Dugan Smith's parents when he recommended that their 10-year-old son have a dramatic surgery called rotationplasty.  The procedure is recommended for active, growing children who have an osteosarcoma around the knee. Surgeons remove the knee, then reattach the lower portion of the leg rotated 180 degrees so that

the ankle joint replaces the knee. It creates a biological joint that grows with the child, who is able to run and jump on a prosthetic lower leg. Or in Smith's case, return to his passion: baseball.

Only about a dozen rotationplasties are done each year in the United States. Most patients in Smith's position get an above-knee amputation and are fitted with a prosthesis that requires expending about 70 percent more energy to walk. Some patients are candidates for a limb-salvage operation that uses an endoprosthesis – usually a metal replacement part for the bone that must be removed. These patients' limbs look normal except for a big scar and can function almost normally for walking and even swimming. But the activity required to play most sports will shred the metal and plastic parts of an endoprosthesis.

Rotationplasty seemed the best option for Smith, whose father coached him as pitcher of his Little League team. "Even for a well-adjusted child like Dugan, it's a difficult emotional thing to do because your body looks very different from everyone else," Mayerson says. Three years later,  an ESPN video shows Smith hitting a double and running the bases.

Children like Smith represent an even rarer population of sarcoma patients, but they bring special challenges to the sarcoma team. Mayerson and the team have met those challenges by pioneering a new endoprosthesis technology that grows with children and lowers their risk of infection. In the past, children needed expansion surgeries



**MIKE PRINDLE** *shortly after his innovative pelvic reconstruction.*

every other year to lengthen their limb by about one centimeter until they finished growing. That could mean up to seven, four-hour surgeries and three- to four-day hospital stays. Worse yet, each expansion surgery carried a 10-percent risk of infection, with half of all infections resulting in amputation.

In 2002, in another "first," Mayerson performed a full femur replacement on a 10-year-old using a high-tech solution for lengthening limbs, the Repiphysis non-operative expandable prosthesis. By applying an external magnetic field, surgeons can heat and melt a plastic tube inside the device that releases the tension on a portion of a coiled spring. While there is some discomfort, the procedure requires no surgery or hospital stay, and it dramatically lowers the risk of infection.

## BEYOND SURGERY FOR SARCOMAS

Even with advanced surgical techniques and prosthetic technologies that improve patients' functional outcomes, Mayerson notes that survival rates for sarcoma patients have plateaued in the last 25 years. "We've made people more

functional – those who are living – but we haven't increased the percentage of survivors," he says.

Because they are both rare and diverse, sarcomas lack chemotherapy options. Pharmaceutical companies are unwilling to invest hundreds of millions of dollars to produce a drug for a few thousand patients each year. And research to learn which genetic mutations drive various types of sarcoma has been slow.

But the OSUCCC – James team aims to rectify that. "Our next biggest challenge is to classify these tumors based on their genomic expressions, and then to tailor treatment on an individual level," says Scharschmidt. "I absolutely think that will lead to improving our patient outcomes in the next five to ten years."

In collaboration with Peter Houghton, PhD, director of the Center for Childhood Cancer at Nationwide Children's Hospital, the team has been building a living-tissue bank of human sarcoma tumors. For every soft tissue sarcoma tumor resected, a sample is transplanted into an immunocompromised mouse, where it will grow and maintain its particular set of gene mutations. The researchers will characterize the genetic profile of these tumors, which eventually will serve as a test bed for new therapies targeted to the specific mutations.

Boehmler also sees potential for tissue engineering for orthopaedic oncology. He notes that when a tumor affects nerves and large blood vessels in a limb, it almost always leads to amputation. In contrast to bone, no replacement parts exist for nerves and vessels.

Instead, Boehmler says, regrowing a patient's own nerves and other tissues would preserve more functional limbs. And regenerating live bone to form, say, a 3-D half of a pelvis would be more advantageous than "spare parts surgery," he says. "The field of regenerative medicine will be a key contributor to the recovery and rehabilitation of these patients."

For now, Boehmler and his peers thrive on the surgical problem-solving of complicated cases like the pelvic reconstruction. "It's the ultimate teamwork to do surgery of this magnitude," notes Mayerson.

Considering the ordeal Prindle endured, his recovery was equally impressive. Mayerson recalls that Prindle left the hospital just 34 days after surgery with only a dose of Tylenol. He was eventually fitted with a state-of-the-art "smart" prosthesis with computerized hip and knee joints that learn his gait and automatically adjust to make walking easier.

"If you can give people a reasonable chance to be as functional as possible, a lot of people will take that chance," says Mayerson. "Mr. Prindle is an amazing person," he adds, with a hint of awe still in his voice. It's probably safe to assume that the feeling is mutual. ■

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

## OHIO STATE'S SARCOMA TEAM

Procedures such as a radical pelvic reconstruction are truly team efforts. In addition to the lead surgeons **Joel Mayerson, MD, Thomas Scharschmidt, MD,** and **James Boehmler, MD,** it takes more than 500 people to care for these patients, including physicians from the blood bank and laboratory medicine; scrub technicians; operating-room, floor and clinic nurses; and a musculoskeletal oncology physician's assistant. The OSUCCC – James sarcoma team also includes six medical specialties.



**Surgical Oncology**  
Carl Schmidt, MD



**Plastic Surgeon**  
Pankaj Tiwari, MD



**General Surgery**  
Peter Muscarella II, MD



**Plastic Surgeon**  
Michael Miller, MD



**Neurosurgery**  
Ehud Mendel, MD



**Plastic Surgeon**  
Albert Chao, MD



**Urology**  
David Sharp, MD



**Plastic Surgeon**  
Ergun Kocak, MD



**Anesthesiology**  
Matharbootham Mani, MD



More at [cancer.osu.edu/about/publications/frontiers/](http://cancer.osu.edu/about/publications/frontiers/)



# The Power of

BY BOB HECKER  
ARTWORK BY  
RICHARD LILLASH

The adage that “an ounce of prevention equals a pound of cure” carries substantial weight in the realm of cancer control.

