TURNING CANCER DISCOVERIES INTO TREATMENTS

FRONTIERS

WINTER | 2014

Inside:
INFLAMMATION AND CANCER

New Neuro-oncology director

Thyroid cancer research

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

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

UPFRONT

The Director's Perspective

A Summer of Progress

A beautiful autumn followed a summer of successes at the OSUCCC – James.

Our fifth annual Pelotonia bicycling event, held in August, attracted a record 6,723 riders from 41 states and nine countries, plus 3,451 virtual riders and more than 2,300 volunteers.

Every dollar raised by Pelotonia supports research at the OSUCCC – James. That work is furthered by outstanding recruits such as Raphael Pollock, MD, PhD, whom we recruited from MD Anderson Cancer Center to serve as director of the Division of Surgical Oncology and as chief of surgical services at the OSUCCC – James.

This issue of *Frontiers* includes a story about Vinay Puduvalli, MBBS, our new director of the Division of Neuro-Oncology. Dr. Puduvalli specializes in treating gliomas and other primary brain tumors. His experience and success in patient care, clinical trials, and basic and translational research make him an outstanding addition to our faculty.

Read here also about Matthew Ringel, MD, and his collaborators who have received an $11.3 million, five-year renewal of their Program Project Grant from the National Cancer Institute (NCI) to help meet the growing challenge of thyroid cancer. The NCI has also awarded Matt a prestigious Specialized Program of Research Excellence (SPORE) grant for thyroid cancer. This is a collaborative grant with MD Anderson Cancer Center. The SPORE is centered at Ohio State with Matt as principal investigator. This issue's cover story describes progress by OSUCCC – James researchers in understanding inflammation and cancer, work that could lead to new approaches for preventing and treating malignancies.

In August, we mourned the passing of Bertha A. Bouroncle, MD, a pioneer in Ohio State cancer research. In 1958, Dr. Bouroncle first identified the malignancy now called hairy cell leukemia and later helped develop an effective therapy for it. With her passing we lost a great scholar and friend and a caring physician.

The caring and commitment of our nursing team was recently recognized by the American Nurses Credentialing Center with their highly prestigious Magnet® designation. The award recognizes quality patient care, nursing excellence and innovations in professional nursing practice. Only 392 hospitals out of more than 6,000 across the United States have earned Magnet status. This was a well-deserved honor for all our James nurses, who work daily toward achieving our vision of a cancer-free world.

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

FRONTIERS

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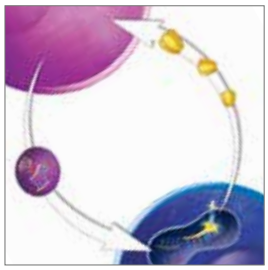
FEATURES



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THE SUPREME COURT GENE-PATENTING DECISION HAS FAR-REACHING CONSEQUENCES

By **REBECCA NAGY, MS, CGC,** *clinical associate professor of Human Genetics and president of the National Society of Genetic Counselors*

On June 13, 2013, the United States Supreme Court ruled that naturally occurring DNA cannot be subject to patent. The unanimous decision ended a four-year court battle between the petitioners in the case, the Association for Molecular Pathology, and molecular genetic testing company Myriad Genetics Laboratories, Inc. Myriad Genetics has been the only laboratory offering clinical genetic testing for the *BRCA1* and *BRCA2* genes for almost two decades, after obtaining numerous patents on everything from test methodology to the DNA sequence itself.

The petitioners argued that genes are a product of nature and, thus, patents held by Myriad Genetics on the *BRCA1* and *BRCA2* sequence were invalid. The Court agreed, ending Myriad's 17-year long monopoly on the *BRCA* genetic testing market.

The ruling has far-reaching consequences for patients, clinicians, researchers and the biotechnology industry. The impact was felt immediately in the clinic, where patients with a suspected elevated risk for breast, ovarian and other cancers receive genetic counseling and testing. Within hours of the decision several laboratories announced that they would immediately offer *BRCA1* and *BRCA2* testing at significantly lower prices.

With test costs dropping, more insurers may be willing to cover the service, which could give more patients access to testing. Testing may also be more comprehensive and provide a more complete risk profile. The *BRCA1* and *BRCA2* genes can now be included in multi-gene panel testing, in which multiple genes known to contribute to a specific disease are tested at the same time.

For hereditary breast and ovarian cancer, panel testing has been problematic since Myriad's patents prevented the inclusion of the two genes responsible for the majority of the disease. This forced women who qualified for testing to do so in a step-wise fashion, testing for *BRCA1* and *BRCA2* first and, if negative, proceeding to additional panel testing, often at a total cost of $6,000-$8,000 or more.

Since the ruling, several laboratories have added the *BRCA1* and *BRCA2* genes to their panels, and patients can now have testing for about 25 different cancer genes at a cost less than that of *BRCA1* and *BRCA2* testing prior to the ruling.

Clinicians should proceed with caution, however. There is little or no clinical information available for many genes included in cancer genetic testing panels, and most do not have published practice guidelines to assist clinicians when they receive abnormal results. The rate of inconclusive or unclear results is significant, and interpretation can be challenging even for seasoned experts.

Pre-test counseling and risk assessment are also more complex. Clinicians will need to collect and review the family history, be familiar with the spectrum of cancers that might be associated with the various genes and their

mutations, and then determine which test might provide the best assessment for that particular family.

Furthermore, it is critical to provide effective pre- and post-test genetic counseling and to interpret test results accurately. Individuals must receive correct and up-to-date information to help them make informed decisions, some of which are irreversible and life-changing. Many busy clinicians may also find it challenging to incorporate ever-changing genetic information into patient care. However, it is crucial that the benefits of increased access that may result from this ruling not be diminished by inappropriate genetic testing and misinterpreted results.

Exactly how the Supreme Court decision will affect the biotech industry remains unclear, and experts have come down on both sides. Those critical of the ruling claim it will stifle discovery and innovation. Those in favor claim that the ability to patent specific testing methods and synthetic DNA, such as cDNA, which remain patent-eligible, allows enough freedom for the diagnostic testing market to remain profitable.

Whatever the outcome, it is likely that the issue of patents as they apply to DNA and genetic testing methodology will come before the courts again. Indeed, on July 9, 2013, Myriad filed a lawsuit against two of the companies now offering *BRCA1* and *BRCA2* testing, claiming infringement on the remaining patents that were not challenged by the original lawsuit. One of these labs, Ambry Genetics, counter-sued Myriad, claiming violation of anti-trust laws. A preliminary hearing took place in early September.

Although the story of the *BRCA1* and *BRCA2* gene patents may not be over, this ruling is a victory for patients. Physicians and other healthcare providers can now offer patients more options to assess breast and ovarian cancer risk, and women with hereditary breast and ovarian cancer and their families now have greater access to high quality, affordable genetic testing.

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

BRCA1 AND BRCA2 CANCER RISK AND GENETIC TESTING

- A woman's risk of developing breast and/or ovarian cancer is greatly increased if she inherits a deleterious mutation in *BRCA1* or *BRCA2*.
- Men with these mutations also have an increased risk of breast cancer, and both men and women who have harmful *BRCA1* or *BRCA2* mutations may be at increased risk of additional types of cancer.
- Genetic tests can check for *BRCA1* and *BRCA2* mutations in people with a family history of cancer that suggests the presence of a harmful mutation in one of these genes.
- If a harmful *BRCA1* or *BRCA2* mutation is found, options are available to help a person manage cancer risk.

Clinical Implications

New Agent Shows Promise in CLL and MCL

JOHN C. BYRD, MD,
professor and director of the Division of Hematology, and a CLL specialist at the OSUCCC – James

KRISTIE BLUM, MD,
associate professor in the Division of Hematology and head of the OSUCCC – James lymphoma program

The New England Journal of Medicine (*NEJM*) reported on exciting findings from two studies co-led by researchers at the OSUCCC – James and MD Anderson Cancer Center regarding the targeted experimental drug ibrutinib as an effective treatment for patients with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL). The articles reported the outcome of two phase II clinical trials of ibrutinib, which is showing exceptional effectiveness against both malignancies.

The CLL study co-leader at Ohio State was John C. Byrd, MD, professor and director of the Division of Hematology, and a CLL specialist at the OSUCCC – James. The Ohio State co-leader of the MCL study, which involved 18 sites, was Kristie Blum, MD, associate professor in the Division of Hematology and head of the OSUCCC – James lymphoma program. *NEJM* first published the two studies together online with an accompanying editorial. The CLL study and the MCL study were then featured in the July 4 and Aug. 8 *NEJM* print editions, respectively. Read more online.

Watch online

Visit the OSUCCC – James CLL Experimental Therapeutics Laboratory.

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

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BREAST CANCER

Gene Enabler

Stress Gene Facilitates Breast Cancer Metastasis

In an unexpected finding, scientists have linked the activation of a stress gene in immune-system cells to breast cancer metastasis and patient outcome.

Senior author and OSUCCC – James researcher Tsonwin Hai, PhD, professor of Molecular and Cellular Biochemistry, says the study suggests that the gene, called *ATF3*, may be a crucial link between stress, cancer and a tumor cell's ability to metastasize.

The results provide important insights into how tumor cells co-opt immune cells to enhance breast cancer metastasis, and they suggest that the stress gene could be a valuable drug target for inhibiting metastasis, Hai says. Additional research must confirm these results. Previous public health studies have shown that stress is a risk factor for cancer, and researchers already knew that *ATF3* is activated, or expressed, when cells are stressed. Under typical circumstances, *ATF3* activation can cause normal and benign cells to self-destruct if stressors such as irradiation or a lack of oxygen irrevocably damage the cells.

This research suggests that cancer cells coax immune cells present in the tumor to express *ATF3*. This then somehow causes the immune cells to act erratically, enabling tumor cells to escape to other areas of the body.

Hai and her colleagues first linked *ATF3* expression in tumor-associated immune cells to worse outcomes among a sample of almost 300 breast-cancer patients. They followed that with animal studies and found that mice lacking *ATF3* had fewer metastatic tumors to the lungs than did normal mice that expressed the gene.

