SUMMER | 2013

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

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

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

inside ▸▸ FOCUS ON MELANOMA | COLORECTAL CANCER ▸

Helping Ourselves

One of the most exciting projects recently launched and led by Ohio State's cancer program is a statewide initiative to screen newly diagnosed colorectal cancer (CRC).

About 3 percent of CRC cases stem from Lynch syndrome (LS), which is characterized by inherited mutations in one of four genes for DNA-repair proteins. Each CRC patient with LS has, on average, three relatives with LS, heightening their risk for cancer. As you will read in "Going Statewide" in this issue of *Frontiers*, these screenings, embodied in the Ohio Colorectal Cancer Prevention Initiative (OCCPI), could save many lives by identifying those at risk so they can take precautionary measures.

Making this project even more extraordinary, it is supported in large part by funds from Pelotonia, an annual grassroots bicycle tour that raises millions of dollars for cancer research at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). In just four years, Pelotonia has become the nation's largest single-event biking fundraiser as measured by the number of riders. Pelotonia 12 drew 6,212 riders from 43 states and three countries, as well as 3,141 virtual riders. Collectively these individuals, along with more than 80,000 donors, raised nearly $16.9 million, bringing the four-year total for this event to more than $42 million.

That's the kind of financial firepower we need to help offset dwindling government allocations for cancer research so we can keep pursuing such innovative endeavors as the OCCPI – especially since the federal funding picture will likely remain dire for the near future.

Harold Varmus, MD, director of the National Cancer Institute (NCI), reported in May that the NCI budget for the current year will be about $4.78 billion, or $293 million less than in fiscal 2012 – a 5.8-percent reduction. He said this is attributable mainly to sequestration, the automatic across-the-board cuts in federal spending that began last March, along with further reductions mandated by the Department of Health and Human Services to support various Departmental obligations.

These cuts require us to do what we can to help ourselves. Pelotonia 13 will unfold from Aug. 9-11 in central Ohio, and I strongly encourage anyone who shares our vision of creating a cancer-free world to join us as a rider, virtual rider, donor or volunteer. More information is available at www.pelotonia.org. I hope to see you on the road.

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

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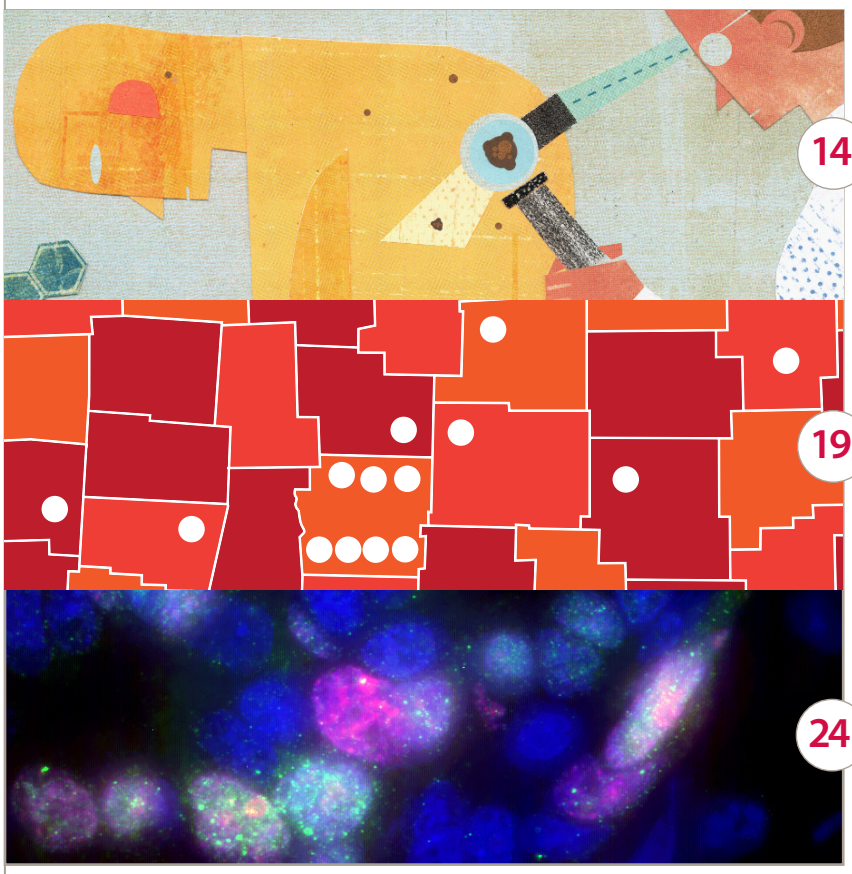

FEATURES

ON THE COVER:
The OSUCCC – James offers research-based melanoma care.
Story on page 14.

A Game-Changer

THE PERSONAL CANCER GENOME AND PRECISION CANCER TRIALS

Genomic research is turning cancer into multiple orphan diseases, which poses challenges for how we do clinical trials.

By **SAMEEK ROYCHOWDHURY, MD, PhD,** *assistant professor of Internal Medicine and of Pharmacology*

Clinical trials traditionally have been designed to treat patients with a specific disease and to treat all patients on the trial the same way. For example, we would evaluate a new drug for breast cancer by giving the agent to a group of breast-cancer patients, and if enough of them benefited, we would judge the drug a good one. If few patients benefited, the drug would likely be abandoned.

During such disease-based trials, a small number of participants, maybe 1-10 percent, can benefit amazingly from the drug, but further development of the agent is unlikely because clinical trials as usually done are impractical for small numbers of patients.

Genomics is now helping us understand why some patients respond differently to therapy; although all the women in our hypothetical trial have cancer of the breast, not all breast cancers are the same.

Traditionally, we diagnose breast cancer, leukemia or prostate cancer by examining the way cells appear under a microscope. This tissue-of-origin approach has provided a histology-based or "microscopic classification" of cancer that has been used for decades.

Histologically, malignancies such as breast and prostate cancer appear to be homogenous. But cancer genomic studies, such as The Cancer Genome Atlas, demonstrate that these cancers are heterogeneous, with sets of mutations and other genetic changes that allow their grouping into subtypes (breast cancer may have more than 25). Each subtype may be a different disease that requires different therapy based on the tumor's genomics. These molecular subtypes are driving the development of targeted drugs and influencing how we do clinical trials.

For example, a genetic pathway called PI3 kinase (PI3K) is genomically altered or mutated in up to 25 percent of breast cancers, and we have disease- and mutation-based trials such as OSU-12127 evaluating a *PI3K* inhibitor for breast-cancer patients with a mutation in a *PI3K* gene. In this trial, a smart drug specifically inhibits the *PI3K* kinase gene pathway. In contrast, in other cancers, genomic targets are less common, amounting to just 1-10 percent of cases, which effectively turns most cancers into multiple "orphan diseases."

But how do we complete clinical trials for a gene mutated in only 1 percent of breast cancer or across many different cancers? If a trial needs 100 patients, 10,000 patients must be screened. That's very challenging; traditional clinical trials are not feasible. Such orphan diseases will require a personalized therapeutic approach, and, consequently, clinical-trial designs are being developed to accommodate this new reality.

Some cancer centers, including the OSUCCC – James, are

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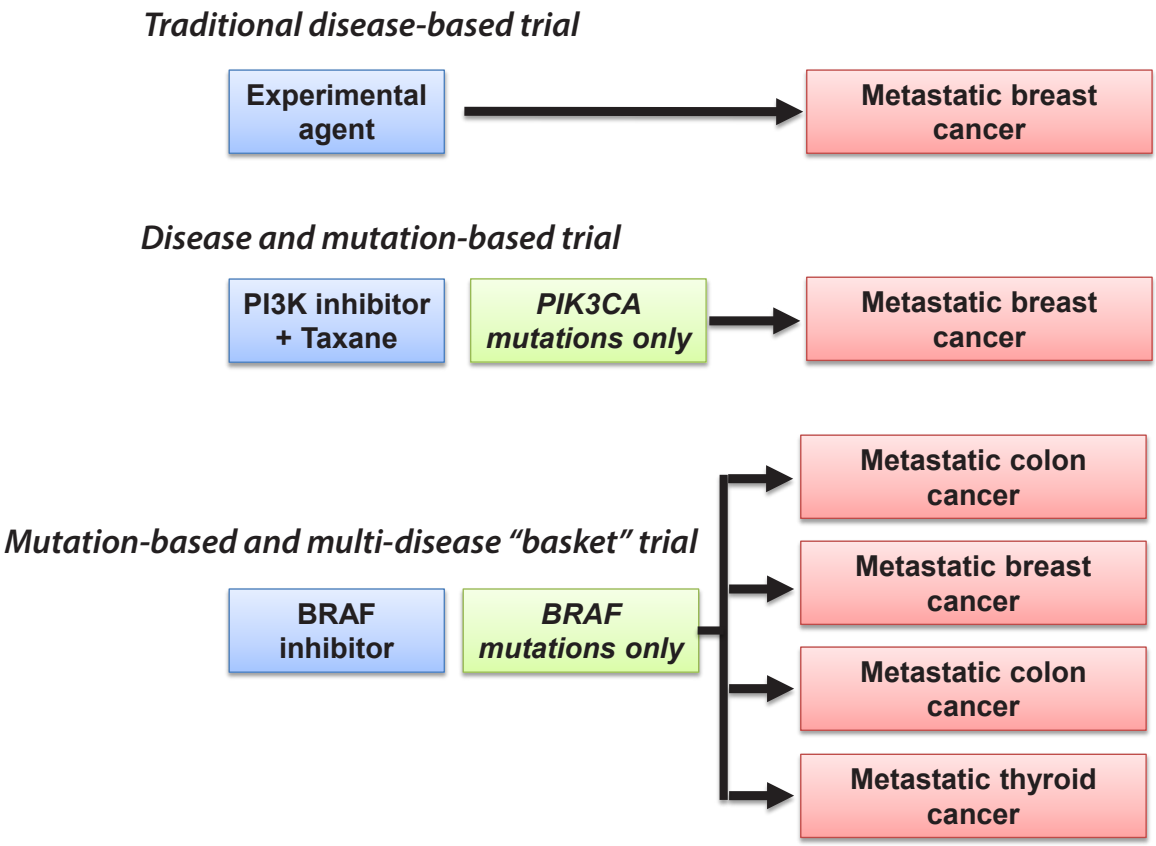
PRECISION CANCER TRIALS



developing a new type of trial design that "baskets" together different diseases that share a molecular target in one trial (see figure).

In some instances, if we know enough about the molecular subsets of a disease, we may be able to enroll patients into trials that have a drug that matches the molecular makeup of their cancer. To facilitate these trials, cancer centers must be capable of providing a personalized molecular view of an individual's cancer.

Gene sequencing technology called next-generation sequencing will enable oncologists to determine which of 200-plus significant genes are altered in a patient's cancer and to use this information to guide therapy. Ohio State is among the leaders in the country in promoting and championing this precision oncology strategy.

In summary, to move forward into the age of precision oncology we need to accomplish four objectives:

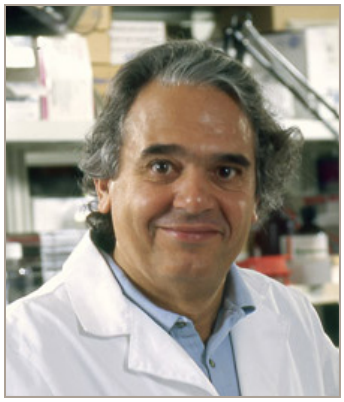
1. Complete the molecular characterization of cancer;
2. Develop drugs that target the molecular defects that drive cancer;
3. Implement next-generation sequencing to molecularly characterize the tumors of patients in the clinic;
4. Launch innovative clinical trials that utilize these molecular portraits.

