SPRING | 09

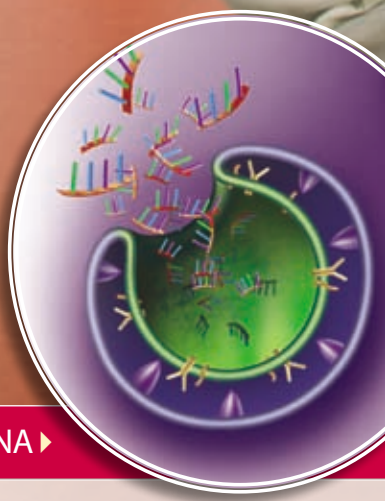
The James
Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

WHERE THERE'S NO SMOKE...

A greater proportion of lung cancer patients are never-smokers. It's a different disease and may require different therapy.



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

MICHAEL A. CALIGIURI, MD
DIRECTOR, COMPREHENSIVE CANCER CENTER
CHIEF EXECUTIVE OFFICER, JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE
THE OHIO STATE UNIVERSITY

FULL TEAM AHEAD

The OSUCCC welcomes two new outstanding researchers

In 2000, a study of 250 cases of squamous cell carcinoma of the head and neck produced strong evidence that human papilloma virus (HPV) positive oral cancers are a distinctly different disease from HPV-negative tumors and have a markedly better prognosis. The first author on that exciting paper, Maura Gillison, MD, PhD, has since become a world authority on HPV-associated oral cancer.

I am very pleased to announce that Maura has been recruited to The Ohio State University and to the OSU Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute (OSUCCC-James) as a member of the Cancer Control and Viral Oncology programs.

Maura, who comes from Johns Hopkins University School of Medicine, is establishing a translational research program that will apply her discoveries at the bench to the prevention and treatment of HPV-associated cancers. She holds the Jeg Coughlin Chair in Cancer Research.

David Symer, MD, PhD, is another outstanding new recruit. He is an assistant professor and researcher in the Department of Molecular Virology, Immunology and Medical Genetics and a physician in the Division of Hematology and Oncology.

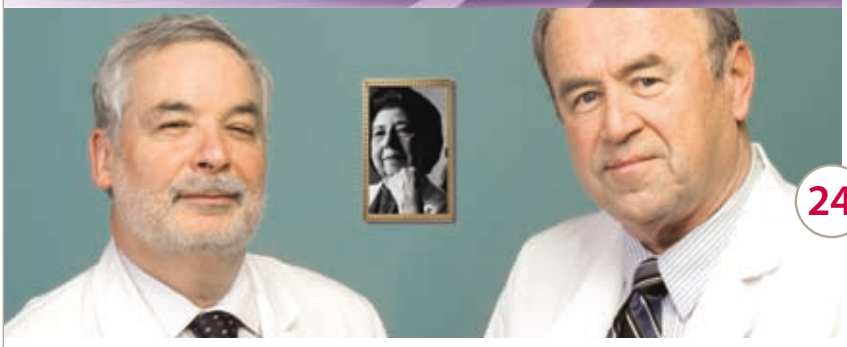
David formerly headed the Epigenetics Section at the National Cancer Institute. He and his laboratory study the influence of retrotransposons and epigenetic controls that drive genetic variation in mouse and human cancer.

To help fund the top-notch research being done by OSUCCC investigators we are introducing Pelotonia, a bike tour with one goal: to end cancer. Driven by the passion of its cyclists and volunteers, and their families and friends, Pelotonia will be an annual event of hope, energy and determination. Thanks to a transformational gift from NetJets Inc., Pelotonia can direct 100 percent of every dollar raised to research at the OSUCCC-James. Honorary chairman of the event, world renowned cyclist Lance Armstrong, will join the 100-mile ride to Athens, Ohio. To learn more about the August 28-30 inaugural event, see page 29 and visit *www.pelotonia.org*.

Top-notch cancer research is necessary to find cures and save lives, but it requires substantial funding.

