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

WINTER | 2012

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

SURVIVORSHIP 2012

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

UPFRONT

The Director's Perspective

Cancer Care Past, Future, Present

Many research-based advances in cancer care have been made since the signing of the National Cancer Act 40 years ago, and they have steadily improved survivorship rates and quality of life for survivors and their families.

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

Since 1971, the number of survivors has increased nearly four-fold, and the American Association for Cancer Research (AACR) reports that 68 percent of the approximately 12 million adult cancer survivors in the United States today are living five or more years after initial diagnosis, compared with just 50 percent four decades ago. Moreover, the AACR says some 15 percent were diagnosed 20 or more years ago.

Our cover story for this issue of *Frontiers* examines national progress in cancer survivorship, including a relatively new definition of the concept and a clinical approach to cancer that has evolved from an almost exclusive focus on treatment to a full continuum of care that integrates survivorship as an essential component. The story also touches on survivorship research at Ohio State that is designed to improve quality of life by reducing stress and clinical depression.

We describe our commitment to P4 medicine in the story "A Quiet Evolution." We believe this approach to cancer care will further improve outcomes and quality of life through its emphasis on prediction, prevention, personalization of therapy and greater patient participation in healthcare decisions.

Finally, our story "Foreign Occupiers" presents some of the research under way at Ohio State to understand and halt one of the most intractable challenges in present-day oncology: metastatic cancer, which is responsible for about 90 percent of cancer deaths and often causes enormous suffering.

These stories reflect just some of our exciting efforts to raise the threshold of hope for patients and their families and friends as we work together to create a cancer-free world.

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

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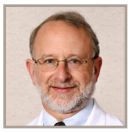
Winter | 2012

FEATURES

04 FRONTLINE



RICHARD M. GOLDBERG, MD
Genetic predictors of tumor aggressiveness can often help make treatment decisions.

06 BREAKTHROUGH

12 OF NOTE

29 BENCH TO BEDSIDE

WILLIAM E. CARSON III, MD
A Phase I/II Trial of Cetuximab in Combination with Interleukin-12 Administered to Patients with Unresectable Primary or Recurrent Squamous Cell Carcinoma of the Oropharynx

30 NEED TO KNOW

ON THE COVER:
PHOTOS OF CANCER SURVIVORS WITH FOUR OSUCCC – JAMES FACULTY. FRONT: JOE FLYNN, DO, MPH, AND SUSAN BROWN, RN, PHD. SECOND ROW: BARBARA ANDERSEN, PHD, AND CHARLES SHAPIRO, MD.

Ready for PRIME TIME

Genetic predictors of tumor aggressiveness can often help make treatment decisions

By **RICHARD M. GOLDBERG, MD,** *physician-in-chief, Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute*

When practicing oncologists make treatment decisions, they use their clinical skills to assess patients for their robustness, comorbidities and ability to tolerate treatment, and they size-up the tumor by staging and grading it. Such factors help determine whether a patient requires aggressive or moderate treatment, can be managed with a single treatment approach such as surgery or needs more than that.

Today, genetic factors that relate to tumor aggressiveness can often contribute to this critical decision. This possibility has emerged from research in genomics and tumor molecular biology, and it has moved into the clinic where it is allowing individualized treatment of patients and is making P4 medicine possible (see *A Quiet Evolution*, page 24).

Patients and tumors share many genes, of course, because tumors are derived from a patient's own tissues. But tumor cells show radical genetic differences from healthy cells, including inactivated tumor-suppressor genes (analogous to defective brakes on a car) and hyper-activated tumor-promoting genes (analogous to a stuck accelerator pedal). Gene marker research—one area of focus here at the OSUCCC – James—is revealing molecular points of vulnerability in tumor cells, and medicinal chemists are developing rationally designed agents that target them.

Notable examples of these agents are inhibitors designed to block single driving mutations that are responsible for tumor growth in a subset of cancers. One such drug is imatinib, which inhibits the tyrosine kinase encoded by the *BCR-ABL* oncogene in chronic myelogenous leukemia and c-KIT tyrosine kinases overexpressed in gastrointestinal stromal tumors (see illustration). Taking this pill can convert these tumors from life threatening to chronic diseases.

Research is also showing that patients' genetics can predict how efficiently they will metabolize certain drugs and perhaps even help gauge their ability to tolerate treatment, a field known as pharmacogenetics.

When Lance Armstrong developed testicular cancer, the odds were good that he would withstand the rigors of treatment because he had tolerated the rigors of the Tour de France. An emerging science now seeks to identify genetic markers that will help determine which patients are the Lance Armstrongs and good candidates for aggressive therapy, and which patients are better managed with milder treatment options.

The burgeoning science of pharmacogenetics is revealing genetic differences that influence a patient's ability to metabolize drugs, and we can test for these in a growing number of cases. For example, genetic testing is now routinely done to determine the dosing of the blood thinner warfarin.

Similarly, a genetic test is available for the drug irinotecan, which is used in the treatment of colorectal cancer, my clinical and research specialty. The drug

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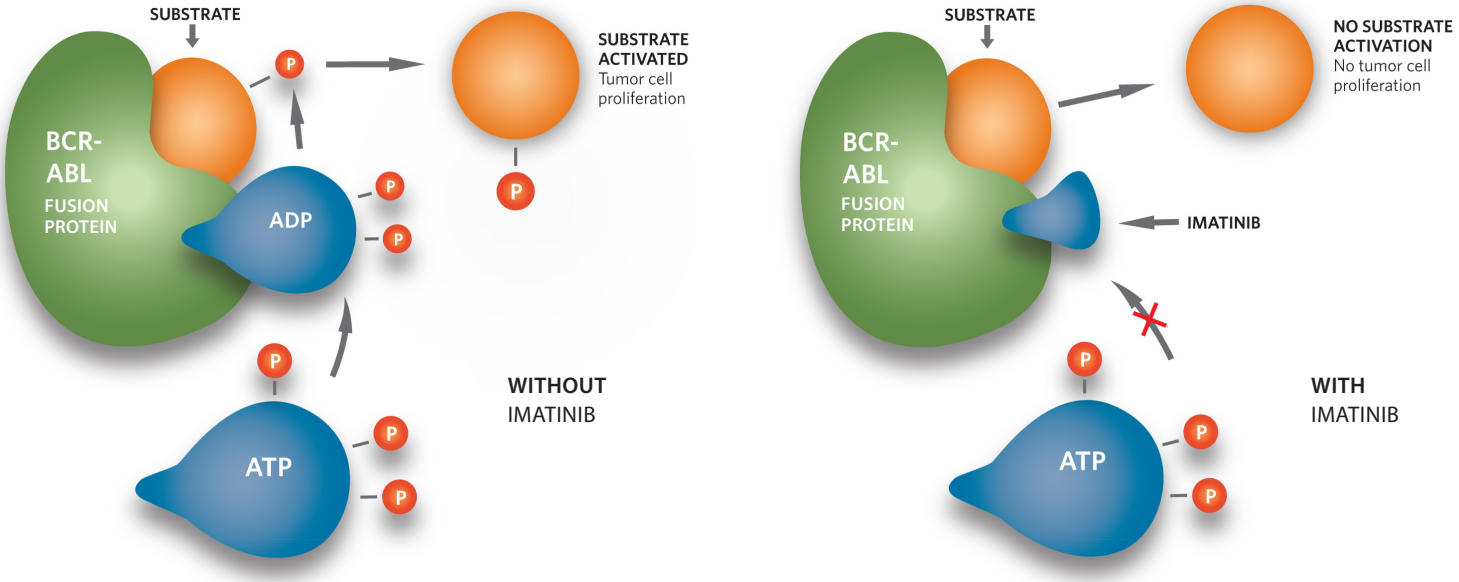
EXPLOITING A MOLECULAR VULNERABILITY

The targeted drug imatinib (Gleevec®) inhibits the tyrosine kinase encoded by the BCR-ABL oncogene in chronic myelogenous leukemia (CML), and c-KIT tyrosine kinases that are overexpressed in gastrointestinal stromal tumors. The drug is designed to bind to the active site of the BCR-ABL fusion protein. This prevents phosphorylation and activation of the substrate and blocks tumor-cell proliferation.



is broken down by the enzyme uridine glucuronyl transferase (UGT). About 10 percent of the American population has a less efficient form of UGT, causing the activated form of irinotecan to remain longer in their system and cause problems such as diarrhea and low blood counts. Today, we can test patients for UGT, allowing us to individualize the dosage of the drug.

Sometimes genetic markers can indicate that further treatment is unnecessary. About 15 percent of colorectal cancers arise through a genetic alteration in one of four or five DNA mismatch repair genes. Patients with a defect in one of these genes have a better prognosis than the 85 percent of colon cancers that arise through chromosomal instability, the more common pathway.

For this reason, patients with early-stage colon cancers and microsatellite instability (a marker for a DNA mismatch repair defect) often don't require chemotherapy after surgical removal of the tumor because outcomes are so good without it and are no better with drug therapy.

These advances all came about through research. These investigations require the proper collection and processing and storage of tumor tissue. At the OSUCCC – James Biorepository and Biospecimen Shared Resource, tumor and tissue specimens are frozen, rather than preserved in formaldehyde. This allows interrogation of the genetic structure of tumors for common genetic abnormalities and their use to develop treatments.

DNA was discovered in the 1950s, the human genome project was completed early in the 21st century, and the pace of progress related to unraveling the genome continues to accelerate. But the science is just in its infancy. Tools to look at the genome are available now, and we are still learning how to exploit them.

The knowledge we are gaining from this work is already revolutionizing the practice of medicine and will continue to do so for decades to come. But even today, genetic markers of tumor aggressiveness are being used in the clinic to identify individualized treatments that can be more effective and safer for our patients.

MULTIPLE MYELOMA

ADVERSE INTERACTION

Study Urges Caution With Lenalidomide Dosage

MITCH PHELPS, PhD,
OSUCCC – James Experimental Therapeutics Program

A multiple myeloma study at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) unexpectedly showed that lenalidomide interacts with a protein in cells, affecting the drug's dosage level.

Lenalidomide is an anti-inflammatory, and more than 390 clinical trials have been initiated to study its activity in cancer and other diseases.

This phase I clinical trial found that lenalidomide interacts with P-glycoprotein (Pgp), a molecule that pumps potentially toxic chemicals out of cells and aids in removing these chemicals from the body. Abnormally high levels of Pgp in cancer cells can be an important cause of drug resistance for many cancer patients.

The findings could lead to safer dosing of lenalidomide in a variety of diseases.

"This is the first report showing that lenalidomide interacts with Pgp, and our clinical data suggests this may be an important consideration for proper dosing of the drug," says study leader Mitch Phelps, PhD, of Ohio State's College of Pharmacy. "Some toxicities induced by lenalidomide can be severe and life-threatening."