Traditional clinical trials evaluate agents in groups of patients with the same malignancy based on microscopic examination of tumor cells (top). When agents become available that target a specific mutation, disease- and mutation-based trials recruit patients with the same histologic disease that also has the target mutation (middle). As genomic studies identify more cancer subtypes and reduce the number of patients requiring a particular therapy, new trial designs are needed. The mutation-based, multi-disease "basket" trial (bottom) combines patients with different malignancies driven by the same mutation to evaluate an inhibitor that targets that mutation.

BREAST CANCER

CLINICAL IMPLICATIONS

New Agent May Control Breast Cancer Growth and Spread



CARLO CROCE, MD,
professor and chair, Molecular Virology, Immunology and Medical Genetics; director, Human Cancer Genetics and the John W. Wolfe Chair in Human Cancer Genetics

A study led by researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) suggests an experimental drug can slow breast-cancer aggressiveness, reverse resistance to the drug fulvestrant and maybe improve efficacy of other breast-cancer drugs.

Findings from the laboratory and animal study might offer a new strategy for treating breast cancer. The drug, called AS1411, belongs to a class of agents called G-rich aptamers. It works by blocking the cell's production of microRNA, molecules that help cells control the amount and kinds of proteins they make. Abnormal levels of certain microRNAs are a hallmark of many cancers.

Specifically, the drug inhibits a protein called nucleolin that plays a critical role in the microRNA maturation process.

"This study of the role of nucleolin in microRNA regulation has clear clinical implications," says principal investigator Carlo Croce, MD, director of Human Cancer Genetics at Ohio State and a member of the Molecular Biology and Cancer Genetics Program (MBCG) at the OSUCCC – James.

"It supports a novel treatment for breast cancer that reduces cancer aggressiveness and restores drug sensitivity by inhibiting the processing of specific microRNAs that are highly expressed in cancers."

First author Flavia Pichiorri, PhD, assistant professor of Hematology and also a member of the MBCG Program, notes that nucleolin is a promising therapeutic target for microRNA modulation in cancer cells.

"To our knowledge, this is the first large study to show a clear association between nucleolin and specific microRNAs that are causally involved in cancer," Pichiorri says. "We also believe it's the first study to show that targeting nucleolin with a G-rich aptamer can control breast-cancer metastasis in an animal model through microRNA regulation."

Published in the Journal of Experimental Medicine

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

PROSTATE CANCER

ENZYME INHIBITION

Study Shows How Vitamin E Can Help Prevent Cancer

Researchers at the OSUCCC – James have identified an elusive anticancer property of vitamin E that has long been presumed to exist but difficult to find.

Many animal studies have suggested that vitamin E could prevent cancer, but human clinical trials following up on those findings have not shown the same benefit.

In this study, researchers showed in prostate cancer cells that one form of vitamin E inhibits the activation of an enzyme that is essential for cancer cell survival. Loss of the enzyme, Akt, led to tumor cell death. The vitamin had no negative effect on normal cells.

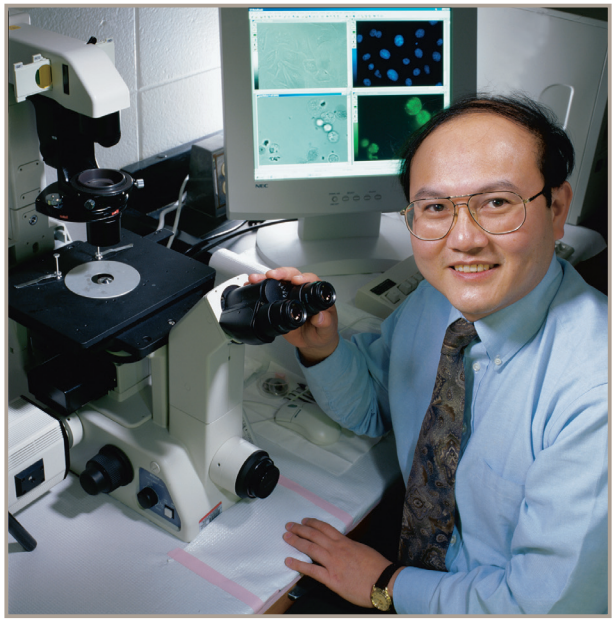
"This is the first demonstration of a unique mechanism of how vitamin E can have some benefit in terms of cancer prevention and treatment," says lead author Ching-Shih Chen, PhD, professor of Medicinal Chemistry and Pharmacognosy at Ohio State, and an investigator in the Molecular Carcinogenesis and Chemoprevention Program at the OSUCCC – James.

But Chen cautions that taking a typical vitamin E supplement won't offer this benefit for at least two reasons: The most affordable supplements are synthetic and based predominantly on a form of the vitamin that did not fight cancer as effectively in this study; and the human body can't absorb the high doses that appear to be required to achieve the anticancer effect.

"Our goal," Chen says, "is to develop a safe pill at the right dose that people could take every day for cancer prevention. It takes time to optimize the formulation and the dose." He has filed an invention disclosure with the University, and Ohio State has filed a patent application for the agent.

Vitamin E occurs in numerous forms based on chemical structure; the most commonly known form belongs to a variety called tocopherols. Of the tocopherols tested in this study, the gamma form had the most anticancer potency.

Published in the journal Science Signaling



CHING-SHIH CHEN, PhD
professor of Medicinal Chemistry and Pharmacognosy, member of the Molecular Carcinogenesis and Chemoprevention Program, and the Lucius A. Wing Chair of Cancer Research & Therapy

SUBSET SIGNATURES

Triple-Negative Breast Cancer Subtypes Identified Using microRNA

CHARLES SHAPIRO, MD,
director of Breast Medical Oncology at the OSUCCC – James and professor of Internal Medicine at Ohio State

A large-scale study of triple-negative breast cancer shows that small molecules called microRNAs can be used to define four subtypes of this aggressive malignancy.

The findings, by researchers at the OSUCCC – James who are working with collaborators in Italy, could lead to new screening methods, prognostic markers and perhaps targeted treatments for this aggressive and often-fatal form of breast cancer.

"Treating women with triple-negative breast cancer is challenging because this malignancy can be very different genetically from one patient to another," says co-senior investigator Charles Shapiro, MD, director of Breast Medical Oncology at the OSUCCC – James and professor of Internal Medicine at Ohio State. "We believe these microRNA signatures define novel subsets of triple-negative breast cancer and offer new insights into the biology of the disease and better ways to treat these patients."

The microRNAs that compose the signatures are involved in regulating cell growth, proliferation and survival, and also in cell movement and migration.

"These findings strongly suggest that microRNAs play an important role in triple-negative breast cancer and might be used to better identify the most effective treatment for a patient's tumor," says co-senior investigator and researcher Kay Huebner, PhD, professor of Molecular Virology, Immunology and Medical Genetics at Ohio State.

"Several of the deregulated microRNAs we found in the cancer samples are involved in chemoresistance or radioresistance. MicroRNA profiles can help us improve and personalize therapies for individual patients," she says.

Triple-negative breast cancer accounts for about 15 percent of all breast cancers. It is characterized by cancer cells that lack estrogen and progesterone receptors, and by overexpression of the HER2 receptor. For this reason, these tumors do not respond to hormone therapies or HER2-targeted treatments.

Published in the journal PLOS ONE

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

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HEAD AND NECK CANCER

RE-EMPOWERING P53

Drug Restores Cell Suicide in HPV-Related Head and Neck Cancer

Researchers have designed a drug to block a newly discovered mechanism by which the human papillomavirus (HPV) causes head and neck cancer. Though more study is needed, they believe the new agent might offer a safer treatment for these tumors when combined with a tapered dose of standard chemotherapy.

HPV-positive head and neck cancer has become three times more common since the 1970s, and it could reach epidemic levels in the future, say researchers at the OSUCCC – James who led the study.

"We believe these findings will help meet the real need for more effective and safer therapy for a growing number of HPV-positive head and neck cancer patients," says principal investigator Quintin Pan, PhD, associate professor of Otolaryngology at Ohio State and a member of the Experimental Therapeutics Program at the OSUCCC – James.

The research, which mainly used head and neck cancer cells, shows that a protein produced by the virus blocks a protein made by the host cell. The cell protein, called p300, regulates a gene called *p53* that both controls cell division and protects the body against cancer by causing cells to die before they become malignant.

By blocking the cell protein, HPV forces the host cell to live instead of die and to proliferate and form tumors. The prospective new drug, called CH1iB, prevents the viral protein from binding with the cell protein. This restores the function of the *p53* tumor-suppressor gene and triggers the death of the cancer cells.

"Our study revealed a new mechanism for *p53* inactivation in HPV-positive head and neck cancer, and this allowed us to develop an agent that disrupts that interaction and reactivates *p53* in this disease," Pan says. "Our preclinical studies show CH1iB can reactivate *p53* and eliminate HPV-positive head and neck cancer cells."

Published in the journal Oncogene

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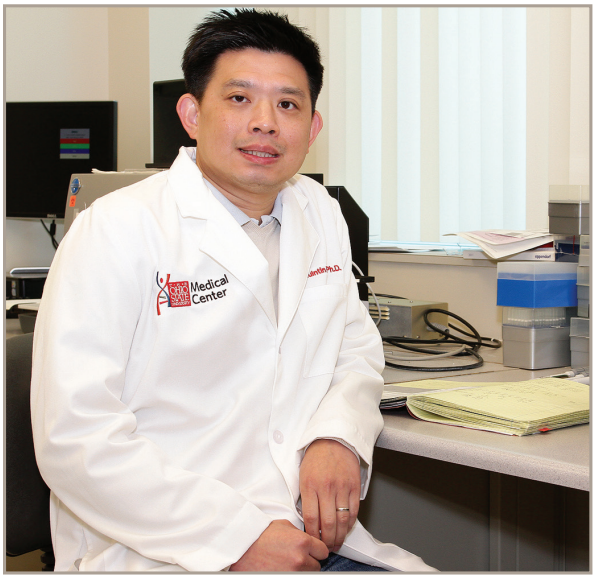

QUINTIN PAN, PhD,
associate professor of Otolaryngology at Ohio State and a member of the Experimental Therapeutics Program at the OSUCCC – James

MOLECULAR MIGHT

Small Molecules in Blood May Gauge Radiation Effects After Exposure

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

OSUCCC – James researchers have identified molecules in the bloodstream that might accurately gauge the likelihood of radiation illness after exposure to ionizing radiation.

The animal study shows that X-rays or gamma rays alter the levels of certain molecules called microRNA in the blood in a predictable way. If verified in humans, the findings could lead to new methods for rapidly identifying people at risk for acute radiation syndrome after occupational exposures or accidents such as the Fukushima Daiichi nuclear reactor incident.

The microRNA markers might also help doctors plan radiation therapy for individual patients by taking into account how different people respond to radiation treatment, the researchers say.

"Our study reports the identification of a panel of microRNA markers in mice whose serum levels provide an estimate of radiation response and of the dose received after an exposure has occurred," says senior author Arnab Chakravarti, MD, professor and chair of the Department of Radiation Oncology at Ohio State, where he also is co-director of the Brain Tumor Program.