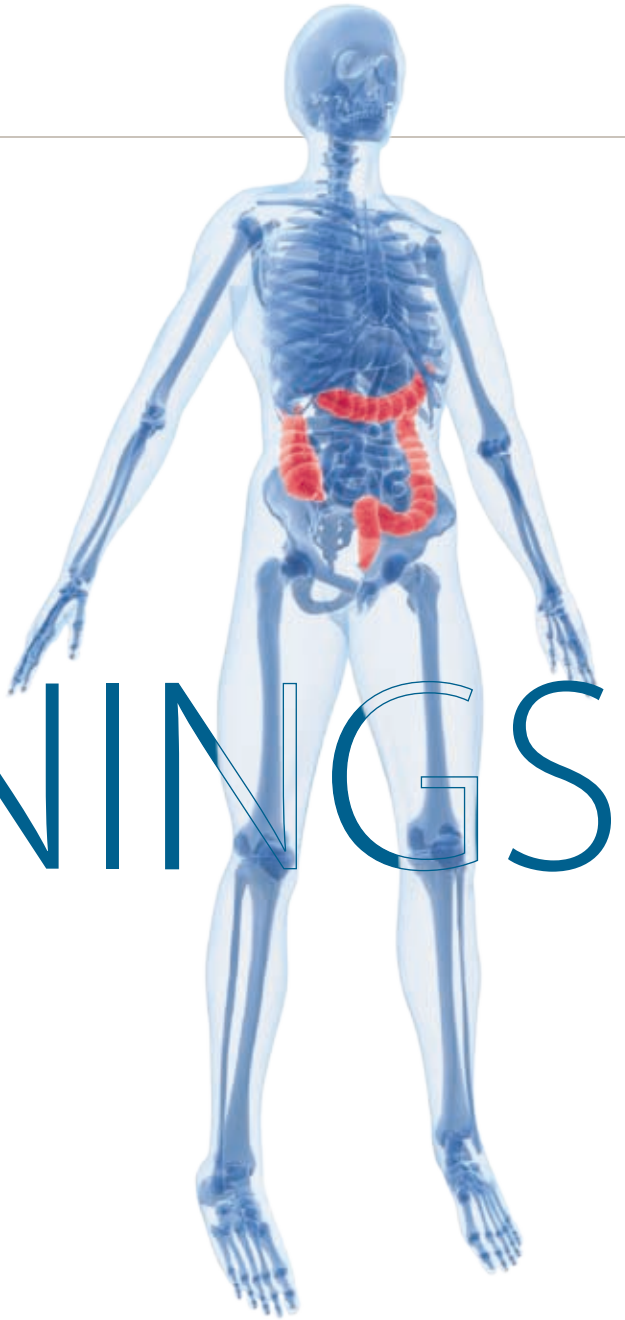
frontiers

SPRING | 09



FEATURES

ON THE COVER: MIGUEL VILLALONA, MD, AND GREGORY OTTERSON, MD. PHOTOGRAPH BY ROMAN SAPECKI.



ADVANCED SCREENINGS

Making sense of conflicting colorectal cancer screening guidelines

By **ROBERT L. POMPA, MD,**
assistant professor of Internal Medicine
James Cancer Hospital and Solove Research Institute

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death in both men and women in the United States. Although most cases of CRC occur in individuals at average risk, there are factors that increase one's risk for the disease. They include increasing age, African-American race and male gender, as well as personal history and first-degree relatives with CRC.

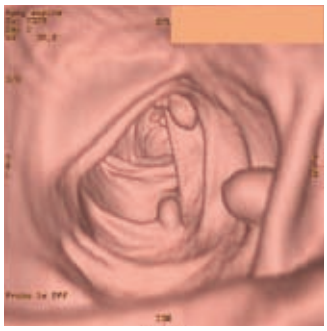
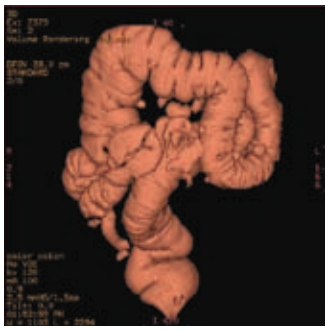
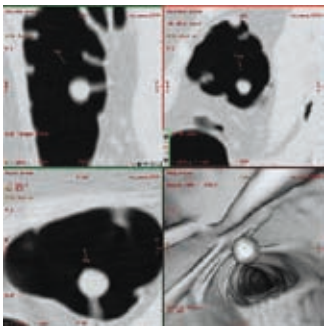
The issue of CRC screening goes beyond whether a patient should have a colonoscopy. Screening intervals can range from three months to 10 years depending on patient characteristics and risk factors. The variety of screening modalities include CT colography ("virtual colonoscopy"), fecal occult blood testing (FOBT), FOBT plus flexible sigmoidoscopy, barium enema and fecal immunochemical DNA testing.