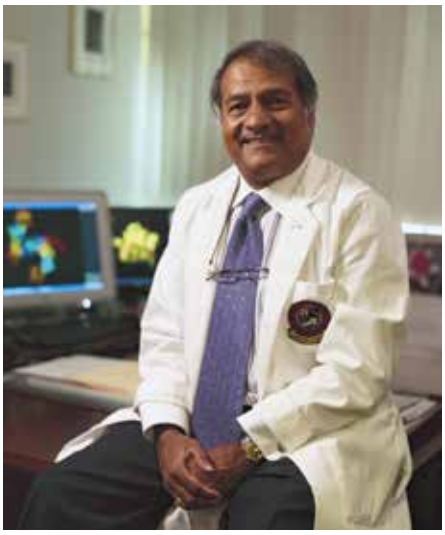
Published in the Journal of Clinical Investigation.

NIH/National Cancer Institute grants CA118306, CA090223; NIH/National Institute of Environmental Health Sciences grant ES021018; National Institutes of Health grant NS045758; research programs in Australia; and a Pelotonia Idea Grant supported this research.

TSONWIN HAI, PhD,
professor of Molecular and Cellular Biochemistry

Anticancer Peptides

HER1 Receptor Targeted for Peptide Cancer Vaccine, Therapeutic Agents



PRAVIN KAUMAYA, PhD,
director of the Division of Vaccine Development and professor of Medicine, of Obstetrics and Gynecology, of Molecular and Cellular Biochemistry, and of Microbiology at Ohio State.

OSUCCC – James researchers led a study focused on the HER1/EGFR receptor as a target for peptide vaccine and therapeutic agents.

HER1 is a member of the epithelial growth factor (EGF) family of cell-surface receptors. The family, which includes the HER2 receptor, plays a central role in the development of a variety of human cancers. It is important for cancer-cell growth and metastasis and an indicator of poor patient survival.

The study, led by Pravin Kaumaya, PhD, director of the Division of Vaccine Development at the OSUCCC – James, identified two regions on the HER1 receptor as potential targets for cancer vaccine or therapeutic peptides. The two regions, defined as sequences 382–410 and 418–435, were the most specific and raised the strongest immune response in test animals.

"The findings could lead to novel peptide vaccines and mimetic inhibitors that target HER1 in tumors of the breast, lung, colon, and head and neck," says Kaumaya, who is also professor of Medicine of Obstetrics and Gynecology, of Molecular and Cellular Biochemistry, and of Microbiology at Ohio State.

They might also overcome many of the significant shortcomings of antibody-based drugs such as cetuximab, he notes. These peptide agents, which are small proteins consisting of 10 to 50 amino acids, might be safer, more effective and less costly than the monoclonal-antibody-based drugs and small-molecule inhibitors now used to treat many malignancies, Kaumaya says.

"Peptide agents might enable the development of combination immunotherapies that avoid the mechanisms of resistance or secondary treatment failures sometimes experienced with antibody treatment," Kaumaya says.

Published in the Journal of Immunology.

NIH/National Cancer Institute grant CA084356 supported this research.

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LUNG CANCER

MicroRNA Tumor-Suppressor

A preclinical study led by OSUCCC – James researchers shows that microRNA-486 is a potent tumor-suppressor in lung cancer

A study led by OSUCCC – James researchers found that microRNA-486 (miR-486) directly targets the insulin growth-factor pathway, which is important for cell survival and proliferation. Alterations in the pathway are believed to play an early role in tumor initiation and progression.

The molecule helps regulate proliferation and migration and the induction of programmed cell death, or apoptosis, in lung-cancer cells.

MicroRNAs are a class of short, non-coding RNAs that regulate the translation or degradation of messenger RNA and therefore the proteins that cells make. Certain microRNAs are frequently dysregulated in cancer.

The researchers further found that miR-486 is itself regulated by the tumor-suppressor gene *p53*, the most frequently altered gene in human cancers, and that activity of miR-486 is partially dependent upon functional *p53*. The study suggests that miR-486 might serve as a biomarker for lung cancer that is likely to respond to insulin-growth-factor inhibitors.

"MiR-486 appears to be a biomarker for lung cancer, but its mechanisms of action remain unclear," says co-corresponding author Patrick Nana-Sinkam, MD, associate professor of Medicine and a researcher with the OSUCCC – James Molecular Biology and Cancer Genetics Program. "These findings show that miR-486 serves a tumor-suppressor function in lung cancer, and that miR-486 action is partially dependent on *p53*."

The partial reliance of one tumor suppressor on another was a surprise, says principal investigator and co-corresponding author Carlo M. Croce, MD, director of human cancer genetics at Ohio State and the John W. Wolfe Chair in Human Cancer Genetics at the OSUCCC – James. "We don't know yet what implications, if any, this might have for the development of targeted therapies."

Published in the Proceedings of the National Academy of Sciences.

NIH/National Cancer Institute grant CA152758 supported this research.

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

PATRICK NANA-SINKAM, MD
associate professor of Medicine and a researcher with the OSUCCC – James Molecular Biology and Cancer Genetics Program

Sarcoma Suppressor

Loss of MicroRNA Decoy Might Contribute to Development of Soft-Tissue Sarcoma

OSUCCC – James researchers have discovered a novel mechanism responsible for the loss of a critical tumor-suppressor gene in rhabdomyosarcoma and other soft-tissue sarcomas. These rare cancers strike mainly children and often respond poorly to treatment; their cause is largely unknown. The discovery of the mechanism could lead to more effective therapies for these malignancies, says principal investigator Denis Guttridge, PhD, professor of Molecular Virology, Immunology and Medical Genetics, and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

DENIS GUTTRIDGE, PhD, *professor of Molecular Virology, Immunology and Medical Genetics, and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program*

Guttridge and his colleagues found that the tumor-suppressor gene called *A20* is silenced not by mutation but because a second molecule is lost, a small molecule called microRNA-29 (miR-29). They also found that miR-29 normally protects *A20* from destruction. When miR-29 is absent, *A20* is degraded. Loss of *A20*, in turn, leads to a dramatic rise in levels of a protein called NF-kB and to tumor progression.

"NF-kB is a known tumor promoter, but we don't know why it is upregulated in many cancers," Guttridge says. The findings identify NF-kB as a therapeutic target in sarcoma, and *A20* and miR-29 as potential biomarkers for sarcoma. First author Mumtaz Yaseen Balkhi, PhD, notes that the findings move research closer to developing miR-29 therapy against NF-kB activation. "Other labs have tried to block NF-kB signaling using pharmacological inhibitors because of the perceived benefits for cancer treatment," he says. "We provide an alternative route, showing that microRNA can do the same job by acting as a decoy."

"The loss of the *A20* tumor-suppressor gene because the microRNA decoy is absent may represent another mechanism to explain why NF-kB is constitutively active in sarcoma cancers," Guttridge says.

Soft-tissue sarcomas make up about 15 percent of pediatric cancer cases. In 2013, about 11,400 cases of sarcoma were expected in the United States, and about 4,400 Americans were expected to die from the malignancy.

Published in the journal Science Signaling.

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BRAIN CANCER

Glioblastoma

Nano Drug Crosses Blood-Brain Tumor Barrier, Targets Brain-Tumor Cells and Blood Vessels

An experimental drug in early development for aggressive brain tumors can cross the blood-brain tumor barrier, kill tumor cells and block the growth of tumor blood vessels, according to a study led by OSUCCC – James researchers.

The laboratory and animal study also shows how the agent, called SapC-DOPS, targets tumor cells and blood vessels. The findings support further development of the drug as a novel treatment for brain tumors.

SapC-DOPS (saposin-C dioleoylphosphatidylserine), is a nanovesicle drug that has shown activity in glioblastoma, pancreatic cancer and other solid tumors in preclinical studies. The nanovesicles fuse with tumor cells, causing them to self-destruct by apoptosis.

Glioblastoma multiforme is the most common and aggressive form of brain cancer, with a median survival of about 15 months. A major obstacle to improving treatment for the 3,470 cases of the disease that were expected in the United States last year is the blood-brain barrier, which protects the brain from toxins in the blood but also keeps drugs in the bloodstream from reaching brain tumors.

"Few drugs have the capacity to cross the tumor blood-brain barrier and specifically target tumor cells," says principal investigator Balveen Kaur, PhD, professor and vice chair for Research of Neurological Surgery.

Kaur and her colleagues showed that SapC-DOPS does both and inhibits the growth of new tumor blood vessels, suggesting that the agent might one day be an important treatment for glioblastoma and other solid tumors, Kaur says. In addition, the agent sensitized hypoxic cells to killing by conventional treatment.

The findings, Kaur says, suggest that SapC-DOPS could have a synergistic effect when combined with chemotherapy or radiation therapy.

Published in the journal Molecular Therapy.

NIH/National Cancer Institute grants CA158372, CA136017, CA136017 and CA171733 supported this research.

BALVEEN KAUR, PhD,
professor and vice chair for Research of Neurological Surgery

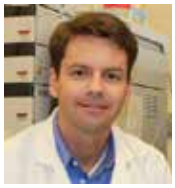
OF NOTE

Recent Recognition of OSUCCC – James Physicians and Researchers

GRANTS

DENIS GUTTRIDGE, PhD, professor of Medicine and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program, has received a four-year, $1.4 million grant (CA180057) from the National Cancer Institute (NCI) entitled Muscle Stem Cells and Cancer Cachexia. The study explores the inability of muscle stem cells to repair muscle injured by a growing tumor and will identify new therapeutic targets.

PETER HOUGHTON, PhD, professor of Medicine and a member of the OSUCCC – James Experimental Therapeutics Program, has received a five-year, $7.8 million grant from the NCI entitled "Studies of Childhood Sarcomas" (CA165995-01A1), which seeks to identify novel therapeutic strategies for childhood sarcoma. The Program Project Grant includes researchers at the University of Virginia, the University of Central Florida and the NCI.



THOMAS SCHMITTGEN, PhD, professor and chair of Pharmaceutics and Pharmaceutical Chemistry, and MITCH PHELPS, PhD, assistant professor of Pharmaceutics and Pharmaceutical Chemistry, both of Ohio State's College of Pharmacy and of the OSUCCC – James Experimental Therapeutics Program, have received a five-year, $3.2 million grant (TR000914) from the National Center for Advancing Translational Sciences. Entitled "Targeted Delivery of microRNA-Loaded Microvesicle for Cancer Therapy," the study will develop new technology for delivering microRNA drugs to tumor cells.

