

TURNING CANCER DISCOVERIES INTO TREATMENTS

# FRONTIERS

WINTER | 2015

Inside:  
**THE NEW JAMES  
IMMUNE THERAPY**

The James Cancer Hospital and Solove Research Institute

The James



THE OHIO STATE UNIVERSITY  
COMPREHENSIVE CANCER CENTER

NCI  
CCC

A Comprehensive Cancer  
Center Designated by the  
National Cancer Institute

# UPFRONT

The Director's Perspective

## Our New Home

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

On Dec. 15, 2014, after a decade of planning and design and three years of construction, we officially opened our new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute—a 21-story, 1.1-million-square-foot, 306-bed facility. It stands as a beacon of hope to all patients and families who turn to us for help after a cancer diagnosis.

When I think of the incredible work that went into creating this hospital—not to mention a superbly orchestrated weekend move of some 220 inpatients from the original James to its transformational successor—I recall the feeling of working with elaborate laboratory equipment that was once state-of-the-art, then moving to the latest, far

more powerful model, enabling us to accomplish so much more.

The new James is doing that for us on a grand scale. There, clinicians and scientists work together closer than ever to translate research discoveries to innovative patient care. I asked the 500 volunteers who assisted with our inpatient move on Sunday, Dec. 14, to think not just of transporting patients in beds and wheelchairs into a new hospital, but across the threshold to a cancer-free world. That's our vision, and I believe that world is within our grasp.

Despite the work involved with opening and occupying our new home — now the nation's third-largest cancer hospital — Ohio State cancer research did not miss



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

a beat. This issue of *Frontiers* also examines some of our studies in immune therapy, one of today's most promising areas of cancer research. You can also read about our Cell Therapy Laboratory located in the new James, which will open exciting avenues of research and treatment.

The work of investigators at Ohio State and elsewhere, plus the promise of the new James, gives cancer patients more reason than ever to hope for a brighter future.

### 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  
**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**

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

Chief Financial Officer  
**JULIAN BELL**

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

Interim Chief Communications Officer  
**MELISSA HALL**

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

#### EDITORIAL BOARD

Stephen Chaykowski  
William Carson III, MD  
Jennifer Carlson  
Jeffrey Fowler, MD  
Melissa Hall  
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.

# FRONTIERS

WINTER | 2015

## FEATURES



14

### THE NEW JAMES

*A 21st-century facility for collaborative, subspecialized and precision cancer care*



### Immune Boosters

22

### IMMUNE BOOSTERS

*Research on immune therapy for cancer turned a corner a few years ago, resulting in treatment strategies that show real promise*

## 04 FRONTLINE



### THREE PERSPECTIVES

*The new James Cancer Hospital and Solove Research Institute*

## 12 OF NOTE

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

## 06 BREAKTHROUGH

### EVASIVE ACTION

*Survival Molecule Helps Cancer Cells Hide From Immune System*

### RISK POTENTIAL

*Researchers Find Possible Link Between Breast Cancer and Salivary Gland Cancer*

### EXAMINING ERLOTINIB

*Study May Explain Why Targeted Drug Doesn't Benefit Patients with Early-Stage Lung Cancer*

### EXPANDING EFFICACY

*Low Doses of Targeted Drug Might Improve Cancer-Killing Virus Therapy*

### INFLUENCING OUTCOME

*Experience Counts with Radiation Therapy for Head and Neck Cancer*

### CURBING COST

*Study Suggests Dopamine is a Safe Antiangiogenic Drug*

## 29 BENCH TO BEDSIDE



### WILLIAM E. CARSON, MD

*A Phase I/II Trial of Cetuximab in Combination with Interleukin-12 Administered to Patients with Unresectable Primary or Recurrent Squamous Cell Carcinoma of the Head and Neck*

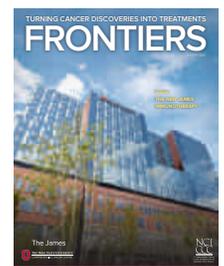
## 30 NEED TO KNOW



### THE CELL THERAPY LABORATORY

## 31 HISTORIC WEEKEND MOVE COMPLETED SAFELY, SMOOTHLY

**ON THE COVER:**  
The New James Cancer Hospital and Solove Research Institute



## THE NEW JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

# THREE PERSPECTIVES

*Editor's note: The new James Cancer Hospital and Solove Research Institute opened Dec. 15.*

*Prior to the hospital's opening, we invited an OSUCCC – James physician, a nurse and a clinical research coordinator to give their perspective on what they found most exciting about the new hospital.*



**RICHARD GOLDBERG, MD**



**AMY TOOTLE, BSN, RN**



**AMBER GORDON, MLS**

### **RICHARD GOLDBERG, MD**

*Physician-in-Chief  
James Cancer Hospital and  
Solove Research Institute*

The new James—it's big, it's beautiful, it's equipped with the latest technology, and it will enable us to provide the most sophisticated care.

When touring the building, I'm reminded at every turn that delivering cancer care these days is a very high-tech proposition. The technological wonders include a dedicated MRI scanner located between the neurosurgical operating rooms, allowing delivery of radiation in the operating room; intensive care beds that have the latest technology; and new linear

accelerators that deliver radiation that is tightly focused on tumors, thereby sparing healthy tissue.

Although the building houses state-of-the-art technology, we also gave thought to the human needs of our patients, their families and friends, and of our teams of cancer experts.

Experts in design helped us engineer the spaces to foster the subspecialty model that we believe 21st-century cancer care demands. Our patient-care areas are designed to bring teams of medical experts trained in delivering all aspects of care together with people who have specific types of cancer. The objective is to help focus the attention of multiple specialized

practitioners on each patient.

We believe the new James will be a magnet for patients and providers from across the Midwest, in the nation and the world. We owe many thanks to the late Arthur G. James, MD, for being the visionary who made this possible.

### **AMY TOOTLE, BSN, RN**

*Assistant Nurse Manager  
Blood and Marrow Transplant Unit  
James Cancer Hospital and Solove  
Research Institute*

The attractive, spacious, state-of-the-art patient rooms offered by the new James provide ideal nursing conditions and a safe, healing environment. Large windows offer breathtaking views that are calming



and comforting. The standardized room-design supports quality care and promotes better patient outcomes. Disease-specific units foster evidence-based practice and innovative care.

Relationship Based Care underpins the practice of nursing at The James. It focuses on care of patients, care of colleagues and care of self. All inpatient rooms include patient lifts to decrease work-related injuries, and all units include respite areas for patients, family members and staff.

The research space on all inpatient units encourages professional team building and professional development.

In addition, multiple spaces are designated for multidisciplinary teams to meet, which should enhance communication, safety and quality. Terrace gardens located on the north and south sides of the building further enhance this caring and healing environment.

Other exciting innovations include an oncology emergency

department that will open this spring. This new facility should enhance patient care and satisfaction. In the end, that is what nursing is all about.

#### **AMBER GORDON, MLS**

*Senior Clinical Research Coordinator  
James Cancer Hospital and Solove  
Research Institute*

As a clinical research coordinator, I constantly look for ways to bring the laboratory and the clinic closer together. I am very excited that the integration of research and clinical care is an important focus of the new James. Each inpatient floor has translational laboratory space so that we can, quite literally, close the gap between bench and bedside.

I'm excited to see how these spaces will help push translational research at The James to a new level. The new building, equipped with the latest technology, along with the growing incorporation of genomic medicine and strong emphasis on targeted-drug development and clinical trials, will improve patient

access to the latest research and technologies that we are using in the fight against cancer.

I'm also impressed about the level of thought that went into effective floor planning. All the operating rooms are on the same floor, which allows for quick equipment transfer, and the clinical trials processing laboratory shares the same floor as the units that administer experimental therapies to patients. This will facilitate good communication, ensure accurate sample collection and expedite specimen processing, all critical factors when developing safe and efficient novel therapeutics.

Overall, the design features of the new James Cancer Hospital and Solove Research Institute will increase the efficiency of our clinical and translational research, which in turn should accelerate the discovery and development of novel therapeutics and their delivery to the patients who need them. It's an exciting time for cancer research at Ohio State! **F**

## Evasive Action

### *Survival Molecule Helps Cancer Cells Hide From the Immune System*



**DENIS GUTTRIDGE, PHD,**  
*professor in the Department of Molecular Virology, Immunology and Medical Genetics and the Department of Molecular and Cellular Biochemistry at Ohio State*

A molecule that helps cancer cells evade programmed self-destruction might also help malignant cells hide from another source of death: the immune system.

A study by researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC –

James) showed that a molecule called nuclear factor kappa B (NF- $\kappa$ B) helps cancer cells suppress the immune system's ability to detect and destroy them. The molecule regulates genes that suppress immune surveillance mechanisms and that lead to the production of cells that inhibit the immune response.