All things considered, who, at what age and how frequently should individuals undergo CRC screening? This can be a complicated and confusing question for many physicians.

A number of societies offer CRC screening guidelines including the American Society of Gastrointestinal Endoscopy, the American College of Gastroenterology, the American Gastroenterology Association, the U.S. Preventive Services Task Force, the American Cancer Society and the American College of Radiology, but collectively, the guidelines can contain inconsistent opinions about the screening process.

CHOOSING A GUIDELINE

How does the physician determine which guidelines are best suited for CRC screening of his or her patients?

CT colography—or virtual colonoscopy—produces vivid 3-D images of the colon, but can also lead to false positive diagnoses of polyps.

ROBERT L. POMPA, MD

"The complexities of choosing a colon cancer screening method can be illustrated by CT colography … Patients and physicians are often drawn to CT colography because it implies a less invasive means of CRC screening … CT colography may find extracolonic abnormalities that require further study, which leads to additional, and sometimes unnecessary, follow-up investigations."

First, the physician must understand the basis on which particular screening guidelines are based. Important factors to consider for any screening test include ease and availability of the test, false positive and false negative rates, the balance between sensitivity and specificity, and cost. Whenever possible, screening recommendations should be based on evidence from multiple randomized controlled trials demonstrating sensitivity, specificity, ease, cost effectiveness and any reduction of morbidity and mortality. For example, despite advances in endoscopic technology, the only CRC screening program that has been shown to decrease mortality is FOBT, followed by endoscopic evaluation of positive FOBT results.

It is also important to consider the source of the guidelines, as each professional society may interpret screening data differently relative to their particular specialty. Variations in data interpretation may significantly influence screening frequency, cost and modality, and add to the complexity of following CRC screening guidelines. These variations can exist even though the randomized controlled trials cited are the same or similar.

For example, published guidelines from cancer-related organizations may tend to favor a more frequent screening interval, regardless of the screening mechanism because the goal of these organizations is cancer detection. Similarly, gastroenterology societies may advocate more frequent or a more endoscopic-based screening recommendation. Similarly, guidelines published by radiology-based organizations may recommend a more prominent role for radiographic screening modalities.

SCREENING METHODS

The complexities of choosing a CRC screening method can be illustrated by CT colography, which can be a very useful tool in colon cancer screening. Patients and physicians are often drawn to CT colography because it implies a less invasive means of CRC screening. Although this procedure does eliminate the risks of endoscopy initially, it nonetheless requires a complete bowel preparation. When suspected polyps are found, colonoscopy is needed to further evaluate the findings, and if the colonoscopy is not available on the same day, then a second bowel preparation on a different day is needed to complete the evaluation. This may be contrary to the patient's expectations for screening and may affect the patient's participation in the screening process and drive up cost.

CT colography may also find extracolonic abnormalities that require further study, which leads to additional, and sometimes unnecessary, follow-up investigations. Other considerations such as sensitivity, specificity, false positive rate, polyp miss rate, cost, interval of screening, radiation exposure, availability and local expertise must also be taken into account.

In summary, following CRC screening guidelines can be challenging. It is important to review the published guidelines and choose those that are best suited for the demographics of your patient population, and the technologic resources and specialty expertise available in your area. This reduces confusion and makes it easier to follow the complex recommendations set forth in these guidelines.

Having good communication and collaboration with a board-certified gastroenterologist is paramount for consulting on special or more complex patients, and it is essential for achieving the highest rate of screening possible for your patient population.