MATTHEW RINGEL, MD, professor of Medicine and member of the OSUCCC – James Molecular Biology and Cancer Genetics (MBCG) Program, was awarded a five-year, $11.3 million Program Project Grant (CA124570) from the NCI. The grant is a continuation of a study that ran from 2008 through 2013 entitled "Genetic and Signaling Pathways in Epithelial Thyroid Cancer." Ringel also has been awarded a five-year, $11.3 million Specialized Program of Research Excellence (SPORE) grant (CA168505-01A1) also to support thyroid cancer research.

REBECCA JACKSON, MD, associate dean for Clinical Research in Ohio State's College of Medicine and a member of the OSUCCC – James Cancer Control Program, has been awarded a $25.4 million grant by the National Institutes of Health to support The Ohio State University Center for Clinical and Translational Science, a collaboration between the University and Nationwide Children's Hospital created to accelerate basic science discoveries into life-saving medical advances. Read more online

AWARDS AND HONORS

MIGUEL VILLALONA-CALERO,MD, professor of Medicine and of Pharmacology and director of the Division of Medical Oncology has been elected a Fellow of the American Association for the Advancement of Science for distinguished contributions in experimental therapeutics and conducting clinical trials for translational research in cancer patients.

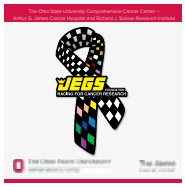
WOLFGANG SADÈE, PhD, professor and chair of the Department of Pharmacology at Ohio State, director of Pharmacogenomics and member of the OSUCCC – James Experimental Therapeutics Program, has been named one of six 2013 University Distinguished Scholars. The award recognizes exceptional scholarly accomplishments by senior professors.

FACULTY AND PROGRAMS

BHAVANA BHATNAGAR, DO, has joined the cancer program as an assistant professor in the Division of Hematology. Her clinical interests include acute myeloid leukemia and myelodysplastic syndromes. Her research interests include experimental therapeutics for myeloid malignancies. She came to Ohio State from the University of Maryland Marlene and Stewart Greenebaum Cancer Center.

AHARON FREUD, MD, PhD, has joined the cancer program as an assistant professor of Pathology. His clinical interests include the diagnosis of leukemia and lymphoma. His research interests include innate lymphocyte biology, and EBV-associated T-cell and B-cell lymphomas. He came to Ohio State from Stanford University Medical Center.

RAPHAEL POLLOCK, MD, PhD, has joined the cancer program as a professor and as director of the Division of Surgical Oncology. His clinical interests include soft-tissue sarcoma. His research interests include sarcoma molecular biology and development of novel therapies for sarcoma. He came to Ohio State from The University of Texas MD Anderson Cancer Center.



THE OHIO STATE UNIVERSITY FOUNDATION has received a gift of $10 million from the JEGS Foundation. The gift to the new 306-bed cancer hospital, due to open in 2014, is intended to help transform cancer treatment and research at the OSUCCC – James. JEGS Foundation was started by the Coughlin family, who own JEGS Automotive Inc.

THE OHIO STATE UNIVERSITY has signed a worldwide agreement with Microlin Bio Inc. to license a large portfolio of Ohio State cancer discoveries. It includes nearly 100 issued and pending microRNA patents related to the diagnosis and treatment of prostate, ovarian, colon and lung cancers. OSUCCC – James researchers Carlo M. Croce, MD, Robert Lee, PhD, and collaborators at the National Cancer Institute and National Institutes of Health developed the technologies. Read more online

LEADERSHIP ACTIVITIES AND ACCOMPLISHMENTS

ARNAB CHAKRAVARTI, MD, professor and chair of the Department of Radiation Oncology and a member of the OSUCCC – James Experimental Therapeutics Program, will serve as scientific program chair for the 2014 American College of Radiation Oncology annual meeting.

RICHARD GOLDBERG, MD, physician-in-chief at the OSUCCC – James, has been appointed to the American Society of Clinical Oncology's (ASCO) Government Relations Committee. The Committee advocates on behalf of the Society's more than 30,000 professional oncology members and the patients they serve.

PIERLUIGI PORCU, MD, associate professor in the Division of Hematology and member of the OSUCCC – James Viral Oncology Program, has been elected to a three-year term as president of the United States Cutaneous Lymphoma Consortium, a multidisciplinary society of physicians who collaborate to improve the quality of life and prognosis of patients with cutaneous lymphoma.

LEIGHA SENTER-JAMIESON, CGC, associate professor in the Division of Human Genetics, has been elected as an at-large member of the 2014 Board of Directors for the National Society of Genetic Counselors. Two other Ohio State faculty serving on the national board are Rebecca Nagy, MS, CGC, immediate past president, and Amy Sturm, MS, CGC, director-at-large. Nagy and Sturm are also associate professors in the Division of Human Genetics.

CHARLES SHAPIRO, MD, director of Breast Medical Oncology and leader of the Breast Cancer Research Program at the OSUCCC – James, has been appointed to serve for a year as chair-elect for the Survivorship Committee of the American Society of Clinical Oncology (ASCO). After his term, Shapiro will become chair for a year and then serve as immediate past chair for another year. Read more online.

IN MEMORIAM

BERTHA A. BOURONCLE, MD, a professor emerita of Medicine at Ohio State who was the first to identify hairy cell leukemia and later helped develop an effective therapy for it, died Aug. 16. "Dr. Bouroncle was a compassionate physician, a superb researcher and a highly respected educator," says OSUCCC Director and James CEO Michael A. Caligiuri, MD. "With her passing, we have lost a great scholar and friend."

A Wound That Never Heals

Research is revealing the intimate links between inflammation and malignancy; the work has important implications for cancer treatment and prevention

A number of OSUCCC – James investigators are involved in inflammation research. Shown above, from left: Michael A. Caligiuri, MD; Anjali Mishra, PhD; Kenechi Ebede, MD; Joanna Groden, PhD; Carlo M. Croce, MD; Esmerina Tili, PhD.

BY DARRELL E. WARD

A cut on the finger oozes blood on the outside; inside, it initiates an acute inflammation response. Macrophages move to the injured area and release chemical messages — cytokines and chemokines — such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), platelet-activating factor and prostaglandin.

The macrophages arrive in M1 mode, killing invading microbes, mopping up cell debris and eliminating dead tissue. They are aided by incoming neutrophils.

As the inflammation response progresses, the area around the cut reddens, swells, feels warm and throbs with pain. And the role of the macrophages changes. They shift to M2 mode. They release cytokines that promote tissue repair, fibroblast proliferation, collagen synthesis and vascular growth. As the wound heals, the macrophages and other immune cells dissipate, and the tissue microenvironment returns to normal.

Inflammation is the immune system's quick response to control infections, eliminate toxins and repair tissue damage. It is essential for life. Chronic inflammation, in contrast, can drive cancer development.

For example, infection by the bacterium *Helicobacter pylori* in the stomach or by the hepatitis

"We want to identify factors that modify cancer risk in IBD and understand the mechanisms of tumor development and progression, and eventually how to better treat these cancers."

JOANNA GRODEN, PHD, *professor of Medicine and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program*

B virus in the liver can create chronic inflammation that leads to gastric cancer and hepatocellular carcinoma, respectively. Long-term inflammation caused by inflammatory bowel disease (IBD) or pancreatitis also can drive cancer development.

In addition, tumor development drives inflammation. Macrophages and other immune cells regularly infiltrate tumors where, instead of attacking the tumor, they often release substances that promote tumor growth, invasiveness and metastasis. This relationship between tumor development and inflammation is so typical that cancer is sometimes described as a wound that never heals.

Researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) are investigating both inflammation-driven cancer and cancer-driven inflammation.

By teasing apart the subtle interactions and intricate chemical conversations that occur between cancer cells, immune cells and the normal structural (stromal) cells within the tumors, they are learning how inflammation promotes tumor growth and then using that knowledge to develop novel, rational strategies for treating and preventing cancer.

DNA REPAIR AND CANCER RISK

It is well known that IBD increases the risk of colorectal cancer (CRC), and that the risk increases with the duration of inflammation. The risk of CRC for people with ulcerative colitis, for example, increases 0.5 percent yearly with a cumulative risk at 30 years of 17.8 percent.

As a clinician, Kenechi Ebede, MD, saw what patients with IBD endure for cancer surveillance, including annual colonoscopies with multiple biopsies from each part of the colonic tract. It was one of the things that drew him to earn a research degree and to work as a postdoctoral researcher in the lab of Joanna Groden, PhD, professor of Medicine and member of the OSUCCC – James Molecular Biology and Cancer Genetics Program.

After 10 years, people with ulcerative colitis are often asked to consider a prophylactic colectomy, Ebede says. "But there might be people who can perhaps wait 20 years, or some who might never need the colon removed. We need to identify markers that will enable us to stratify patients according to risk to improve treatment."

In 2011, Ebede received a postdoctoral fellowship from Pelotonia, an annual grassroots bicycle tour that raises millions of dollars for cancer research at the OSUCCC – James, and began work. "We want to identify factors that modify cancer risk in IBD and understand the mechanisms of tumor development and progression, and eventually learn how to better treat these cancers," Groden says.

Groden and Ebede are using a mouse model of IBD to investigate whether increasing or decreasing DNA-repair capacity affects tumor development. "Funding from Pelotonia helped support the initial studies, and we were surprised by our preliminary results," Groden says.

"This is a way to understand DNA repair and the genetic changes that can lead to colorectal cancer during chronic inflammation," she adds. "We want to understand how some people with IBD might be more susceptible to developing cancer if they have a DNA-repair deficiency."

The researchers are either knocking out or adding copies of a gene involved in DNA repair and replication called *BLM*. The mutation of *BLM* in humans causes Bloom syndrome, a disorder that confers a high risk of cancer.

"Without *BLM*, there is no

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MICHAEL OSTROWSKI, PHD,
OSUCCC – James researcher

"We are comparing human breast-cancer samples and lymph node metastases, and we've found that these miRNAs are more highly regulated in macrophages associated with lymph node metastases than those in primary tumors."

DNA repair," Groden says. "In the absence of inflammation, if we knock out *BLM* and induce tumors, we see more tumors. That makes sense because knocking out *BLM* cripples DNA repair."

The surprise came when Ebede knocked out *BLM* when inflammation was present. "*BLM* was missing, but we got fewer tumors," he says. "That was really interesting, and we don't know why yet."

When they increased *BLM* levels, boosting DNA repair, they got more tumors. "Our findings were very consistent but the opposite of what we expected," Groden says. "We have hypotheses to explain these outcomes, and we're applying for a grant to test them.

