AUTUMN | 10

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

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

Exploring the depths of the genome

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UPFRONT

The Director's Perspective

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

Summer of Progress

Construction begins, the CARE Act is introduced, The James turns 20

This has been an extraordinary summer at The Ohio State University. In June, we broke ground for construction of a 17-story patient tower that will house a new and much larger James Cancer Hospital and Solove Research Institute. It will be the centerpiece of Ohio State's $1 billion ProjectONE medical center expansion. (For more on the groundbreaking, see page 31.)

In July, we helped introduce a piece of landmark federal legislation, the Cancer Centers Assistance for Renovations and Expansion Act of 2010, or CARE Act (HR 5861). The act will provide low-interest loans to fund the expansion of cancer centers and comprehensive cancer centers, as designated by the National Cancer Institute (NCI). These loans will pay the capital costs of projects that improve a center's research, prevention or patient-care infrastructure.

Given the present economic climate, this bill will help centers obtain the resources they need to further cancer research and accommodate the rising number of cancer patients in our aging population.

Our thanks to the bill's sponsor, Rep. Mary Jo Kilroy (OH-15), and its co-sponsors, Reps. Tim Ryan (OH-17), Michael E. Capuano (MA-8), Carolyn Maloney (NY-14) and Kendrick Meek (FL-17).

Also in July, our faculty and staff celebrated the 20-year anniversary of the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. We came together to reflect on our two decades of effort to provide exceptional cancer care at The James, and we looked to the future and to meeting the challenge of creating a cancer-free world.

Finally, we send our best to Dr. John Niederhuber, who in July stepped down as NCI director after guiding the agency through several difficult budget years while keeping cancer research moving forward. And we welcome Dr. Harold Varmus in his new role as the NCI's 14th director.

**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
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Distinguished University Professor
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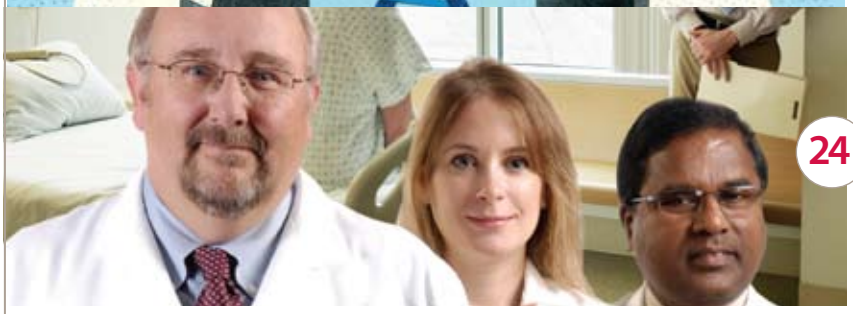

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ON THE COVER: OSUCCC-James researchers (clockwise from lower left) Carlo M. Croce, Jeff Palatini, Hansjuerg Alder and Pearlly Yan.

Accrual BOOSTING

The OSUCCC-James designed a culture-changing program to raise clinical trial participation rates

By **WILLIAM E. CARSON III, MD,**
Associate Director for Clinical Research, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

In 2007, we at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) conducted a comprehensive review of patient participation in therapeutic clinical trials and discovered that our accrual rate had flatlined at about 14 percent per year.

While that rate was significantly higher than the 2-3 percent of adult cancer patients nationally who participate in treatment trials, we wanted to do far better. Clinical trials, after all, are the source of new treatments for our patients, giving them access to the most advanced therapies and the highest standards of care.

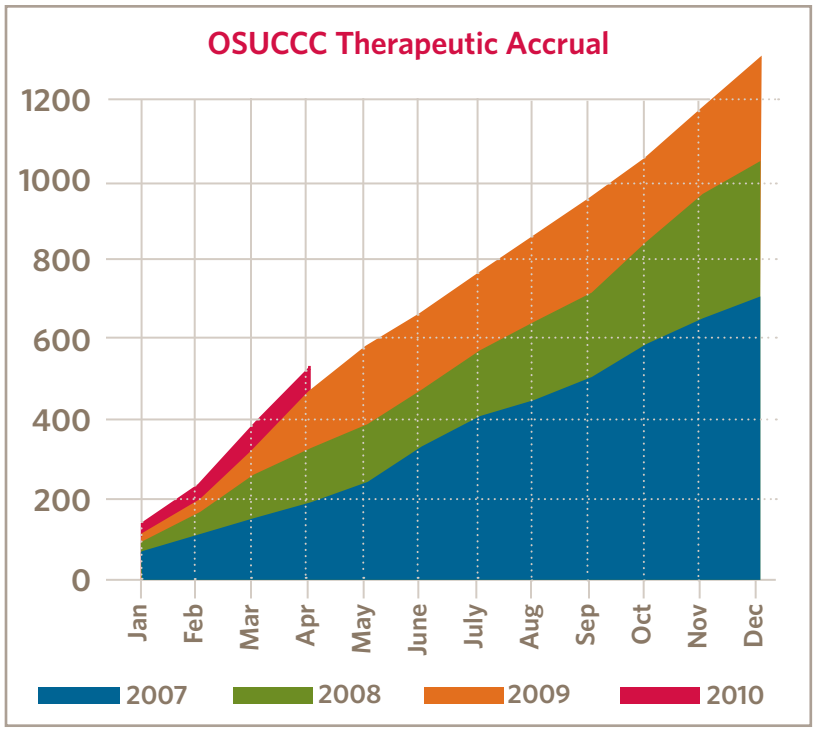
Every agent regarded as the standard of care today was first tested in a clinical trial at some point. High trial-participation rates are associated with many of our greatest achievements in cancer care. Cancers in which we've had the most success, such as childhood cancers and testicular cancer, have high rates of clinical trial participation.

The Ohio State University is an NCI-designated Comprehensive Cancer Center, and clinical trials are where our clinical mission and our research mission intersect, where advances in the laboratory are first applied to patient care. They are not something separate that we do; they are why we are here. We should regard all patients as potential trial participants, and we should provide all patients with an opportunity to participate.

To convey these messages to our physicians and staff, to referring physicians and to our patients and their families, we designed a multipronged campaign titled "2010 by 2010," and launched it in late 2007. Our goal was to accrue 2,010 patients to therapeutic clinical trials by the year 2010, which would represent a 40-percent increase over 2007 accrual levels.

First, Michael A. Caligiuri, MD, director of the OSUCCC and CEO of The James, along with James Thomas, MD, director of our Clinical Trials Office, and I took the campaign to all hospital leaders, division chiefs and staff councils to explain our campaign strategy.

We used several mechanisms to educate patients and families about clinical trials. An updated clinical-trials brochure was placed in new-patient mail packets and made available in clinic waiting areas. Attractive posters with testimonials by clinical-trial participants were displayed near clinic areas, a clinical-trials video ran in a kiosk in The James lobby and in patient rooms, and hospital physicians and staff wore a colorful button that read, "Ask Your Doctor About Clinical Trials."



We reached out to nursing staff by providing information about clinical trials during new-employee orientation, and OSUCCC leadership held a series of informal educational sessions with nursing units and physician groups. Nurses began encouraging patients to ask their doctors about clinical trials at The James.

We reinvigorated faculty by reminding them of the importance of clinical trials through presentations at faculty meetings, during orientation for new physicians, and in one-on-one meetings, and we dedicated a session of the OSUCCC Grand Rounds to the topic. We provided support to top accruers and trial coordinators, and we offered help with protocol development to those who needed it.

Referring physicians received targeted, disease-specific, monthly e-mail updates about our clinical trial activity, and new clinical trials were featured in OSUCCC-James publications.

We reorganized our Clinical Trials Office into disease teams and adopted a management system that enabled us to monitor accrual rates and conduct trials more efficiently. Trial development and implementation was organized along disease-specific lines. The hospital's 10 disease-specific committees were charged with conducting a real-time analysis of accrual progress, regularly evaluating their clinical trials portfolio and examining their protocol activation timelines.

These changes enabled us to open trials faster and accrue patients more efficiently. OSUCCC members were updated on the progress of the campaign through monthly e-mail announcements that provided detailed accrual information.

At the state level, we wrote the Ohio Cancer Clinical Trial Legislation, which requires insurance companies to cover the routine costs of care associated with clinical trials such as physician visits, blood work, hospital stays and X-rays.

The campaign was highly successful. We achieved our goal of accruing 2,010 therapeutic patients in late August 2009, four months ahead of schedule. Furthermore, we surpassed our goal by 695 patients, or 35 percent.

Currently, 27 percent of patients coming to The James for therapy are entering clinical trials. Beyond that, we want to increase our rate to 40 percent and establish a program-wide mindset that regards every patient as a potential participant in a clinical trial.

Our experience shows that a comprehensive campaign to increase accrual to therapeutic trials by educating key stake holders in the clinical trials process can be successful. For more information on our program, please send an e-mail with your questions to **frontiers@osumc.edu.**

BRAIN CANCER

'GROW OR GO' SWITCH

Researchers discover brain tumor mechanism

Researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC-James) have discovered a mechanism that regulates the behavior of glioblastoma multiforme cells.

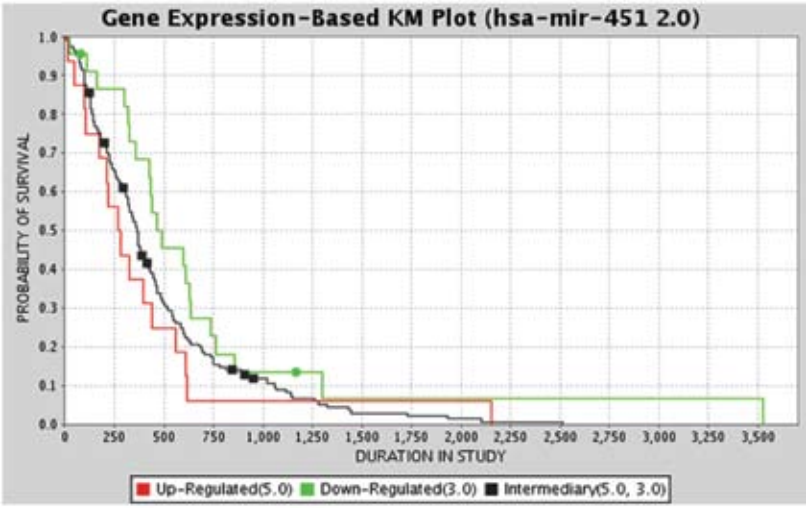
Cancer cells in rapidly growing brain tumors must adapt to periods of energy fluctuation. When glucose levels are high, tumor cells grow and proliferate; when levels are low, the cells grow less and migrate more.

Researchers discovered that the microRNA miR-451 coordinates this "grow-or-go" behavior.

"We found that glioblastoma cells use miR451 to sense glucose availability," says co-author **E. ANTONIO CHIOCCA, MD, PhD,** professor and chair of Neurological Surgery, and co-leader of the OSUCCC-James Viral Oncology Program. "Levels of miR451 directly shut down the engine of the tumor cell if there is no glucose, or rev it up if glucose is plentiful. This suggests that this molecule might be a useful biomarker to predict a glioblastoma patient's prognosis. It also might be used as a target to develop drugs to fight these tumors."