BRAIN TUMORS

MORE IS LESS

Study shows how altering cells may help fight brain tumors

10,000
CASES OF GLIOBLASTOMA ARE DIAGNOSED IN THE UNITED STATES EVERY YEAR. THE AVERAGE SURVIVAL IS ABOUT ONE YEAR FROM DIAGNOSIS.

Cancer researchers at The Ohio State University have found a way to slow the proliferation of cells that drive the growth of glioblastomas. The study discovered that boosting the levels of a particular microRNA in those tumor cells slows their growth by 80 percent and may make them vulnerable to treatment.

"Our findings suggest that if we can get MIR128 into tumor cells of patients, we might help control tumor growth and improve the response to therapy," says **SEAN LAWLER, PhD,** a research assistant professor of Neurological Surgery and an OSUCCC investigator.

The study found that MIR128, present at greatly reduced levels in tumor cells, inhibits a protein needed by certain tumor cells that behave like stem cells. These stem-like cells are believed responsible for the tumor's persistent growth and resistance to therapy.

Low levels of the microRNA in these cells corresponded with high levels of the protein and with tumor cell proliferation. Restoring the microRNA to normal slows the growth of those cells and greatly stunts the growth of tumors when the cells are transplanted into an animal model.

Forced expression of MIR128 in a glioma cell line slowed the cells' growth by 40 percent. In another experiment, tumor cells low in the microRNA grew in culture until they formed large spheres containing thousands of glioma cells. Tumor cells with normal MIR128 expression, on the other hand, grew poorly, forming spheres only one-fifth their size.

Published in the Nov. 15, 2008, issue of the journal Cancer Research.

THE RESEARCHER

SEAN LAWLER, PhD
Research assistant professor of Neurological Surgery

OF NOTE

Recent Recognitions of OSUCCC-James Physicians and Researchers

COLON CANCER

FAMILY MATTERS

Researchers encourage genetic tests of all colon-cancer patients

One in 35 people with colon cancer carry a hereditary form of the disease, according to a study led by OSUCCC researchers. Based on the finding, the researchers recommend screening all colon-cancer patients for Lynch syndrome, the most common inherited form of colon cancer.

The studies involved 1,566 colon-cancer patients who were tested for mutations in one of the four genes responsible for the condition. Lynch syndrome gene mutations were found in 44 patients, each of whom had an average of three family members who also had inherited one of the mutations but had not yet developed cancer. In addition, about half the patients were over age 50, and a quarter lacked a family history of the disease.

"People with a Lynch syndrome gene mutation have an almost 100 percent lifetime risk of cancer," says study leader **ALBERT DE LA CHAPELLE, MD, PhD,** professor of Molecular Virology, Immunology and Medical Genetics. "We recommend that all newly diagnosed colorectal cancer patients be routinely screened for Lynch syndrome."

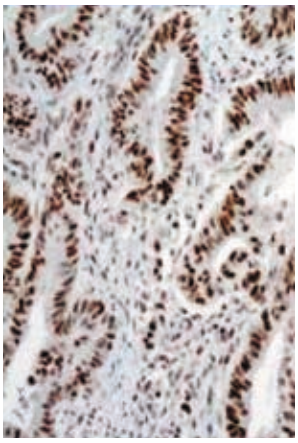
People who inherit a Lynch syndrome mutation have a high risk for colon and uterine cancer, and an increased risk for several other cancers, de la Chapelle says. First-degree relatives of those affected have a 50 percent chance of carrying the same mutation.

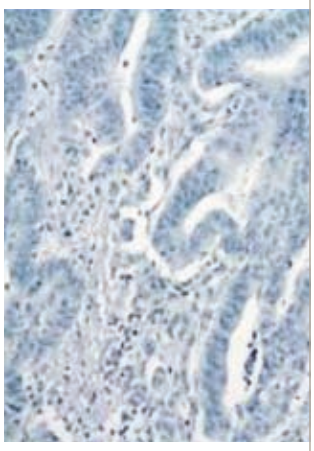
"We were surprised by the number of patients we identified with Lynch syndrome who were diagnosed over age 50 and who did not meet any of the accepted family history criteria," says first author **HEATHER HAMPEL,** a certified genetics counselor with Ohio State's clinical cancer genetics program.