The findings suggest that immune therapy for cancer might be more effective if combined with drugs that inhibit NF- $\kappa$ B. They also provide new details about how interactions between cancer cells and noncancer cells assist tumor growth.

“We’ve long known that NF- $\kappa$ B promotes cancer development by subverting apoptosis, an internal safety mechanism that otherwise would cause cancer cells to self-destruct,” says principal investigator Denis Guttridge, PhD, a professor in the Department of Molecular Virology, Immunology and Medical Genetics and the Department of Molecular and Cellular Biochemistry at Ohio State.

“This study shows that NF- $\kappa$ B might coordinate a network of immune-suppressor genes whose products enable tumor cells to evade adaptive immunity,” adds

Guttridge, who also co-leads the Translational Therapeutics Program at the OSUCCC – James. “Therefore, inhibiting NF- $\kappa$ B might make tumor cells more vulnerable to elimination by the immune system.”

Guttridge credits the paper’s first author, David J. Wang, for developing many of the study’s concepts.

*Published in the journal Cell Reports*

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

## SALIVARY GLAND CANCER |

## Risk Potential

### *Researchers Find Possible Link Between Breast Cancer and Salivary Gland Cancer*

The risk of developing cancer in a salivary gland might be higher in people with mutations in either of two genes associated with breast and ovarian cancer, a study at the OSUCCC – James suggests.

Salivary gland cancer is rare, but this retrospective study suggests it occurs 17 times more often in people with inherited mutations in genes called BRCA1 and BRCA2 than those in the general population.

“Further study is needed to confirm this preliminary result, but I believe that a BRCA-positive patient with a lump in a salivary gland should have that lesion evaluated as soon as possible,” says co-author Theodoros Teknos, MD, professor and chair of the Department Otolaryngology – Head and Neck Surgery at Ohio State.

It is well known that women who inherit mutations in either of the two genes have a higher risk of breast and ovarian cancer than women without the mutation; men with the mutations also are at higher risk of breast cancer. The two mutated genes are linked to prostate, pancreatic and other cancers as well.

Teknos recommends that individuals who carry a BRCA mutation be made aware of this

possible association with salivary gland cancer, and that the study’s findings be considered during genetic counseling of families with inherited BRCA1 or BRCA2 mutations.

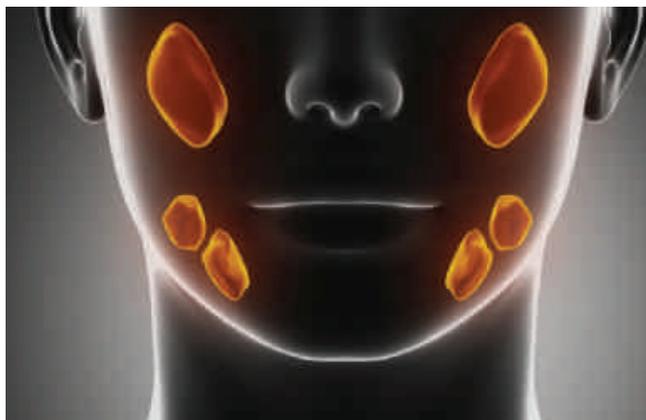
He adds that in the future, patients with salivary-gland cancer and their family members might be referred for BRCA testing, or carriers of BRCA mutations might undergo surveillance for salivary gland cancers.

Cancers of the salivary glands are rare in the United States, with about three cases occurring annually per 100,000 adults in the general population (0.003 percent).

*Published in the journal JAMA Otolaryngology – Head and Neck Surgery*



**TED TEKNOS, MD,**  
*professor and chair of the  
Department of Otolaryngology –  
Head and Neck Surgery at Ohio  
State*



## Examining Erlotinib

### *Study May Explain Why Targeted Drug Doesn't Benefit Patients with Early-Stage Lung Cancer*

The drug erlotinib is highly effective in treating advanced-stage lung cancer patients whose tumors have a particular gene change, but when the same drug is used for patients with early-stage tumors with the same gene change, they fare worse than if they had taken nothing at all.

A study by researchers at the OSUCCC – James and at Cincinnati Children's Hospital might explain why.



**DAVID CARBONE, MD, PHD,**  
*professor in the Division of  
Medical Oncology at Ohio State*

Oncologists use erlotinib to treat lung cancers that have a mutation in a gene called epidermal growth factor receptor (EGFR). The mutation causes EGFR to run like it has a stuck accelerator, and erlotinib blocks the overactive molecule.

The study shows that while erlotinib causes tumors to shrink—suggesting that the drug is helping a patient—it also increases the aggressiveness of the tumor so that cancer-cell growth accelerates when therapy ends. The study found that this is due to a secondary and previously unknown effect of inhibiting EGFR.

The researchers discovered that when erlotinib blocks EGFR, it activates a second signaling molecule called Notch3. Activating that pathway leads to increased development of cancer stem cells among the surviving tumor cells and to accelerated tumor growth.

“Our findings might explain why erlotinib in clinical trials seems to worsen survival in patients with early-stage lung cancer,” says co-corresponding author David Carbone, MD, PhD, a professor in the Division of Medical Oncology at Ohio State and co-leader of the OSUCCC – James Translational Therapeutics Program.

Carbone, co-corresponding author Stacey Huppert of Cincinnati Children's Hospital and their colleagues conducted the study using several cell lines of non-small-cell lung cancer to learn if inhibiting EGFR enhances the activity of the Notch signaling pathway.

“We found that the activated, mutated EGFR directly inhibits Notch signaling,” Carbone says. “Inhibiting EGFR with erlotinib removes this restraint and activates Notch signaling, which suggests that combining an EGFR inhibitor with a Notch inhibitor might overcome this adverse effect.”

*Published in the journal Cancer Research*

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

## Expanding Efficacy

### *Low Doses of Targeted Drug Might Improve Cancer-Killing Virus Therapy*

Giving low doses of a particular targeted agent with a cancer-killing virus might improve the effectiveness of the virus as a treatment for cancer, according to a study led by researchers at the OSUCCC – James.

Viruses that are designed to kill cancer cells—oncolytic viruses—have shown promise in clinical trials for treating brain cancer and other solid tumors. This cell and animal study suggests that combining low doses of the drug [bortezomib](#) with a particular oncolytic virus might significantly improve the ability of the virus to kill cancer cells during [oncolytic virus therapy](#).

“These findings pave the way for a treatment strategy for cancer that combines low doses of bortezomib with an oncolytic virus to maximize the efficacy of the virus with little added toxicity,” says principal investigator Balveen Kaur, PhD, professor and vice chair of research in the Department of Neurological Surgery at Ohio State, and an associate director for shared resources at the OSUCCC – James.

“Because bortezomib is already approved by the Food and Drug Administration, a clinical trial could be done relatively quickly to test the effectiveness of the drug-virus combination,” Kaur says.

Bortezomib inhibits the activity of [proteasomes](#), structures in cells that break down and recycle

proteins. Kaur notes that blocking these “cellular recycling plants” activates a cellular stress response and increases the expression of [heat shock proteins](#). This reaction, which can lead to bortezomib resistance, makes the cells more sensitive to oncolytic virus therapy with little additional toxicity.

For this study, Kaur and her colleagues used a herpes simplex virus-type 1 (HSV-1) oncolytic virus.

“To our knowledge, this study is the first to show synergy between an oncolytic HSV-1-derived cancer-killing virus and bortezomib,” Kaur says. “It offers a novel therapeutic strategy that can be rapidly translated in patients with various solid tumors.”

*Published in the journal [Clinical Cancer Research](#).*

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



**BALVEEN KAUR, PHD,**  
*professor and vice chair of research in the  
Department of Neurological Surgery at Ohio  
State, and associate director for shared  
resources at the OSUCCC – James*

# Influencing Outcome

## *Experience Counts With Radiation Therapy for Head and Neck Cancer*



**EVAN WUTHRICK, MD,**  
*assistant professor of Radiation  
Oncology at Ohio State*



**MAURA GILLISON, MD, PHD,**  
*professor of Internal Medicine  
and Epidemiology at Ohio State*

When it comes to specialized cancer surgery, it's generally true that the more experienced the surgeon, the better the outcome. The same might be true for radiation therapy used to treat head and neck cancer, according to a study by researchers at the OSUCCC – James.

The study was co-led by **Evan Wuthrick, MD**, assistant professor of Radiation Oncology at Ohio State, and **Maura Gillison, MD, PhD**, professor of Internal Medicine and Epidemiology at Ohio State, where she also is a member of the Cancer Control Program at the OSUCCC – James.

The study compared survival and other outcomes in 470 patients treated with radiation therapy at 101 treatment centers through a clinical trial held from 2002 to 2005. The trial was sponsored by the National Cancer Institute and organized by the Radiation Therapy Oncology Group (RTOG).