"The change in miR-451 expression enabled the cells to survive periods of stress caused by low glucose, and it caused them to move, perhaps enabling them to find a better glucose supply," says principal investigator **SEAN LAWLER, PhD,** assistant professor of Neurological Surgery. "The migration of cancer cells from the primary tumor, either as single cells or chains of cells, into the surrounding brain is a problem with these tumors. By targeting miR-451, we might limit the tumor's spread and extend a patient's life."

Published in the journal Molecular Cell.



Kaplan-Meier plot showing that high miR-451 expression is associated with poorer survival in patients with glioblastoma multiforme. The plot was generated using data obtained from The Cancer Genome Atlas. (p = 0.036) Reprinted from Molecular Cell, *37:620, Godlewski J., Nowicki M.O., Bronisz A., et al. MicroRNA-451 Regulates LKB1/ AMPK Signaling and Allows Adaptation to Metabolic Stress in Glioma Cells.*

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THE RESEARCHERS

E. ANTONIO CHIOCCA, MD, PhD,
professor and chair of Neurological Surgery, Dardinger Family Endowed Chair in Oncological Neurosurgery, and co-leader of the OSUCCC-James Viral Oncology Program.

SEAN LAWLER, PhD,
assistant professor of Neurological Surgery

LEUKEMIA

VICIOUS CIRCLE

Molecular network may be therapeutic target for AML

Researchers at the OSUCCC-James have identified a self-feeding "vicious circle" of molecules that keeps acute leukemia cells alive and growing. Their findings suggest a new strategy for treating acute myeloid leukemia (AML) by targeting this molecular network and lowering the amount of a protein called KIT.

The study describes a network of protein and microRNA molecules that, when imbalanced, contributes to increased KIT expression and favors leukemia development. The researchers also were able to target this network with therapeutic drugs.

"We now understand the mechanism responsible for high KIT expression in AML cells, and we believe that targeting that mechanism and reducing KIT levels will prove a more effective therapy than the current standard of care," says study leader **GUIDO MARCUCCI, MD.**

More than 80 percent of AML cases show elevated KIT expression. Doctors treat AML with standard chemotherapy, but drugs that target and block KIT activity are being tested in clinical trials. These agents, tyrosine kinase inhibitors, bind to the protein and stop disease progression, but they can lose their effectiveness when new mutations that arise from the disease alter the protein.

"Our study suggests that the amount of KIT protein in cancer cells is as important as its activity, and we discovered that the amount of the protein is controlled by a circular network of molecules that has many points of entry," says senior co-leader **RAMIRO GARZON, MD.** "These findings provide a strong rationale for developing drugs that target the components of this network rather than focusing on the activity of KIT alone."

Published in the journal Cancer Cell.

THE RESEARCHERS

GUIDO MARCUCCI, MD,
AML specialist and professor of Internal Medicine

RAMIRO GARZON, MD,
AML specialist and assistant professor of Internal Medicine

HEAD AND NECK CANCER

PAPILLOMA PREDICTOR

HPV in oropharyngeal tumors signifies increased survival

THE RESEARCHER

MAURA GILLISON, MD, PhD,
professor of Internal Medicine, Jeg Coughlin Chair in Cancer Research, and her research team

The presence of human papilloma virus (HPV) in oropharyngeal tumors is the most important predictor of patient survival, according to a study at the OSUCCC-James.

This is the first study large enough to show that HPV in tumors accounts for better response to therapy, rather than other favorable factors that may be present, such as young age and small tumors. The second-leading predictor of survival is lifetime smoking history, followed by cancer stage.

The findings suggest that the HPV status and patients' smoking history may be used, in addition to cancer stage, to determine the aggressiveness of therapy.

"Previous studies indicated a relationship existed between the presence or absence of HPV in oropharyngeal tumors and patient survival, but they couldn't determine if other favorable factors present in these patients were responsible for their better outcome," says study leader **MAURA GILLISON, MD, PhD,** medical oncologist and head and neck cancer specialist. "These findings close the door on these questions and will allow the field to move forward with clinical trials to determine how we should use molecular and behavioral factors to personalize therapy."

Gillison says there is insufficient data at this time to indicate how a patient's therapy should be tailored based on these factors.

The research analyzed the tumors and outcomes of 323 patients with stage III or IV oropharyngeal cancer who were part of a Radiation Therapy Oncology Group clinical trial. Of these, 206 had HPV+ tumors and 117 had HPV- tumors. Three years after treatment, 82 percent of those with HPV+ tumors were alive, compared with 57 percent of those with HPV- tumors.

Published in the New England Journal of Medicine.

LEUKEMIA

UP FOR THE CHALLENGE

Stimuli of enriched environment may curb cancer

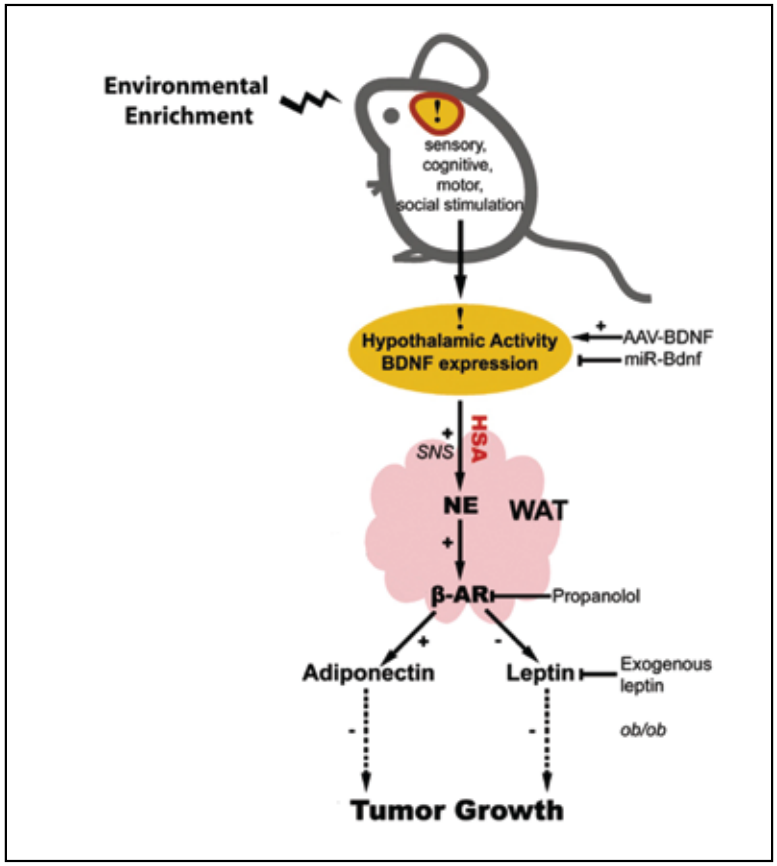
An animal study led by researchers at the OSUCCC-James shows that living in an environment rich with physical, mental and social stimulation – a setting that causes mild stress – may curb cancer growth.

The researchers discovered that an enriched environment activates the hypothalamic-sympathoneural-adipocyte (HSA) axis, a nervous-system pathway that instructs fat cells to stop releasing leptin into the bloodstream. Overall, the study suggests that environmental or genetic activation of the HSA pathway leads to a marked drop in serum leptin levels, and that this inhibits tumor growth.

"People think cancer survivors should avoid stress, but our data suggest this is not completely true," says study leader **MATTHEW DURING, MD, PhD,** professor of Neuroscience, of Neurological Surgery and of Molecular Virology, Immunology and Medical Genetics. "The anticancer effect we observed was not due simply to increased activity, but to social and physical challenges that cause mild stress."

The most dramatic hormonal change observed was the drop in leptin from fat after enhanced housing conditions activated the HSA pathway. The HSA pathway is also present in humans and is likely to be activated by a complex and challenging lifestyle, During notes.

The enriched environment created for this study housed 20 mice in large containers equipped with toys, hiding places and running wheels, along with unlimited food and water. Control mice were housed in groups of five in smaller laboratory containers with unlimited food and water.



An enriched environment inhibits cancer growth in mice. Enrichment stimulates the hypothalamus to produce brain-derived neurotrophic factor (BDNF), which activates the HSA axis. This sympathetic nervous system pathway shuts down leptin production in white adipose tissue (WAT), suppressing cancer growth. Reprinted from Cell, *142:62. Cao L., Liu X., Lin E.-J. D., et al. Environmental and Genetic Activation of a Brain-Adipocyte BDNF/Leptin Axis Causes Cancer Remission and Inhibition.*

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The researchers injected human melanoma cells under the skin in both sets of animals. After three weeks, mice in enriched housing had tumors about half the size of those in control mice. After six weeks of enrichment, those tumors had dropped to one fifth the size of those in control animals, and almost 20 percent of enriched-group mice had no visible tumors. All control animals had visible tumors.

Published as the lead cover story in the journal Cell.

BREAST CANCER

INVALUABLE INTERVENTION

Program helps breast cancer patients long after recurrence

A psychological intervention program for breast cancer patients can reduce the risk of dying if the cancer recurs, new research shows.

The study is the latest in a series at the OSUCCC-James showing that an intervention that teaches patients how to cope with the disease can boost their health, well-being and chances of survival.

In an earlier study, the researchers found that the intervention reduced the risk of dying of breast cancer by 56 percent after a mean of 11 years, and it reduces the risk of recurrence by 45 percent compared with women not receiving the intervention.

The new study shows that women who had a recurrence also benefited from the program. Women with recurrent cancer who received the intervention had a 59-percent reduction in the risk of dying from breast cancer compared with the women who didn't participate.

"Women who took part in the intervention program do better across the board than others, even if they have a recurrence," says lead author **BARBARA ANDERSEN, PhD,** professor of Obstetrics and Gynecology, of Psychology and of Public Health. "They learned how to cope with a cancer diagnosis when they were first diagnosed, and those lessons likely helped them deal with recurrence."

The study is part of the Stress and Immunity Breast Cancer Project at Ohio State, which since 1995 has followed 227 patients treated for stage II or III breast cancer.

Published in the journal Clinical Cancer Research.

BARBARA ANDERSEN, PhD,
professor of Obstetrics and Gynecology, of Psychology and of Public Health

HUMAN CANCER GENETICS

REWIRE ACT

Cancer cells show rewired, fragmented microRNA networks

A multicenter study led by scientists at the OSUCCC-James shows that microRNA (miRNA) molecules work together in single, well-connected networks to control functions in healthy cells, but in cancer cells the networks are rewired and fragmented.

The research introduces a way of discovering cancer genes, identifies new miRNAs that can be used as targets for drug development, and pinpoints possible cancer-related proteins, says study lead **CARLO CROCE, MD,** professor of Molecular Virology, Immunology and Medical Genetics, and John W. Wolfe Chair in Human Cancer Genetics.