"Accurate dose evaluation is critical for making medical decisions and the timely administration of therapy to prevent or reduce acute and late effects," Chakravarti says.

The findings might also one day allow doctors to evaluate radiation toxicity during the course of therapy based on an individual's biology. "This would particularly benefit leukemia and lymphoma patients who receive total body irradiation in preparation for stem-cell transplantation," Chakravarti says.

First author Naduparambil Jacob, PhD, a research assistant professor of Radiation Oncology, says the study could be an important step in the development of biological dosimetry, or biodosimetry, a technology for identifying people at risk for acute radiation illnesses that develop within weeks of radiation exposure, and for cancers and degenerative diseases that can occur months or years later.

Published in the journal PLOS ONE

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

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CHRONIC LYMPHOCYTIC LEUKEMIA

HEMATOLOGIC MALIGNANCIES MARKER UNMASKED

Study Identifies Possible Acute Leukemia Marker and Treatment Target

A study led by researchers at the OSUCCC – James has identified microRNA-155 as an independent prognostic marker and treatment target in patients with acute myeloid leukemia (AML) that has normal-looking chromosomes (i.e., cytogenetically normal AML, or CN-AML).

The study found that, when microRNA-155 (miR-155) is present at abnormally high levels in CN-AML cells, patients are less likely to have a complete remission, and they experience a shorter disease-free period and shorter overall survival. The effect is independent of other known prognostic gene mutations present in the cells.

The findings suggest that miR-155 plays a pivotal role in CN-AML development and could be a target for emerging drugs designed to inhibit microRNAs, says first author Guido Marcucci, MD, a leukemia specialist and associate director for translational research at the OSUCCC – James.

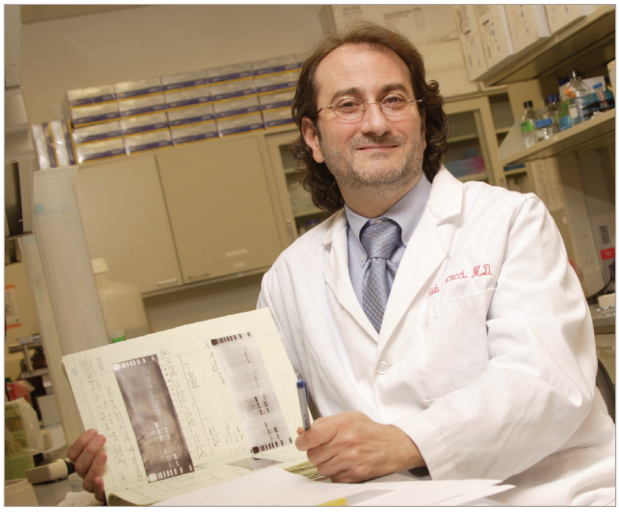
"MiR-155 would be relatively easy to measure at diagnosis," Marcucci says. "We believe it will prove to be a good marker for stratifying patients according to recurrence risk and a good target for emerging compounds designed to inhibit microRNAs."

"Overall, our findings indicate that miR-155 expression is a strong and independent prognostic marker in CN-AML, and they provide clinical validation of data from preclinical models that support a crucial role of miR-155 in leukemia," says principal investigator Clara D. Bloomfield, MD, a Distinguished University Professor who serves as cancer scholar and senior adviser to the OSUCCC – James.

The researchers also note that, because a molecule called NF-kB is believed to regulate miR-155, treatments that inhibit that molecule might also help patients with high miR-155 levels.

Cells use microRNA molecules to help regulate the kinds and amount of proteins they make. Abnormal levels of certain microRNAs are likely to play a key role in cancer development. Abnormally high expression of miR-155 is associated with lymphoma, aggressive chronic leukemias and certain solid tumors, and microRNA levels have been associated with patient survival.

Published in the Journal of Clinical Oncology *with an accompanying editorial and an "Understanding the Pathway" article*



GUIDO MARCUCCI, MD,
leukemia specialist, associate director for translational research at the OSUCCC – James, and The Charles Austin Doan Chair of Medicine

OF NOTE

Recent Recognitions of OSUCCC – James Physicians and Researchers

GRANTS

MICHAEL A. CALIGIURI, MD, *director of the OSUCCC and CEO of The James, and E. Antonio Chiocca, MD, PhD, of Brigham and Women's Hospital in Boston,* **have received a five-year National Cancer Institute (NCI) Program Project Grant of approximately $8.4 million (CA163205-01A1) titled "Circumventing Barriers to Effective Oncolytic Virotherapy of Malignant Gliomas."** *Read more*

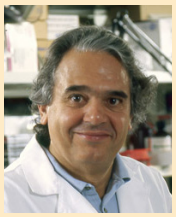
CHANDAN K. SEN, PhD, *professor and vice chair for research in the Department of Surgery, director of the Comprehensive Wound Center and of the Center of Regenerative Medicine and Cell Based Therapies, associate dean for translational and applied research in the College of Medicine, and an OSUCCC – James investigator,* **is co-principal investigator on a five-year, $2.1 million National Institute of Nursing Research grant (NR013898-01) titled "Biofilms and Immunity in Chronic Wounds."**

SUJIT BASU, MD, PhD, *associate professor of Pathology and a researcher in the OSUCCC – James Experimental Therapeutics Program,* **is principal investigator on a five-year, $1.5 million NCI grant (CA169158) titled "Dopamine as a Therapeutic Agent in Stomach Cancer."**

AWARDS AND HONORS

JOHN C. BYRD, MD, *director, Division of Hematology and professor of Medicine, of Medicinal Chemistry and of Veterinary Biosciences, and the D. Warren Brown Designated Chair in Leukemia Research,* **has received the Emil J. Freireich Award for clinical cancer research.** *The award is presented annually by MD Anderson Cancer Center to candidates 55 and younger who have made outstanding contributions to clinical research. Read more*

DAVID CARBONE, MD, PhD, *professor of Medical Oncology and a lung-cancer specialist,* **has received the Sixth Annual Landon Foundation-AACR Innovator Award for International Collaboration in Cancer Research.** *The honor recognizes meritorious research conducted collaboratively by investigators in different countries.*



CARLO CROCE, MD, *professor and chair of the Department of Molecular Virology, Immunology and Medical Genetics, and director of Human Cancer Genetics,* **has been elected to the first class of Fellows of the American Association of Cancer Research (AACR).** *Read more. In addition, he has been awarded the Princess Takamatsu Memorial Lectureship by the AACR, which recognizes an individual whose work has had a far-reaching impact on the detection, diagnosis, treatment or prevention of cancer, and who embodies the dedication of Princess Takamatsu of Japan to multinational collaboration.*

LEADERSHIP ACTIVITIES AND APPOINTMENTS

STEVEN CLINTON, MD, PhD, *professor in the Division of Medical Oncology, and leader of the Molecular Carcinogenesis and Chemoprevention Program at the OSUCCC – James,* **has been appointed to serve on the national 2015 Dietary Guidelines Advisory Committee. Clinton and 14 other nationally recognized experts were appointed to the committee by the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA).** *The committee's recommendations will serve as a basis for the eighth edition of the Dietary Guidelines for Americans, published jointly by HHS and USDA.*

TRAINEE RECOGNITION

PARVATHI RANGANATHAN, PhD, *a postdoctoral research associate at the OSUCCC – James,* **has received a three-year Leukemia & Lymphoma Society Special Fellow Award of up to $65,000 per year to support her research in the laboratory of Ramiro Garzon, MD, assistant professor of Hematology.**

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

FACULTY AND PROGRAMS

FLOOR BACKES, MD, has joined the cancer program as an assistant professor of Obstetrics and Gynecology in the Division of Gynecologic Oncology. *Her clinical interests include all aspects of gynecologic oncology – minimally invasive and radical surgery as well as chemotherapy. Her research interests include clinical trials, sentinel lymph node mapping, and biomarkers for endometrial cancer treatment and outcomes.*

JOSEPH FLYNN, DO, MPH, FACP, *associate professor of Internal Medicine,* **has been named associate physician-in-chief at The James.** *He is serving as co-director of the Division of Hematology and director of clinical operations within the Division.* Read more

JOANNA GRODEN, PhD, *professor of Molecular Virology, Immunology and Medical Genetics,* **has been named vice dean for research for Ohio State's College of Medicine (COM).** *She succeeds OSUCCC – James investigator* **CLAY MARSH, MD,** *who is now vice dean for innovation for the COM.* Read more

CHRISTINA LISCYNESKY, MD, has joined the cancer program as an assistant professor clinical in Ohio State's Department of Internal Medicine, Division of Infectious Diseases. *Her clinical interests include catheter-related bloodstream infections, immunocompromised hosts and hospital epidemiology.*

VINAY K. PUDUVALLI, MD, has joined the cancer program as a professor and director of the Division of Neuro-Oncology in Ohio State's Department of Neurological Surgery. *His clinical interests include the use of new therapies for malignant gliomas. His research interests include identifying ways to accelerate tumor-cell death in brain tumors, and novel therapies for malignant gliomas. Puduvalli was recruited from M.D. Anderson Cancer Center.* Read more

ROBERT STILLMAN, BSN, MA, RN, has joined the cancer program as director of Clinical Informatics. *He came to the OSUCCC – James from Trinity Health in Farmington Hills, Mich., where he served as clinical applications manager.*

JENNIFER WOYACH, MD, has joined the cancer program as an assistant professor in Ohio State's Department of Internal Medicine, Division of Hematology. *Her clinical interests include chronic lymphocytic leukemia (CLL) and other lymphoid malignancies. Her research interests include experimental therapeutics for CLL and other hematologic malignancies.*

The new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute is steadily progressing toward completion in September 2014. It will provide clinicians, trainees and researchers with a collaborative environment that integrates research, education and patient care (see page 31).

THE MOST DEADLY SKIN CANCER

Clinical and translational research at Ohio State and elsewhere are improving care for people with melanoma, one of the few cancers that is increasing in incidence

BY BOB HECKER

Melanoma is the most lethal form of skin cancer, and its incidence has been on the rise for three decades or more in the United States, according to the American Cancer Society (ACS). And though it accounts for less than 5 percent of all skin-cancer cases, it is responsible for the vast majority of skin-cancer deaths. The ACS also notes that:

- An estimated 77,000 people will be diagnosed with melanoma in 2013, and nearly 9,500 will die of the disease;
- Caucasians have a 23-times greater lifetime risk than African-Americans for developing the disease;
- Melanoma incidence rates for Caucasians rose by almost 3 percent per year from 2005-2009.

Despite the upward trajectory and poor survival rates, Kari Kendra, MD, PhD, who leads the expanding melanoma program at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), says there is cause for optimism.

"The FDA has approved three drugs—vemurafenib, dabrafenib and ipilimumab—for melanoma treatment in the past two years," says Kendra, a medical oncologist and researcher who chairs the Melanoma Disease-Specific Committee at the OSUCCC – James. "Before that, there hadn't been a new one approved for about 20 years."

Vemurafenib is approved for treating late-stage disease and targets the BRAF V600E gene mutations. *BRAF* mutations occur

"We've gone from therapies that help a small number of people for a short time to therapies that help a larger number of people for a short time. With additional research, we will develop more therapies that will help larger numbers of people for longer periods of time and bring about better outcomes."

—— Kari Kendra, MD, PhD

KARI KENDRA, MD, PHD, *who leads the expanding melanoma program at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James)*

in about 60 percent of melanomas and signal a poor prognosis. Dabrafenib also targets *BRAF* mutations, and ipilimumab is a monoclonal antibody designed to boost immune responses to melanoma cells.