The findings indicated that patients treated at the less-experienced centers were more likely to have cancer recurrence (62 percent versus 42 percent at five years) and had poorer overall survival compared with those at the highly experienced centers (51 percent versus 69 percent five-year survival, respectively).

“Our findings suggest that institutional experience strongly influences outcomes in patients treated with radiation therapy

for head and neck cancer,” says Wuthrick, the paper’s first author. “They indicate that patients do better when treated at centers where more of these procedures are performed versus centers that do fewer.”

Radiation therapy for head and neck cancer requires complex treatment planning that can vary considerably among institutions and physicians. In addition, significant short- and long-term side effects can occur that require management by a carefully coordinated multidisciplinary care team.

National Comprehensive Cancer Network guidelines recommend that head and neck cancer patients receive treatment at experienced centers, but whether provider experience affects outcomes was previously unknown.

*Published in the Journal of Clinical Oncology*

# Curbing Cost

## *Study Suggests That Dopamine is a Safe Antiangiogenic Drug*

Angiogenesis inhibitors—drugs that block the formation of blood vessels in tumors—are used in the treatment of many forms of cancer. But currently used drugs are expensive and can cause serious side effects, precluding their use in some patients.

A new study led by scientists at the OSUCCC – James suggests that the inexpensive drug dopamine, used to treat heart, vascular and kidney disorders, can be safely used in cancer treatment to curb the growth of tumor blood vessels.

In the study, dopamine prevented the growth of blood vessels in two animal models without causing many of the serious side effects of the far-more expensive antiangiogenic drugs in current use.

The agent also prevented the neutropenia (drop in the number of neutrophils) that is often caused by the chemotherapy drug 5-fluorouracil when used to treat colon, stomach, pancreas and breast cancers.

“This study demonstrates for the first time that the inexpensive drug dopamine lacks the serious side toxicities commonly seen with the antiangiogenesis drugs presently used in the clinic,” says principal investigator Sujit Basu, MD, PhD, professor of Pathology and of Medical Oncology at Ohio State. “Furthermore, dopamine can prevent the low-neutrophil

count that is often induced by a very common anticancer drug used for the treatment of gastrointestinal cancers,” says Basu, who is in the OSUCCC – James Translational Therapeutics Program.

Basu notes that dopamine is being used in clinics to treat other disorders, so these findings can be rapidly transferred to the clinic for the treatment of cancer patients.

Earlier studies by Basu and others have shown that dopamine blocks the growth of new tumor blood vessels by inhibiting the action of vascular endothelial growth factor-A (VEGF-A), a hormone-like substance that plays a critical role in the initiation and progression of solid tumors.

“Most antiangiogenic drugs now in use have anti-VEGF-A actions,” Basu says. “Our study will help to rapidly translate the use of this inexpensive but effective anti-angiogenic drug, dopamine, for the treatment of cancer in the clinics.”

*Published in the [International Journal of Cancer](#)*

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



**SUJIT BASU, MD, PHD,**  
*professor of Pathology and  
of Medical Oncology at Ohio  
State and a member of the  
Translational Therapeutics  
Program at the OSUCCC – James*

# OF NOTE

Recent Recognition of OSUCCC – James Physicians and Researchers

## GRANTS



**MICHAEL A. CALIGIURI, MD**, director of The Ohio State University Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute, has received a five-year, \$2.56 million Oncology Training Grant renewal ([CA009338](#)) from the National Cancer Institute (NCI) to support Ohio State's postdoctoral oncology training program.



**RAMIRO GARZON, MD**, associate professor in the Division of Hematology, was awarded a five-year, \$1.59 million NCI grant ([CA188269](#)) to develop a new class of drugs called CRM1 inhibitors for treatment of acute leukemia.



**BALVEEN KAUR, PHD**, professor of Neurological Surgery and associate director for shared resources at the OSUCCC – James, has received a five-year, \$1.7 million grant from the National Institute for Neurological Disorders and Stroke ([NS064607](#)) for a study evaluating changes in the tumor microenvironment induced by oncolytic viruses (OV) and their effect on OV therapy.

**FEN XIA, MD, PHD**, professor of Radiation Oncology, and **ARNAB CHAKRAVARTI, MD**, professor and chair of Radiation Oncology, have received a five-year, \$2.09 million NCI grant ([CA188500](#)) to study the molecular mechanisms involved in the response of glioblastoma multiforme (GBM) cells and brain neurons to DNA damage caused by radiation therapy. The goal is to improve the therapeutic index in GBM treatment.

**RAMESH GANJU, PHD**, professor of Pathology, has received a five-year, \$1.23 million NCI grant ([CA109527](#)) to further characterize the role of several chemokine-receptor pathways in regulating breast tumor growth, angiogenesis and metastasis.



**METIN GURCAN, PhD**, associate professor of Biomedical Informatics and director of the Clinical Image Analysis Lab, and **GERARD LOZANSKI, MD**, associate professor-clinical of Pathology, have received a four-year, \$1.09 million NCI grant ([CA134451](#)) for a computer-based assessment of the tumor microenvironment in follicular lymphoma.



**NORMAN LEHMAN, MD, PHD**, associate professor-clinical and director of the Division of Neuropathology, has received a \$1.8 million, five-year grant from the National Institute of Neurological Disorders and Stroke ([NS081125](#)) to study Aurora-A, a protein that helps drive cell division, as a novel therapeutic target in glioblastoma.

**STEVEN CLINTON, MD, PHD**, professor, Division of Medical Oncology, College of Medicine; **PURNIMA KUMAR, MDS, PhD**, associate professor, Division of Periodontology, College of Dentistry; **STEVEN SCHWARTZ, PhD**, professor of Food Science and Technology, College of Food, Agricultural and Environmental Sciences; and **CHRISTOPHER WEGHORST, PHD**, professor and associate dean for research, Division of Environmental Health Sciences, College of Public Health, have received a five-year, \$3.1 million NCI grant ([CA188250](#)) to investigate the interactions between black raspberry phytochemicals and tobacco on the oral microbiome and how they influence early oral carcinogenesis.

## AWARDS AND HONORS

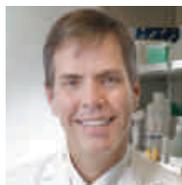


**DONALD BENSON, MD, PHD**, associate professor, Division of Hematology, has been elected a member of the [Henry Kunkel Society](#), which is dedicated to fostering patient-oriented research, particularly in the field of immunology.



**CLARA D. BLOOMFIELD, MD**, Distinguished University Professor, and cancer scholar and senior adviser to the OSUCCC – James, has been honored as one of 50 American Society of Clinical Oncology (ASCO) [Oncology Luminaries](#). Bloomfield was recognized for her years of “practice-changing leukemia and lymphoma research.”

**BLOOMFIELD** and **CARLO CROCE, MD**, professor and chair of the Department of Molecular Virology, Immunology and Medical Genetics, and director of Human Cancer Genetics at the OSUCCC – James, are among 14 faculty and staff at Ohio State's Wexner Medical Center to appear on the 2014 list of Highly Cited Researchers presented by Thomson Reuters, a mass media and information firm.



**JOHN C. BYRD, MD**, director, Division of Hematology, has been chosen clinical advisory editor for hematology/oncology for *Oncology Times*. In addition, Byrd has been appointed chair of the Alliance for Clinical Trials in Oncology Leukemia Correlative Science Committee.



**DELIANG GUO, PHD**, assistant professor of Radiation Oncology, has received the 2014 Scholar Award from the American Cancer Society. It includes a four-year, \$792,000 grant that will help support Guo's examination of cholesterol metabolism in promoting glioblastoma.



**EHUD MENDEL, MD, FACS**, professor of Neurological Surgery and of Orthopaedics, is listed among "230 Spine Surgeons to Know – 2014," compiled by *Becker's Spine Review*. Mendel directs Ohio State's Spine Oncology Program and is clinical co-director of the university's Spinal Biodynamics and Ergonomics Laboratory.



**ASHLEY ROSKO, MD**, assistant professor, Division of Hematology, has received an NCCN Foundation Young Investigator Award. Presented by the National Comprehensive Cancer Network (NCCN) Foundation, it includes a \$150,000 grant over two years for a study titled "NCCN Senior Adult Oncology:

Myeloma Comprehensive Geriatric Assessment and Biomarkers of Aging Investigation."



The OSUCCC – James **BLOOD AND MARROW TRANSPLANT UNIT** has been awarded a Bronze Beacon Award by the American Association of Critical-Care Nurses (AACN). Beacon Awards recognize exceptional care of patients and a positive and supportive work environment for nurses.

**OHIO STATE'S WEXNER MEDICAL CENTER** has been recognized as a "Best in Class" hospital by the Institute for Diversity in Health Management, an American Hospital Association affiliate. The recognition came following a national survey called "Diversity and Disparities: A Benchmarking Study of U.S. Hospitals." More than 1,100 hospitals responded to the survey.