"This work will help us learn how cells acquire or protect themselves from gene mutations. It should lead to better strategies for preventing or treating tumors caused by chronic inflammation."

MACROPHAGES AND METASTASIS

Inflammatory cells, particularly macrophages, are consistently found in the tumor microenvironment, where they influence tumor growth and metastasis, says OSUCCC – James researcher Michael Ostrowski, PhD. "But little is known about the cellular mechanisms involved."

Ostrowski, who is chair of Molecular and Cellular Biochemistry, and a leader of the OSUCCC – James Molecular Biology and Cancer Genetics Program, is working to learn how tumor-associated macrophages promote breast-cancer invasion and metastasis.

"During normal inflammation, macrophages in the M2 remodeling phase help resolve a wound and then disperse," Ostrowski says. "But in cancer, macrophages in the tumor microenvironment remain in the M2 phase, and they engage in chemical conversations with tumor cells, fibroblasts and epithelial cells, which promotes angiogenesis and fibrosis." Ostrowski and his collaborators want to interrupt this cross-talk and perhaps block cancer progression and metastasis.

In a 2010 study published in the journal *Cancer Research*, Ostrowski and his colleagues showed that a protein called ETS2 regulates genes in tumor-associated macrophages that promote the growth of both primary tumors and lung metastases.

In addition, the researchers identified a 133-gene signature in the mouse that is also seen in human breast cancer, and found that this expression signature retrospectively predicted survival of breast-cancer patients. "More research is needed, but this could be of significant clinical importance to human disease," Ostrowski says.

Ostrowski's current work explores the role of ETS2 when macrophages transition from M1 to M2 phase. The transition involves a factor called CSF1, or M-CSF (macrophage colony stimulating factor). "CSF1 is important for normal macrophage differentiation and growth, but its role in tumor-associated macrophages is unclear," he says.

Using experimental models, the researchers showed that CSF1 initiates a signaling cascade in tumor-associated macrophages that eventually activates ETS2, which then directly upregulates a set of microRNAs (miRNA).

MiRNAs are short, non-coding RNAs that regulate the translation or degradation of messenger RNA, and therefore the proteins that cells make.

"Our work suggests that CSF1 is important for the M1/M2 transition, and that turning on these miRNAs is part of that transition," Ostrowski says.

These studies also link these miRNAs to metastasis.

"Overexpressing or removing these miRNAs raises or lowers rates of metastasis in the mouse model," Ostrowski says.

The findings are likely relevant to humans as well. "When we compare human breast-cancer samples and lymph node metastases, we find that these miRNAs are more highly regulated in macrophages associated with lymph node metastases than with primary tumors," he says.

Expression levels of the genes

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targeted by these miRNAs also correlated with patient outcome, making the findings potentially clinically important. "We are bioinformatically comparing our mouse and human signatures," he says. "And a subset of genes regulated indirectly by these miRNAs is also present in the human samples, and they correlate with patients who don't do as well."

In addition, the researchers have detected macrophage-precursor cells called monocytes in patient blood samples.

The cells are in the process of differentiating into macrophages. "That doesn't happen in healthy people," Ostrowski says. This work is being done with OSUCCC – James researcher Jeffrey Chalmers, PhD, director of the Analytical Cytometry Shared Resource.

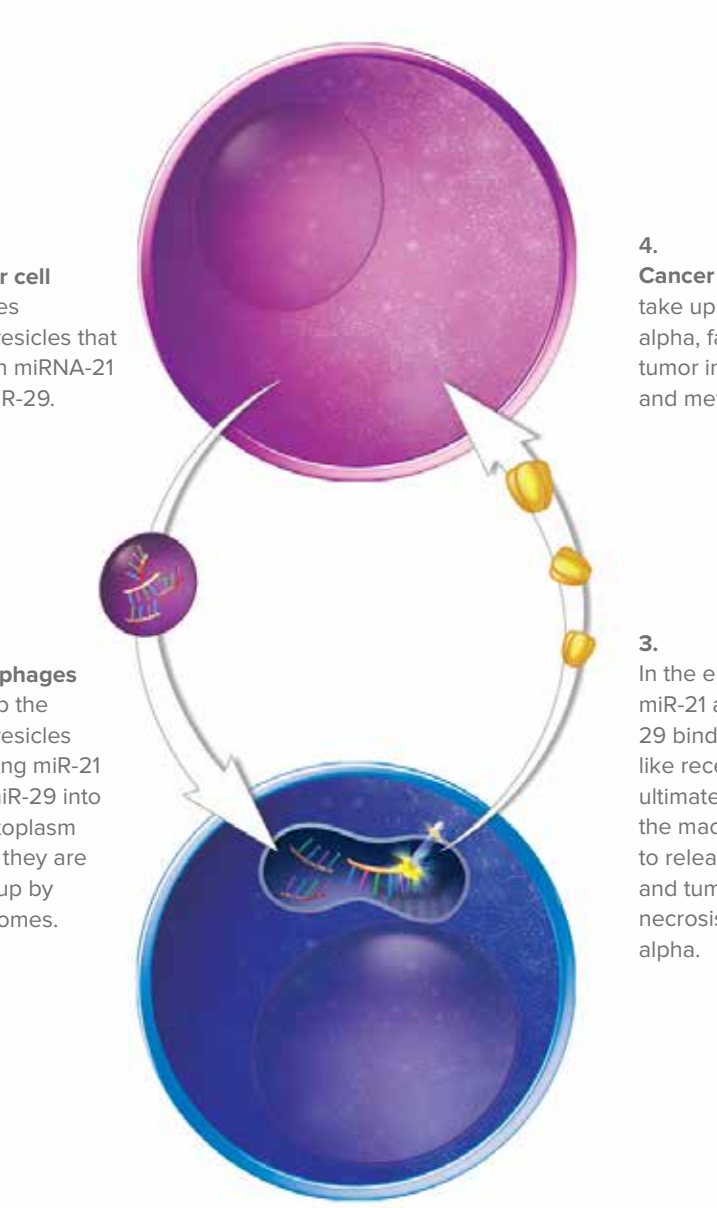
"These miRNAs seem to be upregulated in patients with tumors that have already metastasized to distant loci compared with patients without metastases," Ostrowski says. "Such patients might benefit from anti-CSF1 drugs. Our work might one day enable us to stratify them into treatment groups and help us learn how well those drugs are working."

miR MECHANISMS

MiRNAs characteristically target multiple genes. MiR-155 and miR-21 target genes that encode tumor-suppressor proteins and DNA-repair proteins. Their

MILKING MACROPHAGES IN THE MICROENVIRONMENT

Using microRNAs to communicate with the immune system, cancer cells can regulate the tumor microenvironment and promote tumor growth and spread.



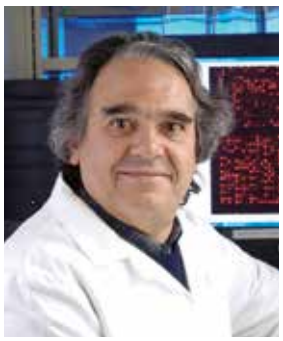
1.
Cancer cell releases microvesicles that contain miRNA-21 and miR-29.

2.
Macrophages take up the microvesicles releasing miR-21 and miR-29 into the cytoplasm where they are taken up by endosomes.

3.
In the endosome, miR-21 and miR-29 bind with toll-like receptors, ultimately causing the macrophage to release IL-6 and tumor-necrosis factor alpha.

4.
Cancer cells take up IL-6/TNF-alpha, facilitating tumor invasion and metastasis.

CARLO M. CROCE, MD,
professor and chair of Molecular Virology, Immunology and Medical Genetics, and director of the Human Cancer Genetics program



"This could be a crucial step in the formation of a tumor microenvironment that could potentially favor tumor growth. If so, targeting that mechanism might offer a new strategy for treating cancer and perhaps diseases of the immune system."

prolonged overexpression can lead to cancer. Both are under study by OSUCCC – James investigator Carlo M. Croce, MD. "Overexpression of these miRNAs can shut down and cripple DNA repair," Croce says.

"In healthy cells," he adds, "if levels of miR-155 and miR-21 increase, DNA damage also increases. When this damage hits a tumor-suppressor gene or activates an oncogene, cancer can occur. It is one way chronic inflammation can lead to cancer over time, perhaps 10, 20 or 30 years."

For example, Croce, who is professor and chair of Molecular Virology, Immunology and Medical Genetics, and director of the Human Cancer Genetics program, led a 2011 study published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*) showing that inflammation stimulated a rise in levels of miR-155. That, in turn, led to a drop in levels of DNA-repair proteins, resulting in a higher rate of spontaneous gene mutations.

"That study showed that inflammation upregulated miR-155, and that overexpression of miR-155 increased the spontaneous-mutation rate, which can contribute to tumor genesis," says first author Esmerina Tili, PhD, a researcher in Croce's lab. "The findings also suggest that drugs designed to reduce miR-155 levels might improve the treatment of inflammation-related cancers."

"Inflammation increases the probability of accumulating mutations that will lead to cancer," Croce says. "Every cell has a probability of acquiring mutations. High levels of miR-155 and 21 increase that probability much more. That might explain why colorectal cancer patients who present with high miR-155 and miR-21 expression have a generally poor prognosis.

"In fact, we can say that inflammation creates genomic instability because of its action on these microRNAs. So we immediately see a connection between chronic inflammation and the induction of cancer."

CANCER-DRIVEN INFLAMMATION

In a 2012 PNAS study, Croce and his colleagues described a novel mechanism by which miRNA promotes cancer growth and spread.

The study found that lung-cancer cells release microvesicles that contain miR-21 and miR-29, two cancer-causing miRNAs. The vesicles can fuse with macrophages and other cells in the tumor microenvironment. Inside the cells, the miRNAs bind with receptors called toll-like receptors. This, in turn, causes the host cell to release interleukin-6 and tumor necrosis factor-alpha, two proinflammatory cytokines that facilitate tumor invasion and metastasis.

"Through this mechanism, tumor cells use miRNAs to communicate with the immune system, regulate the tumor microenvironment and promote tumor growth and spread," Croce says.

"The release of cytokines through this mechanism could enable cancer cells in metastatic sites to attract inflammatory cells and establish a nurturing microenvironment," he notes. "This could be a crucial step in the formation of a tumor microenvironment that could potentially favor tumor growth."

If so, targeting that mechanism might offer a new strategy for treating cancer and perhaps diseases of the immune system, he says.