The clinical trial, which involved 21 patients with relapsed multiple myeloma, combined lenalidomide with temsirolimus, a drug that researchers knew from the start interacted with Pgp. During the study, lenalidomide levels in patients' blood were often higher than expected, and some patients experienced such side effects as electrolyte imbalances and rashes that were also greater than expected.

To the investigators' surprise, laboratory experiments showed that lenalidomide was removed from cells by Pgp, and the rate of removal was reduced when temsirolimus was included in the experiments. That suggested the two drugs interact via Pgp and potentially explained the altered lenalidomide levels in patients' blood.

Phelps says pharmacokinetic interaction between the two agents, along with greater side effects than expected, led researchers to conclude that the interaction of the agents with Pgp may cause increased toxicity.

Published in the Journal of Clinical Oncology.

Watch online

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

BRAIN CANCER

ENCOURAGING COMBINATION

Immunogene Therapy Plus Standard Treatment Found Safe

Researchers at Ohio State have learned through a clinical trial that a type of gene therapy is safe for treating a deadly brain cancer, even when combined with radiation therapy.

The phase I-B trial, conducted at the OSUCCC – James and at Methodist Hospital in Houston, involved a novel treatment that uses an adenovirus vector called AdV-tk. The vector is taken up by cancer cells, where it activates a drug that kills the cells. The vector is applied in the operating room after removal of tumors such as glioblastoma multiforme, the most common and dangerous form of brain cancer.

The findings suggest that this therapy might also stimulate an immune response against the tumor.

"This is the first time a gene therapy approach was combined with radiation in patients with a newly diagnosed glioblastoma," says first author E. Antonio Chiocca, MD, PhD, professor and chair of Neurological Surgery at Ohio State. "There had been a concern that combining these two treatments could be too toxic, but this was not the case. We don't know yet if this will improve survival, but these findings are encouraging."

Glioblastomas annually occur in about 18,500 Americans and kill nearly 13,000. Glioblastoma multiforme is the most common and lethal form of the malignancy, with an average survival of 15 months after diagnosis.

E. ANTONIO CHIOCCA, MD, PhD,
professor and chair of Neurological Surgery and co-leader of the OSUCCC – James Viral Oncology Program

The tumors often recur because cancer cells typically migrate into adjacent brain tissue. This study, which involved 10 patients with glioblastoma multiforme and two with anaplastic astrocytoma, examined an immunogene therapy approach that is designed to kill these undetected cancer cells and prevent recurrence.

In addition to improved overall survival, the study revealed a significant rise in T lymphocytes in the tumors, suggesting that the gene therapy stimulated an immune response against the tumor, producing an "immunogene therapy" effect.

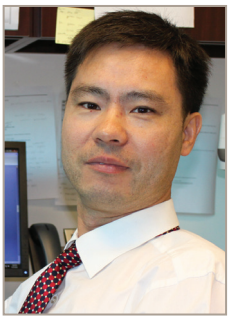
Published in the Journal of Clinical Oncology

Watch online

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

PROMISING APPROACH

Starving Cancer Cells of Cholesterol Could Help Treat Glioblastomas



DELIANG GUO, PhD,
assistant professor of Radiation Oncology

Research suggests that blocking cancer cells' access to cholesterol may offer a new strategy for treating glioblastoma, the most common and deadly form of brain cancer, and perhaps other malignancies.

This treatment could be appropriate for tumors with a hyperactive PI3K signaling pathway, which accounts for up to 90 percent of glioblastoma cases.

Investigators at Ohio State and UCLA's Jonsson Comprehensive Cancer Center who led the study discovered that the hyperactive signaling pathway is linked to cholesterol metabolism, and that inhibiting this pathway leads to the death of glioblastoma cells in an animal model.

"Our research shows that the tumor cells depend on large amounts of cholesterol for growth and survival, and that pharmacologically depriving tumor cells of cholesterol may offer a strategy for treating glioblastoma," says first author Deliang Guo, PhD, of the Department of Radiation Oncology at Ohio State.

"This study uncovers a mechanism that links a common oncogene with altered cell metabolism, and it potentially offers a strategy for blocking that mechanism and causing specific tumor-cell death without significant toxicity," says principal investigator Paul Mischel, MD, professor of Pathology at UCLA and adjunct professor of Radiation Oncology at Ohio State. "Our findings suggest that developing drugs to target this pathway may lead to more effective treatments for patients with this cancer."

Glioblastomas are difficult to surgically remove because malignant cells invade surrounding brain tissue. Also, genetic differences make some glioblastoma cells in the tumor resistant to chemo- and radiation therapy.

"Glioblastomas are among the most treatment-resistant of cancers, so new strategies are greatly needed," Guo says.

Published in the journal Cancer Discovery.

BRAIN CANCER

TWO FOR ONE

Novel Technique Reveals Both Gene Number & Protein Expression

Researchers have discovered a fluorescence microscopy technique for simultaneously visualizing gene number and protein expression in individual cells.

The new technique, called the fluorescent *in situ* gene protein assay, combines traditional fluorescent *in situ* hybridization (FISH) with the *in situ* proximity ligation assay, which is capable of resolving individual protein molecules.

The technique could permit a detailed analysis of the relationship between gene status and expression of the corresponding protein in cells and tissues. Study leaders say this may bring a clearer understanding of cancer and other complex diseases.

"To my knowledge, this is the first technique that allows us to concurrently address gene activity and corresponding protein expression in the same cells," says co-principal investigator Arnab Chakravarti, MD, chair of Radiation Oncology at Ohio State and co-director of the Brain Tumor Program at the OSUCCC – James. "The ability to resolve gene- and protein-expression changes across a tumor could help us understand what drives tumor behavior overall."

For this study, principal investigator Markus Bredel, MD, PhD, associate professor at the University of Alabama-Birmingham and adjunct associate professor of Radiation Oncology at the OSUCCC – James, along with Chakravarti and their collaborators, first assayed fixed human glioblastoma tumor cells, then paraffin-embedded human glioblastoma tissue. In both cases, they assayed for overexpression of a mutant form of the epidermal growth factor receptor gene, *EGFRvIII*, and for levels of its truncated protein in glioblastoma.

"This method has potential to perform a detailed analysis of the relationship between cancer gene status and corresponding protein expression in cells and tissues," Bredel says. "We demonstrate that the fluorescent *in situ* gene protein assay methodology is capable of resolving cancer gene and protein patterns simultaneously on a cell-by-cell basis, which is particularly important in heterogeneous diseases such as cancer."

Published in the journal Neuro-Oncology.

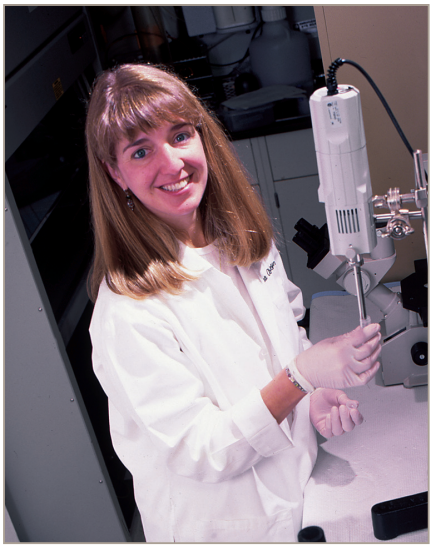
To refer a patient, please call The James Line New Patient Referral Center toll free: 1-800-293-5066.

ARNAB CHAKRAVARTI, MD,
Max Morehouse Chair in Cancer Research, and a member of the OSUCCC – James Experimental Therapeutics Program.

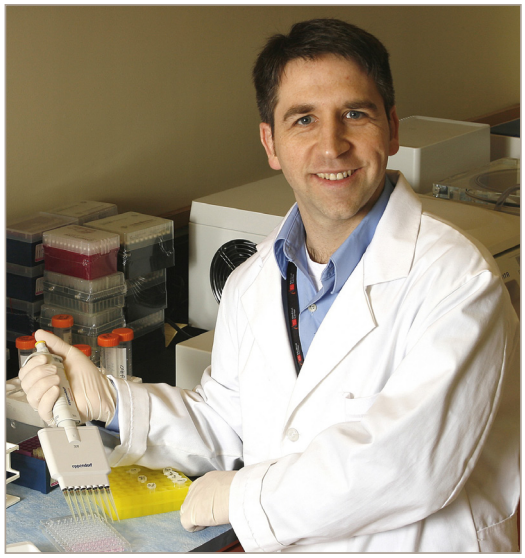
SKIN CANCER

GENDER DIFFERENCE

Lower Catalase Level Might Explain Higher Skin-Cancer Rate



TATIANA OBERYSZYN, PhD,
OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program



GREGORY LESINSKI, PhD,
OSUCCC– James Innate Immunity Program

Men are three times more likely than women to develop a common form of skin cancer, and a study by researchers at the OSUCCC – James may help explain why. The investigators found that male mice had lower levels of an important skin antioxidant than female mice and higher levels of certain cancer-linked inflammatory cells.

The antioxidant, a protein called catalase, inhibits skin cancer by mopping up hydrogen peroxide and other DNA-damaging reactive-oxygen compounds that form during exposure to ultraviolet B light (UVB), a common source of sunburn and cancer-causing skin damage.

The findings suggest that women may have more natural antioxidant protection in the skin than men, perhaps raising men's risk of skin cancer, say study co-leaders Gregory Lesinski, PhD, a member of the OSUCCC – James Innate Immunity Program, and Tatiana Oberyszyn, PhD, of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program.

The UVB exposure also caused an inflammatory white-blood-cell population called myeloid-derived suppressor cells to migrate from the bone marrow into the exposed skin. Higher numbers of these cells moved into the skin of male mice than female mice.

"These cells might be a novel source of UVB-induced immune suppression," says first author Nicholas Sullivan, a research scientist in Oberyszyn's lab. The research suggests that these UVB-induced inflammatory cells contribute to the genesis of skin tumors and perhaps other tumors rather than simply facilitating cancer progression, as generally thought, Sullivan notes.
The researchers conducted the study using a strain of hairless mice that develops squamous cell carcinoma of the skin – the second most common skin cancer in humans – when exposed to UVB.

Published in the journal Cancer Research.

Watch online

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

MELANOMA

HEREDITARY CANCER SYNDROME

Researchers Discover Hereditary Predisposition to Melanoma of the Eye

Ohio State University researchers have discovered a hereditary cancer syndrome that predisposes certain people to a melanoma of the eye, along with lung cancer, brain cancer and possibly other cancers.

An inherited mutation in a gene called *BAP1* (BRCA1- associated protein-1) causes the hereditary syndrome, researchers say. The findings suggest that *BAP1* mutations cause the disease in a small subset of patients with hereditary uveal melanoma and other cancers.