MiRNAs are noncoding RNAs that control cell functions such as growth, proliferation and differentiation. Abnormal miRNA expression plays an important role in cancer development. This study found that miRNAs in healthy cells interact in a network that, when mapped, resembles a family tree with dozens to hundreds of members. Each cell type has its own network, with particular miRNAs serving as central hubs within the network.

In cancer cells, the single network is replaced by subnetworks that usually include small detached clusters of two to six miRNAs. "These small groups that exist outside the main network were unexpected," Croce says. "Some of these miRNA outliers are well-known cancer genes, but the involvement of others in cancer was unknown."

The study suggests that key cancer genes can be identified on the basis of their relationship to other genes, as well as on their overexpression or loss.

Published in the journal Genome Research.

OF NOTE

Recent Recognitions of OSUCCC-James Physicians and Researchers

GRANTS

TIM H.-M. HUANG, PhD, *professor of Molecular Virology, Immunology and Medical Genetics,* **has been awarded an $8.6 million, five-year renewal grant from the NCI** *for computational genome analysis for breast, ovarian and prostate cancers.*

ELECTRA D. PASKETT, PhD, *associate director for Population Sciences at the OSUCCC-James,* **has been awarded a $10 million, five-year grant from the National Institutes of Health** *to continue funding the Center for Population Health and Health Disparities.*

AMANDA TOLAND, PhD, *assistant professor of Molecular Virology, Immunology and Medical Genetics,* **has received a $1.25 million, four-year NCI grant** *for a study examining genetic interactions in colorectal cancer susceptibility.*

JOHN BYRD, MD, *director of the Hematologic Malignancies Program, associate director for Translational Research and holder of the D. Warren Brown Professorship in Leukemia Research,* **has been awarded a five-year, $6.25 million Specialized Center of Research (SCOR) renewal grant from The Leukemia & Lymphoma Society.** *The grant involves five other OSUCCC-James investigators and four clinical trials.*

AWARDS AND HONORS

JOHN BYRD, MD, *director of the Hematologic Malignancies Program,* **has received the first Richard L. Schilsky CALGB Achievement Award.** *The award honors exceptional individuals whose research has transformed cancer-patient care.*

CHING-SHIH CHEN, PHD, *Lucius A. Wing Chair of Cancer Research & Therapy, Professor of Medicinal Chemistry, of Internal Medicine, and of Urology,* **has received an Ohio State University Distinguished Scholar Award,** *which recognizes exceptional scholarly accomplishments by senior professors.*

CARLO M. CROCE, MD, *professor and chair of Molecular Virology, Immunology and Medical Genetics, director of the Human Cancer Genetics Program and the John W. Wolfe Chair in Human Cancer Genetics,* **has been elected to the American Society of Arts and Sciences,** *one of the nation's oldest and most prestigious honorary societies.*

JOSEPH FLYNN, DO, MPH, *co-director of the Division of Hematology,* **has been appointed to the 2010 Board of Examiners for the Malcolm Baldrige Quality Award.** *The award is the highest level of national recognition that a U.S. organization can receive for performance excellence.*

CHANDAN SEN, PhD, *professor of Surgery, associate dean for Research in the College of Medicine,* **has been recognized along with members of Ohio State's Davis Heart and Lung Research Institute (DHLRI) for decade-long excellence in sharing scientific discoveries and advancing the field of redox biology through the journal *Antioxidants & Redox Signaling*.** *Sen is the founder and editor of this journal, which is housed in the DHLRI and recently was recognized as one of the top scientific publications nationwide.*

SMITHA PILLAI, PhD, *a postdoctoral fellow in Feline Cancer Pathogenesis in Ohio State's College of Veterinary Medicine,* **received an Amanda Feline Fellowship from the Morris Animal Foundation to study oral cancer treatment.** *Pillai will receive $100,000 for the two-year fellowship, which is one of only two awarded nationally this year. She works in the laboratory of Thomas Rosol, DVM, PhD, a professor in the Department of Veterinary Biosciences.*

FACULTY AND PROGRAMS

VINCENZO COPPOLA, MD, *assistant professor in the Department of Molecular Virology, Immunology and Medical Genetics, and a former staff scientist with the NCI's Mouse Cancer Genetics Program,* **has joined the OSUCCC-James as director of the University's Mouse Modeling Core Facility.**

JOSEPH FLYNN, DO, MPH, *clinical director of Hematology at the OSUCCC-James,* **has been named co-director of the Lance Armstrong Foundation Survivorship Center of Excellence at Ohio State and medical director of the survivorship clinics.**

MARK B. LANDON, MD, has been named chair of Ohio State's Department of Obstetrics and Gynecology. *Landon specializes in maternal-fetal medicine and is an internationally recognized authority on gestational diabetes and cesarean delivery.*

CHRISTOPHER PELLOSKI, MD, has been named first director of Pediatric Radiation Oncology at the OSUCCC-James. *He also directs the Radiation Oncology residency program and medical student education and holds a joint appointment with Nationwide Children's Hospital for Pediatric Radiation Oncology.*

JEFF WALKER, MBA, has returned to Ohio State to become the first executive director of the OSUCCC-James. *Walker came from Roswell Park Cancer Institute in Buffalo.*

Richard D. White, MD, has been appointed professor and chair of Ohio State's Department of Radiology *and director of the Imaging Signature Program.*

THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER-ARTHUR G. JAMES CANCER HOSPITAL AND RICHARD J. SOLOVE RESEARCH INSTITUTE celebrated its 20-year anniversary July 27. *The James opened in July 1990 as the patient-care component of Ohio State's Comprehensive Cancer Center.*

OHIO STATE'S CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE AND COLLEGE OF MEDICINE have opened a Laser Capture Molecular Core. *For more information visit* **https://lcm.osu.edu/.**

THE OHIO STATE UNIVERSITY MEDICAL CENTER AND SEATTLE'S INSTITUTE FOR SYSTEMS BIOLOGY have established the P4 Medicine Institute (P4MI), *a consortium dedicated to accelerating the emergence and adoption of health care that is predictive, preventive, personalized and participatory.*

LEADERSHIP ACTIVITIES AND APPOINTMENTS

STEVEN M. DEVINE, MD, *director of the Blood and Marrow Transplant Program,* **has been appointed chair of the CALGB Transplant Committee.**

LYNN O'DONNELL, PhD, *director of the Cellular Therapy Lab at the OSUCCC-James,* **has been elected to the Executive Committee of the International Society for Cellular Therapy.**

WILLIAM E. CARSON III, MD, *associate director for Clinical Research,* **has been named to the National Comprehensive Cancer Network Board of Directors.** *He succeeds Clara D. Bloomfield, MD, a Distinguished University Professor at Ohio State.*

JOYCE HENDERSHOTT, LISW-S, ACSW, *clinical program manager for Patient Education at the OSUCCC-James,* **was appointed to the editorial board of Oncology Times,** *an independent, award-winning newspaper mailed to 45,000 cancer specialists nationally.*

Deep Thinking

Using next-generation gene sequencing to explore the depths of the genome

PEARLLY YAN, PHD,
technical director of the OSUCCC Nucleic Acid Shared Resource

BY DARRELL E. WARD
PHOTOGRAPHY BY
ROMAN SAPECKI

Leukemia research reached a milestone in 1994 with the discovery of the *MLL PTD* gene mutation in patients with cytogenetically normal acute myeloid leukemia (CN-AML). Presence of the mutation in leukemic cells identifies a subtype of CN-AML that responds poorly to chemotherapy alone but well to chemotherapy plus autologous stem cell transplantation.

The mutation became the first prognostic marker in this large group of AML patients who lack the chromosomal damage that otherwise would be used to guide treatment decisions and predict relapse risk.

The mutation was discovered by a team of investigators that included Michael A. Caligiuri, MD, Clara D. Bloomfield, MD, and Carlo M. Croce, MD, who are all now at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James).

To investigate the mutation's contribution to leukemia development, the researchers developed an *Mll-PTD* mouse model. They then crossed that mouse with a strain that had a mutation in a gene called *Flt3*, another mutation subsequently discovered in CN-AML patients by a different research group.

This strain of mice with both mutations developed leukemia usually 50 weeks after birth, a time considered to be "older-aged" for mice. The question was, why did it take so long?

The researchers hypothesized that DNA methylation changes were gradually silencing tumor-suppressor genes. Recently, they began designing experiments to look for differences in DNA methylation patterns in younger and older-aged mice with the *Mll PTD* only, with *Flt3 ITD* only and with the two mutations together.

"We want to elucidate the contribution of DNA methylation to leukemogenesis in our novel AML mouse model," says Susan Whitman, PhD, an OSUCCC-James research scientist in the laboratory of Caligiuri, who is director of the OSUCCC and CEO of The James Cancer Hospital and Solove Research Institute.

They chose to do the study using next-generation sequencing (NGS).

Compared with other well-tested single-gene approaches, "next-generation sequencing is less expensive on a per-gene basis, and it allows us to look at methylation changes throughout the genome," Whitman says.

"With NGS, we can ask questions we could never ask before," says Hansjuerg Alder, PhD, director of the OSUCCC-James Nucleic Acid

JEFF PALATINI, PhD,
technical director of the OSUCCC Microarray Shared Resource

Shared Resource, which offers gene sequencing using the Illumina platform. "It makes it far easier to discover potential biomarkers for predicting disease prognosis, progression and drug response, and for molecular diagnosis.

"Each individual with cancer has different genetic changes, and this technology can identify those differences," Alder says. "NGS will enable us to better classify cancers and to tell which patients might respond to a therapy and which probably won't. All of this will help make personalized medicine for cancer possible."

Ohio State is committed to personalized medicine, says Clay Marsh, MD, senior associate vice president for Health Sciences Research and executive director of the Center for Personalized Health Care. "Health care at Ohio State will utilize gene-based information to understand each person's individual requirements for the maintenance of his or her health and prevention of disease, with therapy tailored to that individual's genetic uniqueness. Ideally, it also includes incorporating knowledge of their environment, health-related behaviors, culture and values."

Alder notes that some leaders in the field believe personalized medicine will eventually involve using a patient's genome sequence data the way information from blood tests is used today.

"NGS could change medicine in a way comparable to noninvasive imaging," says Jeff Palatini, PhD, technical director of the OSUCCC Microarray Shared Resource, which offers gene sequencing using the SOLiD platform. "Just as the ability to see the internal organs without doing surgery changed medicine, NGS enables us to identify changes at the molecular level that we can't see any other way."

The experience of Alder, Palatini and other researchers at the OSUCCC-James shows that NGS—also called second-generation sequencing, deep sequencing and massively parallel sequencing—is revolutionizing cancer research.

First-generation genome sequencing technology made the Human Genome Project possible. Completing that groundbreaking effort took 13 years and the involvement of 18 countries. Sequencing alone cost $400 million. It revealed for the first time the sequence of the 3 billion base pairs that make up human DNA. NGS, in contrast, can do the same thing and more in 10 days and with greater accuracy for about $10,000.