## FACULTY AND PROGRAMS

**OHIO STATE'S CENTER FOR RETROVIRUS RESEARCH** in the College of Veterinary Medicine has awarded its 2015 Distinguished Research Career Award to PAUL BIENIASZ, PhD, a Howard Hughes Medical Institute Investigator, head of Rockefeller University's Laboratory of Retrovirology, and a faculty member at the Aaron Diamond AIDS Research Center. His Distinguished Seminar will be held April 30.

**THE OSUCCC – JAMES** has awarded the 21st Herbert and Maxine Block Memorial Lectureship Award for Distinguished Achievement in Cancer to CAROL GREIDER, PhD, a Nobel Laureate and the Daniel Nathans Professor and director of the Department of Molecular Biology and Genetics at Johns Hopkins University School of Medicine. Greider helped discover telomerase, an enzyme that maintains telomeres, which form the ends of chromosomes.

## LEADERSHIP ACTIVITIES AND APPOINTMENTS



**PIERRE GIGLIO, MD**, former director of neuro-oncology at the Medical University of South Carolina, has joined Ohio State's College of Medicine as an associate professor in the Department of Neurological Surgery, Division of Neuro-Oncology. [Read more](#)



**THEODOROS (TED) TEKNOS, MD**, a professor and surgical oncologist at Ohio State since 2008, has been named chair of the Department of Otolaryngology – Head and Neck Surgery in the College of Medicine. [Read more](#)



**JEFF WALKER, MBA**, senior executive director of the OSUCCC – James, has been elected treasurer of the Association of American Cancer Institutes (AACI), which comprises 93 leading cancer research centers in the United States. They include NCI-designated centers and academic-based cancer research programs that receive NCI support.



THE OHIO STATE UNIVERSITY  
WEXNER MEDICAL CENTER

The James Cancer Hospital and Solove Research Institute



# The New James Cancer Hospital and Solove Research Institute

*A 21st-century facility for collaborative, subspecialized and precision cancer care*

On Sunday, Dec. 14, 500 volunteers joined physicians, nurses and staff at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) to make Ohio State history.

That day, the group followed a well-coordinated process of transferring 182 patients from the original 12-story Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, which opened in July 1990, to the new 21-story, state-of-the-art James Cancer Hospital and Solove Research Institute.

The \$750 million, 1.1-million-square-foot, 306-bed hospital—which officially opened the following day—is the third-largest

cancer hospital in the United States and among the most well-designed in the world.

“This is a carefully planned facility, specially designed to integrate our three-part mission of patient care, research and education,” says Michael A. Caligiuri, MD, director of The OSUCCC and CEO of The James.

“We’ve created a highly collaborative, subspecialized cancer-care environment.”

Standout features of the new James include 14 state-of-the-art operating rooms, six interventional radiology suites, an above-ground radiation oncology center containing seven linear accelerators for radiation therapy, and a dedicated early-phase clinical trials unit.

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

**ARNAB  
CHAKRAVARTI, MD**

professor and chair of  
Radiation Oncology and  
co-director of the Brain  
Tumor Program



*“We do have the latest and best equipment...But it’s really the physicians, therapists, nurses and staff who make this a special place.”*

To facilitate translational research, a wet and a dry laboratory is located on alternating patient floors. “We believe this proximity of bench to bedside is unique in the United States, and we’re really proud of that,” Caligiuri says.

**Precision Cancer Medicine**

Each inpatient unit has its own cancer focus—such as gastrointestinal, head and neck, breast, genitourinary and hematologic malignancies. The oncologists, nurses, pharmacists and genomic experts on each unit treat just that type of cancer, collaborating with researchers to look at each patient’s genes and tumor DNA to determine the best

treatment and help speed research discoveries.

This approach, called precision cancer medicine, uses next-generation sequencing and other high-throughput technologies to identify the gene and molecular changes that drive a patient’s malignancy or increase the risk of recurrence or resistance to therapy.

“Next-generation sequencing can identify which of 200-plus significant genes are altered in a patient’s cancer, and we can use that information to guide therapy or match patients to clinical trials,” says Sameek Roychowdhury, MD, PhD, director of precision cancer medicine at the OSUCCC – James. “Ohio State is among the leaders

in the country in promoting and championing precision oncology.”

The new hospital further integrates precision cancer medicine into patient care at the OSUCCC – James, applying it to a growing number of malignancies.

**Radiation Oncology Center**

The hospital’s custom-designed radiation oncology center features seven linear accelerators and one brachytherapy vault. Top radiation oncologists and radiation oncology researchers at the center specialize in specific types of cancer, says Arnab Chakravarti, MD, professor and chair of Radiation Oncology and co-director of the Brain Tumor Program.



Importantly, the center’s second-floor location distinguishes it from most others worldwide and provides soothing natural light to promote patient healing and comfort.

“We do have the latest and best equipment,” says Chakravarti, who holds the Max Morehouse Chair in Cancer Research and helped design the center. “But it’s really the physicians, therapists, nurses and staff who make this a special place.”

**A Standout Surgical Suite**

The expansive new OSUCCC – James surgical suite features advanced technology and a forward-thinking design. The 14 operating rooms, including six interventional operating suites, are each equipped

**Principles That Guided the Design of the New James Cancer Hospital and Solove Research Institute**

- **Patient Care** – single-occupancy rooms, organized into neighborhoods of 10-12 rooms
- **Allow family support 24/7**
- **Bedside technology** – point-of-care support
- **Patient safety** through room design
- **Support and facilitate caregiver efficiency and productivity**
- **Research** – clinical research throughout inpatient facility
- **Education** – Two priorities:
  - Patient:* **Central family resource center** with on-demand, patient-specific education
  - Student:* **Dedicated meeting space**
- **Healing environment** – an interior design with natural light, soothing colors and various art forms



**RAPHAEL E. POLLOCK, MD, PHD,**

director of Ohio State's Division of Surgical Oncology and chief of surgical services at the OSUCCC – James



*“The 14 operating rooms, including six interventional operating suites, are each equipped to perform minimally invasive robotic surgery and state-of-the-art microvascular reconstructive surgery. They were built intentionally large to accommodate future technology and equipment.”*

to perform minimally invasive robotic surgery and state-of-the-art microvascular reconstructive surgery. They were built intentionally large to accommodate future technology and equipment, says Raphael E. Pollock, MD, PhD, director of Ohio State's Division of Surgical Oncology and chief of surgical services at the OSUCCC – James.

Equipment and electrical outlets are secured to the ceilings of each operating room, a feature that dramatically increases usable floor space.

Two of the surgical suites are

connected to a 3-Tesla MRI machine, allowing patients to be imaged during surgery.

**An Active Clinical Trials Unit**

As one of a few cancer centers in the nation funded by the National Cancer Institute (NCI) to conduct phase I and phase II clinical trials of NCI-sponsored anticancer agents, the OSUCCC – James has a well-established and experienced clinical trials program. One in four OSUCCC – James patients is enrolled in a clinical trial, a rate five times greater than the national average (which, historically, has

been 5 percent or less).

The new hospital will broaden the clinical trial program's reach and expand patients' access to it. The new James Clinical Trials Unit will eventually oversee hundreds of cancer clinical trials.

**A Fully Integrated Cancer Emergency Department**

Once home, cancer patients can develop acute medical conditions due to acquired infections, the side effects of therapy or other causes. These cases can require emergency care and present a clinical challenge .

The new OSUCCC – James



addresses this problem with a fully integrated cancer emergency department, to open in March 2015. The department will bring together emergency medicine specialists and clinical oncologists to provide optimal care for cancer patients in crisis. The cancer emergency room will feature 15 treatment stations staffed by teams of emergency medical and cancer specialists, as well as highly trained nursing teams.

**An Advanced BMT Unit and Lab**

The new James incorporates a 36-bed blood and marrow transplant unit supported by a cell therapy laboratory that meets good-



**The New James in a Nutshell**

- Total floors 21
- Square feet 1.1 million
- Beds
  - Acute care 276
  - Cancer critical care 30
  - Total** **306**
- ORs 14
- Interventional radiology suites 6
- Outpatient exam rooms 43
- Clinical trial stations 16
- Radiation oncology
  - Linacs 7
  - Imaging 3
  - Exam rooms 24
- Chemotherapy stations 40
- Blood and Marrow Transplant inpatient beds 36
- Oncology ED beds 15
- Translational research lab on each inpatient floor
- Retail pharmacy
- Patient resource center



**MICHAEL A. CALIGIURI, MD**

director of The Ohio State University Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute



*“We put a lot of thought into planning the new James... This integration of patients, researchers, clinicians, students and visitors is truly inspiring and we believe sets a model for 21st-century cancer care.”*

manufacturing standards (see page 30). Located on the hospital’s 14th floor, the unit features large windows that provide patient rooms and common areas with abundant natural light.