The uvea involves the iris, ciliary body and choroid layer of the eye. Uveal melanoma is the most common eye tumor in adults. It arises from pigmented cells called melanocytes that reside within the uvea, giving color to the eye.

"We are describing a new cancer genetic syndrome that could affect how patients are treated," says first author and cancer researcher Mohamed H. Abdel-Rahman, MD, PhD, assistant professor of Ophthalmology and of Medicine in the Division of Human Genetics at Ohio State.

"We are working with researchers at Nationwide Children's Hospital to develop a clinical test to screen for the *BAP1* mutation," he says.

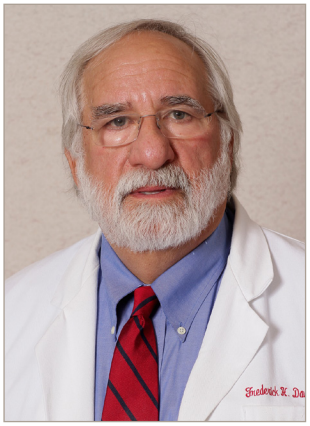
The research involved 53 unrelated uveal melanoma patients with high risk for hereditary cancer. Of these patients, three had germline variants in *BAP1*.

Study leader Frederick H. Davidorf, MD, professor emeritus of Ophthalmology at Ohio State, explained that *BAP1* seems to play an important role in regulating cell growth and proliferation, and that loss of the gene helps lead to cancer.

"If our results are verified, it would be good to monitor these patients to detect these cancers early when they are most treatable," says Davidorf, who treats ocular oncology patients at Ohio State along with Colleen Cebulla, MD, PhD.

The findings are reported in the Journal of Medical Genetics.

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



FREDERICK H. DAVIDORF, MD,
professor emeritus of Ophthalmology at Ohio State

THE RESEARCHERS

MOHAMED H. ABDEL-RAHMAN, MD, PhD,
assistant professor of Ophthalmology at Ohio State

OF NOTE

Recent Recognitions of OSUCCC – James Physicians and Researchers

AWARDS AND HONORS

MARTHA ANN BELURY, PhD, *professor of Human Nutrition, of Endocrinology, Diabetes and Metabolism, and of Public Health,* **has been elected an American Association for the Advancement of Science (AAAS) fellow** *for contributions to the field of human nutrition, particularly for elucidating cellular mechanisms of dietary compounds that influence metabolism, inflammation and carcinogenesis.*

E. ANTONIO CHIOCCA, MD, PhD, *professor and chair of Ohio State's Department of Neurological Surgery, and co-leader of the OSUCCC – James Viral Oncology Program, has been named the* **2011 Distinguished Alumnus for The University of Texas Graduate School of Biomedical Sciences at Houston.**

CARLO CROCE, MD, *director of Human Cancer Genetics at Ohio State,* **has been named to the Institute of Medicine of the National Academies**, *one of the highest honors in medicine. Croce has* **also received the Association for Molecular Pathology Award for Excellence in Molecular Diagnostics.**

ARNAB CHAKRAVARTI, MD, *professor and chair of Radiation Oncology and co-director of the Brain Tumor Program, is part of an international team of investigators that has* **received the National Brain Tumor Society's 2011 Award for Clinical Research Excellence.** *The team was recognized for research identifying methylation of the MGMT gene as a key predictor of outcome in patients with newly diagnosed glioblastoma.*

REBECCA NAGY, MS, *a certified genetic counselor and assistant professor of Clinical Internal Medicine,* **has been named president-elect of the National Society of Genetic Counselors.** *She will move to the role of president in 2013.*

ELECTRA PASKETT, PhD, MSPH, *Marion N. Rowley Professor of Cancer Research, director of the Division of Cancer Prevention and Control, and associate director for Population Sciences at the OSUCCC – James,* **has received the American Society of Preventive Oncology's Distinguished Achievement Award for 2012.** *The award recognizes excellence in research related to cancer prevention and control.*

AMY STURM, MS, *certified genetic counselor and assistant professor of clinical internal medicine in the Division of Human Genetics,* **has received the National Society of Genetic Counselors' 2011 Outstanding Volunteer Award,** *which recognizes dedication and significant contributions to the organization.*

CHRISTOPHER PELLOSKI, MD, *associate professor of Radiation Oncology at the OSUCCC – James and Nationwide Children's Hospital,* **received a $100,000 Hope Grant from Hyundai Hope on Wheels and the Columbus Hyundai Dealers** *to support a program for pediatric radiation oncology translational research.*

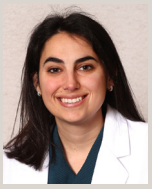
GRANTS

BARBARA ANDERSEN, PhD, *a professor of Psychology and researcher with the OSUCCC – James Cancer Control Program, has received a $1.6 million grant from the National Cancer Institute (NCI) to train mental health professionals in a biobehavioral intervention to help cancer patients cope with the stresses of diagnosis and treatment.*

QIANBEN WANG, PhD, *assistant professor of Molecular and Cellular Biochemistry, has received a $1.6 million, five-year grant from the NCI to study the regulation of androgen receptor function by H3K4 methylation in prostate cancer.*

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

FACULTY AND PROGRAMS



VIRGINIA DIAVOLITSIS, MD, *has joined the cancer program as an* **assistant professor of Radiation Oncology.** *Her clinical and research interests are in thoracic, head and neck, and breast oncology.*

RICHARD M. GOLDBERG, MD, *professor of medicine and a GI medical oncologist,* **has been named physician-in-chief at the OSUCCC – James.** *His responsibilities include leading the transition into the new James Cancer Hospital and Solove Research Institute, which opens in 2014.*

CHARLES SHAPIRO, MD, *director of Breast Medical Oncology and professor of Internal Medicine,* **has been named to lead the breast cancer research program at the OSUCCC – James.** *He will lead an interdisciplinary team of clinical and research scientists whose sole focus is the study and treatment of breast cancer.*

CYNTHIA TIMMERS, PhD, has been selected to develop and direct the new OSUCCC – James Solid Tumor Translational Science Shared Resource. *The new shared resource will design and develop biomarker and diagnostic assays to support correlative studies associated with early-phase solid-tumor clinical trials.*

TERENCE WILLIAMS, MD, PhD, *has joined the cancer program as an* **assistant professor of Radiation Oncology.** *His research interests include novel therapeutic methods to radiosensitize cancer cells, identifying biomarkers that predict outcome and response to therapy, and investigating processes that lead to metastasis.*

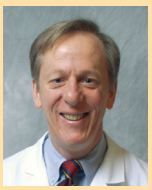
EVAN WUTHRICK, MD, *has joined the cancer program as an* **assistant professor of Radiation Oncology.** *His clinical interests include radiation therapy (RT) for cancers of the GI tract, liver, skin, lung, bladder and prostate. His research interests include early-phase clinical trials; RT and immune-modulatory drugs in melanoma; and RT with novel radiosensitizers, radioprotectors and targeted agents.*

FEN XIA, MD, PhD, *has joined the cancer program as an associate professor of Radiation Oncology. Her clinical interests include comprehensive brain tumor treatment using intensity modulated radiation therapy, image-guided radiotherapy, brachytherapy and stereotactic radiosurgery. Her research interests include DNA damage repair, mechanisms of resistance and identifying molecular targets to enhance brain tumor treatment.*

Ohio State's **CENTER FOR RETROVIRUS RESEARCH** *is granting its 2012 Distinguished Research Career Award to Warner Greene, MD, PhD, director of the Gladstone Institute of Virology and Immunology, and professor of Medicine, Microbiology and Immunology at the University of California, San Francisco. He is well known for research on the molecular biology, immunology and pathogenesis of HIV-1 and HTLV-1.*

OHIO STATE'S MEDICAL CENTER, WHICH INCLUDES THE OSUCCC – JAMES, *completed its conversion to an electronic medical records system, called the Integrated Healthcare Information System, in mid-October.*

LEADERSHIP ACTIVITIES AND APPOINTMENTS



ROBERT BAHNSON, MD, *chief-of-staff at The James Cancer Hospital and Solove Research Institute, has been installed as first vice president of the American College of Surgeons. Bahnson is professor and chair of the Department of Urology and holds the Dave Longaberger Endowed Chair in Urology.*

Today, more people are surviving longer after cancer treatment, and more of their needs are being addressed by research and included in the continuum of care.

SURVIVORSHIP 2012

BY BOB HECKER

When Joe Flynn, DO, MPH, considers cancer survivorship statistics since the National Cancer Act was signed in December 1971, he thinks of his mother.

"Mom had chronic lymphocytic leukemia (CLL) in 1989-90, and in 1991 we started seeing the impact of the 'war on cancer,'" says Flynn, co-director of the Division of Hematology at The Ohio State University. "1991 was the first year that cancer deaths in the U.S. started leveling off."

"WITH HELP FROM A GREAT PATIENT ADVOCACY GROUP, WE ARE PLANNING A SURVIVORSHIP SUPPORT CLINIC THAT WILL HOUSE, IN ONE LOCATION, SEVERAL SUPPORTIVE SERVICES"

– JOE FLYNN, DO, MPH

Flynn's mother was on a clinical trial involving essentially the only drug available then for CLL. "But it was too little too late."

Although CLL remains incurable, medical scientists have since learned much more about this and other cancers. Many CLL-specific clinical trials are under way at institutions around the world, including Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), where Flynn is medical director of survivorship clinics.

The trials involve chemotherapies, immunotherapies, targeted therapies that disrupt molecules involved in tumor growth, and bone marrow transplants. "Today we have multiple agents targeted to specific cancers based on their molecular signatures," Flynn says. "Not a day goes by when I don't wonder, 'If she got that disease now, how would she fare?'"

The answer may lie within statistics that reflect the growing legions of cancer survivors in the United States.

In its *AACR Cancer Progress Report 2011*, the American Association for Cancer Research says 68 percent of adult cancer patients today are living five or more years after initial diagnosis, up from 50 percent in 1975. The five-year survival rate for all childhood cancers combined is up from 52 percent in 1975 to 80 percent.

The AACR report also states that, between 1990 and 2007, death rates in the United States for all cancers combined dropped 22 percent for men and 14 percent for women, resulting in an estimated 898,000 fewer deaths from cancer.

And of nearly 12 million cancer survivors currently in this country, the AACR says the majority were diagnosed more than five years ago, and approximately 15 percent were diagnosed 20 years ago or more.

"In signing the (National Cancer Act) and announcing the war on cancer, President Richard Nixon stated, 'As this year comes to an end, cancer remains one of mankind's deadliest and elusive enemies,'" said Electra Paskett, PhD, MSPH, associate director for population sciences at the OSUCCC – James, during her presidential address at the 35th annual meeting of the American Society of Preventive Oncology

(ASPO) in 2011. Paskett was ASPO president from 2009-11.