An NGS investigation begins with amplification of DNA fragments, tagging each base in the fragments with one of four fluorescent colors and reading the sequence of colors, a process carried out by a tabletop-sized machine. This base identification yields the raw sequence data, a string of 'A's, 'C's, 'G's and 'T's. Depending on the question being asked, NGS data will be analyzed by bioinformaticians and computational scientists using vastly different approaches. (See page 15 for a summary of the sequencing process.)

"NGS is extremely powerful," says Palatini. "It enables the sequencing of entire genomes, both coding (exons) and noncoding (introns) regions, which was not practical before."

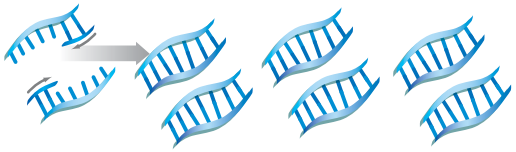
Or, he says, one can examine just DNA regions that are methylated, also called the epigenome; all RNA transcripts—the transcriptome— or just certain transcripts, such as microRNAs. "We can study the genome, the epigenome and the transcriptome at the same time, and we can get information about the depth and expression of transcripts, as well

Steps in NGS sequencing and analysis

Prepare DNA Library

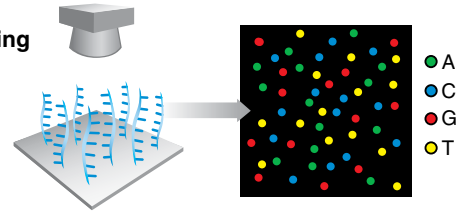
Prepare DNA library: Fragment long strands of DNA, RNA or cDNA into required lengths.

Amplification of DNA



DNA Amplification: Amplify fragments to select for reads that will produce high-quality sequencing results.

Perform Sequencing

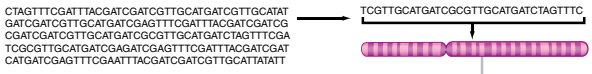


Sequencing: Affix fragments to sequencing platform. CCD camera captures fluorescent signal from bases in succession from end(s) of fragments.

Data Storage

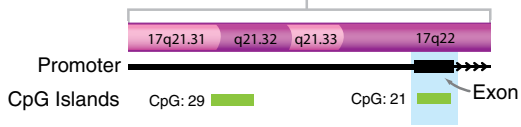
Data storage: Requires terabytes and petabytes of capacity.

Primary Data Analysis



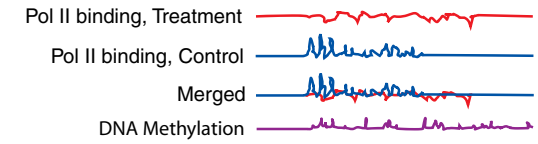
Primary Data Analysis: Convert CCD images into bases, then into strings of bases, and then align them to a reference genome.

Secondary Data Analysis



Secondary Data Analysis: Categorize sequence reads, e.g., as promoters, coding or noncoding regions, CpG islands, SNPs or insertions.

Tertiary Data Analysis



Tertiary Data Analysis: Compare between samples or integrate diverse sequencing data sets, e.g., compare samples across time points for changes in methylation status, or compare different "-omics" data.

Validation

Validation: Confirm finding using a different assay and evaluate functional consequence of observed changes, e.g., determine the importance of a putative tumor-suppressor gene using an animal model.

Clinical Verification

Verify in a clinical setting: e.g., evaluate patient samples for the gene change.

JEFF PALATINI, PhD

"We can study how cancer cells regress to a more primitive state, or dedifferentiate, which may someday enable us to reverse this process in malignant cells, offering a new treatment for cancer."

as their sequence," Palatini says.

"NGS can reveal whether genes are methylated or mutated or both, and we can look at such questions simultaneously to learn what's actually happening," he says. "We can study how cancer cells regress to a more primitive state, or dedifferentiate, which may someday enable us to reverse this process in malignant cells, offering a new treatment for cancer."

It can also improve the accuracy of new targeted therapies, he notes. Administering a DNA methylation inhibitor to one cohort and not another could reveal if the agent is acting on the intended target gene and adversely affecting other genes.

Depth equals confidence

Once genomic DNA, RNA or cDNA is fragmented in preparation for sequencing, the fragments are amplified to increase signal intensities. Depending on the size and complexity of the genome—cancer genomes have many more changes than normal genomes, for example—different amounts of sequencing data must be collected to assure the accuracy of the resulting profile. In general, each region of a normal genome should be sequenced at least 30 times for adequate coverage and to establish confidence, says Pearlly Yan, PhD, technical director of the OSUCCC Nucleic Acid Shared Resource and a sequencing specialist.

When only an expanse of DNA is examined, one can achieve very high coverage, often to a depth of tens of thousands of times, thereby allowing researchers to examine rare mutations or difficult-to-amplify regions.

"The human genome has about 3 billion base pairs, so to achieve 30 times coverage, we need to obtain at least 3 billion x 30, or more than 90 billion base pairs," Yan says. "That's a lot of data. The amount of information produced by each genome experiment requires different computational approaches to uncover the wealth of biology hidden in it."

Because the OSUCCC-James is a research institution, its sequencing facilities can offer investigators the latest, most informative sequencing approaches and many options for sample preparation to obtain the needed information at the desired depth, Yan says.

"More depth and diverse approaches are required to accurately detect rare events, small changes, or when sequencing certain areas of the genome such as regions with repetitive sequences," she says.

Storing and transmitting all this data requires a sophisticated infrastructure. One full sequencing run on the SOLiD platform can produce 9 terabytes (TB) of data, Palatini says. (One TB equals 1,000 gigabytes. For perspective, the Library of Congress had almost 160 TB of data in its collection as of February 2010.)

Then comes data analysis, which cannot be done in the traditional ways on most laboratory PCs. "In some cases, software packages are available that make it easier for biologists to carry out some secondary analyses, but in most cases computing power and bioinformatics collaborators are essential for success," Yan says.

Complex analyses require close collaboration among wet-lab biologists, biomedical informaticians and computational scientists who can spot subtle variations in sequence data and write algorithms for identifying patterns. Biostatisticians are needed to determine statistical significance.

"The challenge is to find the important details in reams of sequencing data," says Jeffrey Parvin, MD, PhD, interim chair of

the Department of Biomedical Informatics and director of the Biomedical Informatics Shared Resource.

"If you look at the Manhattan skyline for the most important object, your eye might be drawn to the Empire State building. But actually a lot of important things are happening in other buildings that you don't see when looking at the skyline. Other kinds of analyses are needed to pick up that information."

The Biomedical Informatics Shared Resource can write computer programs that automate many of the analyses or modify current software to make analysis easier in the future, Parvin says. "This is *a la carte* work. Every biologist needs something special, and we provide solutions for that special need."

microRNA sequencing

"The OSUCCC-James is a top-tier center for small RNA sequencing," Palatini says. "We pioneered much of the microRNA sequencing chemistry and beta testing for the country, as well as the workflow pipeline and computational methods of data analysis."

Much of this work was driven by the research of OSUCCC-James investigator Carlo M. Croce, MD, professor of Molecular Virology, Immunology and Medical Genetics, and director of the Human Cancer Genetics program.

Croce, who also directs the Microarray Shared Resource, is using NGS to investigate the mechanism of disease in chronic lynphocytic leukemia (CLL). For example, he and his lab are looking at microRNA changes and DNA sequences simultaneously to identify the molecular mechanism involved in progression and the points of therapeutic intervention to prevent indolent CLL from becoming aggressive.

OSUCCC sequencing facilities can build DNA libraries to suit every need and sequencing platform, Palatini says, including methylation libraries, targeted sequencing libraries, fragment libraries, paired-end and mated-pair libraries, small RNA libraries, ChIP-seq libraries and Sure-Select libraries.

ChIP seq

Chromatin immunoprecipitation (ChIP) technology allows the location of sites where proteins bind with DNA. When this method is coupled with NGS, called ChIP seq, genomewide investigations of changes in transcription sites and modification to chromatin structure are possible.

Michael Ostrowski, PhD, professor and chair of Molecular and Cellular Biochemistry, and co-leader of the OSUCCC-James Molecular Biology and Cancer Genetics Research Program, and his colleagues study changes in the tumor microenvironment and in cancer cells. They use ChIP seq to study the transcription factor Ets in three cell compartments: stromal fibroblasts, macrophages and endothelial cells.

HANSJUERG ALDER, PhD,
director of the OSUCCC-James Nucleic Acid Shared Resource

In addition, they are studying chromatin marks in these three cell compartments during tumor progression. Finally, they are using RNA sequencing technology for gene expression profiling of both mRNA and microRNA in tumor cells and in the same three tumor microenvironment cell compartments.

"We also plan to use NGS to study changes in the tumor-cell genome in response to changes in the microenvironment, including gene loss and amplification," Ostrowski says.

"This technology is exciting because it allows *discovery,* which can lead to testable hypotheses," he explains. "For example, if we find that Ets2 binds to genes involved in specific signaling pathways, we can make testable hypotheses based on

that global data."

ChIP seq technology plus top-notch computational modeling enabled OSUCCC-James investigator Tim Huang, PhD, professor of Molecular Virology, Immunology and Medical Genetics, and his collaborators to discover a new form of estrogen-mediated gene silencing that may contribute to breast cancer.

CARLO M. CROCE, MD,
professor of Molecular Virology, Immunology and Medical Genetics, and director of the Microarray Shared Resource.

Their study, published in the journal *Genome Research,* analyzed transcriptome, methylome and estrogen receptor datasets from normal breast epithelia and breast cancer cells. It uncovered a cluster of 14 genes that are simultaneously silenced in breast cancer cells through a mechanism that brings the promoters of these genes together at one regulatory site for coordinated repression.

The contortions involved in this process produce DNA loops. These loops are temporary in normal cells but fixed in breast cancer cells, resulting in long-term repression of the 14 genes.

Targeted sequencing

Targeted sequencing focuses on just a region of DNA, such as a stretch of chromosome several megabases long, using customized probes that target that region. The method is useful for comparing chromosome regions in people with and without cancer, for example.

Huiling He, MD, an OSUCCC-James research scientist, is working with the Nucleic Acid Shared Resource to apply the technique for targeted DNA sequencing. Albert de la Chapelle, MD, PhD, professor of Molecular Virology, Immunology and Medical Genetics and the Leonard J. Immke, Jr., and Charlotte L. Immke Chair in Cancer Research, leads the study.

"An advantage of deep sequencing is its ability to detect changes that would be missed by other sequencing methods," says He. "We know the mutation is present, but conventional sequencing cannot locate it. We believe the improved coverage offered by deep sequencing will reveal areas that were missed earlier."

NGS technology is progressing rapidly. Third-generation sequencers can generate longer reads without the need to amplify sample fragments. In some cases, the sequencing process can be monitored using an iPhone.