"These cases would be missed altogether unless all newly diagnosed colon-cancer patients are screened for Lynch syndrome," she says. People with Lynch syndrome-related colon cancer generally have a better prognosis, and new research suggests that they often respond better to certain therapies, she notes.

People with Lynch syndrome mutations need closer cancer surveillance, with annual colonoscopies starting at age 25, de la Chapelle says.

Published in the Dec. 10, 2008, issue of the Journal of Clinical Oncology.





Immunohistochemical staining reveals the presence or absence of the DNA repair proteins related to Lynch syndrome. The dark brown stain in a tumor sample (left) shows that the protein is present and the underlying gene is normal. Lack of the stain (right) means the protein is missing and the gene may be mutated.

AWARDS AND RECOGNITIONS

PATRICK L. GREEN, PhD, *co-leader of the OSUCCC Viral Oncology Program and professor of Veterinary Biosciences and of Molecular Virology, Immunology and Medical Genetics, received a* **Distinguished Scholar Award,** *one of Ohio State University's highest recognitions of scholarly excellence. The award includes a $20,000 research grant and a $3,000 honorarium from the Office of Research.*

ROBERT TAYLOR, MD, *medical and fellowship program director for Pain and Palliative Medicine at the James Cancer Hospital and Solove Research Institute, has received the* **annual Friend of Hospice Award** *from the Ohio Hospice & Palliative Care Organization, Ohio Home Care Organization.*

NOTABLE NUMBER

The OSUCCC–James achieved a record level of clinical trial activity in 2008, enrolling **1,025** *patients into therapeutic cancer clinical trials—a* **45 percent** *increase over 2007.*

GRANTS, FACULTY AND PROGRAMS

CARLO M. CROCE, MD, *professor and chair of the Department of Molecular Virology, Immunology and Medical Genetics, director of the Human Cancer Genetics Program and a member of the OSUCCC's Molecular Biology and Cancer Genetics Program, received a* **$2.64 million NCI grant** *for a study of "MicroRNAs as Targets for the Treatment of Hepatocellular Carcinoma."*

SUSAN MALLERY, DDS, PhD, *of the OSUCCC Molecular Carcinogenesis and Chemoprevention Program received a* **$1.52 million NCI grant** *for a project called Chemoprevention of Head and Neck Cancer Using Controlled Release Polymers. This project entails formulating and evaluating selected chemopreventive compounds delivered from biodegradable, locally injectable, controlled-release polymers using a murine model of head and neck squamous cell carcinoma.*

TATIANA OBERYSZYN, PhD, *associate professor of Pathology and a member of the OSUCCC's Molecular Carcinogenesis and Chemoprevention Program, received a*

TIME OF REVIVAL

Dismissed leukemia drug helps CLL patients

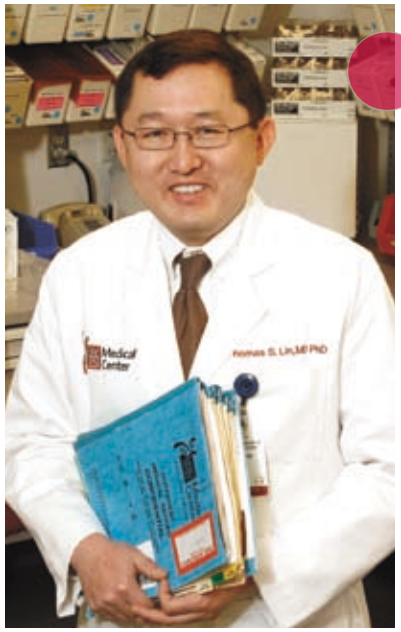
THE RESEARCH

This study was one of five abstracts selected by the American Society of Hematology to be featured during the joint symposium with the American Society of Clinical Oncology.

A drug once dismissed as ineffective in patients with chronic lymphocytic leukemia (CLL) has shown promising results in two phase I and II clinical trials, according to researchers at The Ohio State University Comprehensive Cancer Center–James Cancer Hospital and Solove Research Institute.

Together, the trials involved 116 patients with advanced CLL who were treated with the drug flavopiridol (alvocidib). Responses were seen in approximately half of patients, many of whom had chromosomal abnormalities that made it unlikely they would be helped by standard therapies.