“You are the answer to cancer,” says Electra Paskett, PhD, MSPH, a cancer prevention and control expert at The Ohio State University. A newly released federal report on cancer status in the United States supports her contention.

When Paskett was president of the American Society of Preventive Oncology (ASPO), she gave a talk focusing on the many ways one person can help end cancer globally, from conducting scientific research, to avoiding environmental risks, to changing lifestyle behaviors.

The [\*Annual Report to the Nation on the Status of Cancer, 1975-2008\*](#), released in March 2012 by the National Cancer Institute (NCI), builds on the



# Prevention

lifestyle aspect of Paskett's talk by highlighting the effects of excess weight and physical inactivity on cancer risk. The report states that several cancers – including esophageal, colorectal, kidney, pancreatic, endometrial, and breast cancer among postmenopausal women – are associated with being overweight or obese, and that some of these cancers also are linked with insufficient physical activity. In addition, the report says there is some evidence that excess weight is associated with thyroid, gallbladder and hematopoietic (e.g., leukemia, myeloma) cancers.

“For more than 30 years, excess weight, insufficient physical activity and an unhealthy diet have been second only to tobacco use as preventable causes of disease and death in the United States,” the report states. However, it points out that since the 1960s tobacco use has declined by a third while obesity rates have doubled, “significantly impacting the relative contributions of these factors to the disease burden.”

Noting that obesity and inactivity are avoidable causes of cancer, the report contends that, for people who do not smoke, maintaining a healthy weight and getting enough exercise may be among the most important ways that individuals can help prevent this disease. Paskett, associate director for population science at Ohio State's Comprehensive Cancer Center – James Cancer Hospital

and Solove Research Institute (OSUCCC – James), concurs. She lists the “obesity epidemic” as one of several high-priority areas for cancer prevention. She also leads a five-state initiative to help people of Appalachia reduce cancer risk by combating obesity (see page 21).

But despite growing knowledge of preventable cancer risk factors, progress in cancer prevention has been seemingly slow and “somewhat disappointing,” according to Peter Shields, MD, deputy director of the OSUCCC – James and current president of ASPO.

Shields says epidemiology studies have made only incremental advances, inherent in this type of science, and subsequent intervention studies too often do not validate expected outcomes. This leaves early detection as “the best, and often the only, option for reducing the cancer burden. While there is a lot of promise in early detection, early detection is a back-up. We need to fight cancer when those young cancer cells look happy and normal, or at least just a little sick.”



For real progress in cancer prevention, he says, continued research is critical. “We need a deeper understanding of cancer's causes, then we must use that understanding to focus behavioral change and develop clinically useful markers of cancer risk and evidence-based reasons for choosing interventions.”

This story and sidebar offer examples of innovative cancer-prevention research led by scientists at the OSUCCC – James who, both individually and as collaborators, are serving as “the answer to cancer.”

## PROMISING PATCH

Investigators at the OSUCCC – James hope to begin clinical applications in 2013 with a mucoadhesive medicated patch that releases a chemopreventive drug directly into precancerous oral lesions over an extended time without systemic toxicity.

The study (grant CA129609) is led by principal investigator (PI) Susan Mallery, DDS, PhD, and co-PIs Peter Larsen, DDS, and Gary Stoner, PhD, emeritus professor in Medical Oncology at Ohio State and former

*The patch – designed in the lab of Steven Schwendeman, PhD, a pharmaceutical chemist at the University of Michigan and a collaborator with Mallery and Larsen's team – has three layers: a disk saturated with fenretinide and polymers to make the drug more soluble in saliva; an adhesive ring to hold the disk in place; and a backing to hold in the medication.*



member of the OSUCCC – James. The team has tested the patch in simulated saliva and laboratory models with the drug fenretinide, a synthetic derivative of vitamin A that has promising anticancer properties. In both scenarios, therapeutic doses comparable to levels needed in humans were achieved with none of the drug escaping into the system or into surrounding healthy tissue.

Before that study, scientists had failed to achieve a therapeutic systemic dose of fenretinide because of drug toxicity and rapid loss from the body. Mallery says the medicated patch, with its good adherence and Tegaderm backing, “is so secure that no systemic levels of fenretinide are achieved...ergo no systemic toxicity.”

The patch – designed in the lab of Steven Schwendeman, PhD, a pharmaceutical chemist at the University of Michigan and a collaborator with Mallery and Larsen’s team – has three layers: a disk saturated with fenretinide and polymers to make the drug more soluble in saliva; an adhesive ring to hold the disk in place; and a backing to hold in the medication.

Mallery says the next steps will depend on how the U.S. Food and Drug Administration (FDA) views the team’s Investigational New Drug application, which must be approved prior to human clinical uses. “As fenretinide is already an FDA-approved drug, we hope our application will be considered under the ‘device’ category, since the delivery method is the new component,” she explains.

If the FDA approves metabolic studies to determine the amount of drug that penetrates the human oral mucosa and the time of patch application necessary to achieve therapeutic levels, and if it also authorizes a phase IIb pilot study on patients with oral precancerous lesions, “We will move directly into this area,” Mallery says, adding that researchers would enroll some 20 patients.

“We would then evaluate tissues before and after treatment for light-microscopic diagnosis, size and clinical appearance of the lesion, and for molecular indicators associated with progression of precancerous oral lesions, such as loss of heterozygosity and methylation of promoter sites,” she

says, noting that this work “has the potential to change the treatment paradigm for these lesions.”

## BAKING BETTER BREAD

Data analysis continues in an OSUCCC – James study comparing the ability of two functional foods developed at Ohio State to prevent or slow recurrence of prostate cancer among men treated for this disease.