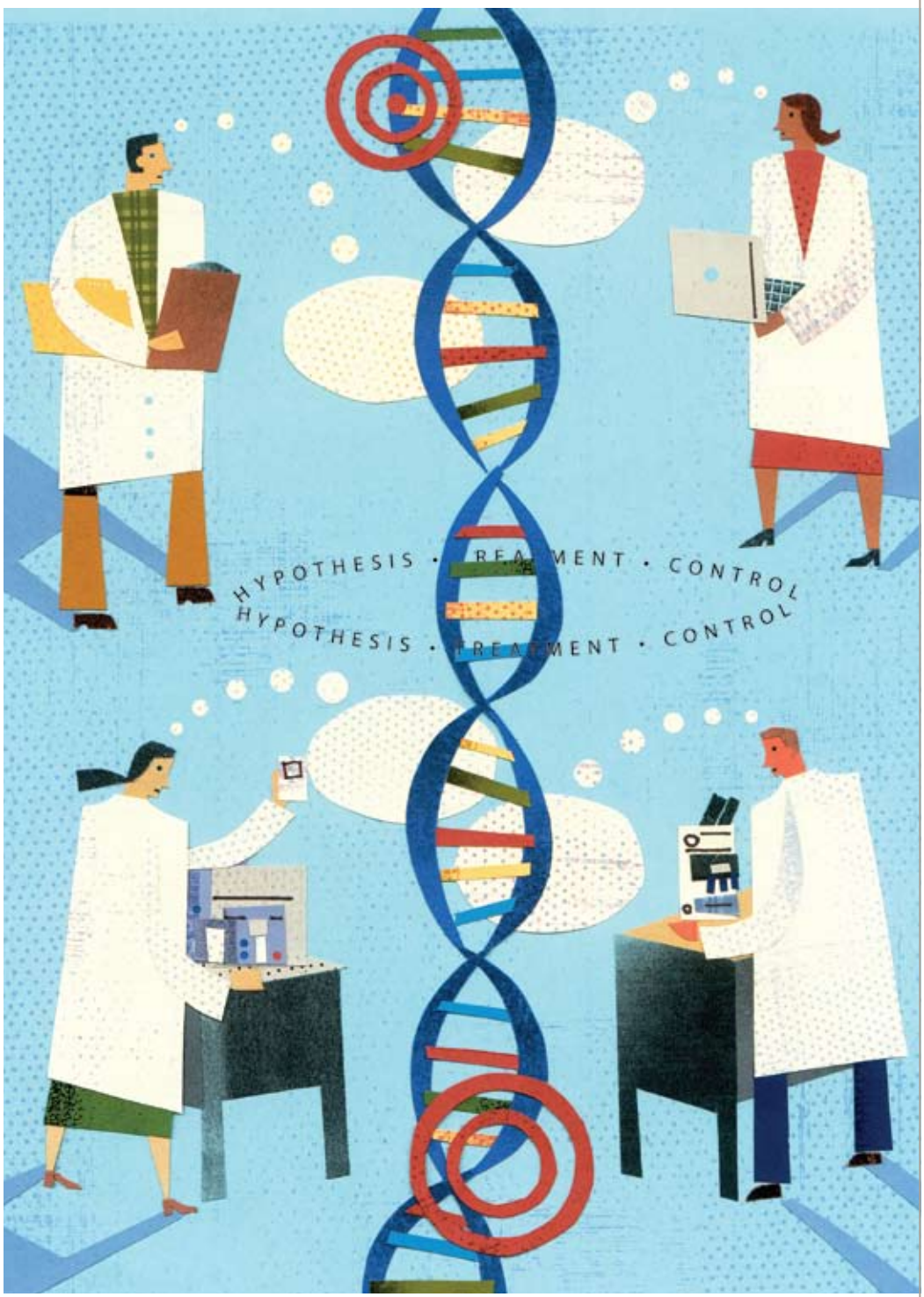
Keeping pace with the technology is an expensive challenge, says Jeff Walker, executive director of the OSUCCC-James. "It's not only the cost of purchasing and maintaining the instrumentation and supporting facility, but also of the bioinformatics expertise and infrastructure required to interpret the massive amount of data generated."

To solve the problem, the OSUCCC-James is exploring the formation of a local consortium that brings together academic centers and industry to support a single genomics infrastructure. "This would give our investigators ready access to the newest NGS technology," Walker says.

"Clearly," he says, "NGS is a critical tool for developing new approaches to diagnosing and treating cancer, and for personalizing clinical care."

ONE FOR ALL

When specialized technology and expertise is needed, OSUCCC-James researchers turn to the cancer center's shared resources



BY DARRELL E. WARD
ILLUSTRATIONS BY RICH LILLASH

Mutations in a gene called *BLM* cause Bloom syndrome, a rare autosomal recessive, chromosome-breakage disorder characterized by small stature, sun-sensitivity, immune deficiency and predisposition to multiple cancers.

Joanna Groden, PhD, a molecular geneticist at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James), was part of the team that discovered *BLM* in 1995.

Groden has since learned much about the gene's function and the protein it encodes. In 2009, for example, her work revealed that the BLM protein interacts with topoisomerase II, a cell cycle enzyme that untangles double-stranded DNA during DNA repair and mitosis.

She and her colleagues have also

MICHAEL D. LAIRMORE, DVM, PhD

"Working with multiple colleges–medicine, pharmacy, veterinary medicine, agriculture and others–brings different areas of expertise to bear on a single problem: cancer. It allows us to synergize, to maximize the strengths of the various colleges."

shown that the interaction of the two molecules prevents chromosome breakage that contributes to many malignancies. They have also identified phosphorylation sites on the protein that regulate its interaction with topoisomerase II and have shown that when these sites are mutated the proteins can't interact. These findings may be important to therapy; they could be used to increase the amount of DNA damage that occurs when treating tumors with radiation or DNA-damaging agents.

To make these discoveries, Groden required advanced technologies such as proteomic assays, fluorescent and confocal microscopy and analytical cell sorting, none of which are found in the average research laboratory.

Similarly, OSUCCC-James researcher Ching-Shih Chen, PhD, a medicinal chemist in the College of Pharmacy, requires a range of specialized technologies for his research in anticancer drug design.

One novel agent of Chen's targets glucose metabolism in cancer cells. It belongs to a new class of drugs called energy-restricting mimetic agents. Chen and his lab also developed two drugs, AR-12 and AR-42, that are now in phase I testing at the OSUCCC-James. AR-12 inhibits two signaling pathways important in breast, colon, lung and prostate tumors; AR-42 is a histone deacetylase inhibitor active against prostate cancer in animal models.

Developing these agents required analytical cell-sorting capabilities, microarray assays and toxicopathological evaluations of the mouse models that are an essential part of drug discovery.

The advanced technologies, methods and expertise that Chen, Groden and other OSUCCC-James investigators need are provided by 15 cancer center shared resources, each of which specializes in a particular medical or research discipline (see sidebar).

"Our shared resource directors and their staff are absolutely critical to research at the OSUCCC-James," says Michael D. Lairmore, DVM, PhD, professor of Veterinary Biosciences and associate director for Basic Research at the OSUCCC-James.

"Our shared resources are developing the latest, greatest way to do research. They often push the envelope of their science," he says. As experts in their field, shared resource directors help investigators better approach their science and often become partners in the research and co-authors on publications. (For a close look at the OSUCCC-James' genomics resources, see "Deep Thinking," page 13.)

In 1999, the OSUCCC-James had six shared resources. The growth in number since then reflects the expansion of the cancer center's research programs over the past 10 years.

"Our number one concern is to develop the shared services that support the highest-quality science," Lairmore says. "The range of services we provide reflects the science that we do here and the needs of our investigators and research programs."

The Behavioral Measurement Shared Resource, for example, supports investigators doing population studies. "Expertise is available for everything from how to retrieve data to how to accrue patients to a study," Lairmore explains.

New shared resources are developed as needs change. The Pharmacoana-

lytic Shared Resource, for example, was added in 2004 to support the rapidly expanding OSUCCC-James Experimental Therapeutics Research Program and a growing number of investigator-initiated clinical trials.

Pharmacokinetic and pharmacodynamic analyses are now a common part of clinical trials and preclinical pharmacologic studies at the OSUCCC-James," says Michael R. Grever, MD, professor and chair of the Department of Internal Medicine, Charles Austin Doan Chair of Medicine and co-leader of the Experimental Therapeutics Program. "These correlative studies are important for synthetic agents and natural products, as well as immune-based therapies. This unit has also been extremely helpful with investigational studies of oncolytic viruses.

"The Pharmacoanalytic Shared Resource gives us a centralized facility that offers sample procurement, processing and storage, the development and validation of bioanalytical methods, and expertise in data analysis and interpretation," he says.

PARTNERSHIPS

The OSUCCC-James developed the Pharmacoanalytic Shared Resource in collaboration with the College of Pharmacy. "We often develop shared resources in partnership with Ohio State's various colleges," Lairmore says. "It's one of the advantages of being a cancer center embedded within a major university."

In fact, OSUCCC-James investigators come from 11 of Ohio State's 14 colleges.

"Working with multiple colleges—medicine, pharmacy, veterinary medicine, agriculture and others—brings different areas of expertise to bear on a single problem: cancer," Lairmore says. "It allows us to synergize, to maximize the strengths of the various colleges."

The cancer center has two shared resources in development. The new Medicinal Chemistry Shared Resource (MCSR) is being developed in conjunction with the College of Pharmacy under the direction of Ching-Shih Chen, who is the Lucius A. Wing Chair of Cancer Research & Therapy, professor of Medicinal Chemistry, of Internal Medicine, and of Urology, and a member of the OSUCCC-James' Molecular Carcinogenesis and Chemoprevention Program.

The new shared resource integrates the disciplines of medicinal chemistry, process chemistry, computational chemistry and molecular pharmacology.

OSUCCC SHARED RESOURCES

THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER – ARTHUR G. JAMES CANCER HOSPITAL AND RICHARD J. SOLOVE RESEARCH INSTITUTE HAS 15 SHARED RESOURCES THAT OFFER THE COMPLEX, SOPHISTICATED TECHNOLOGIES AND EXPERTISE REQUIRED TO CONDUCT HIGH-LEVEL CLINICAL, BASIC AND TRANSLATIONAL CANCER RESEARCH.

Analytical Cytometry and Cell Sorting – Offers cutting edge flow cytometry analysis and cell sorting and assists investigators with experimental design, assay development, education and instrument training.

Behavioral Measurement – Assists with designing behavioral variables for proposed or ongoing research, supporting the accrual of underserved groups to clinical trials, designing an assessment package suited to the investigator's aims and hypotheses and supporting behavioral data interpretation for publication.

Biomedical Informatics – Provides state-of-the-art informatics tools, high-quality informatics analysis and computational biology consultative services.

Biorepository and Biospecimen – Obtains patient-informed consent to procure malignant and normal tissues from solid tumors and matching peripheral blood products for distribution to OSUCCC-James members. The BBSR maintains the central tissues biorepository, provides quality control of the research specimens through direct interaction with pathologists and assists researchers with tissue procurement.