"Overall, we have seen many successes in the war on cancer," added Paskett, who also leads the Cancer Control Program at the OSUCCC – James. "Many malignancies are now curable. We have better treatments for many cancers, including chemotherapy, surgery, radiation therapy, etc., and we have addressed symptoms and quality of life for cancer patients. Five-year cancer rates document our progress."

Julia Rowland, PhD, director of the National Cancer Institute's Office of Cancer Survivorship (OCS), says the number of survivors will continue to rise.

"Since 1971, there has been an almost four-fold increase in the number of survivors," Rowland and colleagues wrote in "Cancer Survivors: A Booming Population," which appeared in the journal *Cancer Epidemiology, Biomarkers & Prevention*, in October 2011. "This is a testament to the many advances in cancer detection, treatment and supportive care in the intervening decades."

With age being the most important risk factor for cancer, Rowland and colleagues concluded that population aging and improved survival will converge to generate a growing number of older-adult cancer survivors with needs complicated by co-existing health conditions.

Even the definition of a survivor has changed. Until late in the 20th century, a "cancer survivor" was someone who had been disease-free for five years. Now, Rowland says, individuals are considered survivors from diagnosis through the rest of their lives.

ADDRESSING NEEDS

Susan Brown, RN, PhD, chief nursing officer at the OSUCCC – James and supervisor of all survivorship activities there, lends historical perspective.

"Forty years ago, clinicians focused entirely on treating the cancer, and the rest of these patients' lives took a back seat," Brown says. "Now that so many patients are living longer, cancer influences every facet of their existence—emotional, psychological, social, financial—and they forever face fears of recurrence."

Brown says caregivers recognize "that we can't just treat them and then leave them alone to cope with the concerns of life, like getting back to work, dealing with chronic pain and fatigue, raising children, adjusting financially and re-establishing relationships. Survivors need help facing the sequelae of cancer."

Addressing survivors' needs has opened cancer survivorship as a new academic field, says Charles Shapiro, MD, director of Breast Medical Oncology and member of the Cancer Control program at the OSUCCC – James, where he also leads the breast cancer research program.

"In 1970, there were only two or three academic papers on survivorship, compared with thousands today," he says.

"Survivorship care has become extremely important to promote optimal health for this growing population and to accommodate their expectations for a better quality of life."

"NOW THAT SO MANY PATIENTS ARE LIVING LONGER, CANCER INFLUENCES EVERY FACET OF THEIR EXISTENCE—EMOTIONAL, PSYCHOLOGICAL, SOCIAL, FINANCIAL—AND THEY FOREVER FACE FEARS OF RECURRENCE." – SUSAN BROWN, RN, PHD

Forty years ago, patients lacked such expectations, and many were reluctant even to talk about their illness.

"People were much more secretive about their diagnosis and condition," says Patricia Ganz, MD, a professor in the UCLA schools of Medicine and Public Health who has devoted more than 25 years to studying quality-of-life outcomes in cancer and other diseases. "There was little or no accommodation in the workplace, there was little understanding of the disease itself, and there was no psychosocial support available."

Cancer has since gone public. "In the '40s, '50s and '60s, patients and

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

families often were embarrassed about a cancer diagnosis," says Barbara Andersen, PhD, a professor of Psychology at Ohio State and member of the Cancer Control Program at the OSUCCC – James. "Now it's the subject of movies, books, major advocacy efforts and huge fundraisers. An explosion of information about cancer in the popular press and on the Web has made cancer more knowable and helped people feel more in control."

"AT LEAST 25 PERCENT OF NEWLY DIAGNOSED CANCER PATIENTS HAVE CLINICAL STRESS AND ANXIETY DISORDERS; IT'S A PROBLEM THAT IS OFTEN UNRECOGNIZED OR IS UNDERTREATED."

– BARBARA ANDERSEN, PHD

This has paralleled a shift toward psychosocial concerns, both among professionals and patients.

"Over the past 25 years, professional caregivers have started writing more about psychosocial adjustments to cancer," Andersen says. "There are still certain aspects of cancer and treatment that are less discussed, such as sexuality, but 25 years ago there was no talk."

UNRECOGNIZED NEEDS

Despite this shift, she says, a gap remains between the prevalence of emotional distress over cancer and the awareness of services for treating it.

"At least 25 percent of newly diagnosed cancer patients have clinical stress and anxiety disorders; it's a problem that is often unrecognized or undertreated," Andersen says. "Almost no studies have looked at how to help the cancer patient with clinical depression."

From Cancer Patient to Cancer Survivor: Lost in Transition, a 2005 Institute of Medicine (IOM) report, notes that primary care physicians and other healthcare providers "often are not extremely familiar with the consequences of cancer and seldom receive explicit guidance from oncologists." The IOM report contends that a "lack of clear evidence for what constitutes best practices in caring for patients with a history of cancer" contributes to the problem.

The report recommends establishing cancer survivorship as a distinct phase of care and calls for oncologists to provide patients with an individualized, comprehensive "Survivorship Care Plan" that the IOM believes should be reimbursed by third-party payers. Ganz has long promoted this idea.

She says that even when cancer treatment has been successful, patients should be followed for recurrence or late treatment effects. "They may experience persistent fatigue or pain that must be managed," Ganz says, "and they are at high risk for second cancers, so promoting health behaviors that reduce that risk is important.

"There has been increasing uptake and use of these plans, mostly among early adopters," Ganz adds. "And the American College of Surgeons has revised its guidelines to include preparation of treatment summaries and Survivorship Care Plans for patients by 2014 for accreditation purposes. This is pushing things forward."

Shapiro says the medical world is in transition between two survivorship models.

"Whereas 10 to 20 years ago the focus was almost entirely on treatment, and survivorship was more of an uncoordinated, non-integrated afterthought, we now recognize that survivorship must be integrated into the continuum of cancer care from the outset, and that it must include health promotion and psychosocial support," he explains.

Flynn says the OSUCCC – James follows IOM survivorship recommendations by using nurse practitioners who provide patients with a summary of their treatment history and an individualized Survivorship Care Plan.

"The nurse practitioners provide transition educational materials and direct patients to specialty services offered by the OSUCCC – James, Ohio State's Medical Center and the community," Flynn says.

"With help from a great patient advocacy group," he adds, "we are planning a Survivorship Support Center that will house, in one location, supportive services that include pain management, genetic counseling, spiritual counseling, nutrition counseling, psychosocial care –

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

information that caters to their needs."

But such comprehensive services are usually provided only at academic medical institutions, Brown notes. "Some 70 to 80 percent of cancer patients are treated in community hospitals, and many private practitioners don't have the wherewithal to offer ongoing survivorship support," she says. "Survivorship programs generally don't produce revenue, so it's hard for institutions to provide them.

"We need to work with third-party payers on broadening their coverage, especially in complementary or alternative medicine—which they generally don't cover but that can benefit cancer patients, such as exercise programs to combat chronic fatigue."

To reduce costs, Andersen believes institutions must focus on the patients who are most in need.

"There's a subset that have the financial resources and the know-how to access interventional services and don't need help from people like myself," she says. "My focus as a psychologist and cancer researcher is on patients in greatest need of help."

SURVIVORSHIP RESEARCH

Andersen and collaborators have garnered national attention with a psychological intervention for women treated for breast cancer. The research involved 227 women surgically treated for regional breast cancer. After a median 11-year follow up, the study showed that the intervention improved survival and reduced recurrence.

William Carson III, MD, a surgical oncologist at the OSUCCC – James who collaborated with Andersen on this work, says the data "show that reducing patients' stress boosted the immune system, perhaps enabling it to destroy small tumor deposits that escaped chemotherapy." He believes the study supports the idea that mental health mediates physical health.

Andersen has since acquired a $1.6 million NCI grant to train psychologists, mental health nurses and social workers to provide the intervention to breast cancer survivors.

She also has received NCI grants to study interventions for patients with recurrent cancer and for women treated for gynecologic cancer who have sexual difficulties. In addition, she has completed a pilot study of an intervention for cancer survivors with clinical depression.

Andersen is working as co-investigator and mentor with Joanne Lester, PhD, CRNP, a clinical assistant professor in the College of Nursing and member of the Cancer Control Program at the OSUCCC – James, on a randomized control trial to study the effect of survivorship care planning on distress in leukemia and breast cancer survivors.

"Prolonged stress among cancer patients can reduce quality of life and affect a host of physical factors, possibly including the risk of metastatic disease," Lester says. She and colleagues will examine the level and nature of self-reported distress in early survivorship, measure the effect of the physician's office visit on distress, and gauge the effect of survivorship care planning over time.

Brown says survivorship research is invaluable to caregivers and patients.

"By focusing on issues that may occur after treatment, this research may also teach us what we can do better during treatment, such as intervening earlier to alleviate distress, to avoid problems later.

"SURVIVORSHIP CARE HAS BECOME EXTREMELY IMPORTANT TO PROMOTE OPTIMAL HEALTH FOR THIS GROWING POPULATION AND TO ACCOMMODATE THEIR EXPECTATIONS FOR A BETTER QUALITY OF LIFE."

– CHARLES SHAPIRO, MD

"We want to develop a model of survivorship care that can be replicated in any setting and a stronger evidence base for survivorship interventions," Brown adds.

Today, the ability to better diagnose and treat cancer, and to help patients cope with life after treatment, has given patients new hope, Flynn says. "It's more than just whether they can be cured, although that's always the goal. It's also about having a good quality of life, which many more survivors now have.

"So really the difference between life for cancer survivors in 1971 and today is like the difference between driving a horse-and-buggy and a Ferrari."

More at cancer.osu.edu/about/publications/frontiers/

FOREIGN *Occupiers*

Metastatic tumors cause the vast majority of cancer deaths. Bone metastases are particularly debilitating. OSUCCC – James researchers are working to understand how they happen and how to block them.

BY DARRELL E. WARD
PHOTOGRAPHY BY ROMAN SAPECKI

Inject metastatic prostate cancer cells into an animal model and within 15 minutes tumor cells localize to the brain, eyes, lung, kidneys and bone. All will soon die except those in bone.

Thomas Rosol, DVM, PhD, professor of Veterinary Biosciences, and his laboratory tracked these events in a mouse model using cancer cells carrying the protein that makes fireflies glow. "The metastatic cells probably interact with the bone microenvironment and create a fertile environment that enables them to grow," Rosol says.

Most invasive cancer cells don't cause metastatic tumors. "Most cancer cells die after entering the bloodstream," he says. Twenty days into the experiment, only two cells capable of causing bone metastases remained, one in the leg and one in the back.