Kendra says these agents and others in development, including some by OSUCCC – James investigators, are offering more options for biologic therapies that enhance the body's antitumor responses and for targeted therapies based on mutational analysis.

"If we can identify genetic mutations in tumors, we can apply a therapy that targets them," she explains. "With newer therapies, we are seeing enhanced response rates, and we are working toward obtaining better survival rates." (See box.)

COMPREHENSIVE PROGRAM

The comprehensive, multidisciplinary and research-based melanoma program at the OSUCCC – James provides patient care that involves innovative immunotherapies, targeted therapies with novel mechanisms of action, and programs that offer patient education and support.

"What sets us apart is the quality and number of our clinical trials, which make promising new drugs and treatment strategies available to patients," Kendra says. "We also take innovative approaches to therapy and have an incredible support team for patients during treatment."

"We have the support people necessary to handle melanoma cases and deal with any problems that may arise, and we hold interactive discussions in at least five multidisciplinary patient conferences per month," adds Thomas Olencki, DO, a medical oncologist and researcher who specializes in cutaneous and ocular melanoma, and other skin cancers.

Patient volume for ocular melanoma at the OSUCCC – James has tripled in the past few years following the addition of ophthalmologist Colleen Cebulla, MD, who has clinical and research interests in ocular oncology, Olencki notes.

Surgical oncologist, clinical geneticist and researcher Doreen Agnese, MD, often provides the initial treatment after a melanoma diagnosis. "I assess cutaneous, subcutaneous and nodal masses and resect metastatic disease," she says.

"Surgeons, medical oncologists, radiation oncologists and dermatologists work closely to provide coordinated care for our melanoma patients, including close surveillance of future skin lesions," says Evan Wuthrick, MD, radiation oncologist and clinical researcher.

Wuthrick notes that radiation therapy is used to treat melanoma in: areas of the body where surgery would be difficult or risky; metastatic tumors in the brain and spine to improve quality of life; and lymph node chains after surgery in patients at high risk of recurrence in the nodes.

WHY THE RISING INCIDENCE?

Risk factors for melanoma include a personal or family history of the

Melanoma Survival Rates

Stage	5-year	10-year
I	91	89
II	70	55
III	45	35
IV	10	5

Average survival for metastatic melanoma: **6-9 months**

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disease, the presence of atypical or numerous moles (more than 50), and immune suppression. Added to that are environmental, social and dietary factors that might increase melanoma incidence, Olencki says. These include depletion of Earth's ozone layer, widespread use of tanning devices, prolonged exposure to sunlight without proper protection, and nutrition low in fruits and vegetables, many of which have anticancer properties.

Tatiana Oberyszyn, PhD, a research pathologist who studies skin cancer at the OSUCCC – James, examines the effects of ultraviolet (UV) radiation in sunlight on the skin.

"UVB, which causes sunburn, was once believed to be the most important wavelength in the development of skin cancer, so initial sunscreens were designed to block UVB but not the longer wavelength, UVA, which penetrates deep into the skin," Oberyszyn explains. "We now know that UVA exposure is also a factor, and most sunscreens today block both wavelengths.

"But there was a period when people used sunscreens that blocked only UVB and were actually exposing themselves to more UVA, which may translate to the increases we've seen in the past 30 years."

Oberyszyn says indoor tanning beds and sun lamps are another big factor, particularly among women, pre-teens and teenagers, who are developing skin cancers at earlier ages. Kendra says she has treated melanoma patients as young as age 14.

In 2009, the International Agency for Research on Cancer (IARC), part of the World Health Organization, classified UV-emitting tanning devices that emit ultraviolet radiation as "carcinogenic to humans." The IARC noted that, "Combined analysis of over 20 epidemiological studies shows that the risk of cutaneous melanoma is increased by 75 percent when the use of tanning devices starts before age 30."

People also tend to wear fewer layers of clothing when outdoors in warm weather and mistakenly believe that the clothes they do wear protect them from UV exposure, Oberyszyn says. "And then there's the past promotion by the media that people look better and healthier with a tan," she adds.

CUTANEOUS ONCOLOGY CENTER

"The OSUCCC – James Cutaneous Oncology Center encompasses melanoma, non-melanoma skin cancers and rare tumors of the skin," says Shannon Campbell Trotter, DO.

- The Pigmented Lesion Clinic, directed by Trotter, specializes in skin surveillance of those at risk for melanoma or with a history of the malignancy. The clinic offers full body photography, or mole mapping, to create a baseline for observing changes in existing moles or new lesions for earlier detection. Patients can take copies of the photos home for comparison when performing skin self-exams.
- The High Risk Clinic focuses on skin surveillance in high-risk populations, including organ transplant recipients and patients with chronic lymphocytic leukemia, HIV and genetic conditions like Lynch syndrome and basal cell nevus syndrome that predispose to skin cancer.
- The Rapid Access Clinic reserves daily appointments for quick evaluation of potential skin cancers. This is available for internal referrals as well as for community physicians who need expedient evaluation of a patient's lesion.

Trotter says patient volume has expanded in the clinics, which are available four days a week. "We can communicate directly with other members of the patient's care team and collaborate on clinial trials. We treat patients as individuals with a customized therapeutic plan that meets their needs," she adds.

CLINICAL TRIALS

"Clinical trials are necessary to improve overall survival in melanoma patients and to improve their quality of life," Kendra says. "It is only with these studies that we have a chance to find that durable response, that 'cure.'"

The number of patients accrued to melanoma clinical trials at the OSUCCC – James increased 10-fold from 2005-10 and continues to rise, she says.

"We've maximized accruals by providing trials that meet our patients' needs and by making community physicians aware of the trials we offer," Kendra explains. "We currently have six trials open and seven pending, meaning they have been funded and will soon start accruing.

"Our goal is to keep increasing the number of National Cancer Institute (NCI)-funded trials and the number of trials initiated by OSUCCC – James investigators."

For a sampling of clinical trials, see the sidebar on page 17.

TRANSLATIONAL RESEARCH

Clinical innovations in melanoma care at the OSUCCC – James are closely tied to the work of translational scientists such as Gregory Lesinski, PhD. Lesinski and his laboratory team are studying interactions between the host immune system and tumor cells in hopes of developing therapeutic or chemopreventive treatments and to improve existing therapies. That work includes collaborating with other OSUCCC – James investigators to develop small-molecule inhibitors that target oncogenic pathways such as STAT3 and XPO1.

"We have discovered that structural derivatives of the natural product curcumin are potent inhibitors of the STAT3 pathway, and we are testing optimized versions of these compounds," Lesinski says. "We hope to gather data that will allow us to develop drugs with potential for clinical-trials testing.

"Another project focuses on a small molecule that targets a nuclear export protein called XPO1, which has undergone preclinical testing in our lab. We have discovered that it has cytotoxic activity against melanoma cells both *in vitro* and in animal models, so we are pursuing a clinical trial of this drug in an expanded cohort of melanoma patients."

Another project involves PRMT5, a protein expressed at higher levels in melanoma than in normal skin. "Knocking down this protein by siRNA (small interfering RNA) in human melanoma cell lines leads to effects on cell growth," Lesinski says. (siRNA is designed in the lab

Examples of Clinical Trials for Cutaneous Melanoma at the OSUCCC – James

ECOG-E1609 – A national phase III trial comparing ipilimumab with high-dose interferon alfa-2b in patients with high-risk stage III or IV melanoma after surgical removal.

Local principal investigator (PI): Kari Kendra, MD, PhD

OSU-12047 - A national phase III trial comparing dabrafenib plus trametinib to vemurafenib in patients with unresectable or metastatic melanoma that is BRAF V600E/K mutation-positive.

Local PI: Thomas Olencki, DO

OSU-12129 - The High-Dose Aldesleukin (IL-2) "Select" Trial: A multicenter prospective tissue-collection protocol to investigate predictive models of response to high-dose interleukin-2 (IL-2) treatment in patients with advanced melanoma.

Local PI: Thomas Olencki, DO

OSU-05127 - A multicenter phase III trial of sentinel lymphadenectomy and complete lymph node dissection vs. sentinel lymphadenectomy alone in patients with evidence of metastases in the sentinel node.

Local PI: Doreen Agnese, MD

OSU-12055 – A national study of minimally invasive inguinal lymph node dissection for patients with melanoma is determining whether an educational training program is successful in teaching surgeons a new operative technique and whether that technique is safe for patients with melanoma in an inguinal nodal basin.

Local PI: Alicia Terando, MD

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

to interfere with messenger RNA so the cell can't make the protein.)

Lesinski says an OSUCCC – James research team led by Robert Baiocchi, MD, PhD, is developing small molecule inhibitors against PRMT5, "which we plan to test preclinically as a potential new drug target in a subset of melanomas."

Constant communication between basic scientists and clinicians allows for sharing data on key oncogenic pathways "that might support acquiring new compounds for the clinic," Lesinski says. "This interaction enables us to rapidly translate research findings to clinical trials so patients can benefit from cutting-edge science in real time."

PATIENT SUPPORT

Phuong Hoang, MSN, RN, CNP, and Nancy Stasik, PA-C, help support the medical oncology clinics led by Kendra and Olencki and several other functions. For example, they collaborated with Ohio State's Pharmacy Department on a retrospective review of supportive-care measures for melanoma patients receiving chemotherapy.

Hoang also leads a monthly melanoma support group through the OSUCCC – James with active patient, physician, psychologist and nutritionist involvement. "We have received very positive feedback and want to make this group known to other patients in central Ohio," she says.

In conjunction with The Melanoma Research Foundation, Hoang coordinates an annual Melanoma Patient Education Symposium hosted by the OSUCCC – James to present the latest in melanoma prevention, diagnosis and treatment. The second annual symposium was held May 4; the third is set for April 26, 2014.

"We have received much positive feedback from these free symposiums," Hoang says, adding that feedback drives the agenda. "The first-year attendees wanted more support information, such as symptom management, psychological support and patient testimonies. We provided that this year."

The OSUCCC – James also hosts a melanoma symposium for referring physicians to increase awareness of the melanoma program. This symposium draws more than 125 attendees from five states. "We anticipate the next one will be in February 2014," Kendra says.

Kendra and Olencki believe continued educational efforts about the dangers of melanoma and ways to prevent it, along with ongoing development of better therapies—especially for later-stage disease—give patients and referring physicians reason to hope.

"We are able to see new patients quickly, usually within five or six business days of the call," Olencki says. "We are very attentive to getting patients in for comprehensive care as soon as possible."