Biostatistics Core – Offers a centralized resource for expertise in the biostatistical analysis and design of clinical, basic and population-based research.

Clinical Trials Office – A centralized resource of comprehensive management services that enables OSUCCC-James investigators to conduct successful clinical trials in a methodologically sound, expedient and cost-effective manner.

Clinical Treatment Unit/Clinical Trials Processing Lab – Supports investigators conducting phase I and phase II clinical trials. The CTU, an ambulatory unit in The James, specializes in treating patients on phase I trials who require intense monitoring or complex correlative sample collection and processing. The CTPL provides dedicated staff for high-volume procurement, processing, storage, delivery and shipment of research specimens critical to clinical trial correlative studies.

Comparative Pathology & Mouse Phenotyping – Provides expert, affordable, experimental pathology support to investigators using animal models to study human disease. Services include characterization of newly produced lines of genetically engineered mice, as well as hematology, clinical chemistry, radiography, routine frozen and paraffin slide preparation, tissue microarray preparation and special histochemical and immuno-histochemical staining.

Leukemia Tissue Bank – Facilitates the translation of basic leukemia research to the clinical setting via an extensive repository of tissue samples and accompanying pathologic, cytogenetic and clinical data for ready correlation of clinical and biological results.

Microarray – Provides custom microarray design and fabrication, commercial microarrays and next-generation sequencing. Services include whole genome epigenetic analysis, mRNA, microRNA, non-coding sRNA and whole transcriptome analysis; RNA/DNA-seq; whole and targeted genome re-sequencing, SNP genotyping, genomic DNA gain/loss detection, microRNA genomic gain/loss detection, RNA/DNA characterization and data analysis.

Microscopy – Offers state-of-the-art microscopy, including live-animal, multiphoton microscopy. Services include a wide range of sample preparation methodologies, investigator training and research collaboration.

Nucleic Acid – Provides centralized instrumentation and expertise for Sanger-based and non-Sanger-based DNA sequencing, genotyping, DNA methylation analysis and gene expression analysis. Also offers quantitative measurement and quality control of nucleic acids, nucleic acid purification and nucleic acid imaging. Investigators have unlimited access to training, consultation, troubleshooting and assistance in experimental design.

Pharmacoanalytical – Supports pre-clinical and clinical drug development with high-quality, cost-effective and reliable bioanalytical method development, quantitative sample analysis, and pharmacokinetic/pharmacodynamic/pharmacogenetic experimental design and data analysis.

Proteomics – An interdisciplinary unit that offers state-of-the-art instrumentation and expertise needed for identifying proteins, quantifying protein expression levels and the discovery of protein modifications and protein biomarkers.

Small Animal Imaging – Offers small-animal imaging using state-of-the-art, high-resolution equipment, and expertise in small-animal handling and in analytical quantitative image analysis.

For more on OSUCCC-James shared resources, visit cancer.osu.edu/research/cancerresearch/sharedresources

MICHAEL D. LAIRMORE, DVM, PhD

"Shared responsibility and shared use translate into more efficient use and higher-quality research. And that's what's required if we are to defeat a disease as complex as cancer."

"The MCSR will serve as a platform to translate basic science findings into the design and synthesis of small-molecule agents for testing individual hypotheses, and it will expedite the application of basic research findings to the clinic," Chen says, adding that it also will help physician scientists develop research collaborations through a partnership with Ohio State's Medicinal Chemistry and Chemistry programs.

Also in development is the Nutrient and Phytochemical Analytic Shared Resource (NAPASR), which will provide an analytical infrastructure to support the OSUCCC-James' "crops to clinic" research efforts. It will help investigators develop methods and techniques to quantitate nutrients and phytochemicals in foodstuffs, and to identify these compounds and their metabolites in tissue samples obtained from clinical trials and preclinical studies. NAPASR was initiated with support from the OSUCCC-James and the Ohio Agricultural Research and Development Center.

"The Nutrient and Phytochemical Analytic Shared Resource will guide the development of functional-food products for cancer prevention, monitor compliance in dietary interventions, conduct absorption and bioavailability studies and investigate the interactions of genes with nutrients and phytochemicals," says Director Steven J. Schwartz, PhD, the Carl E. Haas Endowed Chair in the Department of Food Science, College of Food, Agricultural and Environmental Sciences, and a member of the OSUCCC-James Molecular Carcinogenesis and Chemoprevention Research Program.

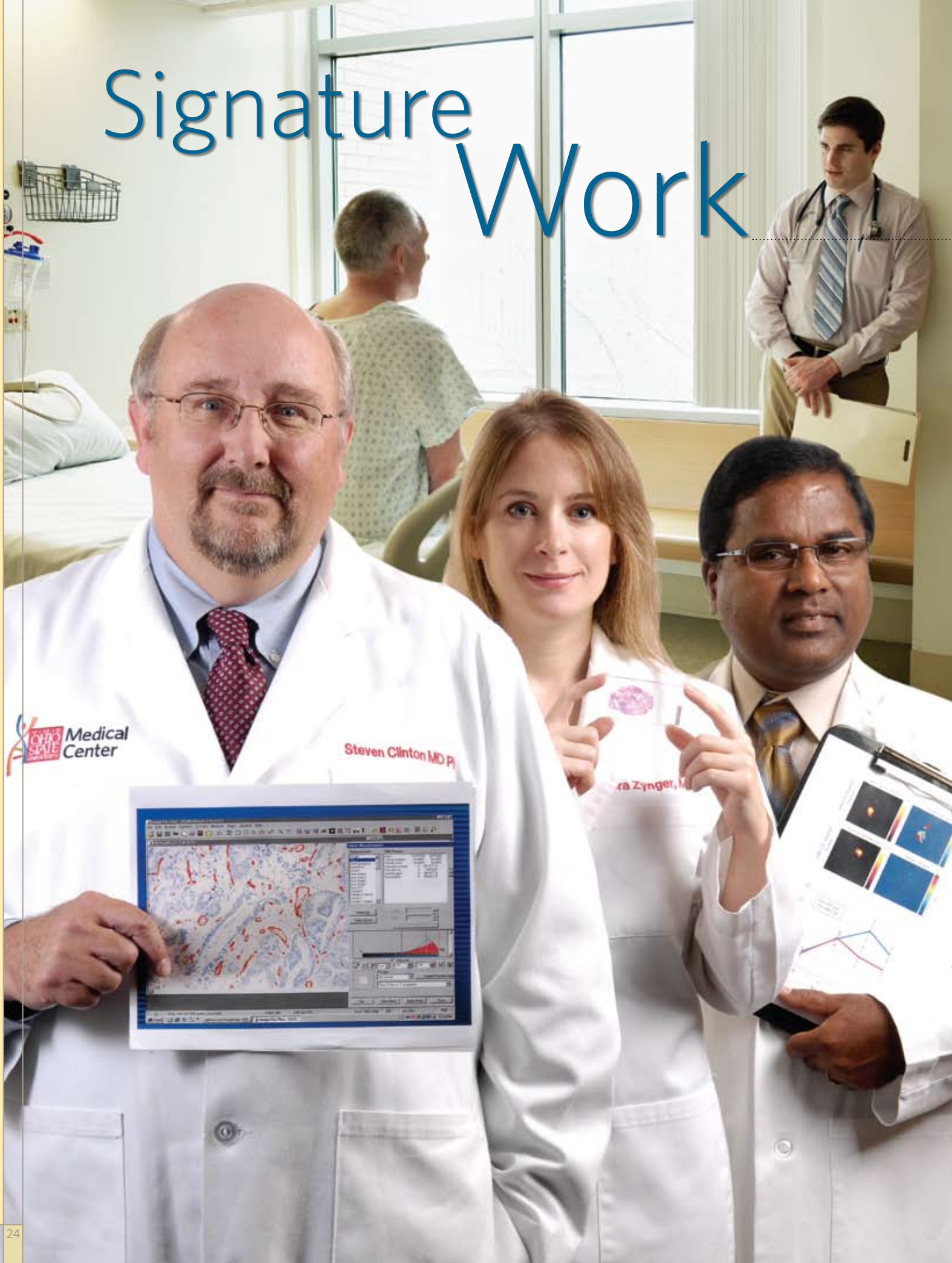
In addition, it will provide analytical tools for investigating the role of metabolites in cancer prevention or therapy and serve as a training facility for graduate students and postdoctoral associates.

Keeping pace with emerging technologies and controlling their costs are significant challenges for a major cancer center, Lairmore notes. About 30 percent of the cancer center's shared resources are funded by the OSUCCC-James' Cancer Center Support Grant from the National Cancer Institute. The remaining support comes from partnerships with various University colleges and departments, and from user fees.

"Our shared resources are available to investigators throughout the Ohio State campus and at other institutions," Lairmore says. "As we look to the future, we are reaching out to other institutions and even to industry. When it comes to rapidly changing, expensive technology such as genome sequencing and imaging technology, we are trying to create a more regional sequencing shared resource.

"The term 'shared' is really important for success in our shared-resources formula," he says. "Shared responsibility and shared use translate into more efficient use and higher-quality research. And that's what's required if we are to defeat a disease as complex as cancer."

Signature Work



Ohio State's Prostate and Genitourinary Oncology Clinic offers interdisciplinary care backed by research

Pictured left are (L to R):

STEVEN CLINTON, MD, PhD,
prostate cancer specialist and researcher and director of the Prostate and Genitourinary Oncology Clinic

DEBRA ZYNGER, MD,
urologic pathologist

PERIANNAN KUPPUSAMY, PhD,
director of Ohio State's Center for Biomedical EPR Spectroscopy and Imaging

BY BOB HECKER
PHOTOGRAPHY BY ROMAN SAPECKI

Men who have been diagnosed with cancer that is thought to be contained in the prostate are benefitting from an evolution toward integrated multidisciplinary care backed by research that will yield more accurate prognoses and determine better treatment plans.

The Prostate and Genitourinary (GU) Oncology Clinic at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) specializes in evaluating men who are trying to determine their best treatment options. The clinic team particularly focuses on patients who are at high risk for recurrence, and it is a leader in accruing participants to clinical trials that integrate treatment modalities, seek prognostic biomarkers and search for novel approaches to curing the cancer or delaying recurrence.

GU Clinic Director Steven Clinton, MD, PhD, a prostate cancer specialist and researcher, believes many advancements lie ahead as medical scientists identify high-risk biomarkers involving tumor angiogenesis, gene expression, proteomics and microRNAs.

"Prostate cancer is highly heterogeneous," says Clinton, who is also professor of Medical Oncology and of Public Health and associate professor of Human Nutrition. "We need better tools to predict whether patients have a form that is aggressive, average or indolent so we can better define a course of treatment – surgery, chemotherapy, radiotherapy, hormone therapy or possibly new drugs that target angiogenesis – that is specific to each person's disease. New biomarkers also will define who has an indolent cancer and can be spared the complications and risks of aggressive therapy.