CHRONIC INFLAMMATION AND LEUKEMIA

A link between inflammation and hematologic malignancies is revealed by research led by OSUCCC – James researchers and co-senior authors Guido Marcucci,

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MD, and Michael A. Caligiuri, MD. Their preclinical study shows that high levels of the inflammatory cytokine interleukin-15 (IL-15) alone can cause large granular lymphocytic (LGL) leukemia, a rare and usually fatal form of cancer. In addition, the researchers developed a treatment for the leukemia that showed no discernible side effects in the animal model.

"This study shows one way that inflammation can cause cancer, and we used that information to potentially cure the cancer," says Caligiuri, who is director of Ohio State's Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute.

Published in the journal *Cancer Cell*, the study showed that exposing normal, human, large granular lymphocytes to high levels of IL-15 for prolonged periods causes cell proliferation, chromosomal instability and DNA hypermethylation.

"Normally, IL-15 stimulates the development and proliferation of natural-killer cells, innate immune cells that destroy malignant and virus-infected cells," says first author Anjali Mishra, PhD, a postdoctoral researcher in Caligiuri's lab. "But our study shows that excessive IL-15 activates the *Myc* oncogene in large granular lymphocytes." Chronic exposure to IL-15 and overexpression of *Myc*, in turn, led to chromosomal instability, additional mutation and DNA hypermethylation and malignant transformation (see diagram online).

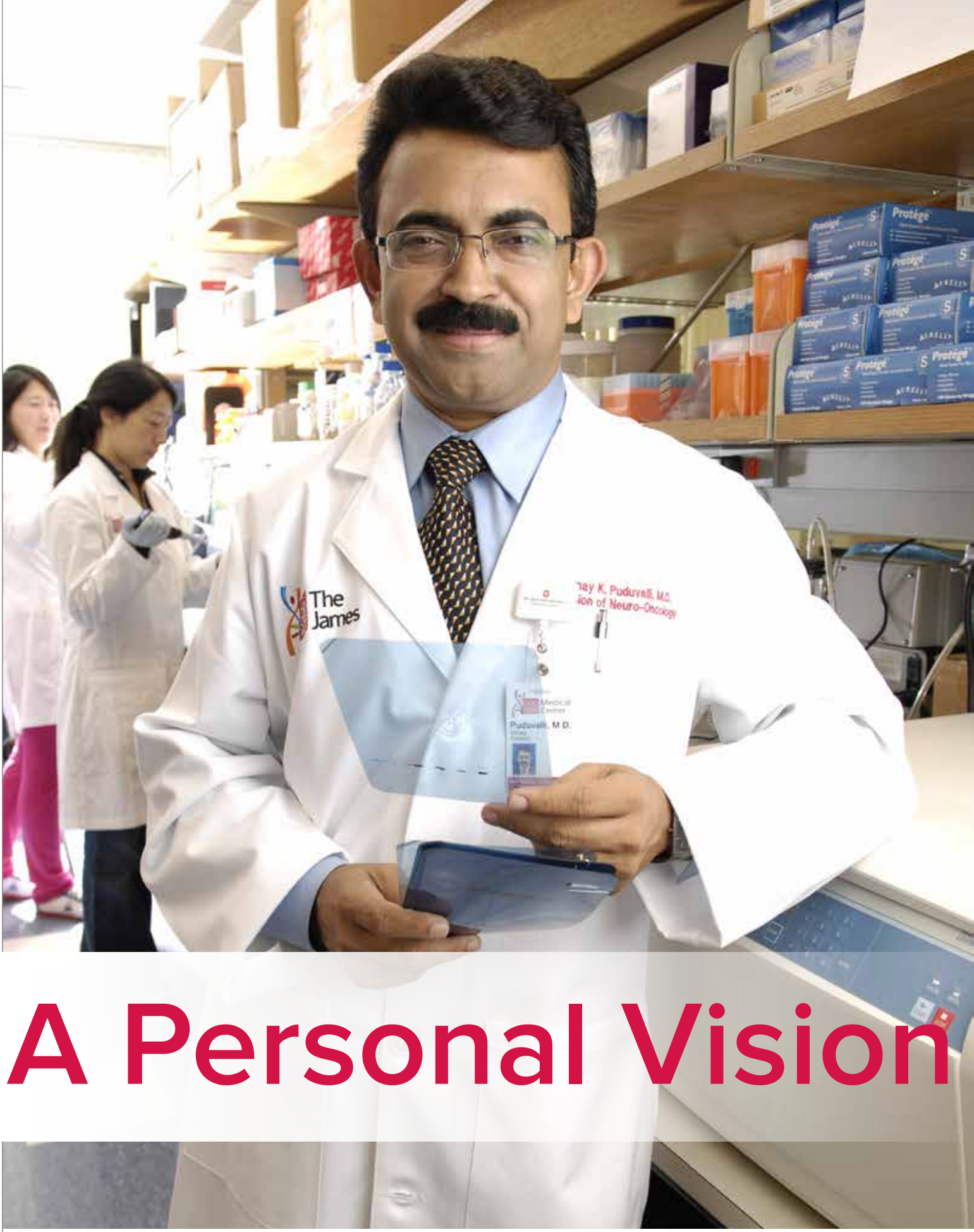
"This study showed how genetic instability and microRNAs can lead directly to cancer," says Marcucci, who is associate director for translational research at the OSUCCC – James.

Co-author Robert Lee, PhD, professor of Pharmaceutics and Pharmaceutical Chemistry in Ohio State's College of Pharmacy, led development of a liposomal formulation of bortezomib, a proteosome inhibitor that shuts down the cancer-causing pathway, potentially curing the malignancy in the animal model.

Leukemic mice treated with the liposomal bortezomib showed 100 percent survival at 130 days versus 100 percent mortality at 60-80 days for control animals. The researchers also found that IL-15 is overexpressed in patients with LGL leukemia, and that it causes similar cellular changes, suggesting that the treatment should also benefit people with the malignancy. "We now plan to develop this drug for clinical use," Marcucci says.

Such studies by OSUCCC – James researchers and their collaborators underscore the importance of treating chronic inflammation early when possible, and of vaccinating against infectious agents such as HBV that can cause it. Their work could also lead to novel treatments that delay tumor growth and spread.

Overall, research on the links between inflammation and cancer is another example of how OSUCCC – James investigators, with help from Pelotonia funding, are working to create a cancer-free world. F



A Personal Vision

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The new director of Neuro-Oncology favors team research and new clinical-trial designs to develop novel drugs for brain tumors

BY BOB HECKER

Vinay Puduvalli's career trek from medical school in his native India to director of the Division of Neuro-Oncology at The Ohio State University was born of biological intrigue and patient compassion.

"As a house officer, I helped care for a 29-year-old woman with a highly malignant brain tumor, a glioblastoma," recalls Puduvalli, MBBS, who recently was recruited from The University of Texas MD Anderson Cancer Center to Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). "She'd become a new mother shortly before her diagnosis, and then she learned that she had less than a year to live.

"It was heart-wrenching. I became deeply interested in brain tumors overnight," he adds. "The fundamental intellectual challenge of understanding why a cell goes off-track in the brain and develops into this malignancy, combined with the intensely human aspect of cancer, fueled my interest in neuro-oncology."

After earning his medical degree, Puduvalli journeyed to the United States to study and practice both neurology and oncology. "In those days, in India, clinical demands were high and the idea of doctors doing research was alien; there was no infrastructure for it and no one to guide someone who wanted to do this," he says.

After a year of basic research training at the University of Texas Medical Branch in Galveston, he completed a residency in neurology at the University of Texas Health Sciences Center and a fellowship in neuro-oncology at MD Anderson. He joined the MD Anderson faculty in 1999 and eventually became director of clinical research in the Department of Neuro-Oncology before coming to Ohio State in January 2013.

"With his wealth of experience and success in cancer patient care, clinical trials, and basic and translational research, Dr. Puduvalli is an outstanding addition to our faculty," says Russell Lonser, MD, chair of the Department of Neurological Surgery, which contains the Division of Neuro-Oncology.

"Dr. Puduvalli has expertise in developing treatments for brain and spine malignancies using a combined approach of targeted therapies, innovative clinical trial designs and rational combinations of anticancer agents," says OSUCCC Director and James CEO Michael A. Caligiuri, MD. "His expertise includes clinical care of patients with brain and spine malignancies, as well as neurological complications of cancer. He also has a lab program focused on understanding the role of epigenetics in brain tumor and glioma stem cell biology, and translating these findings to new treatment options. His knowledge and skills are contributing to our vision of creating a cancer-free world."

Arnab Chakravarti, MD, chair and professor of Radiation Oncology, co-director of the Brain Tumor Program, and the Max Morehouse Chair in Cancer Research, describes Puduvalli's recruitment to Ohio State as a "game-changer" for the neuro-oncology program. "Dr. Puduvalli brings a wealth of experience both in the clinical and translational sciences and brings with him fundamentally new strategies to find curative therapies for tumors, some of which are almost universally fatal."

The American Cancer Society (ACS) expected more than 23,000 new cases of brain and other nervous system cancers in the United States in 2013 and an estimated 13,000 deaths from these malignancies. About 42 percent of all brain tumors are gliomas, and at least 80 percent of malignant gliomas are glioblastomas. These high-grade astrocytomas are the most common and deadliest of adult malignant primary brain tumors. The median survival is 15 months.

The problem, Puduvalli notes, is that these tumors are highly invasive and impossible to entirely remove surgically. Even with radiation and chemotherapy, there is only limited control of the tumor. The tumors grow within the protected environment of the brain and are highly resistant to most treatments. Furthermore, the number of treatments available for

"Our ultimate goal is to rapidly and effectively translate research findings into better treatments and to become the 'go-to place' for malignant brain- and spine-tumor treatment in the region and, eventually, nationally."

— Vinay Puduvalli

these and other central nervous system malignancies is limited.

Puduvalli's research is directed toward developing new targeted therapies for these tumors and designing innovative clinical trials that rationally combine novel and standard anticancer agents. He is leading several trials involving epigenetic therapies and novel targeted agents. He and his laboratory personnel are investigating brain-tumor and glioma stem-cell biology with a focus on drug resistance and accelerating apoptosis (programmed cell death). His lab works closely with other Ohio State investigators to launch multidisciplinary efforts to fight brain cancers.