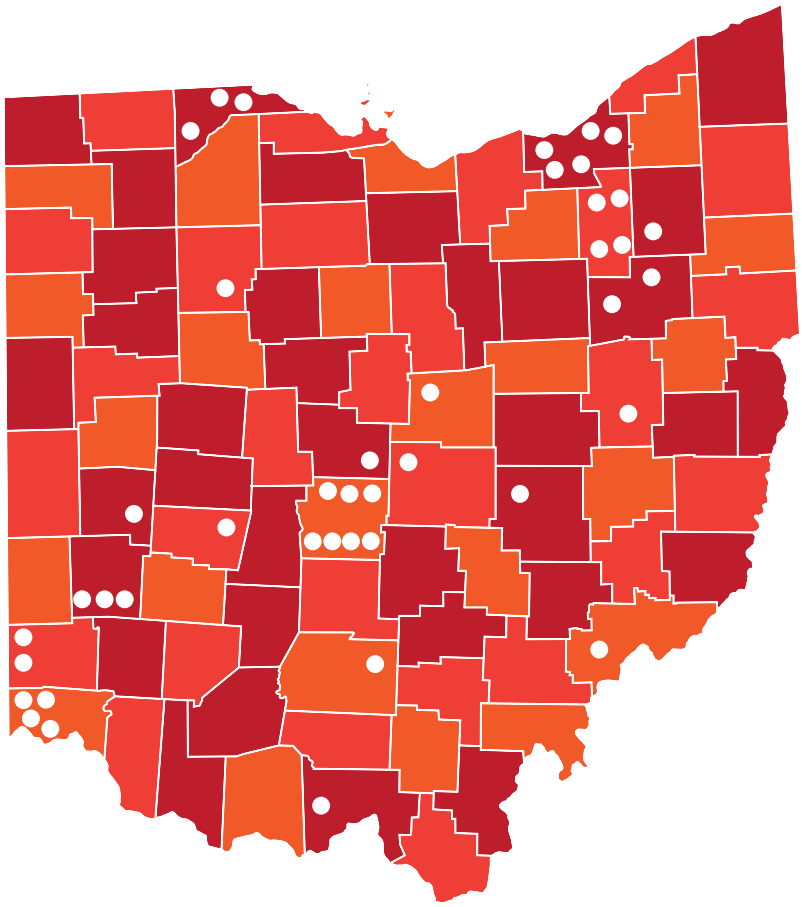
"We are making progress against melanoma," Kendra adds. "We've gone from therapies that help a small number of people for a short time to therapies that help a larger number of people for a short time. With additional research, we will develop more therapies that will help larger numbers of people for longer periods of time and bring about better outcomes."

Ohio State's melanoma program includes a comprehensive, collaborative range of disciplines and services:

- Medical, surgical and radiation oncologists
- Dermatologists and dermatologic clinics, with specialists in Mohs micrographic surgery
- Head and neck surgical oncologists
- Neurosurgeons specializing in melanoma metastatic to the brain and spine
- Reconstructive surgeons
- Pathologists
- Basic and clinical researchers
- Certified nurse practitioners, including one who leads a melanoma support group

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

A cancer research and prevention effort supported by Pelotonia is designed to reduce morbidity and mortality from colorectal cancer in Ohio



GOING STATEWIDE

BY KENDALL POWELL

For the past two years in August, Jenny and Ed Ostendorf have driven an hour and a half from Cincinnati to Columbus to rise early the next day and ride in Pelotonia, an annual cycling event to raise money for cancer research at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James).

Jenny, a 1982 Ohio State graduate who works in human resources for Proctor & Gamble, and Ed, a residential remodeling subcontractor, are committed to Pelotonia because they know that 100 percent of the money they raise will support cancer research at the OSUCCC – James…and because they enjoy the thrill of cycling among a throng of riders. In 2012, more than 6,200 riders raised almost $17 million.

One of the most far-reaching OSUCCC – James projects funded by Pelotonia is the Ohio Colorectal Cancer Prevention Initiative (OCCPI).

"Pelotonia has been a resounding success," says Heather Hampel, MS, CGC, genetic counselor and associate director of the Division of Human Genetics, who heads the OCCPI. "Riders from all over Ohio participate, and this study uses some of the money they raise to help everyone in the state by reducing the incidence of colorectal cancer in Ohio."

Colorectal cancer (CRC), the

"There is no question that we can help the at-risk LS relatives who are walking around with no idea that they have up to an 85-percent risk of CRC —we can absolutely save their lives."

— Heather Hampel

HEATHER HAMPEL, MS, CGC *genetic counselor and associate director of the Division of Human Genetics, head of the OCCPI*

ALBERT DE LA CHAPELLE, MD, PHD, *Distinguished University Professor, the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research*

third most common cancer in the United States, will affect one in 20 Americans. At 51 cases per 100,000 people, the incidence of CRC in Ohio is slightly higher than the national average. This year, 6,370 new CRC cases and 2,456 deaths from the disease are expected in the state.

CRC is one of the most preventable and, when caught early, treatable forms of cancer. The U.S. Centers for Disease Control and Prevention recommends that everyone should be screened for CRC using high-sensitivity fecal occult blood testing, sigmoidoscopy or colonoscopy beginning at age 50 and continuing to age 75.

But, says Hampel, "There is a lack of knowledge in the general public that colonoscopies can prevent CRC by removing polyps in the colon before they become cancerous." She notes that there is even less awareness that close relatives of CRC patients can be at increased risk of developing cancer.

The overall goal of the OCCPI is to reduce CRC morbidity and mortality and to increase awareness of CRC screening in the state of Ohio.

OHIO-SIZED INITIATIVE

The OCCPI is working with more than 40 hospitals across Ohio to screen all newly diagnosed CRC patients and their biological relatives for Lynch syndrome (LS), an inherited cancer syndrome that predisposes people to CRC, uterine, ovarian, gastric, kidney and other malignancies.

The ambitious initiative has three arms:

- **Universal CRC Screening for LS**: This study will test the tumor tissue from 4,000 newly diagnosed CRC patients at participating hospitals for characteristics of LS. It also will evaluate whether a concerted statewide effort to screen all CRC patients for LS will enhance case identification.
- **Adherence to Colorectal Cancer Screening**: This arm will follow the same 4,000 newly diagnosed CRC patients and their first-degree relatives—siblings, parents and children—to learn whether education about the benefits of colonoscopy and receipt of a personalized prescription for colon cancer screening will improve colonoscopy screening rates and prevent future cancers.
- **Molecular Epidemiology of Colorectal Cancer**: This arm will build a biorepository of patient samples obtained from participants in both the universal screening and the adherence arms of the project. The repository will include epidemiological data, and blood, tumor and saliva samples. Participating hospitals will have access to samples and data from all 4,000 cases and their relatives. These materials will be studied for novel methods of CRC prevention and treatment.

UNIVERSAL CRC SCREENING

People are diagnosed with LS if they inherit a mutation in one of four DNA-mismatch-repair genes. About 3 percent of newly diagnosed CRC patients carry LS mutations.

"That percentage might sound small, but it represents nearly 4,300 people per year in the United States," notes Albert de la Chapelle, MD, PhD, a Distinguished University Professor at Ohio State and co-leader of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James, who oversees the genetic-screening arm of the project.

The OSUCCC – James has screened all CRC patients for LS since 2006. Based on that experience, de la Chapelle and Hampel calculate that for every patient diagnosed with LS, three more people on average in their family also carry the mutation. "That translates to nearly 13,000 people per year in the U.S.," says de la Chapelle, who estimates that as

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many as 95 percent of LS cases are undiagnosed.

Relatives who learn they have LS can increase surveillance to prevent cancers such as CRC, uterine and ovarian from occurring or to catch them early, at more treatable stages. Increased surveillance includes colonoscopies beginning at age 20 to 25 and repeated every one to two years thereafter; women may choose to have a hysterectomy and oophorectomy to eliminate the risk from uterine and ovarian cancer.

"If you know you have LS, you don't need to die from cancer; but if you don't know it, you run a pretty big risk of dying from cancer," de la Chapelle says.

In addition, he notes, "An equal number or more family members will not have the mutation. Knowing this is a great bonus psychologically but also financially, because these individuals require no more surveillance than the average person."

The Universal CRC Screening arm of the study will test every new CRC patient's tumor for LS using immunohistochemistry (IHC) and microsatellite instability, genetic markers for possible LS mutations. These screening tests will be compared for effectiveness.

Suspected cases of LS will be confirmed by sequencing 13 genes that include the four LS genes and genes responsible for other cancer syndromes, such as APC, the cause of familial adenomatous polyposis (FAP), and TP53, which causes Li-Fraumeni syndrome.

If LS is confirmed, the results will be conveyed to the collaborating physicians, and genetic counseling will be offered to patients and their relatives about the need for LS testing and cancer surveillance.

Universal screening of colorectal cancer cases for Lynch syndrome (LS) could save thousands of lives annually

The OSUCCC – James has screened all colorectal cancer (CRC) patients for LS since 2006. If this practice were adopted nationally, it could potentially save thousands of lives, particularly because for every patient diagnosed with LS, three more family members on average also carry the mutation. Here's how the numbers work out if all CRC cases nationally were screened for LS:

143,000

the number of new CRC cases expected in 2013.

4,300

the **3 percent** of people with CRC that universal screening would show have LS.

Could *potentially* save

12,900

The total number of people with LS who could be identified annually and whose lives could potentially be saved through universal CRC screening followed by genetic counseling and testing to identify affected family members.

Increased surveillance of people with LS can prevent CRC, uterine and ovarian cancer from occurring or can catch them at early, more treatable, stages. Increased surveillance includes colonoscopies beginning at age 20 to 25 and repeated every one to two years.

The CDC already recommends universal screening for LS, but the practice is not widespread. In a 2010 paper in *Genetics in Medicine*, Hampel and colleagues showed that universal screening using IHC and sequencing of the four LS genes is cost-effective by U.S. healthcare system standards. They showed that protocol had an incremental cost effectiveness ratio of $22,552 per year of life saved; generally, any intervention below $25,000 is considered cost-effective.

"It's not only a question of the value of life, but also of how much money we save when LS patients don't develop cancer," de la Chapelle says.

The OCCPI team estimates that the universal screening arm of the study alone will save 390 years of life among the Ohio CRC patients and their relatives, Hampel says. "There is no question that we can help the at-risk LS relatives who are walking around with no idea that they have up to an 85-percent risk of CRC—we can absolutely save their lives."

TACKLING COMPLIANCE

The Adherence to Colorectal Cancer Screening (ACCS) arm of the study examines whether screening interventions increase the rates of appropriate CRC screening.

"Nationally, only probably half of the people who should get a colonoscopy for cancer prevention actually get one," says Electra Paskett, PhD, MSPH, associate director for population sciences at OSUCCC – James and leader for the ACCS arm. Screening rates in Ohio, especially in the Appalachian region, are even lower, she says. Colonoscopies take time away from work, require unpleasant colon-cleansing preparations and involve sedation, which means someone must drive the patient home. All these factors contribute to poor compliance—a major reason that less than 40 percent of CRCs are caught early, when survival rates are above 90 percent.

"The number one reason that people get screened is because their doctor recommended it, so we're hoping to help initiate that conversation," says Paskett. "But what we don't know is the compliance of people with LS or other increased hereditary risk. Do they seek screening at the appropriate age and frequency? Do they get an exam when they need to, and not get one if they don't need one? We don't have data on that."

In the adherence-to-screening arm of the OCCPI, enrolled relatives are directed to a website to complete a simple five-minute survey. They enter information about themselves such as age and screening and polyp history. Information on the relative with CRC is already in the database. The website then returns a personalized prescription that includes colonoscopy-screening recommendations. Guidelines for lowering CRC risk are provided, and the participant can access a link to find the location of local gastroenterologists.

In addition, half of the participants are randomly assigned a patient navigator who will call them to follow up five days later. The navigator, a trained lay health adviser from the OSUCCC-James, checks to see if the relative understands the prescription and helps the person overcome barriers to making or attending a screening appointment.

Paskett and her team want the website and navigator system to become a model for wider use. "We hope to develop something that can be used by all oncologists and their CRC patients and family members, with the overall goal to decrease mortality from and incidence of CRC."