The study, which involved 32 patients, is testing whether consuming soy-almond bread will improve preventive and treatment benefits over consuming soy bread alone. Both breads were created by a team led by Yael Vodovotz, PhD, a physical chemistry researcher and food scientist. Vodovotz is PI for the study ([grant CA125909](#)). Steven Clinton, MD, PhD, a medical oncologist and researcher who specializes in treating and preventing prostate cancer, directed the clinical trial, which was closed in spring 2011 so researchers could start analyzing blood and urine samples from participants who consumed the breads.

The study is based on the belief that isoflavones in soy can inhibit hormone-dependent cancers such as prostate cancer. Since soy is not commonly consumed in the Western diet, the researchers tried to better incorporate it by placing it in bread. They later added almonds to improve the taste and boost the health benefits of soy isoflavones.

“Almonds are a rich source of the beta-glucosidase enzyme,

*The study is based on the belief that isoflavones in soy can inhibit hormone-dependent cancers such as prostate cancer. Since soy is not commonly consumed in the Western diet, the researchers tried to better incorporate it by placing it in bread.*





which converts the isoflavones to a chemical form that is theoretically better absorbed in the body,” Vodovotz says. “We added almonds to produce a bread with a chemical composition that was better absorbed than our original bread.”

For eight weeks, half of the participants daily ate three slices of soy bread and half ate three slices of soy-almond bread. Then, after a two-week period of consuming no soy, the groups switched bread types and repeated the pattern for another eight weeks.

“Analysis of samples is not complete, and we hesitate to make any major preliminary conclusions at this time,” Clinton says. However, the team reports that study compliance was outstanding and the bread was easily incorporated into the diet “with very good taste characteristics.”

They also observe that participants show several different patterns in their metabolism of soy components. “Our analysis suggests that the metabolic profile of soy metabolites and their potential to impact cancer risk is influenced by other foods you consume and by your genetics,” Clinton says.

“It is likely that the genes impacting how we respond to anticancer drugs also impact the metabolism of many dietary components,” Vodovotz adds. “All of these issues could affect how soy may work to reduce cancer risk.”

When sample analysis is complete, the researchers will publish their findings. They also are working



to commercialize their breads for wider consumption.

### FAITH-BASED OBESITY BATTLE

A transdisciplinary health disparities research team is partnering with churches in a five-state region to refine and test a previously piloted faith-based intervention program to promote health and reduce cancer risk by addressing obesity.

Electra Paskett is PI for the project, which is the research component of the larger Appalachian Community Cancer Network (ACCN), funded at \$6.13 million over five years by the NCI. The research component, “Faith-Based Initiative to Promote Health in Appalachia,” is funded at \$2.7 million (grant CA153604).

The intervention will employ community-based participatory research strategies aimed at two behavioral causes of obesity: sedentary lifestyle and unhealthy diet. The target region is mainly rural and contains medically underserved populations characterized by low income, education deficits, poor health, increased rates of obesity and high cancer incidence.

*“The research component, ‘Faith-Based Initiative to Promote Health in Appalachia,’ is funded at \$2.7 million.*

*The intervention will employ community-based participatory research strategies aimed at two behavioral causes of obesity: sedentary lifestyle and unhealthy diet.”*

“An obesogenic environment promotes obesity by encouraging physical inactivity and limiting healthy food choices,” Paskett says. “The goal of this project is to test a faith-based intervention in 10 churches compared to a comparison program in 10 additional churches where participants will receive information and cancer-screening tests.”

Participants in the intervention churches will receive help in increasing physical activity and consuming healthier foods, including more fruits and vegetables daily.

Paskett says part of the intervention involves an e-health computer program that tracks the number of steps per day by participants and provides them with tailored messages and information about increasing physical activity and changing their diets. “We will also explore the willingness of participants to provide biomarkers and biospecimens to further understand the effects of the intervention on markers of obesity and to establish a biospecimen bank within Appalachia,” she adds, noting that the two-year e-health program was supported by a \$100,000 “idea” grant from

Pelotonia, an annual grassroots bicycle tour that raises money for cancer research at the OSUCCC – James.

“That money helped us secure NCI funding to do the whole research study in 20 churches throughout the ACCN region,” Paskett explains. “The project has started and we are recruiting participants. We hope to be in all 20 churches by this time next year.

“We believe this project will have an immediate impact among members of the participating churches,” she says, “and the successful strategies could be used to improve the health of residents in other states throughout Appalachia in the future.”

### STUDYING STRAWBERRY STRENGTHS

OSUCCC – James investigators have nearly finished a clinical study examining the inhibitory activity of whole foods in the earliest stages of oral cancer in humans. The team is applying a strawberry-based confection to the high-risk oral cavity of current smokers, believing that anticancer compounds in the

berries will cause cigarette smoke-altered genes to resemble the genes of never-smokers, thus favoring cancer prevention.


“Compounds such as ellagic acid, quercetin, ferulic acid and beta-carotene found in various berries have been shown to possess cancer-preventive mechanisms: reducing oxidative damage to genetic material; inhibiting cell proliferation and oncogenic expression; promoting expression of tumor-suppressor genes; inducing death of precancer and cancer cells; and preventing formation of blood vessels that sustain tumor cells,” says PI Christopher Weghorst, PhD. “With this in mind, we’re applying a food-based approach that emphasizes the potential for complex mixtures of preventive agents to inhibit multiple processes of carcinogenesis.”

The two-year study, also funded by a \$100,000 Pelotonia “idea” grant, enrolled 20 healthy individuals, half of whom are smokers. Participants received either a strawberry-based or placebo confection for seven days. Then, after 14 days of no treatment,

the groups were reversed to receive either a strawberry-based or placebo confection. Blood, urine and mouth-scrape samples were collected before and after each treatment for analysis.

Weghorst says the team – which includes co-PIs Steven Clinton, MD, PhD; Yael Vodovotz, PhD; and Steven Schwartz, PhD – is determining the expression of 41 cigarette smoke-altered genes that were previously identified as being differentially expressed in the oral cavities of 40 smokers as compared with 40 never smokers. That study was conducted and reported by research groups from Memorial Sloan Kettering Cancer Center and Cornell University.