NEW DIRECTIONS

Puduvalli's vision for the Division of Neuro-Oncology is to translate more discoveries into treatments and to do so in a way that takes into account patients' quality of life. Ohio State, he says, has the multidisciplinary resources and the will to help realize this vision. He believes this will bring together the strong efforts in clinical care, patient support and survivorship already established at the university.

"Leadership at the OSUCCC – James is strongly invested in the success of its faculty," he says. "In addition, the OSUCCC – James administration has a single-minded focus on excellence that is supported by extensive resources and talent in the medical center and the university."

Puduvalli will strengthen the integration of clinical neuro-oncology research with the existing brain-tumor research group housed primarily in the Dardinger Neuro-Oncology Center. Their work involves preclinical models, viral therapies, tumor profiling and targeted-agent identification. Puduvalli plans to collaborate closely with the Department of Neurological Surgery, the Department of Radiation Oncology, and Ohio State's Neurosciences Signature Program, led by Ali Rezai, MD. Recognizing the impact of brain tumors in pediatric patients, his group is developing collaborations with Nationwide Children's Hospital. He will also work closely with the departments of Pathology, Radiology, Physical Medicine and Rehabilitation, and Psychiatry.

"We are part of a major land-grant university, and we want to make best use of this unique resource," Puduvalli says. "Neuro-oncology must connect with the many university groups involved in cutting-edge research, such as pharmacy, veterinary medicine, bioengineering, biomedical informatices and newer areas such as nanotechnology. We can then achieve the critical mass that creates synergy. When appropriate, we will work with pharmaceutical companies to bring novel treatments for our patients.

"Our ultimate goal is to rapidly and effectively translate research findings into better treatments and to become the 'go-to place' for malignant brain and spine tumor treatment in the region and, eventually, nationally."

RESEARCH DIRECTIONS

"Gliomas are the most devastating of primary brain tumors," Puduvalli says. "Basic research is giving us a deeper understanding of their biology. As a result, the next generation of treatments will be tailored to the molecular features of brain tumors rather than to their pathological characteristics. One area of our research is the role of epigenetic changes in tumor biology."

Epigenetics refers to chemical changes in genes that affect their expression but do not involve changes in the DNA sequence such as mutations. Consequently, epigenetic changes in tumors are potentially reversible.

Puduvalli and his lab are investigating whether epigenetic mechanisms help cancer cells survive, proliferate and resist therapy. "We use insights gained from our lab research to generate clinical trials using drugs that modify epigenetic responses in malignant glioma," he says. "This concept drives a significant part of the basic and clinical components of my research." Puduvalli currently leads clinical trials that utilize some of these agents in combination strategies for patients with glioblastoma.

One of his trials (NCT00555399)

focuses on overcoming resistance to the therapeutic agent cis-retinoic acid. The drug pushes malignant cells to develop more benign behavior, but epigenetic changes in the cells can thwart the process. "So we're combining the drug with a class of epigenetic-targeting agents called histone deacetylase (HDAC) inhibitors to overcome the resistance and enhance the therapy," Puduvalli says.

A second trial (NCT01266031) uses the HDAC inhibitor vorinostat to help patients overcome resistance to bevacizumab, an angiogenic inhibitor that tumors often evade. "There is a huge opportunity for developing drugs that target and shut down epigenetic mechanisms in specific contexts so that even conventional therapies can work better," Puduvalli says.

"Cancer cells hijack normal cell mechanisms to their benefit. Their ability to use normal growth factors, blood vessel development, signals from surrounding tissues and immune suppression works to their advantage for growth and proliferation. Much of our research is directed toward disabling the mechanisms they use to hijack these processes without affecting normal cells. Gaining insights into various aspects of tumor biology is a powerful tool for doing that."

INNOVATIVE TRIALS

Puduvalli's research also addresses the need for advanced

OSUCCC – JAMES NEURO-ONCOLOGY TEAM

Neurosurgical Oncology

Mario Ammirati, MD, professor of Clinical Neurological Surgery, director, Skull Base Surgery

James B. Elder, MD, assistant professor of Neurological Surgery

John McGregor, MD, assistant professor of Clinical Neurological Surgery and of Clinical Radiology

Ehud Mendel, MD, professor of Neurosurgery, Oncology and Orthopedics Justine Skestos Chair in Minimally Invasive Neurological Spinal Surgery

Daniel Prevedello, MD, associate professor of Neurological Surgery

Medical Neuro-Oncology

Robert Cavaliere, MD, assistant professor of Neurology, Neurological Surgery and Oncology

Herbert Newton, MD, FAAN, professor of Neurology and Oncology Esther Dardinger Endowed Chair in Neuro-Oncology

Vinay Puduvalli, MBBS, professor of Neuro-Oncology director, Division of Neuro-Oncology

Radiation Oncology

Arnab Chakravarti, MD, professor and chair of Radiation Oncology Max Morehouse Chair in Cancer Research

John Grecula, MD, associate professor of Radiation Oncology

Michael Guiou, MD, assistant professor clinical of Radiation Oncology

Fen Xia, MD, PhD, associate professor of Radiation Oncology

Neuroradiology

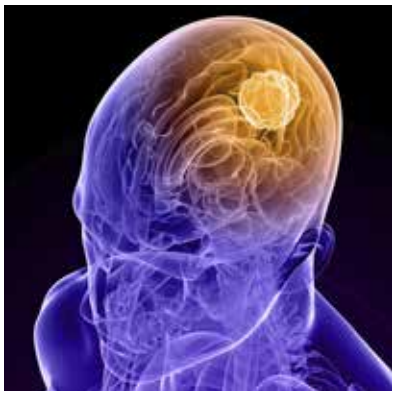
Donald Chakeres, MD, professor and director of Neuroradiology

H. Wayne Slone, MD, associate professor, clinical director of MRI

Neuropathology

Abhik Ray Chaudhury, MBBS, assistant professor of Pathology

Norman Lehman, MD, PhD, associate clinical professor of Pathology



"More molecular-based data are emerging for selecting the best therapies for patients, but these are not easily accessible in the community setting. I think we as an academic medical center have a strong obligation to fill that gap..."

—Vinay Puduvalli

clinical trial designs when evaluating targeted drugs.

"Traditional clinical trial designs are built around the older chemotherapeutic agents, but most of the newer agents don't quite fit that model," he says. "There are so many new agents emerging that, if we use traditional models, we would spend decades determining which drugs make the cut for further study. If you take into account drug combinations, there are even more options to explore.

"It's imperative that we use new clinical trial designs to screen these agents more efficiently," Puduvalli adds.

In one case he and his group are using a Bayesian adaptive study design, which uses interim data to influence the ongoing trial.

"In traditional trial models," Puduvalli says, "you must complete the study to gain the full power of analysis of comparison and do not use the information gained along the away. A Bayesian design uses information as it emerges to inform the decision-making of the trial in real time. This potentially allows the trial to be completed in a more efficient way and helps pick the winner among several treatments."

Such designs can also be used in phase I trials to more efficiently identify the right dose for a new drug and in phase II trials to identify the right patients for the right treatments.

"We also can test whether a patient's specific tumor markers will predict responses to targeted treatments," he says. "In fact, we can test multiple markers and agents within the same trial. Combined with insights into tumor biology from lab studies, this is the way toward personalized and highly effective treatments for malignancies, which is the holy grail of cancer research."

Puduvalli believes it is the Division of Neuro-Oncology's mission and responsibility as part of Ohio State's nationally recognized cancer program to offer the community the widest possible array of evidence-based treatments. This involves a team approach with close partnerships between Neurological Surgery and Radiation Oncology.

"More molecular-based data are emerging for selecting the best therapies for patients, but these are not easily accessible in the community setting. I think we as an academic medical center have a strong obligation to fill that gap," Puduvalli says. "Given the paucity of standard treatment options for brain tumor patients, our patients deserve access to every reasonable cutting-edge therapy available. We will continue developing new treatments that improve life span and maintain patients' quality of life, and we will do more to connect with academic partners regionally and across the country to make innovative care available to all. Ohio State aims to be a leader in that effort."

Puduvalli, Lonser and Caligiuri agree that this trend should be exciting to community oncologists and their patients.

"It's all about translating basic science findings to the application of effective therapies," Lonser says. "It's leading to more and more clinical trials at Ohio State for neuro-oncology patients."

"Doctors will find us to be willing and collaborative partners who will open doors for their patients to receive the latest treatments," Puduvalli adds. "We view this as a true collaboration to benefit patients no matter where they are referred from."

For incentive, he need only remember the young woman in India whom he helped treat for glioblastoma many years ago as a neurosurgery house officer.

After assisting in her surgery, Puduvalli was assigned to inform her family of both the severity of the tumor and that the surgery could not remove it all. Her only remaining option at that time was radiation therapy to prolong her life. "Beyond that, we had nothing to offer her, a fact I found very frustrating."

Through team research and the pursuit of science-based therapies, he hopes to erase such scenarios.

Seeking Answers *for Thyroid Cancer*

Renewed NCI funding supports bedside-to-bench research driven by the needs of patients

BY BOB HECKER

Thyroid cancer incidence in the United States is rising at the fastest rate of all solid tumors, producing an increasingly important public health problem. Researchers at The Ohio State University are working to understand why this is happening and how to better treat and prevent the disease.

In 2013, a team of researchers led by Matthew Ringel, MD, co-director of the Thyroid Cancer Unit at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James), received an $11.3 million, five-year renewal of a Program Project Grant first awarded in 2008 at $11.9 million by the National Cancer Institute (NCI) to study "Genetic and Signaling Pathways in Epithelial Thyroid Cancer" (grant number CA124570-06)

OSUCCC Director and James CEO Michael A. Caligiuri, MD, has called the grants "a landmark achievement in NCI funding for Ohio State's thyroid cancer program that represents the best in translational science."

"To our knowledge, this is the only Program Project Grant currently funded by the NCI that focuses entirely on thyroid cancer," says Ringel, the Ralph W. Kurtz Professor of Medicine, director of the Division of Endocrinology, Diabetes and Metabolism at Ohio State, and a member of the OSUCCC – James Molecular Biology and Cancer Genetics Program (MBCG).

The grant has four interacting research projects that share four core services. This design reflects the multidisciplinary nature of the OSUCCC – James' Thyroid Cancer Unit, which addresses all aspects of care, including determining genetic predisposition, improving diagnosis and treatment, and managing side effects.

"We also offer therapeutic clinical trials for patients with non-responsive or progressive disease," Ringel says. "I'd describe our translational-research program as 'bedside to bench' rather than 'bench to bedside,' because it's so much driven by the clinical needs of our patients."