UNEARTHING ROOT CAUSES

The Molecular Epidemiology of CRC study arm focuses on genetic and environmental factors

PETER SHIELDS, MD, *deputy director of the OSUCCC – James and leader of the molecular epidemiology arm of the study*

"We hope to identify risk factors for CRC that will enable us to tell patients whether they are at high risk or low risk, and if it is high, what kind of screening and prevention are needed to keep this person and family from getting CRC."

—Peter Shields, MD

"If you know you have LS, you don't need to die from cancer; but if you don't know it, you run a pretty big risk of dying from cancer. An equal number or more family members will not have the mutation. Knowing this is a great bonus psychologically but also financially because these individuals require no more surveillance than the average person."

— Albert de la Chapelle, MD, PhD

ALBERT DE LA CHAPELLE, MD, PHD,
a Distinguished University Professor who oversees the genetic-screening arm of the project

that increase CRC risk. "This is an opportunity to understand the causes of CRC that affect the general population," says Peter Shields, MD, deputy director of the OSUCCC – James and leader of the molecular epidemiology portion of the study. "Ultimately, we want to have good blood or saliva tests that will predict who is most at risk for CRC."

But first, Shields explains, a CRC research infrastructure is needed that includes a biorepository that can be mined for the molecular causes of this disease. Both the CRC patients identified in the universal screening arm and the relatives in the adherence arm of the study will be asked to participate in the molecular epidemiology arm and contribute samples to the biorepository: CRC patients will provide blood, mouthwash and tumor samples; their relatives will provide a mail-in mouthwash sample, which will contain cells from the oral lining for DNA analysis.

Those samples, combined with the lifestyle and environmental questionnaire completed by participants, plus the tumor and blood samples from the relative with cancer, and pathology from polyps removed during relatives' colonoscopies, will provide one of the most comprehensive clinical and genetic CRC databases in the world.

"If you take all the CRC risk, about 30 percent is estimated to be due to genetics," says Amanda Toland, PhD, associate professor of Molecular Virology, Immunology and Medical Genetics. "But we've only identified genes responsible for somewhere around five to six percent of cases."

Both Toland and Shields are leading efforts to identify other factors responsible for this "missing heritability." Shields is investigating the relationship between a specific bacterial infection and CRC, as well as genomewide association studies, to determine which genetic variants, in combination with environmental factors such as diet, exercise, smoking and alcohol use, increase CRC risk. Toland's group is investigating parent-of-origin effects, where certain genetic mutations might increase CRC risk only if inherited from a particular parent.

"There's a lot we don't know about how CRC develops," Shields says. "This effort will build the research infrastructure we need to better understand how this disease happens."

That knowledge should, in turn, improve screening and treatment. In particular, it could lead to faster and cheaper genetic tests that further personalize care by identifying patients who might need colonoscopies at age 40 and those who could safely wait until age 60.

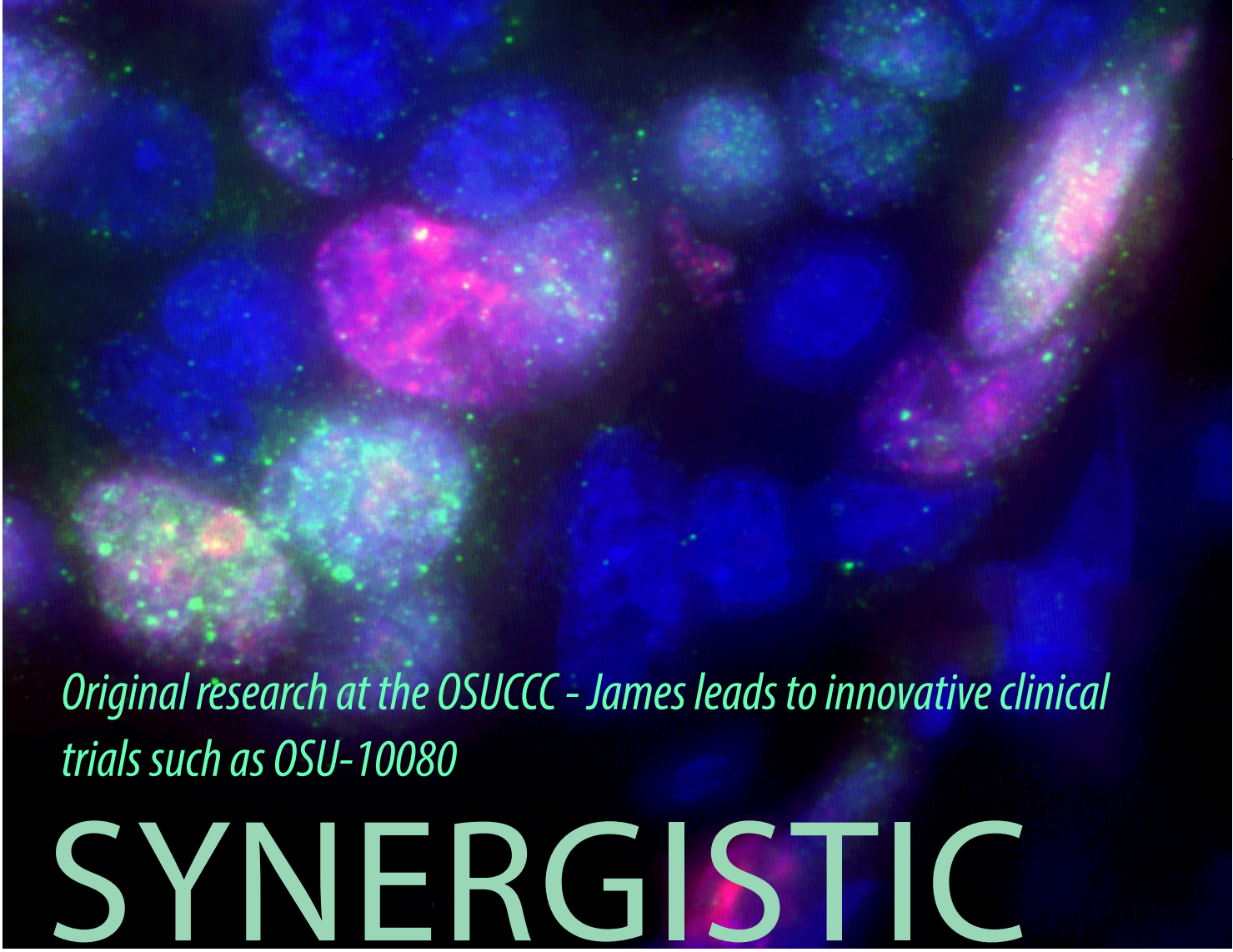
"We hope to identify risk factors for CRC that will enable us to tell patients whether they are at high risk or low risk, and if it is high, what kinds of screening and prevention are needed to keep this person and family from getting CRC," Shields says.

He acknowledges that the scale of the OCCPI—thousands of participants enrolled from more than 40 hospitals in a year and a half—is ambitious. "To get big answers, you have to do big studies," he says. "You have to do team science, and this team is composed of a very diverse set of multidisciplinary investigators. And answering questions about cancer risk requires large numbers of patients—we have to go to the whole state."

The Ostendorfs, in their early 50s, ride in memory of both of their fathers, who died of cancer, and in honor of both of their mothers, who are breast-cancer survivors. Jenny lost her father to colon cancer and says she's glad to know Pelotonia funds will be increasing awareness about the inherited risks of CRC.

"My family has lived it. My father's oncologist told my cousins, siblings and me that we really needed to stay on top of that. We get regular screenings—going every five years—and then my cousins and I trade colonoscopy stories!"

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



Original research at the OSUCCC - James leads to innovative clinical trials such as OSU-10080

SYNERGISTIC SCIENCE

BY DARRELL E. WARD

Women diagnosed with triple-negative breast cancer face significant challenges.

Triple-negative breast cancer (TNBC) is characteristically more aggressive and has fewer treatment options than other types of breast cancer. The reason is biological. These tumors lack estrogen (ER) and progesterone receptors (PR), and they do not overexpress the human epidermal growth factor receptor (HER2). This "triple-negative" quality leaves them unresponsive to hormone therapy and to HER2-targeted therapy, which have greatly improved survival in women with ER/PR-positive and HER2-positive tumors. TNBC treatment is typically limited to chemotherapy, and the tumors tend to recur quickly.

TNBC accounts for about one-fifth of the 1 million breast-cancer cases that occur annually worldwide. It mainly affects women age 40 and younger, especially African-American women and women who inherit mutated *BRCA1* and *BRCA2* (*BRCA1/2*) genes.

"These are devastating cancers, and new therapies are badly needed for them," says breast oncologist Bhuvana Ramaswamy, MD, MRCP, an assistant professor in the Division of Medical Oncology at Ohio State, and co-medical director of the Clinical Trials Office at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC — James).

When the National Cancer Institute (NCI) issued a request for proposals to evaluate a new targeted therapy that might improve the treatment of TNBC, Ramaswamy gathered with collaborators at the

OSUCCC – James and developed a protocol that the NCI approved in 2012.

Titled "A Phase 1 Dose-escalation Study of ABT-888 (veliparib) in Combination with Carboplatin in HER-2-negative Metastatic Breast Cancer," OSU-10080 evaluates the safety and identifies the maximum tolerated dose of the PARP inhibitor veliparib in combination with the chemotherapy drug carboplatin in women with metastatic TNBC (see the sidebar for an overview of the trial).

"Other centers chosen by the NCI to evaluate this agent designed trials that combine veliparib with two or three chemotherapy drugs, but we chose instead to use one chemotherapy agent and a higher dose of veliparib," says Ramaswamy, principal investigator for the trial.

OSU-10080 also incorporates original OSUCCC – James research that makes this PARP inhibitor trial particularly innovative:

- **An immunofluorescence assay** developed by Miguel Villalona, MD, Wenrui Duan, PhD, and colleagues to detect tumors with functional Fanconi Anemia defects enabled the trial to include certain patients with ER/PR-positive breast tumors;
- **FLT-PET imaging** with an experimental marker of proliferation to predict tumor response, led by Michael Knopp, MD, PhD, director of Ohio State's Wright Center of Innovation;
- **Monitoring response to therapy in real time** using circulating tumor cells (CTCs) from patient blood samples and technology developed by Jeffrey Chalmers, PhD, in Ohio State's College of Engineering and by Maryam Lustberg MD, assistant professor of Medical Oncology in the College of Medicine;
- **Applying microRNA research** by Carlo M. Croce, MD, to learn if changes in microRNA expression influence response to treatment.

First and foremost, OSU-10080 was designed to evaluate the safety of the PARP inhibitor veliparib combined with the chemotherapy drug carboplatin and to identify the maximum tolerated dose in women with metastatic TNBC. But like most clinical trials, correlative studies were added to answer other questions related to the drug.

Following is a look at the agent being evaluated by OSU-10080 and at the OSUCCC – James research that sets this trial apart from other veliparib trials.