"In the future," he adds, "prognosis and treatment of prostate cancer will be defined by molecular signatures that will give us a far better classification of risk for each patient."

Clinton and colleagues in the GU Clinic – which includes specialists in medical, urologic and radiation oncology – believe interdisciplinary collaboration will help make this a reality.

"The most patient-relevant research advances are achieved only if physicians and scientists with different specialties collaborate," says urologic pathologist Debra Zynger, MD. "Urologic oncology research at the OSUCCC-James involves team members from multiple disciplines who integrate their clinical expertise and participate in patient-care clinics and conferences to optimize treatment."

This level of integrative care is relatively new in prostate cancer, Clinton notes.

Historically and nationwide, he explains, patients with confirmed prostate cancer were left to negotiate a complex and difficult pathway to choose a treatment plan. Options ranged from watchful waiting to surgery to multiple types of radiation therapy.

"The history of prostate cancer has few examples in which urologists, radiation therapists and medical oncologists got together to conduct randomized studies to compare one treatment with another. There was not that level of collaboration," Clinton says. "But under the new paradigm, patients with biopsy-confirmed cancer can come to our clinic and on the same day receive assessments from urologists, radiation oncologists and medical oncologists who work together to provide a unified approach toward options for care, which may include clinical trials."

Patients receive personalized therapy, which can range from watchful waiting, to single modality

care for low-risk patients, to multimodality care for those at higher risk for recurrence. "In high-risk care," Clinton says, "we may integrate therapies, such as surgery with adjuvant radiation and hormone therapy, or surgery with neoadjuvant chemotherapy and hormone therapy."

Until risk can be defined by newer molecular signatures, prostate cancer risk of recurrence is determined using tumor grade (Gleason score), stage (amount/size and location), prostate specific antigen (PSA) level and findings on digital rectal exam. This information is plugged into a computerized prostate nomogram – a mathematical model that helps estimate outcomes such as probability of recurrence after treatment, probability of survival after prostatectomy and treatment success for salvage radiation therapy in men whose cancer has recurred after prostatectomy.

"We integrate all of these elements to produce an overall determination of risk," Clinton says, "but these tools can be greatly improved. In the future we will include data relating to gene expression signatures and other biomarkers such as angiogenesis. We don't yet have the biomarkers for prostate cancer that we have for breast cancer, which is several years ahead of prostate cancer in that regard, but we're moving rapidly through basic research and clinical trials."

Prostate Prognostication

Zynger agrees. "If we can identify biomarkers that will stratify prostate tumors and predict their behavior, many men may be able to delay treatment or completely avoid it, while others will be steered toward more aggressive and effective multimodality care."

Angiogenesis may offer one example. A recent study led by the OSUCCC-James in collaboration with the Harvard School of Public Health suggests that prostate cancer behavior is predicted by the size, shape and number of tumor blood vessels.

The study, published in the *Journal of Clinical Oncology*, analyzed microvessel morphology as a predictor of prostate cancer mortality in 572 men with localized disease who underwent prostatectomy. Researchers immunostained tumor block sections for endothelial marker CD34 and assessed microvessel density, vessel size (area and diameter) and irregularity of vessel lumen using computer-assisted image analysis.

"They first determined how to more accurately measure angiogenesis in prostate tumors," Clinton says. "Typically, the approach has been to manually count the vessels we see using a microscope. But we wanted a more precise and consistent assessment of tumor blood vessels. We chose computerized digital analysis, which gives better quantitation of vascular architecture and more objective data."

After an average follow-up of 10 years, 44 of the 572 men had developed metastatic cancer or died of their disease. Men whose tumors had smaller vessel diameters were six times more likely to have aggressive cancer and die from it, and those with the most irregularly shaped vessels were 17 times more likely to develop lethal cancer. The findings were independent of traditional markers (Gleason score, stage, PSA level).

The investigators concluded that aggressive tumors "form vessels that are primitive in morphology and function, with consequences for metastasis."

"It's as if aggressive prostate cancers are growing faster, and their blood vessels never fully mature," Clinton says.

If these findings are validated, particularly in biopsy specimens, the measurement of tumor blood vessel architecture might help patients determine their optimal choice of therapy and improve long-term survival. "It really is about personalized health care," Clinton says.

Pleased as PUNCH

The "Pre-surgical Study Using Neoadjuvant Chemotherapy (PUNCH)" is a national, randomized, phase III clinical trial that compares progression-free survival in men with high-risk localized prostate cancer who undergo prostatectomy with or without six months of presurgical chemohormonal therapy (docetaxel and the androgen-deprivation agents leuprolide acetate or goserelin).

Clinton notes that Ohio State leads the nation with nearly 30 accruals to this Cancer and Leukemia Group B (CALGB) clinical cooperative group study.

"This trial should determine the benefits of aggressive combination

chemotherapy and hormonal therapy prior to surgery in patients who have a 40 percent or more five-year risk of recurrence," he says. Five to 10 years of follow-up will be needed to learn if the treatment improves survival, he adds, although "some short-term outcomes may be determined sooner, such as how the grade and stage were affected by the neoadjuvant therapy."

Clinton attributes Ohio State's success in PUNCH accruals to the GU Clinic's multidisciplinary structure, in which patients are quickly informed of their options, and to the skill and reputation of colleagues such as Ronney Abaza, MD, director of Robotic Urologic Surgery.

"Dr. Abaza is now a major referral center for robotic prostate surgery, so we're seeing a larger number of high-risk candidates for this trial," Clinton says.

OSU ANGIOGENESIS RESEARCH FURTHERS FOLKMAN'S LEGACY

Steven Clinton, MD, PhD, believes researchers at The Ohio State University who study angiogenesis in cancer or other medical disciplines have a special bond with the founder of the field.

"Our work with angiogenesis has an historical link to Dr. Judah Folkman, one of the greatest scientists OSU has produced," Clinton says. "The field of angiogenesis research owes so much to his pioneering work."

Folkman, who died in 2008, was a former central Ohio resident who graduated from Ohio State in 1953 and earned his MD at Harvard Medical School. He later became a surgeon and researcher at Harvard and at Children's Hospital Boston, where he directed the Vascular Biology Program.

In a 1971 paper in the *New England Journal of Medicine*, Folkman hypothesized that all tumors depend on angiogenesis for sustenance, an idea that opened global avenues of investigation for thwarting this process and inhibiting tumor growth. "But his hypothesis was not widely supported, and it was nearly two decades before his persistent and careful research stimulated an explosive growth in the field," Clinton says.

In 1998 The *New York Times* reported that two anti-angiogenesis agents Folkman had developed – angiostatin and endostatin – had eradicated cancer in mice with no toxic effects. This news dramatically elevated public hopes for an imminent cure for human cancers even though Folkman was cautious about the promise of these agents.

"In the mouse models those agents were potent, but such findings don't always translate immediately to the more complex human system," says Clinton, who trained at Harvard and served on the faculty from 1988-98.

Clinton, who knew Folkman and often discussed science with him, was first motivated to study angiogenesis through his own observations coupled with those of Folkman. "I noticed in the lab that when cancer was developing in the prostate, there was a large vascular pattern in and around the tumor," he recalls. "Through my exposure to Dr. Folkman, I realized he had similarly observed this as a surgeon and was making progress toward understanding the process."

Based on Folkman's pioneering findings, "We have seen in recent years an evolving approach to using small molecule drugs and antibodies that target angiogenic growth factor signaling," Clinton says. "Some of these, such as Avastin, have made their way into the clinic, and others are being developed that wholly or partially target angiogenesis signaling."

Clinton considers Folkman a humble visionary and an outstanding scientist who always encouraged anyone interested in angiogenesis. "He simply wanted to see the field move forward to help more patients. We've not yet appreciated the full potential of targeting angiogenesis for prevention and therapeutic purposes. It's up to us to learn how we can best translate the basic science into clinical care, but certainly Dr. Folkman's legacy will be seen as a key contributor to a cancer-free world."

STEVEN CLINTON, MD, PhD

"Our mission is to move promising lab findings into the clinic to help realize our vision of creating a cancer-free world sooner rather than later."

Imaging Innovations

The basic laboratory of Periannan Kuppusamy, PhD, a member of the Experimental Therapeutics Program at the OSUCCC-James, develops imaging technologies for tumor oxygenation and therapeutic drugs that target hypoxic tumors.

Along with OSUCCC-James researchers Tim Eubank, PhD, and Clay Marsh, MD, Kuppusamy's lab has shown how *in vivo* imaging of tumor oxygenation (tissue pO_2) can be used as a marker of tumor-growth inhibition by anti-angiogenic therapy.

Published in the journal *Cancer Research*, this study "was performed using a mouse model of breast cancer with the administration of granulocyte macrophage colony-stimulating factor (GM-CSF) as an anti-angiogenic agent," Kuppusamy says. "We used a nanoprobe-based electron paramagnetic resonance (EPR) imaging technology developed by my group to monitor reduction in tumor oxygenation following GM-CSF treatment."

Kuppusamy, who directs Ohio State's Center for Biomedical EPR Spectroscopy and Imaging, also is developing EPR oximetry for clinical applications.

"Oxygen concentration is an important determinant of treatment outcome in radiation and chemotherapy in solid tumors, including prostate cancer," he says. "Since vascularity and angiogenesis are directly related to tumor oxygen levels, our goal has been to use oxygen concentration as a surrogate endpoint to assess anti-angiogenic therapy. We believe this would help us make better prognostic decisions and monitor treatment."

Chemopreventive Ploys

Prostate cancer researchers at the OSUCCC-James also are developing and testing drugs to delay recurrence in high-risk patients or to treat more advanced disease.

In 2008, investigators led by Ching-Shih Chen, PhD, and Clinton reported in the journal *Cancer Research* that a drug designed by Chen blocks prostate cancer progression in an animal model with an aggressive form of the disease.

The agent, called AR-42 (OSU HDAC42) is a histone deacetylase inhibitor that has been shown in animal studies to reactivate epigenetically silenced tumor-suppressor genes. It prevented mice with prostatic intraepithelial neoplasia from developing advanced prostate cancer. "This study showed that an agent with a specific molecular target can dramatically inhibit prostate cancer development in a very aggressive model of the disease," Clinton says.

Favorable Future

With one foot rooted in the lab and the other in the clinic, Clinton has a perspective that enables him and his collaborators to expedite science-based care, particularly for high-risk prostate cancer patients.

"Medicine is moving toward therapies that are increasingly individualized," Zynger says. "If we take steps to further target our therapeutic approach in prostatic adenocarcinoma, we may reduce morbidity while enhancing cure in a large number of men."

"Our mission is to move promising lab findings into the clinic to help realize our vision of creating a cancer-free world sooner rather than later," Clinton says. "Over the next decade I believe we will see clear benefits of integrating multidisciplinary treatment plans into a personalized care plan for each patient and increasing our cure rates for high-risk patients."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU-09067 – Phase II Trial of Temsirolimus and Bevacizumab in Patients with Carcinoid Cancer

HYPOTHESIS: Temsirolimus (CCI-779) and bevacizumab (Avastin) combined will induce stable disease in patients with carcinoid cancer.