“We are also preparing a Program Project Grant application to the NCI for an integrated and multiproject research program at Ohio State that will focus on black raspberries and the reduction of oral cancer risk,” Weghorst says, noting that Ohio State studies with animal models have found strawberries and black raspberries to be equally effective in inhibiting oral cancer.

“If awarded, the NCI grant will enable us to fill any knowledge gaps we need to address before initiating a large-scale national cooperative phase III trial for preventing oral cancer with whole foods,” he adds. “This approach may ultimately prove to be an effective, safe and natural method of cancer prevention.” 

*“Compounds such as ellagic acid, quercetin, ferulic acid and beta-carotene found in various berries have been shown to possess cancer-preventive mechanisms . . .”*



## GRANT SUPPORTS U.S.-CHINA COLLABORATIVE CANCER STUDY

Researchers in China and at the OSUCCC – James are studying biomarkers of precancerous lesions of the esophagus that could lead to chemopreventive strategies for esophageal cancer.

The study is funded by an international collaborative research grant from the National Institutes of Health (NIH) and the National Natural Science Foundation of China. Principal investigator Tong Chen, MD, PhD, a researcher at the OSUCCC – James, says the \$79,109 grant supplements a previously awarded parent grant from the NIH titled “Combinatorial Approaches to the Chemoprevention of Esophageal Cancer” (grant CA131073).

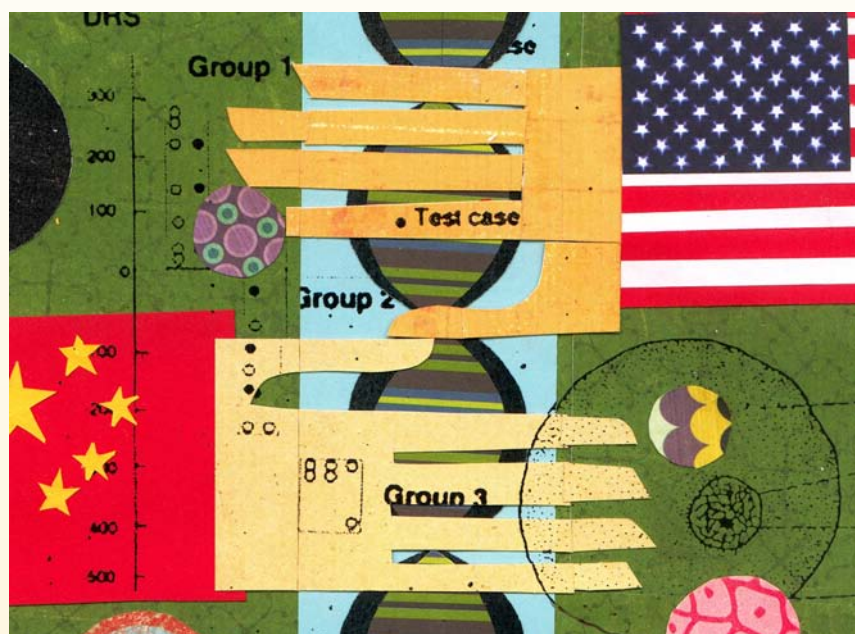
Chen says esophageal squamous cell carcinoma (SCC) is among the most common malignant neoplasms. In the United States, this disease has an overall five-year survival rate of only 13 percent, which is close to the observed survival rates in high-risk countries such as China and other global regions.

Chen believes an association between esophageal dysplasia (precancerous lesions) and SCC risk suggests that a shift in dysplasia grade can help evaluate potential chemopreventive agents. “Because symptoms of esophageal SCC typically remain absent until tumors are advanced, there is an urgent need to investigate molecular alterations in dysplastic lesions and to identify preventive agents that target those changes,” she says.

The researchers will study the roles of mitogen-activated protein kinase (MAPK) and nuclear factor- $\kappa$ B (NF- $\kappa$ B) in animal models (at Ohio State) and in humans (in China) while also examining functions of oxidative stress pathways in esophageal dysplasia in animals (at Ohio State) and in humans (in China).

“A successful outcome will provide important information and rationale to target MAPK, NF- $\kappa$ B and oxidative stress pathways in chemoprevention strategies for esophageal cancer,” Chen says.

“Although the supplement grant is not a huge amount, it is very competitive and meaningful. We hope it will open doors for other collaborations with China.”



*“Although the supplement grant is not a huge amount, it is very competitive and meaningful. We hope it will open doors for other collaborations with China.”*



**ROBERT BAIOCCHI, MD, PhD,**  
assistant professor of Medicine  
and a member of the OSUCCC –  
*James Viral Oncology Program*

**CHENGLONG LI, PhD,**  
associate professor of Medicinal  
Chemistry and Biophysics, and a  
member of the OSUCCC – *James  
Experimental Therapeutics  
Program*

**SAÏD SIF, PhD,**  
associate professor of Molecular  
and Cellular Biochemistry, and  
a member of the OSUCCC –  
*James Experimental  
Therapeutics Program*

# Drug Design *in silico*

BY DARRELL E. WARD



*OSUCCC – James researchers have used computers and computation to develop a new class of drugs that targets a key enzyme they discovered 10 years earlier in cancer cells.*

The enzyme PRMT5 is a key regulator of cell growth and proliferation during embryonic development. When the gene's assigned task is over, the cell reduces its expression, and the enzyme's levels become barely detectable.

As cells become cancerous, however, the low levels of mRNA of this dormant gene are translated more efficiently, and the enzyme is produced in abnormal abundance. In 2003, Saïd Sif, PhD, a molecular biologist and biochemist with The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), showed that overexpression of the gene is key to the hyperproliferation of cancer cells.

PRMT5 is an enzyme that adds methyl groups to histones and other proteins. Specifically, Sif showed in 2004 that it adds methyl groups to histone proteins H3 and H4, and that this leads to the shutdown of important tumor-suppressor genes and promotes tumor growth.