OSU-10080 SYNOPSIS

ClinicalTrials.gov identifier: NCT01251874

The trial was open to patients with

- Triple-negative breast cancer
- ER/PR+, HER2- metastatic breast cancer with defects in Fanconi anemia pathway
- BRCA1/2 germline mutations

Trial objectives

- Determine a safe, effective dose for a phase II trial, toxicity and preliminary efficacy of veliparib in combination with carboplatin
- Evaluate pharmacodynamic markers possibly associated with PARP inhibition in tumor, including FLT-PET changes, circulating tumor cells (CTCs) for the induction of the histone variant gamma H2AX, and PAR levels in peripheral blood mononuclear cells
- Evaluate biomarkers in primary tumor that could predict antitumor response following PARP inhibitor treatment

Hypothesis

- Higher doses of veliparib will be better tolerated when combined with single-agent carboplatin alone
- FLT-PET uptake will reliably predict antitumor responses
- Higher induction of gamma H2AX in CTCs will reflect higher doses of veliparib

Correlatives

- Use of FLT-PET to assess tumor response (with FDG-PET-CT scan to evaluate radiological response)
- Isolation of peripheral blood mononuclear cells to assess PAR levels
- Assess the induction of gamma H2AX in CTCs as a measure of veliparib to induce DNA damage in a dose-dependent fashion
- Assess primary tumor tissue for BRCA1/2 protein miR-155 expression

PARP INHIBITION

Many chemotherapy drugs and ionizing radiation kill cancer cells by causing breaks in one or both strands of the DNA helix. Such breaks also occur commonly in healthy cells from natural causes. If these breaks are not repaired, the cell dies. Consequently, cells have acquired elaborate systems to stitch up damaged DNA. In cancer cells, ramped-up DNA repair can be an important component of drug resistance.

One important mechanism of DNA repair relies on an enzyme complex called poly (ADP-ribose) polymerase (PARP). Cancer cells often show high PARP-repair activity, which might enable them to survive DNA-damaging chemotherapy and radiation.

PARP inhibitors are a new class of drugs that block the PARP mechanism. "It's believed that inhibiting PARP will sensitize tumor cells to DNA-damaging chemotherapy such as carboplatin and enhance the ability of these agents to kill them," Ramaswamy says.

The agents should be particularly effective in cancer cells that have pre-existing damage to a DNA-repair mechanism such as *BRCA1/2* mutations. *BRCA1* is a component of a mechanism called homology-directed repair. That mechanism is crippled in cancer cells with *BRCA1* mutations. These cells then rely on PARP for survival.

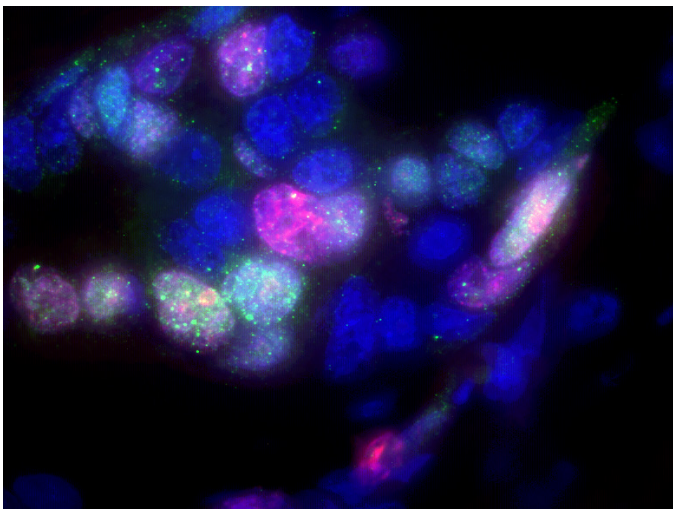
"TNBCs often have defective DNA-repair mechanisms, which is one reason we are hopeful that PARP inhibitors will help these patients," Ramaswamy says, noting that some patients entering the trial do not have documented *BRCA* mutations. Tumor cells from these patients are therefore assessed for *BRCA1/2* protein levels to determine if a tumor has a functional *BRCA* pathway.

"This data should give us additional biomarkers that can be used to identify tumor subtypes that will benefit from PARP inhibitor therapy," Ramaswamy says.

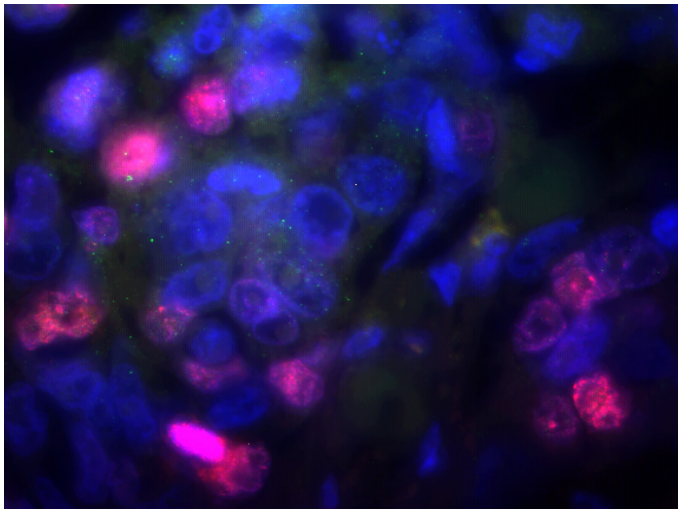
THE FATSI ASSAY

Women with ER/PR-positive breast cancer can also have damaged DNA-repair mechanisms and may be treatable with PARP inhibitors. About 20 percent of the women enrolled in OSU-10080 have defects in the Fanconi anemia DNA-repair pathway. The trial evaluates whether these tumors are susceptible to PARP inhibitors.

For all patients entering the trial, tumor tissue was tested for Fanconi anemia functional defects using the FA Triple Stain Immunofluorescence (FATSI) assay developed by OSUCCC – James researcher Miguel Villalona, MD, professor of Internal Medicine and of Pharmacology, and director of the Division of Medical Oncology, Wenrui Duan, PhD, who heads Villalona's laboratory, and a group of collaborators. The assay is performed and interpreted in the



Breast cancer cells with a functional Fanconi anemia repair pathway as indicated by the green foci produced by the Fanconi Anemia Triple Stain Immunofluorescence (FATSI) assay. FATSI-positive cancers are unlikely to respond to PARP inhibitors.



FATSI-negative breast cancer cells show few green foci. These cells have a nonfunctional Fanconi anemia repair pathway and are likely to respond to PARP inhibition.

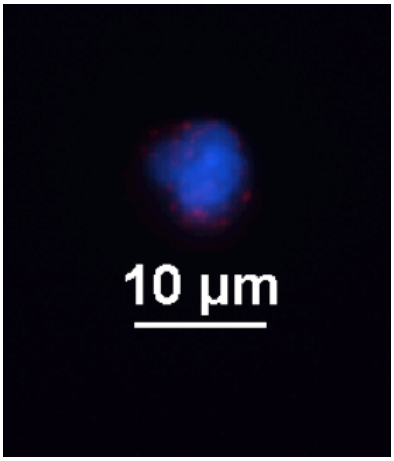
"Tumors that are dysfunctional in any component of the FA network might be susceptible to PARP inhibition... In addition, FA patients have a high incidence of malignancy, and cells from these patients are highly sensitive to DNA cross-linking agents, such as mitomycin C and cisplatin."

CLIA-certified molecular-pathology laboratory of Weiqian Zhao MD, PhD, a researcher in the OSUCCC – James Molecular Biology and Cancer Genetics program.

The FA network involves at least 15 genes and includes *BRCA2*. It regulates DNA-damage responses that help maintain genome integrity. In 2013, Villalona and his collaborators published the method in the journal *Translational Research*, using it to determine the functional status of the Fanconi anemia pathway in tumor cells (see figures, page 26).

"Tumors that are dysfunctional in any component of the FA network might be susceptible to PARP inhibition," Villalona says. "In addition, FA patients have a high incidence of malignancy, and cells from these patients are highly sensitive to DNA cross-linking agents, such as mitomycin C and cisplatin."

Villalona is principal investigator on another NCI-approved trial (OSU-9100; NCI0117640) under way now at the OSUCCC – James. It evaluates veliparib as monotherapy and in combination with mitomycin C in patients with solid tumors with deficiency in homologous recombination repair.



Epifluorescent image of a circulating tumor cell showing the presence of gamma-H2AX (red), a marker of DNA damage. Only the cell nucleus is visible, colored blue by the fluorescent stain DAPI.

Because of the FATSI assay, four patients with ER-positive tumors have also been enrolled on this trial.

"No one else was using PARP in ER-positive tumors," Ramaswamy says. "But including these tumors was a natural next step, and the FATSI test developed at Ohio State made it possible. This also makes our trial different from what other centers were doing."

IMAGING

Another question that OSU-10080 seeks to answer relates to dose of the drug: Does veliparib cause dose-related cancer-cell death or does it plateau after a certain dose?

Trial co-investigator Michael Knopp proposed using an experimental functional-imaging method called F-18 fluorothymidine and positron emission tomography (FLT-PET) to answer the question.

THIS RESEARCH BY
MIGUEL VILLALONA, MD
director of the Division of Medical Oncology and The Dorothy M. Davis Chair in Cancer Research

FLT-PET is a whole-body scan that can reveal multiple metastatic tumors.

FLT works as follows: As proliferating cancer cells make DNA, they take up the radiolabeled FLT as a source of thymidine. Tumors with proliferating cells will appear brighter on the PET image; in tumors with less proliferation, the image will appear dimmer.

Fluorodeoxyglucose PET (FDG-PET) scans, with CT scans, were also used for more traditional radiological screening and measurement of response using RECIST criteria.

During the trial, patients received FLT-PET scans prior to treatment and again after seven days and 14 days of treatment. "That was the original schedule; it called for 14 days of treatment," Ramaswamy says. "Then we went to 21 days of treatment because at 14 days, many patients were showing greater tumor reduction by FLT-PET, so we decided to add another week of treatment.

"That was particularly rewarding," she says, "because we'd chosen to use FLT-PET, which, as a research-imaging modality, was not covered by trial participants' insurance, and it was expensive. But the choice proved to be a good one because it enabled us to make an important clinical decision."

"Our hope is that FLT-PET will become a tool to guide dosing regimens during clinical trials," adds Knopp, who is professor and vice chair of Radiology.

CIRCULATING TUMOR CELLS

There is another question OSU-10080 is investigating: Should veliparib be administered to patients continuously or intermittently?

Here, Ramaswamy turned to OSUCCC – James researcher Jeffrey Chalmers, PhD, professor of Engineering and director of the Analytical Cytometry Shared Resource. Chalmers had developed a method to isolate CTCs using a negative-selection technology based on immunomagnetic tagging and removal of cells that are positive for CD45, the leukocyte common antigen, which is expressed on most/all hematopoietic cells.

At the Analytical Cytometry Shared Resource, the CTCs are isolated from samples of peripheral blood collected before treatment and during the trial. An immunofluorescence assay is used to detect a marker of DNA damage called gamma-H2AX (see figure, page 27).

H2AX is a histone protein and a building block of nucleosomes, molecular spools involved in DNA folding and gene expression. When DNA sustains a double-strand break, the H2AX in the nucleosomes undergoes a chemical change; it is phosphorylated. This phosphorylated form is called gamma-H2AX, and it is a marker of DNA damage.

If the veliparib-carboplatin combination inflicts DNA damage and blocks repair as expected, CTCs should show higher levels of gamma-H2AX with increasing doses of veliparib.

"We hope to learn if we can detect changes in CTCs and whether the drug is really killing the cancer cells," Chalmers says.

The researchers are also monitoring CTCs for the appearance of HER2 markers in patients with TNBC. "We're not the first group to do this, but we are pushing technology to look at this more closely," Chalmers says.