"That's two prostate cancer cells out of 100,000," Rosol says. "We want to learn what's special about those few surviving cells, and we want to learn how to stop them."

Roughly nine in 10 cancer deaths are caused by tumors that spread—metastasize—to organs often far removed from the primary tumor. Metastatic cancer cells are models of the adage, "What doesn't kill you makes you stronger." They have survived chemotherapy, radiation and target agents, selective pressures that leave them resistant to further therapy.

Treating bone metastases is particularly difficult. Surgical control is generally not an option because bones are usually not sites for surgical removal, Rosol says. "In general, once cancer metastasizes to bone, it is incurable."

Lung, thyroid and renal cancers often metastasize to bone, and sometimes melanoma. Prostate and breast cancer and multiple myeloma commonly spread to bone. Rosol has personal experience with the latter. His father died of multiple myeloma at home under hospice care.

"Bone metastases can be devastating and painful," he says. "They can destroy bone and lead to fractures. In the spinal column, they can cause vertebrae to collapse and lead to paralysis. In the leg, arm or ribs, they can cause fractures that won't heal because of the cancer present. They can be very debilitating."

Rosol is working to understand bone metastases in both human and veterinary patients. "A handful of spontaneous cancers are relatively common in dogs and cats, and we treat them at our Veterinary Medical Center," he says.

The cancers include:

- **Breast cancer** – occurs in both dogs and cats;
- **Prostate cancer**, osteosarcoma and lymphoma – occurs in dogs;
- **Oral cancer** – cats commonly develop an aggressive, invasive oral cancer.

Rosol's lab develops cell lines from these cancers for studies in animal models.

The animal models enable translational research that has application for both human and animal patients.

PROCESS AND PATTERNS

While benign tumors tend to remain localized and removable, malignant tumors develop a capacity to invade neighboring tissue and to metastasize, a process that requires several steps (see sidebar).

Research has shown that many of the genes involved in invasion and metastasis are associated with a cell program called the epithelial-mesenchymal transition, a pathway normally activated during early embryogenesis and wound healing. In malignancy, the pathway gives epithelial cells features of mesenchymal cells, enabling them to detach, move through the extracellular matrix, interact with endothelial cells and other stromal cells, and enter the blood and lymphatic systems.

The site of metastasis depends on the type of cancer. Most metastatic cells are transported by the bloodstream, and the preferred metastatic site is often the next organ downstream. But why breast and prostate cancers metastasize frequently to bone is not understood, Rosol says.

The idea that metastases of certain cancers prefer particular tissues was recognized long ago. In 1889,

THOMAS ROSOL, DVM, PhD

"Bone metastases can be devastating and painful. They can destroy bone and lead to fractures. In the spinal column, they can cause vertebrae to collapse and lead to paralysis. In the leg, arm or ribs, they can cause fractures that won't heal because of the cancer present. They can be very debilitating."

the British surgeon Sir James Paget published a paper in the journal *Lancet* proposing the "seed and soil" hypothesis, which likens tumor cells to seeds that require a particular kind of "soil," or organ.

"Today, we think of this as the dynamic interplay between cancer cells and the tumor microenvironment," Rosol says.

Breast and prostate cancers can affect the bone microenvironment in opposite ways: Breast cancer cells destroy bone, a process called osteolytic metastasis, while prostate cancer cells can cause bone production, or osteoblastic metastasis, a pathology that also causes pain and disability (see illustration).

MODELING METASTASIS

Research by Rosol and others has provided insights into how bone metastases happen. In 1987, Rosol was part of a group that discovered parathyroid hormone-related protein (PTHrP), which is released by some types of cancer and can cause dangerously high levels of blood calcium, a condition called hypercalcemia.

PTHrP stimulates osteoclasts, which are cells that occupy and dissolve bone. Normally, osteoclasts work in coordination with bone-building cells called osteoblasts to remodel bones and accommodate changes in mechanical stress. Together, they replace an estimated 10 percent of bone mass annually, or the entire skeleton every decade.

It turns out, Rosol says, that the release of PTHrP by metastatic breast cancer cells induces osteoclasts to resorb bone. "So cancer cells themselves don't destroy bone; they direct normal bone cells to destroy the bone," he says.

Unfortunately, investigating the molecular mechanism underlying these events is notoriously difficult for two key reasons: a lack of animal models (other mammals develop spontaneous cancers, but the tumors produce few metastases), and the difficulty of seeing bone metastases on X-rays.

Rosol and his colleagues have made progress against both problems. A break came in the mid-90s when the technology of bioluminescence was discovered by Christopher Contag, PhD, at Stanford. Rosol immediately recognized its potential for studying metastasis, and he visited Contag's laboratory to learn the technique.

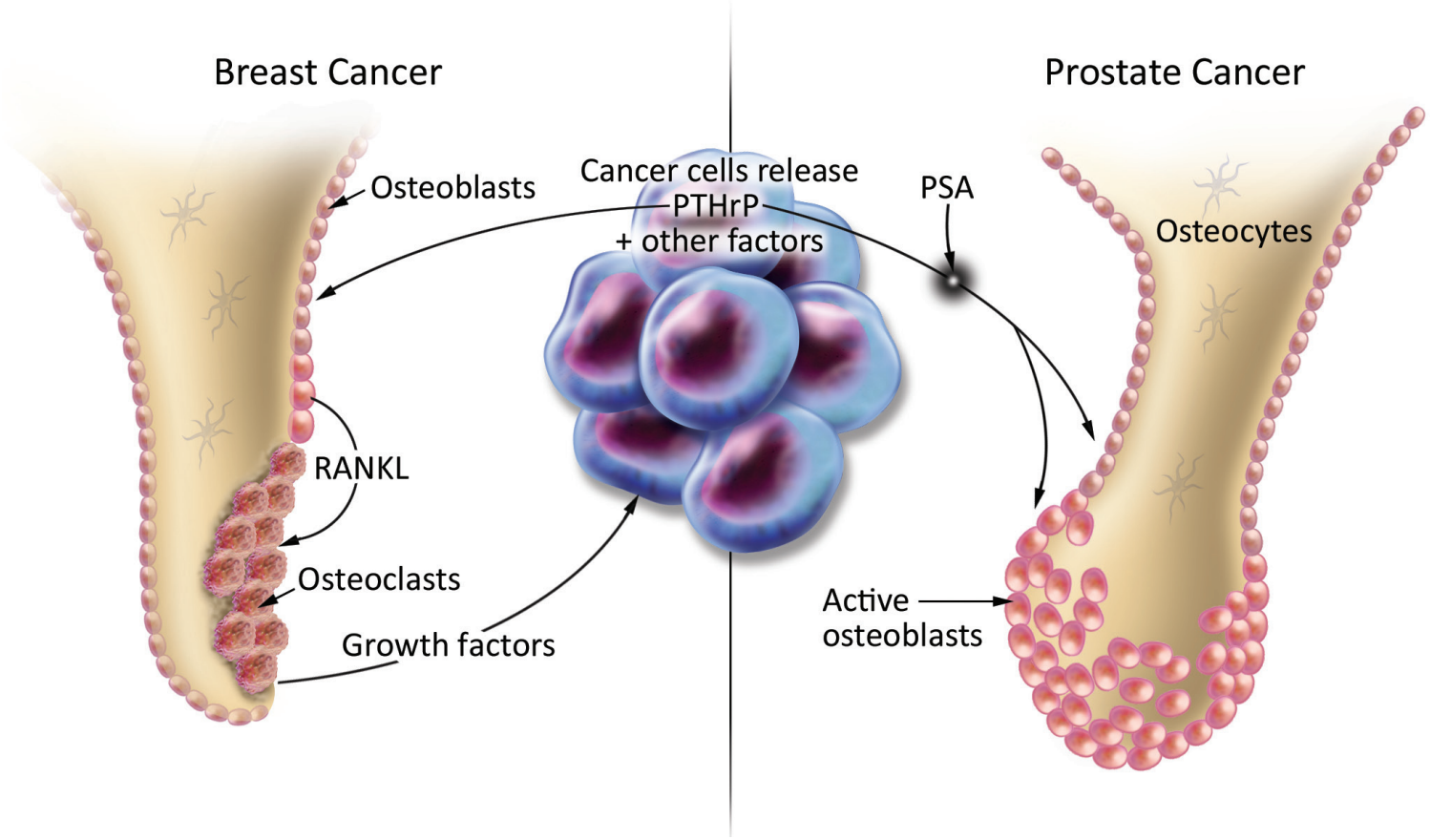
The method uses genetic engineering to add the gene for luciferase, the enzyme that enables fireflies to glow, to lines of human and animal cancer cell lines. "This endows the cells with light just like fireflies," Rosol says. They use a high-sensitivity camera to visualize the glowing cells inside the bones of immunodeficient mice even at a very early stage.

"This was a tremendous advance," Rosol says. "We can count the number of metastases, calculate their growth rate and investigate different treatments to see if they reduce the number or growth of metastases."

Watch online

Rosol now has an inventory of 10 bioluminescent cell lines of canine, feline and human breast cancer; canine and human prostate cancer; canine and human osteosarcoma; and feline and human oral cancer.

"Oral cancer will destroy facial bones," Rosol says. "It's not metastasis; it's local invasion into the bones, and it will destroy the jaw or face. The mechanism of destruction is very similar to that of metastatic cancer, even though the process to get to the bone is different."



OSTEOCLASTIC AND OSTEOBLASTIC BONE METASTASIS

Breast cancer cells that metastasize to bone (left side of figure) release a cytokine called parathyroid hormone-related protein (PTHrP), which causes nearby bone cells called osteoblasts to release a cytokine called RANKL. RANKL, in turn, stimulates bone-absorbing cells called osteoclasts to dissolve the bone. Along with weakening the bone, this action releases growth factors from the bone that stimulate proliferation of the cancer cells and calcium that can lead to hypercalcemia. Prostate cancer cells that metastasize to bone (right side of figure) also release PTHrP, but it's thought that the protein is cleaved by prostate-specific antigen (PSA), and that the resulting truncated PTHrP molecule and other growth factors activate abnormal bone production by osteoblasts.

BREAST CANCER – OSTEOLYTIC METASTASIS

Breast cancer research by Rosol's lab involves mainly human tumors. The researchers hypothesize that metastatic breast cancer invades bone through a vicious cycle of tumor-induced bone resorption.

Their studies and those of others have revealed a chain of events that leads to bone breakdown. It begins when breast cancer cells release PTHrP. This stimulates osteoblasts in the bone to release a cytokine called RANKL (receptor activator of nuclear factor kappa-B ligand), a protein important for bone metabolism. RANKL, in turn, induces osteoclasts to resorb bone. This breakdown releases both calcium, resulting in hypercalcemia, and a variety of growth factors from the bone. "Those growth factors nurture the proliferation of the cancer cells," Rosol says.