About that time, Robert Baiocchi, MD, PhD, joined Sif's laboratory and began cell and animal studies of PRMT5. Baiocchi, who today has his own lab at the OSUCCC – James, and Sif found that overexpression of PRMT5 promotes survival and proliferation in high-grade lymphomas, glioblastomas and melanomas, and in a wide range of cancer cell lines.

They and others have since shown that PRMT5 is astonishingly versatile and a central enzyme in cell growth and cancer development. It regulates several pathways involved in cell growth and survival, epigenetic regulation of tumor-suppressor genes and even the synthesis of cell organelles.

They also have shown that overexpression of PRMT5 promotes invasion and metastasis, and that blocking the enzyme stops cancer-cell growth and prevents migration and invasion.

One summer day in 2008, Baiocchi walked briskly down 12th Avenue, the Medical Center's research corridor, to the College of Pharmacy. There he met with computational biophysicist, *in silico* drug designer and OSUCCC – James researcher Chenglong Li, PhD, about developing a PRMT5 inhibitor using *in silico* drug design methods.

"PRMT5 plays a key role in regulating the cell cycle in cancer cells," Baiocchi explains, "and it is expressed at very low levels in healthy adult cells. It's an ideal target for a small-molecule inhibitor, and a PRMT5 inhibitor could be an effective cancer therapeutic for stopping tumor growth."

Following that meeting, Li, Baiocchi, Sif and a large group of collaborators went on to develop a first-in-class PRMT5 inhibitor that is currently in preclinical testing, and they have a third-generation agent under development.

But it wasn't easy.

## IN SILICO DRUG DESIGN

*In silico* drug design uses the power of silicon-chip computer circuitry to design new targeted agents. Using computers, Li and his lab pull drug molecules apart, sort the fragments by chemical attribute and shower them onto the active site – the business-end – of target molecules. The fragments that stick are potential inhibitors.

It's a dazzling process of computation, but hardly perfect. Nature is complicated. So OSUCCC – James medicinal chemists make small quantities of promising candidate agents and send them to Baiocchi, a biologist, who tests them for specificity and potency using enzyme and cell assays. If one is outstanding, Li and his colleagues computationally fine-tune the molecule to produce a second-generation agent that also undergoes biological evaluation. When all goes well, this process leads to phase I clinical studies and a new anticancer drug.

"Typically, about 5,000 compounds must be discovered and tested to get one FDA-approved drug when *in silico* drug design is not used," Li says. "The use of *in silico* drug design can reduce the number of compounds to 500, or even 100, and produce three to five agents to choose from for preclinical evaluation and possible clinical trials testing."

The accomplishments of Li and his lab include designing three inhibitors for STAT3, a central

signaling protein that is overexpressed in cancers of the breast, prostate, lung and pancreas, and in myeloma, and devising a new docking simulation for modeling molecular binding. The STAT3 inhibitors are in preclinical testing.

## THE TARGET

Anticancer *in silico* drug development begins with a validated target molecule and its atomic structure (see sidebar, page 27), which normally is derived using X-ray crystallography or other technology. PRMT5 was a validated target, but the protein's molecular structure was unknown. That problem had stymied attempts by others to develop an inhibitor for this enzyme.

Li and his colleagues derived the 3-D structure for the PRMT5 active site computationally, basing the model on the crystal structures of four homologous PRMT proteins: human PRMT3, mouse Carm1, and rat Prmt1 and Prmt4.

The active site is the all-important pocket in the enzyme where another

molecule – the enzyme's substrate – docks, or binds, with the enzyme and makes a chemical reaction happen. For PRMT5, that chemical reaction transfers methyl groups to arginine residues in histones H3 and H4.

Li's ultimate goal was to design a small molecule that will readily occupy the PRMT5 active site, blocking the normal molecule from binding with the enzyme. This neutralizes the enzyme and triggers cancer-cell death.

This first “homology model” of PRMT5 was too crude to use for drug-development research, so they fine-tuned its atomic framework using a method called molecular dynamic simulation. In the end they showed – computationally – that their model pocket would bind both the normal human PRMT5 substrate and its cofactor. Their model of the human enzyme was accurate to its very atoms.

Now they could search for a small molecule to gum it up.

## THE FLOOD

Li and his colleagues began the hunt by downloading the molecular structures of more than 1,500 Food and Drug Administration-approved drugs, and 7,000 to 8,000 experimental drugs in clinical trials testing from public databases. Then, Li says, “We used computers to chop these nearly ten thousand drugs into pieces and sort the pieces into subgroups according to structure, solubility, acidity and other properties.”

Then they flooded the active site with 200 to 300 of these fragments, along with nearly 1.5

million organic molecules from a bank of chemical structures that Li maintains. They did this using a computer program developed by Li called Multiple Ligand Simultaneous Docking (MLSD). It matched each molecule against the pocket according to three criteria: binding energy, binding mode and binding statistics. The Ohio Supercomputer Center crunched the numbers almost around the clock for nearly four weeks.

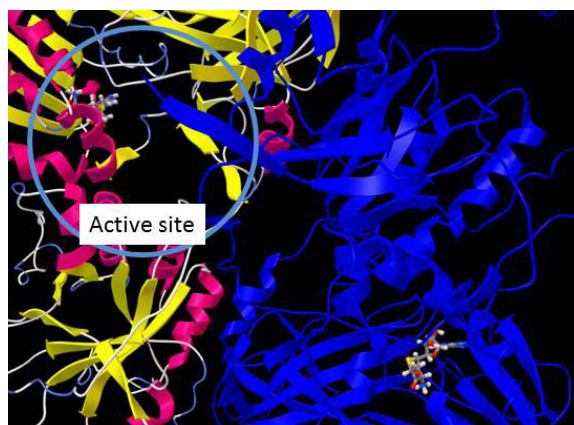
These high-throughput screenings identified eight molecules that fit the pocket.