RATIONALE: Carcinoid tumors arise from diffuse neuroendocrine cells, most often those in the GI tract, the pulmonary bronchi and pancreas. GI sites are primarily the stomach, ileum and appendix. The tumors may be benign or malignant and cause pain, obstruction and bleeding. Carcinoid tumors may be endocrinologically active, producing a variety of hormones, which may cause carcinoid syndrome. The syndrome is often marked by striking skin color changes, abdominal cramps and diarrhea, right-side endocardial fibrosis and increased excretion of the serotonin metabolite 5-HIAA.

Although curative resection of carcinoid tumors is possible, no effective chemotherapeutic regimen is available for systemic spread, but targeted agents hold promise. VEGF is a critical proangiogenic factor in these hypervascular tumors. In one study of 50 cases of human gastrointestinal neuroendocrine tumors, VEGF expression was associated with poor progression-free survival. Neutralization of VEGF by bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells *in vitro*, and decrease microvessel density and interstitial pressure in tumor xenografts *in vivo*.

In patients, preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab. Bevacizumab has shown promising antitumor activity in preclinical and clinical studies of patients with carcinoid tumors.

Temsirolimus is a cytostatic cell-cycle inhibitor with antitumor properties. The agent specifically inhibits the mammalian target of rapamycin (mTOR), a Ser/Thr kinase involved in the initiation of mRNA translation. Temsirolimus inhibits the growth of a histologically diverse range of tumor cells, with the greatest sensitivity shown by cells derived from central nervous system cancers, leukemia (T-cell), breast cancer, prostate cancer and melanoma. Key features of this agent include its tolerability, unique mechanism of action, ability to arrest cells in the G1 phase, and ability to induce apoptosis.

A phase II study of single agent temsirolimus and a phase II study of bevacizumab plus octreotide in patients with advanced progressive neuroendocrine carcinoma also showed moderate antitumor activity. This study evaluates bevacizumab and temsirolimus as combined therapy in patients with metastatic carcinoid tumors.

Note: OSU-09067 is part of NCI Protocol #8233, a single study that examines the same therapy in five diseases using five parallel phase II clinical trials.

The overall purpose of NCI # 8233 is to evaluate the safety and effectiveness of temsirolimus and bevacizumab in patients with endometrial, ovarian, hepatocellular carcinoma, carcinoid or islet cell cancer. Each of the two drugs individually has shown some benefit in each of these malignancies.

NCI # 8233 is supported by the NCI Cancer Trials Support Unit, and participation is restricted to centers with an NCI-supported phase II contract. The study chair is Charles Erlichman, MD, professor and chairman of Oncology at Mayo Clinic.

http://clinicaltrials.gov/ct2/show/NCT01010126?term=temsirolimus+neuroendocrine&rank=6

AT A GLANCE

Clinical trial OSU-09067

PI: **MANISHA SHAH, MD,** director, Neuroendocrine Tumor Clinic Program

Phone: 614-293-8629

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Eligibility: Histologically/cytologically confirmed carcinoid (neuroendocrine) cancer that is locally advanced, recurrent, metastatic or progressing; Age 18 years or older; Must have measurable disease; Radiation therapy must be completed four weeks or more prior to registration if applicable; ECOG 0-1; Must have tissue available from the primary tumor or metastases for tumor studies.

ProjectONE
Construction Kicks Off on Ohio State's New Cancer Hospital

A new era of cancer care and research at The Ohio State University began June 18th when the University broke ground for ProjectONE, a $1 billion initiative that includes construction of a 17-story medical tower that will house a reimagined James Cancer Hospital and Solove Research Institute and an equally innovative critical care hospital.

Completion of the new 276-bed cancer hospital and 144-bed critical care hospital is slated for 2014.

The design of the tower will place cancer researchers near clinicians to promote their interaction and to expedite discovery and its translation to patient care. It emphasizes the education of future healthcare professionals, particularly in "P4 Medicine"—health care that is

predictive, preventive, personalized and participatory.

The largest construction initiative in Ohio State University history, ProjectONE will create 5,000 construction jobs over the next four years and at least 6,000 full-time positions at the University from 2008-15.

OSUCCC Director and James CEO Michael A. Caligiuri, MD, spoke at the June ceremony, noting that the groundbreaking was held nearly 20 years to the day that marked the opening of the present James Cancer Hospital in July 1990.

"We're all here today because a generation of people before us was willing to invest in the future, to create the environment in which we now prosper," Caligiuri said. "Now, it is our turn to build the future for the next generation."

OSUCCC-James events calendar

GASTROINTESTINAL CANCERS 2010: A MULTIDISCIPLINARY APPROACH TO PREVENTION, DIAGNOSIS AND TREATMENT

October 8

OSUCCC-James researchers are applying a novel approach to drug discovery using computational and genomic methods to identify agents that alter tumor behavior by striking several molecular targets at once. Topics include updates on therapeutic procedures, recent advances in the treatment of advanced gastro-esophageal cancers and the management of colorectal and pancreatic cancers.

For more information and to register: http://cancer.osu.edu/research/ researcheducation/meetingsconferences/giconference/pages/index.aspx

THIRD ANNUAL PERSONALIZED HEALTH CARE NATIONAL CONFERENCE: ADVANCING PREDICTIVE, PREVENTIVE, PERSONALIZED AND PARTICIPATORY MEDICINE

October 14-15

Topics include state-of-the-art developments in genomics medicine and their potential in predicting clinical events; developing and implementing a new model of preventive and prospective care; delivering the promise of pharmacogenomics and targeted therapy; and engaging and empowering patients and consumers for participatory health care.

For more information and to register, visit http://phc.osumc.edu.

AFTER WORD

RIDERS REFLECT ON PELOTONIA 2010

Some 4,047 riders participated in the 2010 Pelotonia bicycling event held Aug. 20-22 to raise money for cancer research at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. Here are excerpts from a few of the notes ride organizers received after the event.

We were all lined up to go at the starting line at 7 a.m. There was much excitement as we headed out into the sunrise, and supporters rang cowbells and cheered for us. As we approached the outskirts of the city I really wondered what I had gotten myself into and if I ought to just give up! But right at that time another girl started riding next to me, and we got to talking. She was riding for her dad who had passed away. I thought about all those people who have struggled with their treatments and felt like they could not go on, and I just kept on peddling for them.

Every time along the way I wanted to quit, there was someone cheering on the roadside to spur me on, or another rider saying "You can do it!" (or good-naturedly teasing me about my pathetic cardiovascular conditioning). And I just kept thinking about all of you who have supported me, and about how cancer has touched you, and the people that you want to find a cure for.

I believe that research is leading us to a world where HOPE will be foremost in the minds of everyone who hears the words, "You have cancer." Because the new treatments will be so successful, they will have no reason not to have hope. I believe that this ride, and the money that is going to the James Cancer Hospital and Solove Research Institute, is going to have a profound impact and will bring us closer to that world even sooner than we have dreamed.

Jackie

I rode the 100+ mile route from Columbus to Athens. Last year at this time, I was participating in the Flavopiridol clinical trial. During the trial, I told my wife that if I was able to I'd like to ride in Pelotonia this year. After getting the message from Dr. Byrd on March 1st that I was "stable," I registered for Pelotonia and put in over 1,000 miles on my bike between then and last weekend.

Riding into Athens late Saturday afternoon and making that final turn into the Ohio University campus was a dream come true. My sincere thanks to all who played a part in my treatment.

Walter

I want to share the story of a fellow rider who encouraged me to continue when the going got tough. At our 43-mile lunch stop, my [partner] and I noticed an elderly gentleman who was cycling as well. We thought he must have gone to the wrong lunch tent because it appeared that he was continuing on to do the 102-mile ride, which seemed impossible at his age. However, he was continuing on, and every time I wanted to give up, I thought of him. Not only did we see him at the 102-mile finish later that day, on Sunday we found out that he spent the night in Athens and rode the entire 180 miles, and that he is 80 years old! He even took a wrong turn and did a few extra miles on accident. He says it was the ride of his life for the love of his life – his wife of 57 years who is celebrating her 22nd year as a cancer survivor. Pretty inspiring stuff.

I rode for Grandma, Gary, Betty, Ruth, Anne, Sylvia, and all my friends, co-workers, patients and relatives who have fought cancer, and I learned that nothing is impossible – not even a cancer-free world!

Heather

For more information about Pelotonia, visit **http://www.pelotonia.org.** If you have questions about Pelotonia, please e-mail **questions@pelotonia.org.**

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FUNDRAISING

PELOTONIA

Revenue Funds "Idea Grants" and Student Fellowships at Ohio State

Last year's inaugural Pelotonia cycling tour attracted 2,265 riders and raised more than $4.5 million for cancer research at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC-James).

A portion of that revenue has been awarded as two-year Idea Grants to OSUCCC-James investigators, and as fellowships to promising undergraduate, medical, graduate and postgraduate researchers.

Idea Grants were awarded to 10 teams of OSUCCC-James research groups to pursue high-risk, high-reward studies.

"Pelotonia Idea Grants provide seed funding for ideas that can lead to critical preliminary data, new collaborations, and ultimately discovery – and that, in turn, can lead to breakthroughs in science, prevention and treatments, and to larger grants," says Michael A. Caligiuri, MD, director of the OSUCCC and CEO of The James.

Idea grant applications were judged via a peer-review process that considered potential for discovery, publication, clinical trials, patents and leverage for subsequent funding from the National Cancer Institute.

Twenty-nine Pelotonia fellowships have been awarded to Ohio State undergraduates, one medical student and two postdoctoral researchers. The students will conduct cancer research in various laboratories at the OSUCCC-James during 2010-11. (The selection of graduate and additional postgraduate fellowships was under way at this writing.)

Pelotonia Undergraduate Fellowships were available to all Ohio State University undergraduate students in any field of study. Winning applications were selected by an 11-member committee based on applicant strengths and research potential, mentor qualifications, and relevance of the project to cancer research.

More than 4,000 riders and volunteers participated in this

year's Pelotonia event (see **www.pelotonia.org**). For more about the Pelotonia grant and fellowship awardees, see **http://cancer.osu.edu/research/researcheducation/pelotoniafellowshipprogram/pages/index.aspx**

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

FINDING POSITIVES TO BALANCE A TRIPLE NEGATIVE

Triple Negative Breast Cancer (TNBC) disproportionately affects African-American women and younger women and has few treatment options beyond chemotherapy. OSUCCC-James physicians and researchers are working to identify new molecular biomarkers and new avenues for targeted therapies, and conducting several investigator-initiated clinical trials to improve TNBC therapy.

WHEREFORE E2F?

The E2F family of transcription factors is conserved from roundworms to mammals. Ohio State's Gustavo Leone and his collaborators have shown that much of what has been learned about E2Fs *in vitro* doesn't hold up *in vivo*. Their work has produced more than two dozen papers in top journals, including five in *Nature,* and taken them in unexpected directions.