"Ohio State's success has reinvigorated interest in flavopiridol at the National Cancer Institute and other cancer centers," says **THOMAS LIN, MD, PhD,** a medical oncologist and researcher in the OSUCCC Experimental Therapeutics Program.



THE RESEARCHER

THOMAS LIN, MD, PhD
Medical oncologist and researcher

In the 1980s, animal tests showed flavopiridol to be a potent anti-cancer agent. But in repeated trials using a continuous prolonged infusion, the drug proved ineffective and was essentially forgotten. Ohio State researchers later discovered that flavopiridol binds to proteins in human blood, leaving an ineffective level of free drug in the bloodstream.

"To compensate for this, we devised a new dosing schedule that has increased the drug's anti-tumor activity," says **MICHAEL GREVER, MD,** chairman of the department of Internal Medicine and co-leader of the OSUCCC Experimental Therapeutics program.

"Flavopiridol has bridged the way for several CLL patients to receive a curative stem cell transplant," says **JOHN BYRD, MD,** associate director of Translational Research and principal investigator of the phase II trial.

Ohio State is now participating in a multi-center flavopiridol trial to see if other cancer centers have similar results with the drug. Ohio State researchers are also studying flavopiridol in patients with acute myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma and head and neck cancers.

Presented during the 50th Annual Meeting of the American Society of Hematology (ASH).

GRANTS, FACULTY AND PROGRAMS

NOTABLE NUMBER

The OSUCCC Microarray Shared Resource analyzed over **12,000** *samples last year, almost* **7,000** *for miRNA,* **1,500** *for global gene expression and the rest for sample integrity.*

$1.5 million NCI grant *for a study titled "Importance of Gender in the Chemoprevention of Ultraviolet-Induced Skin Cancer."*

DEHUA PEI, PhD, *professor of Chemistry–Biological Chemistry and a member of the OSUCCC Molecular Carcinogenesis and Chemoprevention Program, received a* **$1.29 million NCI grant** *for a study titled "Substrate Profiling of Protein Tyrosine Phosphatases."*

CHANG-HYUK KWON, PhD, *has joined the cancer program as an* **assistant professor in the Department of Neurological Surgery and a member of the OSUCCC.** *His research is focused on searching for therapeutic clues for glioblastoma, the most frequent and aggressive of brain tumors, by using mouse genetic models and cancer stem cell cultures. Kwon came to OSU from the University of Texas Southwestern Medical Center, where he was an instructor of developmental biology.*

THEODOROS N. TEKNOS, MD, *has joined the cancer program as* **director of the Division of Head and Neck Oncologic Surgery, and as the David E. and Carole H. Schuller Chair in Head and Neck Oncologic Surgery.** *His research interests include angiogenesis, refinements in microvascular reconstructive surgery, development of novel therapeutics for disease treatment, identification of serum and tissue tumor markers and overcoming chemoresistance. Teknos came to Ohio State from the University of Michigan, along with three of the top researchers in his program.*

RITU SALANI, MD, MBA, *has joined the cancer program as an* **assistant professor in the Division of**

MELANOMA

DYNAMIC DUO

Two drugs kill resistant melanoma cells

THE RESEARCHER

GREGORY LESINSKI, PhD
OSUCCC Innate Immunity Program

Combining interferon-alpha (IFN-α) with the drug bortezomib causes melanoma cells to self-destruct by apoptosis, according to an animal and laboratory study by OSUCCC researchers.

The drug combination also significantly increased survival in a mouse-tumor model and cut the growth of transplanted human tumors by half in a second model. The study marks the first time the two drugs have been used together for this disease.

The combination even killed melanoma cells that had high levels of BCL2 and MCL1, two survival proteins that block programmed cell death. The findings led to a phase I clinical trial that is now under way.