Next, medicinal chemists in the College of Pharmacy and the OSUCCC – James Medicinal Chemistry Shared Resource formulated a small quantity of the eight compounds and sent them to Baiocchi and Sif. Sif studied the molecular interactions of the potential inhibitor, and Baiocchi screened them for specificity using an enzyme assay and glioma and lymphoma cell lines. One of the eight proved highly specific for human PRMT5.

That molecule consisted of two molecular fragments, and it became the starting point, the lead (rhymes with “seed”) molecule. The researchers called this first-generation PRMT5 inhibitor BLL1. “We did a lot of work in collaboration with other labs to develop this molecule,” Li says.

## THE BINDING-SITE TANGO

Next, Li and his lab set out to optimize the crude inhibitor for specificity and potency, an inhibitor's two most important qualities. That is, they wanted to



Ribbon diagram of PRMT5 derived by Chenglong Li and his lab. For an animation depicting the motion of the molecule inside the cell, visit [www.youtube.com/watch?v=T2TMf5DCo00](http://www.youtube.com/watch?v=T2TMf5DCo00).



strengthen the bond between the inhibitor and the PRMT5 active site. This interaction involves the six “weak chemical forces” that hold molecules together (see sidebar, page 28). These are noncovalent forces that individually are 10 to 100 times weaker than the covalent bonds that join atoms, but together they can hold molecules together.

“Much of the molecular biophysics in *in silico* drug design

is devoted to simulating the nonbinding interactions between molecules,” Li says. “It is one of the most challenging, computationally involved and intriguing aspects of *in silico* drug design.”

Li uses molecular dynamic simulation to estimate the six forces, and this predicts how long the inhibitor molecule will stick to the active site. “If these forces match, the inhibitor will occupy the active site for a sufficient period; if they don’t,

the drug will fall off quickly,” he says.

The six forces are influenced by molecular motion, Li says, noting that molecules can shoot straight ahead, rotate, flex and vibrate.

“Molecular dynamic simulation accounts for these motions,” he says.

“Inside the cell, the target protein and the drug molecule bounce and weave around one another, but they won’t come together specifically if they don’t recognize each other,” Li says. “If you design a drug that is potent and specific, the drug will move around the protein and at some point the two will hook together.”



The drug doesn’t sit there for long, though. Molecular motion causes it to repeatedly pop in and out of the active site. “The small molecule dances around the binding site,” Li says.

This molecular dance also relates to drug toxicity. “The ideal drug will stick to the target active site, but it could stick to other molecules, too. You don’t know,” Li explains. “The binding of the inhibitor to the target must also be reversible. If something stays there forever, it could be deadly. So we must computationally model this, too.”

If an agent is potent and specific but too toxic, Li and his colleagues will tweak the molecule further. “Changing an atom here or there will sometimes make the agent less toxic or more stable,” Li says, “but then we have to check that it is still potent and specific. If not, we have to start over and redesign the molecule.

“An *in silico* molecule is always an approximation,” Li adds. “This is not like designing a building or a bridge because the nonbinding interactions are extremely hard to predict.”

## IN SILICO DRUG DESIGN IN SEVEN STEPS

1. Identify a validated target molecule such as a tyrosine kinase, cell receptor or a signaling pathway.
2. Generate the 3-D structure of the target molecule’s active site using data from a protein data bank or X-ray crystallography, or derive it computationally.
3. Identify a lead inhibitor molecule by computationally plying the target active site with fragments of known molecules.
4. Evaluate the putative inhibitor for specificity and potency in bioassays.
5. Optimize the lead molecule for specificity and potency to produce a second-generation agent.
6. Evaluate the second-generation inhibitor for specificity and potency in bioassays.
7. Optimize the molecule further to develop third- and fourth-generation agents with greater specificity and potency.

The biological and biochemical evaluations by Baiocchi and Sif showed that the second-generation PRMT5 inhibitor, called BLL54, was stable, water soluble and had low toxicity.

### CURRENT STATUS

BLL1 and BLL54 are in preclinical testing, and Li is developing a more potent third-generation agent. Their studies so far have shown:

- That PRMT5 is overexpressed in mantle cell lymphoma (MCL), Hodgkin's lymphoma, diffuse large B cell lymphoma, Burkett's lymphoma, glioblastoma multiforme, lung (small and non-small cell) and melanoma, suggesting that the target is relevant to aggressive solid and hematologic tumors;
- That PRMT5 partners with other proteins to silence multiple regulatory and tumor-suppressor genes;
- That BLL1 inhibited PRMT5 activity in cancer cells without affecting normal cells, and that this slowed or stopped cancer cell growth;
- That both inhibitors are safe, metabolically stable and effective in an animal model;

They also have developed a transgenic mouse that overexpresses PRMT5 and develops lymphoma, providing a preclinical model for evaluating inhibitors.

At the 2011 American Society of Hematology meeting, Baiocchi presented findings about the use of BLL1 as a novel experimental therapeutic in MCL. Their study,

selected as one of the meeting's top oral presentations, showed that BLL1 greatly reduced the expression of molecules involved in MCL development, and that 46 patient samples examined showed "abundant PRMT5 expression" in both the cytoplasm and nucleus.

In addition, Baiocchi says, "We're using these novel inhibitors as tools to tease out the biology of lymphomagenesis." For example, the Ohio State researchers have shown that PRMT5 is essential for Epstein-Barr virus to transform B cells, and that blocking PRMT5 with BLL1 inhibits that transformation.

Baiocchi, Sif and Li are collaborating with other OSUCCC – James investigators to study the inhibitor in melanoma, breast cancer and glioblastoma. "We're

looking at the role of this enzyme and these inhibitors in a range of solid and hematologic cancers," Baiocchi says. "We hope to begin a phase I clinical trial for one of their PRMT5 inhibitors within five years."

Last but not least, Li and his lab are working with Sif's lab to generate crystals from PRMT5. "We're close to having the first crystal structure of human PRMT5, which would be a huge accomplishment," Baiocchi says. "This will help validate what we've done to date, and it will help us find more potent inhibitors.