Steven Devine, MD, director of the Blood and Marrow Transplant Program, notes that these and other design elements can accelerate patient-recovery times and increase patients’ sense of well-being.

**Facilitating Clinical Care**

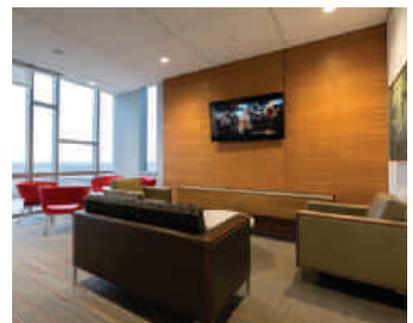
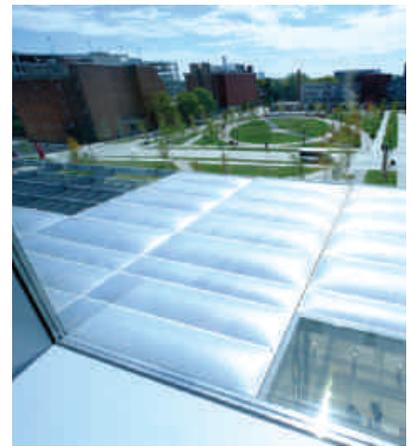
Enhancing that sense of well-being, a patient’s electronic medical records are available at the bedside. Known as MyChart Bedside, the bedside medical records result in faster documentation, fewer errors and seamless sharing by members of the medical team. Patients and family members can see names and photos of their doctors, primary nurse and other key care-team members, along with test results, and they can ask non-urgent

questions and schedule future appointments.

Each inpatient floor has a pharmacist who is part of the care team (oncology pharmacists also staff the first-floor cancer specialty pharmacy), and patient medications carry barcodes that clinicians wirelessly scan prior to dispensing at bedside, to ensure accuracy.

**Patient Rooms**

All inpatient rooms in the new hospital are private, spacious,

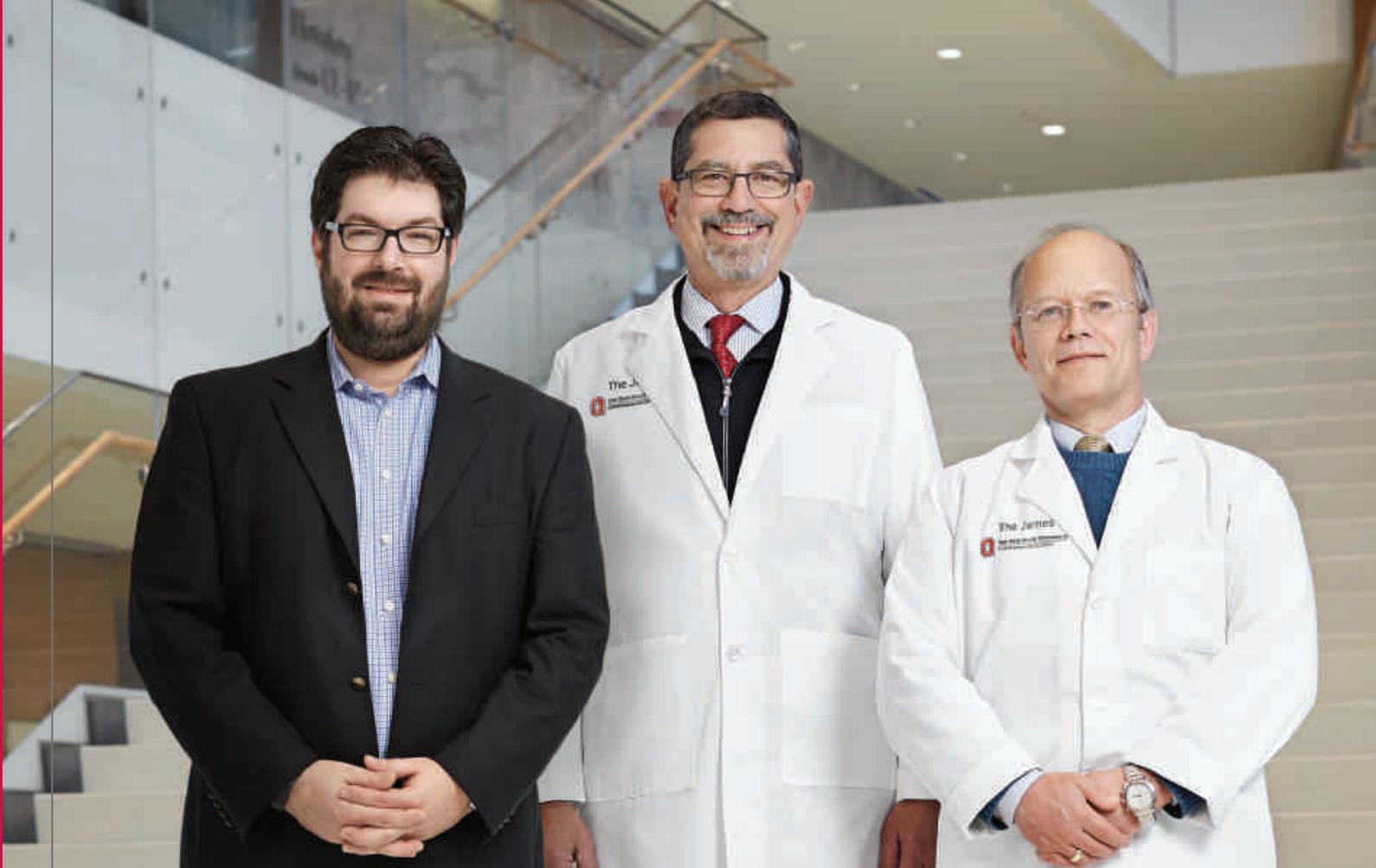


admit comforting natural light and have identical layouts to enhance patient safety. A fold-out bed allows overnight stays by loved ones, and the bathroom includes a full shower. Patients enjoy personalized nutrition through dining-on-demand service.

Added features on every floor include lounges, private consultation rooms, Wi-Fi, TVs, computer terminals and respite areas. Patients, visitors and staff can enjoy outdoor cafes and terrace gardens on the 14th floor, where plantings include vegetables that OSUCCC – James research has shown have cancer-preventive properties.

“We put a lot of thought into planning the new James,” Caligiuri says. “This integration of patients, researchers, clinicians, students and visitors is truly inspiring, and we believe it sets a model for 21st-century cancer care.” 





# Immune Boosters

*Research on immune therapy for cancer turned a corner a few years ago, activating the field and resulting in treatment strategies that show real promise*

**THOMAS MAGLIERY, PHD,**  
*associate professor of Chemistry and Biochemistry, and member of Ohio State's Drug Development Institute*

**DAVID P. CARBONE, MD, PHD,**  
*professor of Medical Oncology, and Barbara J. Bonner Chair in Lung Cancer Research at Ohio State*

**MIKHAIL DIKOV, PHD,**  
*associate professor of Medical Oncology at Ohio State*

BY DARRELL E. WARD

For more than 100 years doctors and researchers have poked, prodded and worked to coax the immune system into eliminating cancer. Then, in the last few years, scientists gained insights into the mechanisms of immune suppression. It was a breakthrough. It brought true clinical successes and energized the field. Today, immune therapy is one of the hottest areas of cancer research.

Clinically evident tumors must have avoided an effective immune response to have survived. But initial attempts to generate a therapeutic immune response to treat those tumors were not very successful because they attempted to induce immunity to cancer, says Mikhail Dikov, PhD, associate professor of Medical Oncology at Ohio State and member of the Translational Therapeutics Program at Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). “Then scientists discovered that, in addition to overactive mechanisms of immune induction, there are mechanisms that suppress the immune system in cancer patients.”

Therapies that reverse that suppression have been fruitful. “Patients with cancers that have been refractory to everything that's been tried, such as non-small-cell lung cancer, are responding to these agents, which is unheard of,” says Gregory Lesinski, PhD, MPH,

associate professor of Medical Oncology at Ohio State and a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program. “The field is expanding rapidly.”

These suppressive modulators include the programmed cell death protein 1 (PD1), a T-cell receptor that inactivates T cells. Another is CTLA4 (cytotoxic T-lymphocyte-associated protein 4), a receptor on T cells that downregulates the immune system.

“New classes of drugs have been developed that inhibit both PD1 and CTLA4,” says William Carson III, MD, professor of Surgery at Ohio State and associate director for clinical research at the OSUCCC – James. “The success of these agents has given immune therapy a tremendous boost.

“Simply by giving a drug that stops one negative pathway on T cells, we're seeing impressive shrinkage of tumors in melanoma and other cancers. The thinking is that those cases can also be treated with immune therapy,” Carson says.