The American Cancer Society expected 60,220 new cases of thyroid cancer and 1,850 deaths from the disease in the United States in 2013. Three out of four of the new cases and more than half the deaths occurred in women. The chance of being diagnosed with this disease is now more than twice what it was in 1990.

Why the incidence is rising is unknown, Ringel says, but one factor may be better detection using technologies such as thyroid ultrasound and fine-needle aspiration.

"There are only a few known environment risk factors, such as radiation exposure for papillary thyroid cancer — the most common form in the United States — and iodine deficiency for follicular thyroid cancer. Some rare genetic syndromes also predispose to follicular thyroid cancer, he says.

The primary goals of the PPG's translational studies are to:

- Better predict who is at risk for the disease, enable earlier diagnosis and predict tumor behavior by identifying genes that predispose to thyroid cancer;
- Identify cell pathways that influence thyroid cancer development and progression for potential drug targeting;
- Identify why patients stop responding to standard therapy, then develop strategies that improve response rates.

"Thyroid cancer typically takes an indolent course when patients are diagnosed early, so with increasing

incidence there is a growing population of long-term survivors," Ringel says. "For patients with more aggressive disease, we need better treatment options."

The renewal funding will enable Ringel and his colleagues to further the most promising earlier findings, those with the greatest potential to improve care or advance thyroid cancer research.

Here is a summary of the renewal grant's four projects and cores.

MATTHEW RINGEL, MD, *co-director of the Thyroid Cancer Unit at the OSUCCC — James*

SPORE Grant Brings Added Support for Thyroid Cancer Research

In addition to receiving five years of renewal funding for an NCI Program Project Grant, **Matthew Ringel, MD,** co-director of the Thyroid Cancer Unit at the OSUCCC – James, has been awarded a five-year, $11.3 million Specialized Program of Research Excellence (SPORE) grant (CA168505-01A1). The SPORE is a collaborative grant with investigators at MD Anderson Cancer Center and centered at Ohio State with Ringel as principal investigator. Its primary goal is to improve the outcomes and lives of patients with thyroid cancer.

Project I: Genes in the Predisposition to Papillary Thyroid Carcinoma (PTC)

In the first grant period, the investigators identified 125 families that have at least three members with PTC, enabling them to apply a "clan genomics" approach and learn whether it can improve identification of inherited gene variations that contribute to PTC development.

"Numerous studies done mainly by others show that the heritability of thyroid cancer is very high, so we set out to find predisposing genes that explain this," says Project Director Albert de la Chapelle, MD, PhD, professor of Medicine and the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research.

"But even with many large families to study, we found very little. This we interpret to mean that high-penetrance genes probably are rare or do not exist," de la Chapelle says.

"We are now concentrating on finding rare, high-penetrance genes that may occur mostly in single patients or families," he adds. "We are doing this using next-generation sequencing of individuals from families in which the inheritance resembles that of high-penetrance genes. We have so far identified at least three promising genes." One of those, for example, was polymorphism rs944289, described in a 2012 paper in the *Proceedings of the National Academy of Sciences (PNAS)*.

De la Chapelle and his colleagues now hope to confirm the involvement of these genes in PTC.

Project II: Genetic Alterations That Initiate Follicular Thyroid Carcinogenesis

This study investigates the genetic causes of inherited follicular thyroid carcinoma (FTC) and sporadic FTC in humans and in a mouse model. The project is directed by Charis Eng, MD, PhD, chair and founding director of the Genomic Medicine Institute of the Cleveland Clinic Foundation, and co-led by Lawrence Kirschner, MD, PhD, professor of Medicine in the Division of Endocrinology, Diabetes and Metabolism, and a researcher with the OSUCCC – James MBCG Program.

The human genetic model used in the study is an inherited cancer syndrome called Cowden syndrome (CS), which is caused by germline mutations in the *PTEN* tumor-suppressor gene and is characterized by high risk for FTC.

"CS presents a unique opportunity to examine the events that are the earliest indicator of FTC," Eng says.

In the first grant period, the researchers accrued more than 3,000 human subjects who met CS or CS-like criteria. "We then created a Web-based *PTEN* risk calculator based on the presence or absence of *PTEN* mutations and clinical characteristics," Kirschner says. Key findings during the first grant period included:

- *PTEN* mutation carriers have a 32-percent lifetime risk of thyroid cancer, much higher than previously estimated;
- Germline mutations of *PTEN* account for 25 percent of CS cases, instead of the widely believed 85 percent from a previous series

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

of accruals, indicating that other predisposition genes must exist. The research team has identified two new CS susceptibility genes so far;

- Thyroid cancer prevalence is higher in patients with *SDHx* gene variants versus those with *PTEN* mutations alone, and *SDHx* variants modify cancer risk in those with *PTEN* mutations.

During the second grant period, Eng, Kirschner and their team will work to identify the earliest events in FTC initiation and predisposing genetic factors useful for predictive testing to risk assessment.

"Based on data from our first grant period, we hypothesize that interactions of *PTEN, SDHx* and *PRKAR1A* play an important role in thyroid neoplasia initiation by modulating mitochondria-associated energetics," Eng says. To investigate this question, the researchers will:

- Analyze the role of *SDHx* and *PRKAR1A* germline variations in modifying risk and the molecular signaling of thyroid cancer in patients with *PTEN* mutations;
- Analyze *PTEN* and *SDHx* interactions;
- Study mitochondrial function in mouse models of thyroid neoplasia.

Project III: Selective Modulation of Thyroidal Radioiodine Accumulation

The ability of thyroid follicular cells to concentrate iodine allows the use of radioiodine to target residual and metastatic thyroid cancer after tumor removal.

"Radioiodine therapy (RAI) can decrease recurrence and improve overall survival in several thyroid cancer patient populations," says Project Director Sissy Jhiang, PhD, professor of Medicine and a member of the OSUCCC – James MBCG Program. "But about 20 percent of patients with differentiated thyroid carcinomas, and most patients with poorly differentiated thyroid cancer, do not respond to RAI therapy because their ability to accumulate radioiodine is reduced or absent."

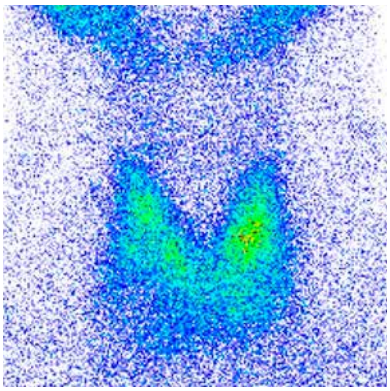
Jhiang's project seeks to improve RAI therapy in these patients by identifying molecular candidates that restore or enhance radioiodine accumulation in thyroid tumors.

During the first grant period, Jhiang's team confirmed that inhibitors for *MEK, BRAF,* and *PI3K* genes could increase radioiodine accumulation in thyroid cells; they learned that *Hsp90* inhibition and *Akt* inhibition selectively increased radioiodine accumulation; and they used small-animal imaging to quantify radioiodine accumulation in thyroid cancer models.

"Several small-molecule inhibitors that target *MEK, BRAF, Akt, PI3K* or *Hsp90* are in clinical trials to treat other types of cancer, and these could be applied to thyroid cancer patients as well," Jhiang says. "We hypothesize that these inhibitors might halt thyroid tumor progression and also sensitize surviving tumor cells to radioiodine ablation."

Project IV: P21-Activated Kinase in Thyroid Cancer

During the first grant period, Ringel's lab discovered a new link between the *BRAF* oncogene, which causes about 40 percent of papillary thyroid cancers and is associated with aggressive disease, and the signaling molecule p21-activated kinase (PAK). This pathway regulates the migration of thyroid cancer cells, and it is independent of the classic *BRAF* target known as *MEK*. In addition, laboratory studies suggested it is sensitive to RAF-kinase inhibitors that are already in clinical testing.

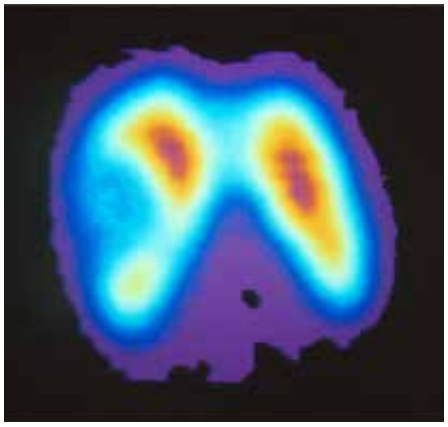


"Radioiodine therapy (RAI) can decrease recurrence and improve overall survival in several thyroid cancer patient populations..."

—Sissy Jhiang, PhD

"Activating mutations in *BRAF* are the most common identifiable genetic mutations in thyroid cancer so far and are associated with poor prognosis," says Project Director Ringel. His team worked with Ching-Shih Chen, PhD, a professor of Medicinal Chemistry and Pharmacognosy at Ohio State and member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program, to develop *PAK* inhibitors.

"We believe *PAK* is critical for *BRAF* signaling, that it is involved



"Activating mutations in BRAF are the most common identifiable genetic mutations in thyroid cancer so far and are associated with poor prognosis."

—Matthew Ringel, MD

in thyroid cancer progression, and that it is a novel therapeutic target to inhibit PTC progression," Ringel says.

"Now, we're trying to understand how *PAK* works at the molecular level, and we're evaluating tumor samples that have shown invasion and metastasis so we can develop inhibitors to treat that kinase."

RESEARCH CORES

The grant also funds four shared-resource cores that support the research:

- **Integrated Clinicopathology and Biorepository Core:** Oversees the biospecimens collected for research and the databases that integrate pathology and laboratory samples with clinical information. The team is led by John Phay, MD, of the Division of Surgical Oncology, and Rebecca Nagy, CGC, of the Division of Human Genetics, and includes Paul Wakely Jr., MD, in the Department of Pathology.

- **Mouse Imaging and Pathology Core:** Provides expertise in mouse thyroid pathology. The team is directed by Kirschner, co-leader of Project II, who has extensive experience in mouse models of endocrine cancer. The researchers use CT/SPECT (computed tomography and single photon emission computed tomography) with ultrasound to quantify iodine uptake in mouse models. The core includes Krista LaPerle, DVM, PhD, a mouse veterinary pathologist at Ohio State.