"We have a great multidisciplinary team working on this inhibitor," he says, "and I think it's going to help push the OSUCCC – James drug-development program to a new level." **f**

## THE SIX WEAK FORCES CONSIDERED IN *IN SILICO* MODELING

While covalent bonds hold atoms together to make a molecule, nonbinding interactions, or weak chemical interactions, hold two molecules together. There are six weak chemical interactions, or forces, that *in silico* drug designers simulate to determine the specificity and potency of a potential targeted inhibitor.

- 1. Van der Waals attractions** This force relates to molecular shape.
- 2. Electrostatic force** These are ionic bonds between atoms.
- 3. Hydrogen bonding** This bond occurs when two electronegative atoms share a hydrogen atom.
- 4. Polarization force** A force produced by shifting densities of moving electrons.
- 5. Desolvation** A layer of water surrounds a target molecule. Desolvation refers to the force required to displace this layer of water when a drug binds to a target molecule. "This is one of the most difficult forces to model," Li says.
- 6. Entropy** This force relates to molecular vibration, rotation and translation.

# BENCH TO BEDSIDE

*From the Laboratory to the Pharmacy*

## An open-label, phase 1b/2, safety and efficacy study of the Bruton's tyrosine kinase (Btk) inhibitor, PCI-32765, and ofatumumab in subjects with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma and prolymphocytic leukemia

**HYPOTHESIS:** Administration of ofatumumab either consecutively or simultaneously with PCI-32765 will improve response rates compared with PCI-32765 alone and prolong survival in people with chronic lymphocytic leukemia (CLL).

**RATIONALE:** CLL, the most common leukemia diagnosed in Western countries, is characterized by an accumulation of leukemic cells that occurs in part because the cells receive survival signals from various receptors activated by ligands. CLL subtypes and related malignancies share common pathways, and this has allowed for the development of targeted therapies such as PCI-32765 and ofatumumab.

This phase 1b/2 study is designed to determine the safety and efficacy of PCI-32765 in combination with ofatumumab in subjects with relapsed or refractory CLL, SLL and related diseases. The combination is expected to be well tolerated by patients; nonetheless, the trial evaluates three dosage schedules. The study will also estimate the efficacy of the combination treatment as measured by overall response rate and progression-free survival.

PCI-32765, which is taken orally, is a selective inhibitor of Bruton's tyrosine kinase (Btk). The Btk protein is expressed mainly in B lymphocytes. It is critical for B-cell development, differentiation and signaling,

and for B-cell proliferation and survival. Individuals who lack functioning Btk lack circulating B cells and are thus unable to produce immunoglobulins or mount humoral immune responses.

Btk plays a key role in B-cell growth and proliferation via the B-cell receptor. A constitutively active mutant can induce IL-5-independent growth in a pro-B-cell line, and a body of evidence suggests that B-cell receptor signaling may be necessary to sustain the viability of CLL and other B-cell malignancies.

The fact that mutational status of the BCR is a strong predictor of disease outcome in CLL emphasizes the importance of the BCR signaling pathway in CLL pathogenesis and suggests the importance of Btk as a therapeutic target.

Ofatumumab is a humanized monoclonal antibody that targets CD20, a B-cell surface protein that is also critical for B-cell

development and differentiation. It is highly expressed on malignant B cells. Ofatumumab shows activity in patients with fludarabine- and alemtuzumab-refractory CLL, including patients previously treated with rituximab. Ofatumumab was chosen for this trial over rituximab, which also targets CD20, for its superior single-agent activity, for superior complement-dependent cell killing and antibody-dependent cell killing, and because it has a weekly dosing schedule.

OSU-10053 has three cohorts. In the first cohort, PCI-32765 is administered for 28 days alone before ofatumumab is added. In the second cohort, the two drugs are started concurrently. In the third cycle, ofatumumab is administered alone for two cycles before PCI-32765 is added. Data from correlative studies will improve the understanding of the mechanism of action of PCI-32765 and of the drug combination.

### AT A GLANCE

Clinical trial OSU-10053

PI: **SAMANTHA M. JAGLOWSKI, MD**

Phone: 614-293-8858

Email: [Samantha.jaglowski@osumc.edu](mailto:Samantha.jaglowski@osumc.edu)

**Eligibility:** Subjects with histologically confirmed CLL, small lymphocytic lymphoma or prolymphocytic leukemia as defined by WHO classification of hematopoietic neoplasms, or Richter's transformation arising out of CLL/SLL. Additional criteria are available upon request.





# NEED TO KNOW

Resources for Professional Development

## » SHARED RESOURCES

### WHEN BEHAVIOR MATTERS

The Behavioral Measurement Shared Resource (BMSR) provides OSUCCC – James investigators with a continuum of services that includes planning and developing research proposals and projects, data collection and behavioral data interpretation to help them integrate behavioral research into their studies.

Director Michael Slater, PhD, MPA, is a member of the OSUCCC – James Cancer Control Program and a Social and Behavioral Sciences Distinguished Professor in Ohio State's School of Communication. He has served as principal investigator on NIH-funded studies representing more than \$11 million in research grants and has more than 100 publications, mostly in the areas of

communication and health behavior and research methodology.

Associate Director Paul Reiter, PhD, is a member of the OSUCCC – James Cancer Control Program and an assistant professor in Ohio State's College of Medicine, Division of Cancer Prevention and Control. His research focuses largely on cancer prevention and control through screening and vaccination.

The BMSR assists in designing and incorporating behavioral variables into proposed or ongoing research. The shared resource can help with the accrual of underserved groups into research studies, in designing and implementing assessment tools suited to the investigator's aims and hypotheses, and in the interpretation of behavioral data for publication.

The BMSR offers services in:

- Research design
- Population-based data retrieval
- Recruitment and accrual, particularly with underserved and minority populations
- Behavioral assessment
- Data collection

The BMSR also collaborates with investigators at outside institutions, assisting in the design and development of data collection forms and processes, recruitment of study participants, interviewer training and data-analysis preparation.