A number of OSUCCC – James researchers are working to improve immune therapy for both solid tumors and hematologic malignancies. Some are investigating mechanisms of immune suppression and how to inhibit them. Others are developing peptide vaccines and inhibitors that generate anticancer antibody responses and induce immune memory to prevent recurrent

disease. One of the vaccines is in clinical testing.

## CANCER VERSUS THE IMMUNE SYSTEM

Studies by Lesinski and his lab focus on how cancer alters the immune system and how to reverse immune suppression. He collaborates with OSUCCC – James clinical researchers studying immune therapies in clinical trials, and he leads translational mechanistic studies that could lead to new treatments.

One long-standing interest is the STAT3 protein. It is almost always turned on in cancer cells, where it promotes survival and inhibits death by apoptosis, Lesinski says. They're learning it's also important for the generation of myeloid-derived suppressor cells (MDSCs), a class of immune cells that curtail immune responses in cancer patients.

“Our evidence suggests that STAT3 promotes both tumor-cell survival and the downregulation of anticancer immune responses we see in patients with advanced cancer,” Lesinski says.

“We're investigating whether inhibiting the STAT3 pathway might be a novel way to enhance immune therapy against cancer. We think that targeting STAT3 might have a dual effect, one on tumor cells and another that restores a degree of immune function that is lost with cancer.”



**GREGORY LESINSKI,  
PHD, MPH,**

*associate professor of  
Medical Oncology at  
Ohio State.*

with soy can lead to immunologic changes,” Lesinski says. “Now we’re addressing whether a simple dietary intervention might alter the immune response in a way that favors anticancer immunity.”

In 2014, the researchers published findings from a study of black raspberry extracts and metabolites. It showed that these compounds might downregulate suppressive immune cells, in part through targeting STAT3.

“They block the ability of proinflammatory cytokines to expand the population of immune suppressive cells that are upregulated in cancer,” Lesinski says. The findings suggest that black raspberries might be a source of compounds for drugs that influence immune function or inhibit STAT3 pathways.

**LUNG CANCER**

PD-1 is a receptor present on activated T cells and a potent mechanism of immune suppression. When tumor cells express one of PD-L’s two ligands—PD-L1 or PD-L2—tumor cells can shut down attacking T cells in the tumor microenvironment.

“Expression of PD-L1 on tumor cells is associated with poor prognosis in non-small-cell lung cancer and other tumor types,” says David P. Carbone, MD, PhD, professor of Medical Oncology and Barbara J. Bonner Chair in Lung Cancer Research at Ohio State. “But tumors expressing these ligands respond better to the new antibodies that target this pathway.”

Carbone chairs the steering committee for a 120-site,

global phase III trial for the drug nivolumab, an anti-PD-1 monoclonal antibody. The trial (NCT02041533) compares this immune therapy with chemotherapy as first-line treatment for lung cancer.

“Anti-PD1 therapy by itself is proving to be extremely important,” Carbone says. “For decades, the paradigm in metastatic lung cancer has been platinum-based chemotherapy first line, with experimental treatments later on.

“But anti-PD1 immunotherapy has generated so much excitement and evidence of clinical benefit that it’s now being tested as first-line therapy, as the sole therapy. This raises the possibility that some lung cancer patients may have durable remissions for metastatic disease that last a long time with minimal toxicity and without ever having had chemotherapy. This large randomized trial compares nivolumab alone head to head with platinum-based doublet chemotherapy for patients with newly diagnosed metastatic lung cancer.

“This is fantastic by itself,” Carbone says, “but it also tells us that immunotherapy can work. Now we need to look at the science and figure out all the other processes that are involved in suppressing the immune response to develop new therapies and new combinations that might be even more effective or work in more people.”

**NOTCH**

Carbone and collaborator Mikhail Dikov are also investigating

**PRAVIN  
KAUMAYA, PHD,**

*professor and  
director of the  
Division of Vaccine  
Development in Ohio  
State’s Department  
of Obstetrics and  
Gynecology*

STAT3 inhibitors are themselves immunotherapy because immune cells rely on the STAT3 pathway, he notes. “We think that those inhibitors may have an underappreciated effect on the immune system.”

Similarly, his lab is exploring other pathways that are targeted in cancer cells and also used by immune cells. “Some of these inhibitors might in reality work by acting on immune cells rather than on tumor cells. We’re exploring that in-depth for several inhibitors.”

**DIETARY IMMUNE  
MODULATORS**

Lesinski’s lab is also investigating dietary and natural products as a novel means to reverse immune suppression or to prevent inflammatory immune changes that can produce smoldering chronic inflammation and then cancer.

One line of an NCI-supported study (CA169363) examines whether dietary soy might change the immune-cell profile in patients with prostate cancer. “We’ve learned that isolated soy components and diets enriched

a mechanism of immune suppression very different from PD-1. It involves an interesting pathway called Notch.

Notch is key for the development and differentiation of T cells and other immune cells, and for immune responses. When certain ligands bind with Notch receptors on T cells, it activates the cells and induces differentiation and immune responses.

Carbone and Dikov have shown that Notch signaling through a molecule called DLL1 is reduced in bone-marrow immune precursor cells both in patients and tumor-bearing animal models.

“We believe that activating the Notch signaling pathway offers a novel strategy for overcoming cancer-induced immune suppression,” Dikov says.

That conclusion is based on the findings of a [2011 study](#) led by Carbone showing that tumor growth can inactivate the Notch pathway and turn off T cells. This immune suppression protects tumor cells from destruction by cytotoxic T cells.

The researchers found that Notch is inactivated by high levels of circulating vascular endothelial growth factor (VEGF). The high levels of VEGF inhibit the expression of two Notch ligands called DLL1 and DLL4 by endothelial and other cells into the bloodstream. Low levels of those ligands shut down the Notch pathway in “use it or lose it” fashion.

They also showed that boosting Notch signaling with a drug they developed in an animal model reversed the tumor-associated

T-cell changes and dramatically slowed tumor growth. “We believe that if we can develop a drug that works in humans to increase Notch signaling, it will have a similar effect in patients,” Carbone says.

Carbone and Dikov are working to develop this new drug for clinical use. “To be active, it will need to consist of a multivalent form of DLL1,” Carbone says. “The idea is to express multimers of the DLL1 binding domain for optimal signaling.”

The researchers are developing the complex agent in collaboration with Ohio State biochemist Thomas Magliery, PhD, associate professor of Chemistry and Biochemistry, and a member of Ohio State’s Drug Development Institute.

“This exciting partnership is taking our findings in an animal model and using them to develop an agent we hope to use in the clinic,” Carbone says.

Studies under way by Carbone and Dikov will provide a deeper understanding of Notch, DLL1 and other Notch ligands in antitumor immunity and will help evaluate their therapeutic and prognostic potential. The work is supported by an NCI grant, “Notch Ligands in Regulation of Anti-Cancer Immunity” ([CA175370](#)). The findings will contribute to the development of the therapeutic DLL1 agent and possible prognostic assays.

## ENHANCING ANTIBODY THERAPIES

The clinical and translational research of William Carson III, MD, focuses on strategies for inhibiting

immune suppressor cells, which act to restrain the immune system. He and his lab are investigating how myeloid-derived suppressor cells, or MDSCs, affect antibody therapy (NCI grant [CA095426](#)). “We want to inhibit the cells that are braking the immune system,” Carson says. “It’s like cutting the brake line—things should go a lot faster and the cancers should shrink more.”

“In many cancers, we can get a general idea of how well patients will do based on whether immune cells are infiltrating the tumor,” he adds. “That suggests that the immune system is working to eliminate these cancers, and that it’s involved in the response to treatments like radiation and chemotherapy. This idea is also supported by the effectiveness of anti-CTLA4 and anti-PD1 immune boosters.”

Carson has long had an interest in investigating the use of immune hormones to enhance the effectiveness of monoclonal-antibody-based drugs.

He is principal investigator on a phase I/II trial ([NCT01468896](#)) that combines the antibody-based drug cetuximab with an immune hormone called interleukin-12 (IL-12) in patients with head and neck cancer. The drug binds to EGFR receptors on the surface of malignant tumor cells. Patients are then given an injection of IL-12. “Our thought is that immune cells like natural killer (NK) cells will attack the antibody-coated cancer cells, and that interleukin-12 will provide an extra boost to the NK cells and help them kill tumor cells more effectively,” Carson says. “It

## CAR T CELLS SHOW PRECLINICAL PROMISE AS MULTIPLE MYELOMA THERAPY



**CRAIG HOFMEISTER, MD, MPH**, assistant professor of medicine and a member of the OSUCCC – James Leukemia Research Program

A recent study by OSUCCC – James researchers provided evidence that genetically modified immune cells might effectively treat multiple myeloma, a disease that remains incurable and accounted for an estimated 24,000 new cases and 11,100 deaths in 2014.

The researchers modified T lymphocytes, or T cells, to target a molecule called CS1, which is found on more than 95 percent of myeloma cells. The modified cells—technically called chimeric antigen receptor (CAR) T cells—were able to identify myeloma cells and kill them.