PROSTATE CANCER – OSTEOBLASTIC METASTASIS

Ahmad Shabsigh, MD, assistant professor of Urology at Ohio State and a collaborator of Rosol's, knows what metastatic disease means for prostate cancer patients.

"The vast majority of men diagnosed with prostate cancer in the United States have local disease,

but still, about 32,000 men died from prostate cancer in 2010, and they all died from metastatic disease," Shabsigh says.

Dogs are the only other mammal known to develop spontaneous prostate cancer, and their disease also metastasizes to bone, Rosol notes. "The biology of prostate cancer metastasis is amazing," he says. "It induces osteoblasts to produce excessive, poor quality bone that can lead to spinal cord compression, pathological fractures and pain."

PTHrP plays a role here, too, he says, but it involves a different portion of the molecule. *In vitro* evidence suggests that prostate-specific antigen (PSA), the protein used to detect prostate cancer, is actually an enzyme, he says. "We think PSA destroys the part of PTHrP that induces osteoclasts, and that the remaining truncated molecule induces bone formation."

In 2007, Rosol had a breakthrough in prostate cancer modeling. A dog with prostate cancer was brought for treatment to Ohio State's College of Veterinary Medicine Hospital for Companion Animals. The disease had metastasized to one leg, which was amputated. Rosol and his team obtained malignant cells from the animal and have developed a cell line that could lead to new treatments for prostate cancer. Watch online

"Most models of metastatic prostate cancer don't induce new bone," he says. "Amazingly, the cell line we developed using this tumor induces new bone just like human disease." They have since published three papers on the cell line, which they call ACE-1. They've shipped the cell line to universities around the United States and the world and licensed it to a major pharmaceutical company for research.

A NEED FOR INHIBITORS

When cancer cells enter bone marrow, they often lie dormant there for years before metastatic tumors develop. "We don't know why it takes so long, or how they come out of dormancy," Rosol says.

At least 30 percent of people with primary breast or prostate tumors and no evidence of metastases have individual metastatic cells in their bone marrow, Rosol says. "They're very rare, but they are there. Some will never develop a metastasis and some will. If we can learn what triggers their growth, we might be able to prevent it. It's an important question but very hard to model."

Currently, no drugs exist that block metastasis, but a growing number of agents are available to inhibit bone loss, he says. Most of these belong to a class of drugs called bisphosphonates, which were originally developed to inhibit bone loss due to osteoporosis. They work by inhibiting osteoclasts, and they've recently been used to treat patients with bone metastases.

"Their effect on metastasis is still unclear, but they do reduce bone destruction, and that is beneficial for a woman with breast cancer," Rosol says. "They are also being investigated for prostate cancer, but we don't know what they will do there."

Newer agents that influence bone loss are in development or have been approved for clinical use by the Food and Drug Administration. They include denosumab, an antibody-based drug that inhibits osteoclasts by targeting RANKL.

LOOKING FORWARD

Preventing metastasis remains a daunting challenge. "One strategy

"That's two prostate cancer cells out of 100,000," Rosol says. "We want to learn what's special about those few surviving cells, and we want to learn how to stop them."

THOMAS ROSOL, PHD

is to prevent activation of those disseminated tumor cells," Rosol says. "There is evidence that the tumor cells displace bone marrow stem cells and compete for the same location, so one idea being considered in the field is to repopulate bone marrow with new stem cells to evict the cancer cells."

In the case of prostate cancer, Rosol is working with Shabsigh; Tarik Khemees, MD, a clinical fellow of Shabsigh's; Michael Knopp, MD, PhD, professor of Radiology and Novartis Chair of Imaging Research; and Michael Tweedle, PhD, professor and Stefanie Spielman Chair in Cancer Imaging, to improve treatment of localized disease and prevent metastasis from occurring.

"There is no cure for advanced prostate cancer or for bone metastatic disease, but no patients die from localized disease," Shabsigh says. "If we can do a better job of treating localized disease, perhaps we can prevent metastasis from occurring."

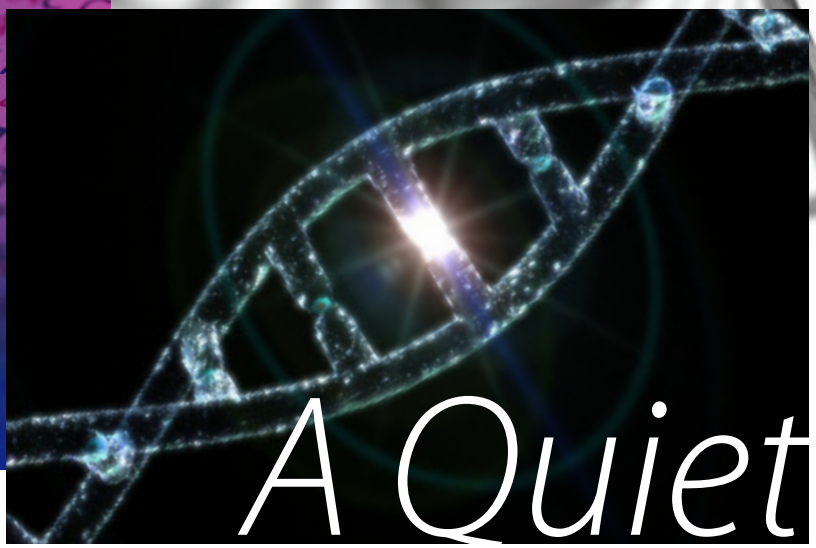
Their goal is to improve the imaging of localized prostate cancer and the focal treatment of the disease using cryotherapy or high-frequency ultrasound.

"We want to develop an animal model that will help us develop techniques to identify exactly where the tumor is within the prostate," Shabsigh says. "That may enable us to treat only the areas of the prostate with cancer and prevent the removal of the whole gland."

A better understanding of the mechanisms of metastasis is essential for developing effective treatments for advanced disease. "The ability to model and image metastasis in mice with human and animal tumors has been an important advance to enable cancer research that will improve the lives of those with late-stage cancers," Rosol says. "We will not be able to prevent cancer deaths until we understand why and how to prevent metastasis and metastatic tumor growth in patients."

METASTASIS REQUIRES SEVERAL STEPS

- Cancer cells invade neighboring tissue, break from the primary tumor and enter the circulation.
- Most circulating tumor cells die; a few are caught in capillaries in a new organ.
- At the secondary site, cancer cells may enter the tissues and experience one of several outcomes:
  - *Solitary tumor cells may die, lie dormant or proliferate.*
  - *Nonvascular micrometastases may die, grow or lie dormant (i.e., cell death and cell proliferation occur equally).*
  - *A micrometastasis may grow and become a vascularized, clinically detectable metastatic tumor.*



A Quiet EVOLUTION

P4 medicine promises to promote wellness, lower healthcare costs and improve treatment outcomes.

BY DAVE SLAYBAUGH

Recent and emerging technologies and several decades of research are transforming the practice of medicine from the primarily disease-based care of today to a wellness-based care model of the future. This new approach is called P4 medicine: It provides care that is predictive, preventive, personalized and participatory (see sidebar).

The principles of P4 medicine are being applied to oncology with a growing emphasis on the use of genomics and other "-omic" sciences to predict cancer risk, prevent cancer development, and develop and guide use of personalized therapy. Along with this, there is growing emphasis on encouraging patients to participate more in treatment decisions and to adhere to survivorship care plans (see "Survivorship 2012," page 14).

The Ohio State University Medical Center and Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) are at the forefront of the P4 medicine movement with research that is advancing clinical care and offering training in P4 medicine for the physicians of tomorrow.

"The OSUCCC – James is committed to personalized health care through research to improve diagnosis and develop targeted therapies, identify clinically useful biomarkers and evaluate new cancer prevention and control strategies," says Michael A. Caligiuri, MD, director of Ohio State's Comprehensive Cancer Center and chief executive officer of The James Cancer Hospital and Solove Research Institute.

Why P4 medicine is important

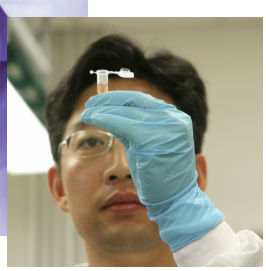
In a presentation at the 2011 Annual Systems Biology Symposium: Systems Biology & P4 Medicine, Clay Marsh, MD, executive director of Ohio State's Center for Personalized Health Care, cited these factors in discussing health care's "need for transformation":

- In 2009, the overall cost of health care in the United States totaled $2.5 trillion, accounting for 17.6 percent of the American economy.
- An estimated 75 to 90 percent of that amount was spent managing and treating preventable chronic illnesses.
- On a per-person basis, U.S. healthcare costs are 50 percent higher than in the nation with the second-highest costs.
- Drugs prescribed for patients are effective in less than 60 percent of treated patients, but development costs have skyrocketed.

Marsh and other P4 medicine advocates say that by engaging patient participation, predicting and preventing disease, facilitating health and creating a personalized wellness plan for each patient, P4 medicine can eliminate much of the labor and cost of treating preventable illnesses while enhancing quality of care.

"We believe that by increasing the precision of health care and ultimately trying to reverse our paradigm from disease to health,

Clay Marsh, MD, *executive director, Ohio State's Center for Personalized Health Care*



from reactive to proactive care, there's a tremendous opportunity to both lower costs and improve outcomes," says Marsh, who is also vice dean and senior associate vice president for research at Ohio State's College of Medicine.

P4M for Cancer Patients

"Cancer is a genetic disease," Caligiuri says, "but the kinds of genetic changes that occur can be different in each patient—even those with the same type of cancer—and they influence how that patient responds to treatment. We want to learn how those changes affect outcome and which ones we should target with existing or new drugs."

Researchers, physicians, geneticists and others at the OSUCCC – James are contributing to each area of the P4 medicine transformation.

PREDICTIVE

As recently as the 1980s, the existence of major hereditary forms of cancer was not universally accepted. Then groundbreaking research by Albert de la Chapelle, MD, PhD, co-leader of the OSUCCC – James Molecular Biology and Cancer Genetics Research Program, and others in the 1990s established that hereditary nonpolyposis colorectal cancer (HNPCC), commonly called Lynch syndrome, is inherited.

Further research led by de la Chapelle on Lynch syndrome mutations showed the following:

- All colon tumors requiring surgery should be tested for Lynch syndrome mutations, and that prescreening for the mutations could be done economically using immunohistochemistry. The study was published in the *New England Journal of Medicine*. Watch online
- About one in 50 newly diagnosed endometrial cancer patients have Lynch syndrome mutations, suggesting that women with endometrial cancer should be screened for the syndrome.
- Some rare skin cancers – sebaceous adenomas, sebaceous adenocarcinomas and keratoacanthomas – may be a sign of Lynch syndrome. The study confirmed that Muir Torre syndrome is a variant of Lynch syndrome. Watch online

Because Lynch syndrome carries an almost 100 percent lifetime risk of cancer, patients or their relatives with the mutation require close monitoring for early cancer detection.