For more information, visit the Behavioral Measurement Shared Resource website at <http://cancer.osu.edu/research/cancerresearch/sharedresources/bm/pages/index.aspx>.

### Events Calendar

#### PELOTONIA 12

**August 10-12, 2012**

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

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

#### CANCER CACHEXIA: MOLECULAR MECHANISMS AND THERAPEUTIC APPROACHES

**Sept. 21-23, 2012, Boston, Mass.**

**FOCUS:** The clinical manifestations of cancer cachexia; mechanisms of skeletal and cardiac muscle wasting in cancer cachexia; common mechanisms of cachexia-promoting conditions; the significance of non-muscle tissue in cancer cachexia; and optimal strategies for treating cancer cachexia

#### 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.

*For more information, contact Pat Fitzwater at Academic Event Management (805) 300-9154, or by email at [pat@academicventmanagement.com](mailto:pat@academicventmanagement.com).*

## » EXPANSION UPDATE

# EXPERIMENTAL THERAPEUTICS PROGRAM HAS SPACE TO CALL ITS OWN

The move is another step toward an Ohio State drug-discovery institute

The burgeoning OSUCCC – James efforts in drug discovery and design took a significant step forward in May when investigators in the cancer center’s Experimental Therapeutics Program began occupying new space on the fourth floor of the 12th Avenue Biomedical Research Tower.

The 25,640 sq. ft. area – nearly 80 percent of which is laboratory space – is the research program’s coordinating center, says Michael Grever, MD, co-leader of the Experimental Therapeutics Program and professor and chair of the Department of Internal Medicine. “This new space is designed to be a hub for new ideas and improved strategies for the treatment of cancer.”

The drug discovery and development unit is ideally located between Ohio State’s new James Cancer Hospital and Solove Research Institute and College of Pharmacy, and across the street from the research laboratories of the Dorothy M. Davis Heart and Lung Research Institute.

“Our location helps us tap into the expertise and talents of a range of people on campus who are interested in drug development,” Grever says.

Overall, the Experimental Therapeutics Program is composed of more than 50 clinical and laboratory investigators from 16

departments within Ohio State’s College of Medicine and College of Pharmacy. Only a portion of them are housed in the new area.

Research under way in the unit includes work in epigenetic therapeutics, biomarkers and targeted therapies for lung cancer, and development of a natural-products anticancer agent. It also houses an office for the cancer program’s emerging drug development program, and space is reserved for the recruitment of new investigators involved in experimental therapeutics research. Embedded in this research area are three key supporting core services:

- The Medicinal Chemistry Shared Resource, which offers expertise in synthetic and process chemistry, molecular pharmacology, purity analyses and custom syntheses.
- The Pharmacodynamic Shared Resource, which provides high-quality, cost-effective method development, quantitative sample analysis, and pharmacokinetic, pharmacodynamic and pharmacogenetic experimental



design and data analysis.

- The Solid Tumor Translational Science Shared Resource, which develops customizable validation assays to provide innovative correlative-science studies associated with early-phase solid-tumor oncology clinical trials.

“In addition to laboratory and office space and essential core services for therapeutics research, we provide open spaces and conference rooms to encourage and facilitate creative interactions among investigators,” Grever says. “The Ohio State cancer program is building a truly robust drug discovery and development program.”

## ABOVE

The OSUCCC – James Experimental Therapeutics Program is occupying new laboratory and office space in The Ohio State University Wexner Medical Center Biomedical Research Tower.

## STAFF RECOGNITION

# Gillison Receives Prestigious AACR Award

Maura L. Gillison, MD, PhD, professor of Medicine, of Epidemiology and of Otolaryngology at the OSUCCC – James, has received the 36th Annual AACR Richard and Hinda Rosenthal Memorial Award from the American Association for Cancer Research.

Gillison, who is also the Jeg Coughlin Chair of Cancer Research, was honored at the association's 2012 annual meeting in Chicago, where she presented a lecture entitled "Clinical Implications of HPV in Head and Neck Cancers."

"It is an honor to receive this award," Gillison says. "Our team strives to generate data that will improve the lives of individuals affected by head and neck cancers, and this is a wonderful validation that we are on the right track."

The AACR noted that Gillison's "seminal research on the role of HPV in head and neck cancers revolutionized the specialty. Her research has demonstrated that HPV infection causes a distinct molecular, clinical and pathological subset of head and neck squamous cell carcinomas."



## NATIONAL RECOGNITION

# NCI Renews Ohio State's 'Comprehensive' Status

The National Cancer Institute (NCI) has again designated The Ohio State University a "comprehensive" cancer center, a status the University has continuously retained since 1976. The NCI awards the title only to cancer programs that substantially contribute at all levels of cancer research – basic, clinical and population sciences – as well as provide patient care and professional and community education.

The University's cancer program was evaluated for scientific impact, improving cancer care and clinical trials enrollment, and service to the community.

"As one of the nation's leading comprehensive cancer centers, our groundbreaking discoveries are changing the way the world diagnoses, treats and prevents cancer," says Michael A. Caligiuri, MD, director of Ohio State's Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute. "We are pleased to maintain our 'comprehensive' status following a rigorous NCI review process, including a site visit by 28 scientists from other universities that led to the OSUCCC's rating of exceptional, which is the highest possible rating."

## IN THE NEXT ISSUE OF **frontiers...**

### CLINICAL TRIALS FOR CANINES

In 2007 The Ohio State University College of Veterinary Medicine set up its own Clinical Trials Office. Recently, that program and the OSUCCC – James began an innovative collaboration to expedite the development of new anticancer drugs for humans and related agents for dogs that develop spontaneous cancer.

### INTERDISCIPLINARY COLLABORATION

Gregory B. Lesinski, PhD, MPH, is an OSUCCC – James bench scientist studying how inflammation leads to cancer. In collaboration with OSUCCC – James researchers in the colleges of Pharmacy and Agriculture, he works to discover new molecular inhibitors and whole-food dietary interventions that modulate the immune system to control a variety of solid tumors.