The researchers grew the modified T cells in the lab to increase their numbers and then injected them into an animal model where they again killed human myeloma cells.

The findings were published in the journal *Clinical Cancer Research*.

“Despite current drugs and use of bone marrow transplantation, multiple myeloma remains incurable, and almost all patients eventually relapse,” says co-principal investigator and multiple myeloma specialist Craig Hofmeister, MD, MPH, assistant professor of medicine and a member of the OSUCCC – James Leukemia Research Program.

“This study presents a novel strategy for treating multiple myeloma, and we hope to bring it to patients as part of a phase I clinical trial as soon as possible,” Hofmeister says.

“In particular, our study shows that we can modify T lymphocytes to target CS1, and that these cells efficiently destroy human multiple myeloma cells,” says principal investigator Jianhua Yu, PhD, assistant professor of medicine and a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program.

“An important possible advantage to this approach is that these therapeutic T cells have the potential to replicate in the body. Therefore, they might suppress tumor growth and prevent relapse for a prolonged period,” Yu says.

Yu, Hofmeister and their colleagues used cell lines and fresh myeloma cells from patients to produce genetically engineered T cells with a receptor that targets CS1. The researchers then tested the capacity of the modified cells to kill human multiple myeloma cells in laboratory studies and an animal model.

*Funding from the National Institutes of Health (CA155521, OD018403), Multiple Myeloma Opportunities for Research and Education, the National Blood Foundation, and an OSUCCC – James Pelotonia Idea Grant supported this research.*



**JIANHUA YU, PHD**, assistant professor of medicine and a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program

works in the test tube, it works in mice, and now we will learn if it works in humans.” (For more about this clinical trial, see page 29.)

A previous phase I trial conducted by Carson evaluated the combination of IL-12 and trastuzumab (Herceptin) in patients with breast and gastrointestinal cancers. The study accrued 21 patients with metastatic HER2-positive tumors. The findings, published in the journal *Molecular Cancer Therapy*, showed that IL-12 in combination with trastuzumab and paclitaxel is safe and has activity in patients with HER2-overexpressing cancers.

## ANTICANCER PEPTIDE VACCINES

OSUCCC – James researcher Pravin Kaumaya, PhD, professor and director of the Division of Vaccine Development in Ohio State’s Department of Obstetrics and Gynecology, is leading the development of five anticancer peptide vaccines and related peptide inhibitors.

The vaccines and inhibitors target EGFR, HER-2, HER-3, VEGF and IGF-1R receptors. The molecules play key roles in cancer-cell growth, proliferation and survival, and they are often overexpressed in breast cancer, including triple-negative breast cancer, and in pancreatic, esophageal and colon cancers. HER-2 overexpression, for example, occurs in 15-25 percent of breast cancers and is associated with aggressive tumor behavior. Kaumaya’s peptide vaccines are designed to provoke an antibody response to the target molecules on tumor cells and to generate memory

that will enable the immune system to respond quickly should the cancer recur.

The peptide inhibitors target the same set of cell-surface receptors. They bind with and inactivate the target molecule, leading to programmed cell death, or apoptosis.

The agents have completed preclinical testing; the HER-2 vaccine is in phase I testing (NCT01376505) in patients with metastatic solid tumors.

“Innovative immune-based therapies that target these receptors are particularly important,” Kaumaya says, “because they might offer long-term control in several tumor types without the toxicities associated with current FDA-approved regimens.

“HER-2-positive patients are treated with humanized monoclonal antibodies such as trastuzumab,” he adds, “but they often develop resistance within a year, rendering the drug ineffective. Prolonged treatment can also lead to serious side effects, and the drugs are very expensive.”

A standard one-year course of treatment with trastuzumab, for example, can cost \$70,000, he notes.

“We believe our new peptide immune-based therapies and strategies will overcome these problems,” he says, noting that the many advantages of peptides over monoclonal antibodies include lower cost, high specificity and potency, ability to penetrate the cell membrane, low immunogenicity and greater overall safety.

Furthermore, preclinical studies conducted by Kaumaya and his collaborators suggest that

combining two peptide vaccines, two inhibitors, one of each or combined with chemotherapy might further improve the agents’ effectiveness.

“We believe that strategies that selectively target both IGF-1R and HER-3 hold great promise for overcoming mechanisms of resistance to HER-1- and HER-2-targeted agents and facilitating tumor regression in a range of tumor types,” Kaumaya says.

“More broadly, we believe our novel immune-stimulatory strategies using peptide vaccines and inhibitors hold the promise of durable clinical benefit for high-risk, recurrent, refractory and metastatic cancers,” he adds.

## HEMATOLOGIC CANCERS

Immune therapy is a long-term focus of the OSUCCC – James Leukemia Research Program. “Our goal is to develop immune therapies for hematologic malignancies as one component of a move away from chemotherapy altogether,” says Jeffrey Jones, MD, MPH, section head for CLL/Hairy Cell Leukemia.

It’s an attainable target made possible, he says, by recent advances in technology that enable new treatment strategies. He notes three approaches to immune therapy for hematologic malignancies:

- Monoclonal-antibodies and other agents that stimulate both the adaptive and innate immune response;
- Monoclonal antibodies tagged with a toxin or a radioactive isotope that kills targeted cells;
- Engineered T cells, or chimeric antigen receptor (CAR) T cells.

Early examples of the first



**JEFFREY JONES, MD,**  
*section head for CLL/Hairy Cell Leukemia*

**WILLIAM CARSON III, MD,**  
*professor of Surgery and associate director for clinical research at the OSUCCC – James*

strategy included native immune stimulants like IL-2 and INF-alpha. But the most notable successes have been the drug [rituximab](#), a monoclonal antibody that targets CD20 on B cells first approved for clinical use in 1997, and next generation “engineered” CD20-targeted antibodies like obinutuzumab. Binding of the antibody on cancer cells attracts natural killer (NK) cells and other innate immune system elements that kill the cells through antibody-dependent cell-mediated cytotoxicity ([ADCC](#)) and the [complement](#) system.

Ongoing studies at the OSUCCC – James are now exploring antibodies directed at new targets, such as B-cell markers CD19 and CD37, as well as checkpoint inhibitors like nivolumab and pembrolizumab recently approved for solid tumor indications but with preliminary data suggesting efficacy in blood cancers, too.

According to Jones, “Combinations of antibodies targeting different markers on the cancer cell surface may better rally the patient’s own immune system to engage their cancer.” Also promising is the potential for combining monoclonal antibody therapy with targeted agents, like the recently approved kinase inhibitors ibrutinib and idelalisib. Jones says the OSUCCC – James Leukemia Research Program will lead several such studies for CLL expected to open later in 2015.

## IMMUNOCONJUGATES

The second approach uses immunoconjugates, antibodies

linked to a toxic agent. Two clinical trials under way at the OSUCCC – James are good examples. Kami Maddox, MD, an OSUCCC – James B-cell malignancy specialist, leads a phase I trial ([NCT01534715](#)) evaluating the immunoconjugate IMGN529 in patients with relapsed or refractory non-Hodgkin’s lymphoma. The toxin, once released into target cells, blocks mitosis and the cells die by apoptosis.

Jones is the local principal investigator on the second trial. The phase III study ([NCT01829711](#)) for patients with relapsed or refractory hairy cell leukemia evaluates an anti-CD22 antibody linked to a pseudomonas toxin. CD22 is a molecule present on essentially all hairy cell leukemia cells, Jones says. The trial evaluates the effectiveness of [moxetumomab pasudotox](#) in killing hairy cell leukemia cells and in producing lasting complete remissions.

## CAR T CELLS

CAR T cells are T cells that are genetically altered to generate a disease-specific immune response. “Success with this novel technology is one of the most exciting developments in hematologic malignancies during the last 10 years,” Jones says. “It tricks the patient’s own T cells to zero in on a new target.”

It is a form of adaptive immune therapy, he notes. This strategy begins by isolating T cells from a patient’s blood, manipulating them genetically to target the patient’s cancer subtype, then infusing the cells back into the patient, where they expand and wage an immune response against leukemia cells.

“Ohio State is one of the designated sites for a multicenter trial that will use CAR T cells to treat acute lymphoblastic leukemia,” Jones says.

“The next step is to combine these new immune therapies with targeted inhibitors,” he adds. “That’s the direction the field is going. Cancer immunotherapy is a very fertile area of investigation.”

Immune therapy today includes not only the cytokines that were used in the 1980s and ‘90s, but also the monoclonal antibodies developed in the 2000s, Carson says. “We also have the newer immune boosters such as anti-PD1 and anti-CTLA4, along with promising cancer vaccines and CAR T cells from the 2010s. We have trickier ways to stimulate the immune system than giving high levels of immune hormones.”