Additional studies have shown that testing for tumor genomics or patient genomics may help predict a susceptibility to other types of cancer, including breast and lung.

PREVENTIVE

"We know that about 5 to 10 percent of all cancers are caused by a genetic mutation that runs in the family and causes an increased susceptibility to cancer," says Heather Hampel, a certified genetic counselor and associate director of Ohio State's Division of Human Genetics.

"If we can identify the gene mutation that is responsible, we can offer predictive testing to at-risk relatives. Those who are found to have a high risk for cancer can follow intensive cancer surveillance and prevention recommendations to either prevent the cancer altogether or to diagnose it early when it is most treatable."

The Division of Human Genetics has counseled nearly 5,000 patients since 1996, and about 2,800 have undergone genetic testing, Hampel says. The testing has identified several hundred individuals with Lynch syndrome and several

"The OSUCCC – James is committed to personalized health care through research to improve diagnosis and develop targeted therapies, identify clinically useful biomarkers and evaluate new cancer prevention and control strategies."

MICHAEL A. CALIGIURI, MD

P4 Medicine ● PREDICT ● PREVENT ● PI

hundred with hereditary breast and ovarian cancer syndrome, enabling their physicians to prescribe appropriate observation and prevention protocols.

Although Lynch syndrome and hereditary breast and ovarian cancer syndrome are the two most common inherited cancer syndromes, Hampel adds, "There are many other hereditary cancer syndromes, and we can evaluate families for any of them."

Because so many people are diagnosed with cancer every year, cancer prevention is an area of P4 medicine that holds tremendous potential for progress. Researchers continue to learn more about cancer-causing genetic mutations, but much is yet to be discovered.

Read about the OSUCCC – James Clinical Cancer Genetics Program here.

PERSONALIZED

"The history of research in cancer-related genetics at the OSUCCC – James spans studies in acute and chronic leukemia that have improved patient stratification and led to new treatments and more individualized treatment," says Caligiuri. Therapies—and clinical trials testing new therapies—for these and other cancers are being personalized based on the genetic profile of patients' cancer cells.

Lung Cancer

Gregory Otterson, MD, a lung cancer specialist and a member of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James, says that lung-cancer clinical trials at The James and elsewhere are matching specific drugs and approaches with specific patients according to the genetic signature of the patient's tumor cells.

"Instead of talking about 200,000 patients per year with lung cancer, we will be talking about 20,000 to 30,000 patients per year with *EGFR*-mutant lung cancer, 8,000 patients with *EML4-ALK* translocated lung cancer and 60,000 to 70,000 patients with *KRAS* mutant lung cancer."

The treatments for each type can be quite different, he says. "Approaches that affect the specific molecular defects of the cancer may be much more effective than the 'old-fashioned' concept of adding Drug A to Drug B to see if it improves treatment."

"Instead of talking about 200,000 patients per year with lung cancer, we will talk about 20,000 to 30,000 patients per year with EGFR-mutant lung cancer, 8,000 patients with EML4-ALK translocated lung cancer and 60,000 to 70,000 patients with KRAS-mutant lung cancer."

GREGORY OTTERSON, MD

Acute Myeloid Leukemia

Guido Marcucci, MD, director of the OSUCCC – James Myeloid Malignancy Program, focuses on drug development and discovery of molecular prognostic biomarkers in acute myeloid leukemia (AML).

"Morphologically, patients with this disease all look the same," he says, "but genetically, they are much different. Every patient is characterized by certain gene mutations or changes in genetic expression, and these impact treatment outcome according to which alterations are present. In other words, a particular mutation may have more or less impact on a patient's prognosis according to whether other mutations are present.

"This is important because we now make treatment decisions based on the mutations that are present," Marcucci says.

Pharmacogenomics

Researchers at the OSUCCC – James and elsewhere have associated scores of genetic alterations with tumors, leading to a wave of novel agents that target specific mutations involved in the growth of particular tumors. However, the mutation is carried by only a portion of patients with a specific cancer.

"This is where pharmacogenomics becomes important," says Wolfgang Sadée, PhD, chair and professor of Pharmacology and director of Ohio

ERSONALIZE ● PARTICIPATE

State's Program in Pharmacogenomics. "The goal is to optimize therapy for each individual patient, rather than applying the same treatment regimen to all. This approach has considerable potential to improve the success of therapy, and it is particularly pertinent to cancer chemotherapy."

Tests that measure gene variation, gene-expression profiles, protein abnormalities and other molecular changes are being used increasingly at the OSUCCC – James to determine therapy. For example, the targeted breast-cancer drug Herceptin is effective only in patients who highly express the growth factor receptor HER2-neu, Sadée says.

PARTICIPATORY

To be successful, proponents say, P4 medicine will require active patient participation. Here are some of the most important facets of this fourth "P":

- Ongoing collection of patients' data – everything from family health history, genetic screenings and personal medical records to information about lifestyle and environment. Such data helps stratify patients into risk groups enabling more precise care and more effective treatments, Marsh says.
- Health literacy – patients must understand their medical information well enough to make appropriate health decisions and to follow prescribed disease prevention and treatment protocols. One study estimates that between $106 billion and $238 billion is lost annually because adults are unable to obtain, process and understand health information.
- Clear and continued communication from healthcare providers to patients. "We must say things in terms patients understand," Marsh says. "This is also about continuity of care and communicating in a variety of ways that include phone, videoconferencing and email, so that patients can continue the conversation with members of their health team. We must make sure patients understand that initial burst of information, and then we must work with them throughout their illness to provide the help they need when they need it.

"As the emphasis of health care shifts to prediction and prevention, health and wellness, and engagement and empowerment," says Marsh, "we want people to go beyond participation based on just following instructions. We want to give people the capacity to drive their lives in ways that will keep them healthy.

"Through personalized medicine, we can transform health care so that it costs less, provides higher quality outcomes and yields better patient satisfaction."

OHIO STATE INITIATIVES THAT SUPPORT P4 MEDICINE

- The Medical Center established its Center for Personalized Health Care in 2005 to encourage research in the field, facilitate the incorporation of this research into patient care, and advocate nationally for the practice of personalized health care. In 2008, the Center began hosting its annual national conference on Personalized Health Care.
- Ohio State is a founding partner in the P4 Medicine Institute, a research organization dedicated to accelerating the emergence and adoption of P4 medicine. The Medical Center and OSUCCC – James will serve as clinical demonstration sites for pilot projects to test innovative ideas and technologies.
- Ohio State, along with five other institutions, participates in the Coriell Personalized Medicine Collaborative™ to study the use of personalized genetic information to improve people's health.
- Ohio State's College of Medicine offers the P4 Scholars Program, a course that encourages students to think about how they would integrate P4 medicine into their future practices. "Our program shifts traditional medical training from sick care to the practice of well care," says Kandamurugu Manickam, MD, a geneticist and director of the P4 Scholars Program.

http://go.osu.edu/H56.

PELOTONIA "HIGH-RISK, HIGH-REWARD" RESEARCH PROJECTS FOR 2011

Six teams of scientists at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) are each receiving two-year, $100,000 Pelotonia Research Awards to fund "high-risk, high-reward" research projects.

The grants are funded with a portion of the $8 million raised during the 2010 Pelotonia cycling tour to support cancer research at the OSUCCC – James. (For information about Pelotonia 2012, visit http://pelotonia.org.)

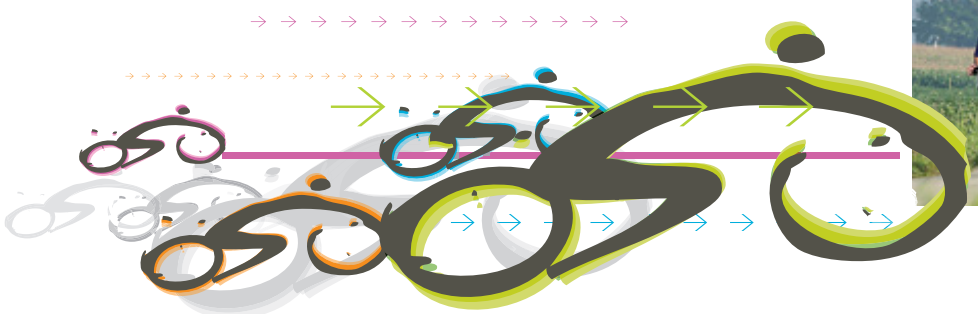
Grant recipients were selected in a highly competitive process from 50 applications. The applications were scored and the top projects were selected for funding by senior leaders at the OSUCCC – James, says Peter Shields, MD, deputy director of Ohio State's Comprehensive Cancer Center.

"I was impressed with the potential these ideas have and the collaborative nature of all the projects," Shields says.

"These Pelotonia research awards encourage our investigators to collaboratively develop novel ideas that can lead to breakthroughs in science, prevention and treatments," says Michael A. Caligiuri, MD, director of Ohio State's Comprehensive Cancer Center and chief executive officer of The James Cancer Hospital and Solove Research Institute. "Pelotonia provides critically needed seed funding for ideas that may one day lead to larger, federally funded grants."

A LIST OF 2011 PELOTONIA RESEARCH AWARD RECIPIENTS AND THEIR RESEARCH OBJECTIVES FOLLOWS:

- **PATRICK GREEN, PHD, AND ROBERT BAIOCCHI, MD, PhD:** Develop a promising therapeutic approach for treatment of an aggressive adult T-cell leukemia by studying a specific cellular protein and testing a new class of drugs in a preclinical model of human ATL.
- **TSONWIN HAI, PhD, JOHN C. BYRD, MD, AND DAVID LUCAS, PhD:** Improve the treatment of chronic lymphocytic leukemia by developing agents to modulate a specific gene pathway in both the organism with cancer and the cancer cells themselves.
- **BHUVANESWARI RAMASWAMY, MD, SARMILA MAJUMDER, PhD, XIAOBAI LI, PhD, LISA YEE, MD, MIKE OSTROWSKI, PhD, AND GUSTAVO LEONE, PhD:** Explore ways to identify breast tumors that have higher risk of developing into invasive cancer, and treat them by blocking a specific signaling pathway involved in breast development.
- **QIANBEN WANG, PhD, AND VICTOR JIN, PhD:** Develop novel therapies to treat hormone-independent prostate cancer by targeting specific gene-signaling pathways.
- **AMANDA TOLAND, PhD, THOMAS OLENCKI, DO, DAWN ALLAIN AND TED TEKNOS, MD:** Identify genomic changes that cause squamous cell carcinoma of the skin to metastasize, in order to develop therapies to treat these aggressive tumors.
- **JIANHUA YU, PhD, AND KALPANA GHOSHAL, PhD:** Develop novel therapeutics and preventive agents for liver cancer by targeting specific gene-signaling pathways.



BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

A Phase I/II Trial of Cetuximab in Combination With Interleukin-12 Administered to Patients With Unresectable Primary or Recurrent Squamous Cell Carcinoma of the Oropharynx

HYPOTHESIS: Administration of IL-12 will enhance the antitumor activity of cetuximab by activating FcR-positive immune cells that recognize cetuximab-coated tumor cells. The trial combines cetuximab with IL-12 in patients with locally recurrent or unresectable HER1-overexpressing squamous cell carcinoma (SCC) of the oropharynx. Correlative laboratory studies will evaluate the ability of this regimen to activate the innate immune system and relate these events to clinical activity.

RATIONALE: More than 90 percent of oropharyngeal squamous cell carcinomas (SCC) overexpress the epidermal growth factor receptor (EGFR, or HER1). Binding to HER1 by epidermal growth factor (EGF) or transforming growth factor (TGF)-alpha leads to cell cycle progression, reduced cell death (i.e., apoptosis), angiogenesis and metastasis. Tumor HER1 expression correlates with a poor prognosis and resistance to therapy.

Cetuximab is a humanized monoclonal antibody that binds with high affinity to HER1 and shows activity as a single agent in patients with HER1-positive oropharyngeal SCC. When cetuximab binds to HER1 on tumor cells, EGF and TGF-alpha cannot activate the receptor, which reduces proliferation, enhances apoptosis and angiogenesis, inhibits invasiveness and metastasis and down regulates HER1 expression.

This Ohio State-originated clinical trial makes use of the fact that cetuximab and other monoclonal antibody agents possess a binding site in the constant or "Fc" region of the antibody, which is located away from its antigen-binding site. Natural killer cells, monocytes and other innate immune cells bear specialized Fc receptors (FcR) that recognize the antibody's Fc region and enable them to distinguish antibody-coated tumor cells, which they often destroy. Laboratory, preclinical studies and phase I trials indicate that IL-12 can activate FcR-bearing immune cells and enhance their ability to recognize and eliminate antibody-coated tumor cells.

In this trial, we hypothesize that IL-12 will increase the anti-tumor activity of cetuximab in patients with inoperable, HER1-overexpressing oropharyngeal SCC. Our preliminary data strongly indicates that the antitumor activity of IL-12 and cetuximab is dependent on NK cells and their production of IFN-γ, the release of which mobilizes a more effective immune response against cancer cells.

The key objectives of the trial are:

- Identify a safe and tolerable dose of IL-12 in combination with cetuximab.
- Test the ability of IL-12 to enhance response rates to cetuximab in patients who have progressed on a cetuximab-containing regimen.
- Characterize the antitumor mechanism of IL-12 and establish biomarkers that will predict patient responsiveness.

Information gained from this trial should directly apply to other monoclonal antibodies that target HER1 and other oncogenes.

AT A GLANCE

Clinical trial OSU-11010

PI: **WILLIAM E. CARSON III, MD,** professor of Surgery, associate director for clinical research and co-leader of the Innate Immunity Program

Phone: 614-293-6306

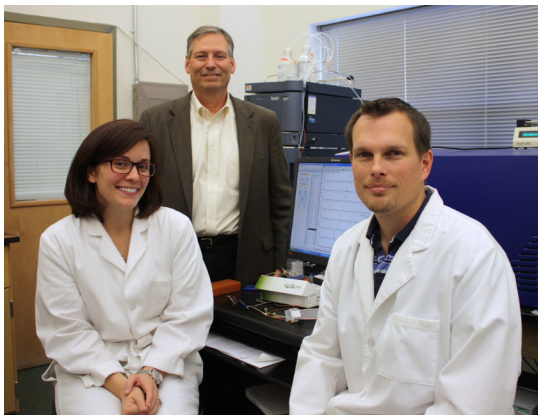
Email: *william.carson@osumc.edu*

Eligibility: Patients must be older than 18 years with histologically proven, unresectable, recurrent or metastatic SCC of the oropharynx; one prior systemic therapy is permitted; patients must have progressed on a cetuximab-based regimen or not have responded to it, have an ECOG performance status less than 2, a life expectancy greater than 6 months and normal organ and marrow function.

SHARED RESOURCES

UNRAVELING PHYTOCHEMICAL QUANDARIES

The Nutrient and Phytochemical Analytic Shared Resource



Nutrient and Phytochemical Analytic Shared Resource Director Steven J. Schwartz, PhD (standing), associate researcher Abby Monnin, MPH, and associate director Ken M. Riedl, PhD.

The Nutrient and Phytochemical Analytic Shared Resource (NPASR) provides the OSUCCC – James and other investigators with expert bioanalytical method development and quantitative analysis of phytonutrients and their metabolites. Director Steven J. Schwartz, PhD, professor and Carl E. Haas Endowed Chair in the College of Food, Agriculture and Environmental Science, Department of Food Science and Technology, is a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program. He also directs the Center for Advanced Functional Foods Research and Entrepreneurship.

Associate Director Ken M. Riedl, PhD, an analytical chemist and research scientist, operates three HPLC-MS platforms, each with unique capabilities for identifying and quantifying phytochemicals and their metabolites. His collaborative work spans disciplines from horticulture to nutrition and clinical research.

THE NPASR PROVIDES:

- Expert development of bioanalytical methods and quantitative analysis of nutrients and phytochemicals in foodstuffs and their metabolites in biological samples from both human clinical trials and animal model investigations.
- Particular expertise in evaluating the bioavailability, metabolism and physiological significance of carotenoids, isothiocyanates and isoflavones.
- Development of analytical methods for a Good Laboratory Practice environment.
- An enhanced understanding of the role of dietary compounds in cancer prevention and control.

For more information about the Nutrient and Phytochemical Analytic Shared Resources, call 614-292-4069.

Conference Calendar

10TH INTERNATIONAL SKIN CARCINOGENESIS CONFERENCE

June 21-24, 2012

FOCUS: The conference covers squamous cell carcinoma, basal cell carcinoma and melanoma. It will feature the most recent advances in our understanding of the biological, cellular and molecular changes that occur during skin tumor development. It will also explore topics such as the skin as a model system for other tumors, stem cells in skin carcinogenesis and molecular-targeted therapies.

For more information and to register or submit an abstract, visit http://cancer.osu.edu/ISCC2012.

EXPANSION UPDATE

THE NEW JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

Growing to meet demands for cancer services

Demand for cancer care is growing, and expected to continue with a projected increase in new cancer cases nationally of 45 percent – from 1.6 million in 2010 to 2.3 million by 2030.

- This rise includes an expected 67 percent increase in cancer incidence among adults 65 years and older due to a growing aging population, and a 99 percent increase among minorities due to aging and growth in minority populations.
- In the state of Ohio, cancer incidence is expected to rise 20 percent by 2030. Increases are expected particularly for melanoma and cancers of the thyroid, liver, pancreas and breast.
- Currently, The James is operating beyond capacity for inpatient and many outpatient services.

The new James Cancer Hospital will ease the burden of cancer.

The new James Cancer Hospital and Solove Research Institute will ease this rising burden of cancer through a larger, state-of-the-art hospital that fosters compassionate care and collaborative, transformational research.

- The new hospital will expand capacity to 276 beds, up from today's 210 beds.
- The new hospital will provide a calming setting designed to promote patient recovery and wellness while integrating research and education.
- The new hospital will offer an environment that inspires and enhances collaboration among OSUCCC – James researchers, who bring ideas and expertise from 11 of Ohio State's 14 colleges.
- The new hospital will help attract and retain leading cancer investigators, talented young minds and the best doctors.
- The new hospital will help revolutionize cancer care and prevention through P4 medicine. (See "A Quiet Evolution," page 24.)

ABOVE Artist's rendering of the new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, scheduled to open in 2014.

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

PELOTONIA '11 Raises a Record $13.1 Million

Pelotonia '11 riders and donors raised a record $13,108,639 for cancer research at the OSUCCC – James, a 68-per-cent increase over the 2010 fundraising total of $7.8 million.

From Aug. 19-21, 4,986 riders from 38 states and four countries rode up to 180 miles on one of four routes during the annual grassroots bicycle tour that was started in 2009. The three-year fundraising total is approximately $25.47 million.

Every dollar raised by riders, virtual riders and donors is invested in research initiatives at the OSUCCC – James, a distinction made possible by Pelotonia's generous funding partners: Limited Brands Foundation; Huntington Bank; Richard and Peggy Santulli; American Electric Power Foundation; Nationwide Insurance; and Cardinal Health Foundation. Pelotonia also benefits from in-kind donations made by numerous locally and nationally based companies, and from the services of some 1,700 volunteers who helped out in 2011.

Pelotonia dollars support research projects that address all aspects of cancer, from diagnosis and treatment to psychosocial issues and prevention. Funds are also used to recruit and retain outstanding cancer researchers to Ohio State and to purchase sophisticated equipment that helps the more than 270 scientists at the OSUCCC – James conduct their research. Details are available online.

Pelotonia 2012 is scheduled for Aug. 10-12. To register, visit www.pelotonia.org.

NATIONAL RECOGNITION

OSUCCC – James Repeats as a Leapfrog 'Top Hospital'

For the third consecutive year and fourth time in five years, the OSUCCC – James has been named among the safest and most effective hospitals in the country by the Leapfrog Group, a national coalition of public and private purchasers of employee health coverage who collectively work to improve healthcare quality.

The James is among 65 hospitals from a field of almost 1,200 to be named 2011 Leapfrog Top Hospitals based on a rating system that provides an up-to-the-minute assessment of a hospital's quality and safety. A complete list of 2011 Leapfrog Top Hospitals can be viewed at www.leapfroggroup.org. The Leapfrog Group is a consortium of about 150 Fortune 500 companies that pay for healthcare needs of an estimated 34 million Americans.

IN THE NEXT ISSUE OF **frontiers**…

ORTHOPAEDIC ONCOLOGY

Joel Mayerson, MD, specializes in bone and soft-tissue tumors of the arms, legs and pelvis, and metastatic bone disease. With extraordinary surgical skill and sensitivity toward quality of life, he has changed an ankle into a knee and returned a child to the playing field.

DRUG DISCOVERY BY COMPUTATION

In silico drug design applies computers, databases, and computational and design software to discover and optimize new anticancer agents. OSUCCC – James researchers are using this fascinating combination of technologies to develop novel and first-in-their-class targeted agents.