- **Biostatistics Core:** Directed by Soledad Fernandez, PhD, of the Department of Biomedical Informatics at Ohio State, this core provides biostatistical support for PPG investigators at all levels of research, from study design to final analyses.

- **Administrative Core:** "This core is structured to analyze and monitor progress in all aspects so we can foster collaborations to enable more rapid progress," says Ringel, the core's director.

OPTIMISTIC OUTLOOK

Ringel notes many reasons why the group's work stands an excellent chance of helping patients. They include support for team science and collaboration by the OSUCCC – James, and the integration of research with longstanding clinical expertise.

"At the same time, we couldn't do this research without the help of our patients," he adds. He cites the leadership of Manisha Shah, MD, who directs Ohio State's Neuroendocrine Tumor Program and is principal investigator for several clinical trials, including some that focus on thyroid cancer. Shah has research and clinical interests in adrenal, neuroendocrine and thyroid cancers.

Ringel also notes other Ohio State faculty who are crucial to the program's success:

- **Jennifer Sipos, MD,** and **Fadi Nabhan, MD,** Division of Endocrinology, Diabetes and Metabolism, experts in thyroid nodules and thyroid cancer and national leaders in thyroid cancer diagnosis and management;
- **Nathan Hall, MD, PhD** and his team in Nuclear Medicine;
- **Paul Wakely, MD, Rulong Shen, MD,** and others in the Department of Pathology;
- **Surgeons in Surgical Oncology and Head and Neck Surgery;**

"We also have the support of a terrific group of nurses and administrators in multiple divisions who support our joint commitment to a true multidisciplinary approach to this work," Ringel says.

"Also important to patients is our ability to minimize many treatment side effects to improve quality of life," he adds. "Today, so many patients are doing well and surviving longer that we need to be cognizant of side effects, particularly in those with early-stage disease."

Yet, much work lies ahead. "The main benefit from our studies might come from the clues they provide to pathways that predisposing genes act through, and from drugs that can be conceived to act on those pathways," adds de la Chapelle, director of Project I. "This might make it possible to halt or cure the disease. Such studies are now beginning."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU-12055: Safety and Feasibility of Minimally Invasive Inguinal Lymph Node Dissection (SAFE-MILND)

HYPOTHESES: That minimally invasive groin dissection is a safe procedure; 2. That the learning curve for minimally invasive inguinal lymph node dissection for those with inguinal lymph node dissection experience will be steep; 3. That pre-course generic laparoscopic technical skills correlate with minimally invasive superficial groin dissection performance in a clinical setting, including operative oncologic standards and safety metrics.

RATIONALE: Regional lymph nodes (LNs) are the most frequent site of melanoma spread. The presence of tumor cells in LNs, if left untreated, can result in disease progression and an increased risk of death. Patients with melanoma that is metastatic to the inguinal lymph nodes may require a complete lymph node dissection.

The standard open inguinal LN dissection involves a long incision that crosses the inguinal crease. The procedure is associated with a high incidence—up to 50 percent in some series—of complications such as wound infection, wound dehiscence, seroma formation, venous thrombotic events and lymphedema. These can result in extended hospitalization, reduced quality of life, delayed return to normal activities and increased healthcare costs. Interventions that attempt to minimize these problems have been unsuccessful. Lymphedema remains a chronic, incurable condition.

This phase I multicenter trial evaluates the benefits and safety of minimally invasive lymph node dissection as a novel approach to inguinal LN staging and treatment. The procedure is performed through three small incisions in the thigh, utilizing a camera and special instruments.

Post-operative evaluation for adverse events will occur after 30 and 90 days. Lymphedema will be assessed using leg-volume measurements at baseline and during postoperative follow-up. Finally, the study assesses the efficacy of a specific didactic and hands-on training program designed to teach surgeons to perform this new procedure.

AT A GLANCE

Trial no.: OSU-11055 (ClinicalTrials.gov identifier: NCT01500304)

PI: ALICIA TERANDO, MD

Phone: 614-293-8890

Email: *alicia.terando@osumc.edu*

Eligibility: Age 18 years or older; malignant melanoma present in an inguinal node basin requiring superficial inguinal lymph node dissection; surgical plan for superficial inguinal dissection; clinical or radiographic evidence of superficial inguinal lymph node disease; able to tolerate general anesthesia; female patients of childbearing age must have a negative pregnancy test, be surgically sterile or post-menopausal for a year or more.

Block Lectureship Award Celebrates 20th Anniversary

In October, the OSUCCC – James celebrated the 20th anniversary of the Herbert and Maxine Block Memorial Lectureship Award for Achievement in Cancer.

The Block family of Columbus established the award to honor the memory of their parents, Maxine and Herbert J. Block, who both died of cancer. It is given annually to a renowned cancer researcher who is invited to the OSUCCC – James to deliver the annual Block Lecture and to accept a monetary prize of $25,000.

"Twenty years ago the Block family met with the director of The Ohio State University Comprehensive Cancer Center to set up a fund designed to drive more advances in cancer through greater engagement and cross-industry collaborations," says Michael A. Caligiuri, MD, director of the OSUCCC and CEO of the James Cancer Hospital and Solove Research Institute. "Today, it is one of the largest and most esteemed prizes awarded by an academic institution in the field of cancer."

The Block Memorial Lectureship is funded by proceeds of the annual Herbert J. Block Memorial Tournament, a golf outing established in 1982 by the Block family to honor their father.

Treating Oncologic Emergencies

A cancer emergency department is among the unique features of the new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, opening in 2014.

The James Cancer Emergency Department (ED) will be contiguous with the traditional Ohio State Wexner Medical Center ED. "It will be among the first fully integrated cancer EDs in the nation," says Richard Goldberg, MD, physician-in-chief at the OSUCCC – James.

"The cancer ED will provide specialized emergency oncology care," says Thomas E. Terndrup, MD, professor and chair of Emergency Medicine. "Those who arrive with a trauma or heart attack will be treated in the Wexner Medical Center ED, coordinated when appropriate with their cancer history and James staff."

ED physicians trained in oncology will staff the department, along with a dedicated team of nurses. They will be expert in treating such oncologic emergencies as treatment-associated infections, tumor lysis syndrome, surgical problems such as bowel or kidney obstruction, or pain or weakness due to brain tumors or spine metastases.

"Additional diagnostic or treatment services will be available just an elevator ride away in The James," says Goldberg, who is also professor of Medicine in the Division of Hematology and the Klotz Family Chair in Cancer Research.

The department will be open 24 hours a day, seven days a week, will have a capacity of 15 patients, and it will have a waiting room designed for patients with compromised immunity.

"The cancer ED will accept patients treated at other centers, but we will be particularly well prepared for James patients needing emergency care," Terndrup says.

Cancer ED physicians will open the patient's electronic chart and immediately learn the patient's history, treatment regimens and other details. "That permits high-quality, personalized care," Terndrup says.

"The James Cancer ED, true to the goals of the new cancer hospital, will enable us to maintain coordinated, integrated care of our patients, while optimizing efficiency and quality of care," Goldberg says.

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$19 MILLION RAISED BY PELONIA 13 – $61 MILLION FIVE-YEAR TOTAL

This year's Pelotonia bicycling tour raised a record $19 million for cancer research at the OSUCCC – James, pushing the five-year total of the annual grassroots event to more than $61 million.

"Every year, I am humbled by the generosity and tenacious commitment of the thousands of Pelotonia riders and volunteers working to help us reach our goal of creating a cancer-free word," says Michael A. Caligiuri, MD, director of The Ohio State University Comprehensive Cancer Center and CEO of the James Cancer Hospital and Solove Research Institute.

"Pelotonia support has been integral to our ability to attract and retain brilliant clinician-scientists; support student and fellowship training; purchase critical research equipment; and fund the new big ideas that will help us better understand each person's unique cancer."

Pelotonia 13, held Aug. 9-11, attracted a record 6,723 riders from 41 states and nine countries, along with 3,451 virtual riders and more than 2,300 volunteers. Riders for the tour chose from assorted routes between central Ohio and Kenyon College in Gambier, Ohio.

Team Buckeye, Ohio State's official superpeloton, had a record 1,178 Ohio State riders in 90 pelotons, 614 virtual riders and 122 volunteers. Its fundraising total stands at nearly $2.3 million.

Thanks to generous sponsors – including Huntington Bank, Limitedbrands Foundation, Peggy and Richard Santulli, American Electric Power Foundation, Nationwide Insurance, Cardinal Health, Harold C. Schott Foundation, Kenyon College and Scotts Miracle-Gro – 100 percent of every dollar raised by Pelotonia supports cancer research at the OSUCCC – James.

Pelotonia 14 is scheduled for Aug. 8-10. Registration opens Jan. 7, 2014. For more information, visit http://pelotonia.org.

US NEWS & WORLD REPORT RANKS OSUCCC – JAMES 20TH IN THE NATION

U.S.News and World Report has ranked the OSUCCC – James among the top 20 on the magazine's annual list of "America's Best Hospitals" for cancer care.

This year, *U.S.News* placed the hospital at No. 20, a significant jump from last year's impressive ranking of 25th. This is the 15th consecutive year that the OSUCCC – James has earned a place on the magazine's prestigious list of the nation's top 50 hospitals for cancer care. The James first made the list in 1999, less than a decade after it opened in July 1990.

The *U.S.News* 2013 rankings, featured online at www.usnews.com/besthospitals, are based on clinical outcomes, patient safety, national reputation and more. Rankings are based on data collected annually from thousands of hospitals by *U.S.News*. The cancer program is among 10 medical specialties at Ohio State's Wexner Medical Center that *U.S.News* ranked among America's best in 2013.

INSIDE THE NEXT FRONTIERS

TOBACCO RESEARCH

Ohio State's new Center for Excellence in Regulatory Science is funded by a five-year, $18.7 million grant from the National Institutes of Health and the U.S. Food and Drug Administration. The developing research program will take into account the biological, psychological, economic and public health implications associated with tobacco use and the marketing of tobacco products. The center's 18 scientists come from the OSUCCC – James and six Ohio State colleges.

PRECISE CANCER MEDICINE

Studies suggest that cancer is a genetically heterogeneous disease, and that personalized therapy will be superior to the "one size fits all" approach. Personalized therapy requires identifying unique and shared genetic changes in patients' tumors. OSUCCC – James researchers are merging clinical and basic science expertise, and sequencing individual cancers in real time, to develop and apply genetic biomarkers through innovative clinical trials. The goal: to bring precision cancer medicine into the clinic.