And there’s more to come, Carson says. “We have new technologies, new ideas, new targets and a renewed realization that the immune system is a powerful tool we must incorporate as new treatment options for cancer patients. Cancer immune therapy is an exciting field full of possibilities.” **F**

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

# BENCH TO BEDSIDE

*From the Laboratory to the Pharmacy*

## *A Phase I/II Trial of Cetuximab in Combination with Interleukin-12 Administered to Patients with Unresectable Primary or Recurrent Squamous Cell Carcinoma of the Head and Neck*

**HYPOTHESIS:** More than 90 percent of squamous cell carcinomas (SCC) that originate in the oropharynx overexpress the epidermal growth factor receptor (EGFR, or HER1). Cetuximab is an anti-HER1 monoclonal antibody that binds to HER1-overexpressing tumor cells and has activity as a single agent when administered to patients with HER1-positive SCC of the oropharynx. We hypothesize that IL-12 administration will enhance the antitumor activity of cetuximab by activating innate immune cells that recognize antibody-coated tumor cells.

**RATIONALE:** This novel protocol exploits the fact that innate immune cells bear specialized receptors for the Fc region on monoclonal antibodies. Evidence suggests that Fc-receptor-dependent mechanisms contribute substantially to the activity of monoclonal antibodies directed against tumor antigens, and that co-administration of immune stimulatory cytokines might enhance their effects. This is particularly true for natural killer (NK) cells.

Once activated, NK cells release cytokines that have antitumor activity and help coordinate innate and specific immune responses. They also release factors that recruit

macrophages and T cells to sites of inflammation.

NK cells express an Fc receptor called FcγRIIIa, which enables them to interact with antibody-coated tumor cells and to mediate antibody-dependent cellular cytotoxicity (ADCC) and the secretion of IFN-γ and TNF-α. The presence of IL-12 markedly enhances this antitumor activity. This protocol evaluates whether administration of IL-12 will enhance the antitumor activity of cetuximab in patients with inoperable HER1-overexpressing SCCs of the head and neck.

• The phase I portion of the study will identify a tolerable dose of IL-12 plus cetuximab;

• The phase II study will determine the response rate to the two agents.

• Additional correlative studies will provide information on the antitumor mechanism of IL-12 and establish biomarkers for predicting patient responsiveness.

Along with characterizing the immunologic effects of IL-12 in combination with cetuximab, this study will provide a better understanding of the NK-cell response to antibody-coated tumor cells and of how to improve the regimen's effectiveness. The information gained from this study should also apply to other monoclonal antibodies currently in use or under development.

### AT A GLANCE

Trial no.: ClinicalTrials.gov identifier: **NCT01468896**

PI: **WILLIAM E. CARSON III, MD**

Phone: 614-293-6306

Email: [william.carson@osumc.edu](mailto:william.carson@osumc.edu)

Eligibility: age 18 or older, histologically proven recurrent or metastatic squamous cell carcinoma of the head and neck that is unresectable (patients in the phase II portion of the trial must have measurable disease), ECOG performance status less than 2 (Karnofsky greater than 60%), life expectancy greater than 6 months, normal organ and marrow function, ability to understand and willingness to sign a written informed consent document.



# NEED TO KNOW

At the OSUCCC—James

## W.W. Williams Company Cell Therapy Laboratory



**LYNN O'DONNELL, PHD,**  
*associate professor of Hematology  
and CTL Director*

The new James Cancer Hospital and Solove Research Institute includes a ramped-up Cell Therapy Laboratory (CTL) that can produce clinical-grade living cells for use in immune therapy research.

The lab follows Good Manufacturing Practices (GMP), which are required for the production of pharmaceutical and biologic agents.

“The new lab expands our capabilities from the traditional preparation of cells for bone marrow and stem cell transplant to

the production of therapeutic cell products for use in immune therapy trials,” says CTL Director Lynn O’Donnell, PhD, associate professor of Hematology.

“The CTL will allow OSUCCC – James investigators for the first time to conduct phase I and phase II clinical trials to evaluate cellular immune therapies that are based on their own preclinical research.”

The 2,500-sq.-ft. facility, located on the hospital’s first floor, has two clean rooms and a highly trained, expert staff.

“Our researchers will drive the types of cells we handle,” O’Donnell says. “If they are studying a cell type that has therapeutic benefit, we will learn how to produce that cell type.”

O’Donnell expects the Cell Therapy Lab to produce cells for two clinical trials during its first year of operation and to open another three or four studies during its second year.

“Patience is essential for these studies,” she says. “A significant amount of work is required to scale up from animal studies to human studies.”

It typically takes one to two years to work through the optimization and scale-up phases of a project.

### HIGHLIGHTS OF THE CELL THERAPY LABORATORY

- The two ISO Class 7 clean rooms are equipped for investigational cell-therapy products, which require a high level of air quality, extensive staff gowning and additional process controls.
- The lab includes a separate quality control room for testing cell therapy products, as required by the FDA.
- It is equipped with cell-selection devices, automated processors, a bioreactor, an eight-parameter flow cytometer, and cryopreservation and storage equipment.
- The lab maintains extensive cleaning and sanitization, environmental monitoring, batch production, materials management and process-validation records.

# Historic Weekend Move Completed Safely, Smoothly

## *New James Open for Business*

The new James Cancer Hospital and Solove Research Institute officially opened its doors as planned on Monday, Dec. 15. The monumental task of transporting 182 acute-care cancer patients from the original 12-story, 228-bed James hospital to the new 21-story, 306-bed facility took place one day earlier.

Some 500 volunteers—faculty and staff, family members and friends of The James—helped with the move. It began at 8:30 a.m. and finished just over nine hours later, ending ahead of schedule and without mishap.

Two days earlier, 39 critical-care patients were moved into the new facility, for a total of 221 patients moved that weekend.

“I want to express gratitude to all of you for your hours of hard work, patience and cooperation in making this world-class hospital a reality,” OSUCCC Director and James CEO Michael A. Caligiuri, MD, told the gathering of volunteers.

“All of us have worked so hard to get to where we are today,” Caligiuri said. “Today is all about our patients. As you assist with this move, think of wheeling them not just into a new hospital but across the threshold to a cancer-free world.”

Toward the end of the Sunday move, nurses and staff in the Acute Leukemia Unit of the original James paused and held a brief ceremony to reflect on their experiences and all they had learned in the former location.

The next day, the new James began its first week of operation. The hospital’s advanced operating rooms, ambulatory clinic spaces, infusion center, imaging suites and radiation oncology center all came on line with no significant problems.



*“Today is all about our patients. As you assist with this move, think of wheeling them not just into a new hospital but across the threshold to a cancer-free world.”*

*—Michael A. Caligiuri, MD*



## **PELTONIA 14 RAISES \$21.5 MILLION, BOOSTS 6-YEAR TOTAL TO \$82.3 MILLION**

Riders, virtual riders and donors in Pelotonia 14, the 14th annual grassroots bicycle tour that generates money for cancer research at Ohio State, raised a record \$21,049,621, surpassing the Pelotonia 13 total of \$19,007,104 and boosting the six-year total for this event to \$82,343,670.

Thanks to Pelotonia's generous sponsors—including L Brands Foundation, Huntington, and Richard and Peggy Santulli—every cent raised by riders, virtual riders and donors supports cancer research at the OSUCCC – James.

The money supports projects that address cancer diagnosis, treatment, psychosocial issues and prevention. Pelotonia funds support a fellowship program for student researchers working in the labs of faculty mentors, "idea" grants for teams of faculty researchers, sophisticated equipment to aid researchers in their work and recruitment/retention of top cancer researchers.

Pelotonia 14 took place Aug. 8-10 on picturesque routes between Columbus and Kenyon College in Gambier, Ohio. The event attracted a record 7,270 riders from 41 states and 10 countries, along with 3,700 virtual riders and more than 2,600 volunteers.

The tour consisted of 276 registered pelotons (riding groups), including 2,362 members of Team Buckeye, the official superpeloton of The Ohio State University. Team



Buckeye consisted of 1,428 riders in 100 pelotons, as well as 732 virtual riders and 202 volunteers. The collective Team Buckeye fundraising total was \$2,727,856.66.

In September, global cancer advocate Doug Ulman was appointed Pelotonia's president and CEO. Ulman, 37, is a three-time cancer survivor and the former president and CEO of the LiveSTRONG Foundation, where he spent 14 years growing the start-up non-profit into an iconic global cancer-survivorship organization. Ulman replaces Tom Lennox, who resigned in January 2014.

In addition to his role as president and CEO of Pelotonia, Ulman works on behalf of the OSUCCC – James to build awareness and support for its work in cancer research, education and prevention.

Pelotonia 15 is scheduled for Aug. 7-9. To register, visit [www.pelotonia.org](http://www.pelotonia.org).

### **UPCOMING EVENTS**

#### **PELTONIA 15**

**August 7-9**

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

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