MICRORNA

Are there still other breast cancer patients whom PARP inhibitors might help? Work by OSUCCC – James researcher Carlo Croce, MD, professor and chair, Molecular Virology, Immunology and Medical Genetics, and director of Human Cancer Genetics, suggests, yes, and they might not be difficult to identify.

Croce has led laboratory and animal studies that link high levels of microRNA-155 (miR-155) to B cell lymphoma and to breast cancer and other solid tumors. The work indicates that overexpression of miR-155 results in the loss of function of several genes involved in DNA repair.

"This suggests that cancer cells that overexpress miR-155 should be extensively sensitive to PARP inhibition," Ramaswamy says. To help answer that question, OSU-10080 includes a correlative study to evaluate primary tumors of patients for miR-155 expression, which will be correlated with tumor responses to therapy.

"Those findings should help us learn if high miR-155 expression in tumor cells is a marker for breast-cancer patients who might benefit from a PARP inhibitor," Ramaswamy says.

In the end, OSU-10080 accrued 44 women with breast cancer; four patients were ER/PR-positive cases identified using the FATSI assay. Overall, 21 percent of tumors tested so far did have defective Fanconi anemia pathway. Since the trial has just completed accrual, the findings of the correlative studies won't be known for some time, although the preliminary toxicity and FLT results were presented in the European Society of Medical Oncology Breast Cancer conference (IMPAKT) in Brussels and at the 2013 ASCO annual meeting.

"Our ultimate goal is to live in a cancer-free world," Ramaswamy says. "OSU-10080 trial is an example of the imaginative, collaborative research and innovative team-science at the OSUCCC – James that will help get us there."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU-11055: Model development to personalize dosing for intravenous melphalan in the setting of autologous transplant for multiple myeloma

HYPOTHESES: Our pharmacokinetic model will predict interpatient variability; melphalan drug exposure will correlate with mucositis and duration of neutropenia; and measurements of DNA damage using patient blood in the laboratory will be directly related to melphalan concentrations, thereby allowing for the creation of a model that will be the first of its kind to personalize chemotherapy dosing in the setting of an autologous hematopoietic stem-cell transplant.

RATIONALE: In multiple myeloma, one of the most effective therapies is the use of high-dose intravenous (IV) melphalan, which is given at either 140 or 200 mg/m2 as an IV bolus followed by autologous stem cell rescue 48 hours after infusion—in the United States we perform more than 5,000 myeloma transplants yearly. Autologous transplant is associated with severe toxicity (1-5 percent transplant-related mortality), a 16-day inpatient stay on average, and a quality of life decrement that lasts nine months on average. There have been no improvements in the basics of autologous transplant for myeloma in the last 20 years because there is extensive interpatient variability in melphalan exposure, and no adequate PK/PD model has been developed.

The No. 1 patient complaint with autologous transplant for myeloma used to be mucositis before the use at Ohio State of oral cryotherapy. Standard ice-chip therapy requires patients to hold one ounce of ice chips in their mouth, then replenishing them when melted, for 30 minutes before and during, and continuously for six hours after melphalan infusion (seven hours total). Prolonged ice-chip therapy is a hardship for patients.

In the setting of an ongoing randomized controlled trial of myeloma patients undergoing autologous transplant comparing the incidence of severe mucositis in two-hour versus six-hour schedules of crushed ice therapy, we are gathering relevant pharmacokinetic data, performing experiments using patients' peripheral blood mononuclear cells (PBMCs) to measure DNA damage (primarily accumulation of p53 protein) with different concentrations of melphalan, and monitoring patients closely for melphalan-related toxicities. The objective is to develop a model that will include covariates that are clinical (mucositis grade, neutropenia duration), pharmacokinetic (melphalan exposure and maximum serum concentration), and pharmacodynamic (*ex vivo* DNA damage) to predict the optimal dose of melphalan. With completion of this study, we will have developed a model that will be validated in a multicenter prospective trial.

AT A GLANCE

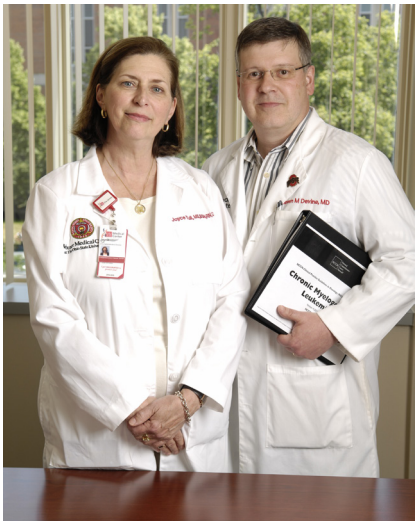
Trial no.: OSU-11055 (ClinicalTrials.gov identifier: NCT01653106)

PI: **CRAIG HOFMEISTER, MD, MPH**

Phone: 614-293-7807

Email: *craig.hofmeister@osumc.edu*

Eligibility: Patients must be diagnosed with multiple myeloma and admitted for autologous stem cell transplantation; Age: 18 years or older; Ability to read and understand informed consent.



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BHUVANA RAMASWAMY, MD,
MEDICAL CO-DIRECTOR

CLINICAL TRIALS OFFICE

The Clinical Trials Office (CTO) provides centralized administration of all clinical trials conducted within The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). The office ensures that clinical trials conducted at the OSUCCC – James are methodologically sound, expedient and cost effective. It currently oversees more than 250 acting and pending trials.

The office specializes in protocol implementation and coordination, data and regulatory management, negotiating clinical trial agreements and developing clinical trial budgets, internal auditing, and clinical trial education.

The CTO assists investigators in the design of well-constructed clinical trials that have good accrual potential and do not overlap with existing trials. This assistance includes:

- Translating discoveries and ideas into formal protocols;
- Preparing protocols for review by institutional review boards and other committees;
- Providing quality-controls to ensure that cancer trials meet federal, state and institutional regulations;
- Training investigators and staff in the development, conduct and analysis of clinical trials;
- Developing budgets and providing financial and contract management services during the trial;
- Facilitating the enrollment of eligible patients, including those from underserved populations;
- Data management;
- Training staff in evaluating and documenting adverse events.

EXPANSION UPDATE

THE NEW JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

Designed to transform a three-part mission to achieve one goal

Patient care, education and research describe the three-part mission of any academic medical center. However, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute combines these to achieve one goal: create a cancer-free world.

All three mission areas have been tightly integrated into the design of the new James Cancer Hospital and Solove Research Institute, which is targeted to open in 2014.

A translational-research laboratory is located on each patient-care floor of the new hospital, with wet and dry labs on alternating floors. Wet labs will be equipped for cancer molecular genetics research. Dry labs will provide space where informatics and computational scientists, for example, can analyze genomics and other data.

The labs will educate, also. Each has a glass front. Patients can look in; researchers can look out. Patients for whom research is an abstract activity will see it under way in their own environment, perhaps instilling greater hope. Researchers who are often isolated from patients will see the consequences of human malignancy, underscoring the importance of their work and strengthening their sense of purpose.

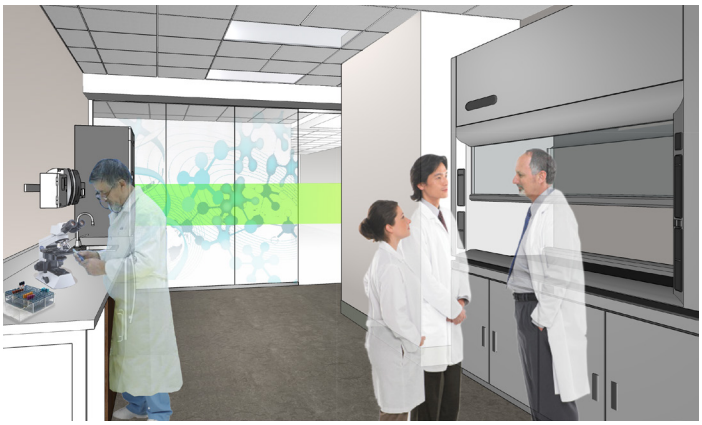
"These laboratories will also enhance our tissue-banking capacity, which is fundamental to our precision cancer medicine program," says David E. Schuller, MD, vice president for medical center expansion and outreach. "Ohio State's cancer program has more than 30 years of tissue-banking experience, and we want to take advantage of that to develop a robust biorepository mechanism."

Each floor of the new hospital will have three care-team education centers. Here, teams of faculty, fellows, residents, medical and nursing students will meet to discuss the care of the patients in their respective patient-care neighborhoods. These rooms will be equipped to support educational activities.

These new spaces will also support Ohio State's new medical-school curriculum, which calls for first-year students to be involved in patient care. "We will also encourage them to be involved in research," Schuller says. "To have research activities in patient-care areas should facilitate that interaction."

This architectural integration of the three mission areas should increase research productivity, enhance education and lead to more effective care as the cancer program continues its quest to create a cancer-free world.

Translational Research dry lab



Translational Research wet lab

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

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FUNDRAISING

Ohio State Cancer Leader Elected to AACR Board of Directors

Michael A. Caligiuri, MD, director of The Ohio State University Comprehensive Cancer Center and CEO of the James Cancer Hospital and Solove Research Institute (OSUCCC – James), is one of five scientists elected by members of the American Association for Cancer Research to serve on the AACR Board of Directors for the 2013 to 2016 term.

The American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to high-quality, innovative cancer research. The organization fosters the exchange of knowledge and new ideas among cancer researchers, provides training opportunities for the next generation of cancer researchers and increases public understanding of cancer.

AACR membership includes more than 34,000 laboratory, translational and clinical researchers, population scientists, other healthcare professionals, and cancer advocates residing in more than 90 countries. The AACR annually convenes more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 17,000 attendees.

Caligiuri holds the John L. Marakas Nationwide Insurance Enterprise Foundation chair in cancer research at Ohio State. He is a professor in the Department of Molecular Virology, Immunology and Medical Genetics, and in the Department of Internal Medicine at Ohio State, and he was chairperson for the AACR Annual Meeting Program Committee in 2009.

NATIONAL RECOGNITION

James Cancer Hospital Launches Online Cancer Community

Cancer patients seeking to connect with others facing similar challenges can join a new social media network called CancerConnect that allows them and their caregivers to share information, inspiration, hope and support.

The OSUCCC – James has partnered with OMNI Health Media to launch The James CancerConnect to bring together cancer patients, caregivers and others in a welcoming and informative online community.

The free site—which offers participants the opportunity to read informational materials and communicate with others—is open to anyone who registers with a user name and password. Members of The James CancerConnect community are invited to participate in more than 60 disease-specific, online national communities for individuals with similar interests at cancerconnect.com/thejames.

Cancer-specific groups are available—as well as groups focused on caregiving, health and wellness, clinical trials, insurance, nutrition and survivorship—to provide support for those affected by cancer.

IN THE NEXT ISSUE OF **frontiers**…

PELOTONIA 13 AUGUST 9-11

Pelotonia is an annual bicycling event that takes riders through bucolic Ohio countryside on routes of varying length. The event attracts thousands of cyclists from across the nation and 100 percent of the funds raised supports cancer research at the OSUCCC – James. For information or to register as a rider or volunteer, visit **http://www.pelotonia.org**.

2013 ERNEST L. MAZZAFERRI THYROID CANCER CONFERENCE

November 15, 2013, The Ohio State University Biomedical Research Tower

FOCUS: A comprehensive review of new diagnostic modalities and recent advances in the treatment of thyroid cancer.
Registration is required for this live, CME-certified educational activity.
Visit http://go.osu.edu/thyroid2013