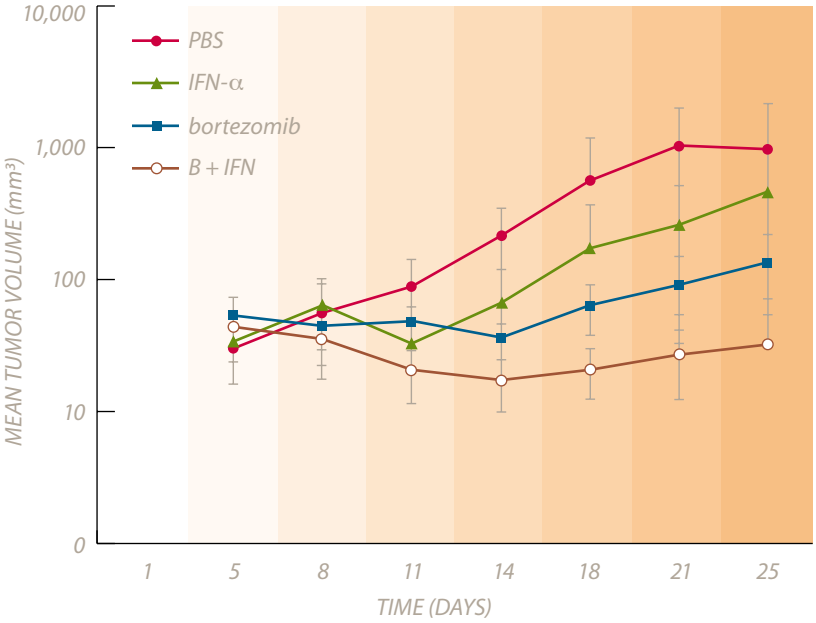
"Advanced melanoma is highly resistant to most chemotherapy drugs, so it is particularly important to investigate new combination therapies for this disease," says principal investigator **WILLIAM E. CARSON, III, MD,** a surgical oncologist, melanoma specialist and leader of the OSUCCC Innate Immunity Program. "Our preclinical data indicates that the anti-tumor effects of this combination are better than either agent alone, and we observed no significant side effects, suggesting that this may be a good treatment strategy for melanoma and possibly other cancers."

"We found that the two drugs synergistically activate complementary cell-death pathways and overcome the usual mechanisms that make melanoma cells resistant to standard therapies," says first author **GREGORY LESINSKI, PhD,** assistant professor of Internal Medicine and a researcher in the Innate Immunity Program.

Published in the Oct. 15, 2008, issue of the journal Cancer Research.

Gynecologic Oncology. *Her clinical interests include minimally invasive surgical techniques, and radical pelvic and abdominal surgery. Her research interests include advanced ovarian cancer, and healthcare quality and outcomes analysis. Salani comes to Ohio State from Johns Hopkins University.*

QIANBEN WANG, PhD, *has joined the cancer program as an* **assistant professor in the Department of Molecular and Cellular Biochemistry.** *His research focuses on how a male steroid hormone controls gene activity in prostate cancer. Wang came to Ohio State from Harvard's Dana-Farber Cancer Institute.*



Bortezomib plus interferon-alpha (IFN-α) inhibits the growth of human melanoma xenografts in athymic mice. Mice were treated with phosphate buffered saline (PBS), IFN-α, bortezomib or both agents combined. Mice treated with both agents had the lowest tumor volume (mm³).

FIGHTING THE RESISTANCE

Study shows how breast cancer cells resist tamoxifen

A study by OSUCCC researchers helps explain why 30 percent of patients taking tamoxifen do not respond or become resistant to the drug. The study found that abnormally high expression of microRNA-221 (MIR221) and microRNA-222 (MIR222) contribute significantly to this problem. The researchers note that the two microRNAs may be potential markers of tamoxifen-resistant tumors.

"If a marker of this kind were available, physicians could identify patients with tamoxifen-resistant tumors and treat them from the beginning with a more effective drug," says co-author **SAMSON T. JACOB, PhD,** professor of Molecular and Cellular Biochemistry and of Hematogy-Oncology and co-leader of the OSUCCC Experimental Therapeutics Program.

"Further study of these deregulated microRNAs could also broaden our understanding of tamoxifen resistance and aid in the design of new therapeutic agents for these patients," says principal investigator **SARMILA MAJUMDER, PhD,** research assistant professor of Molecular and Cellular Biochemistry.

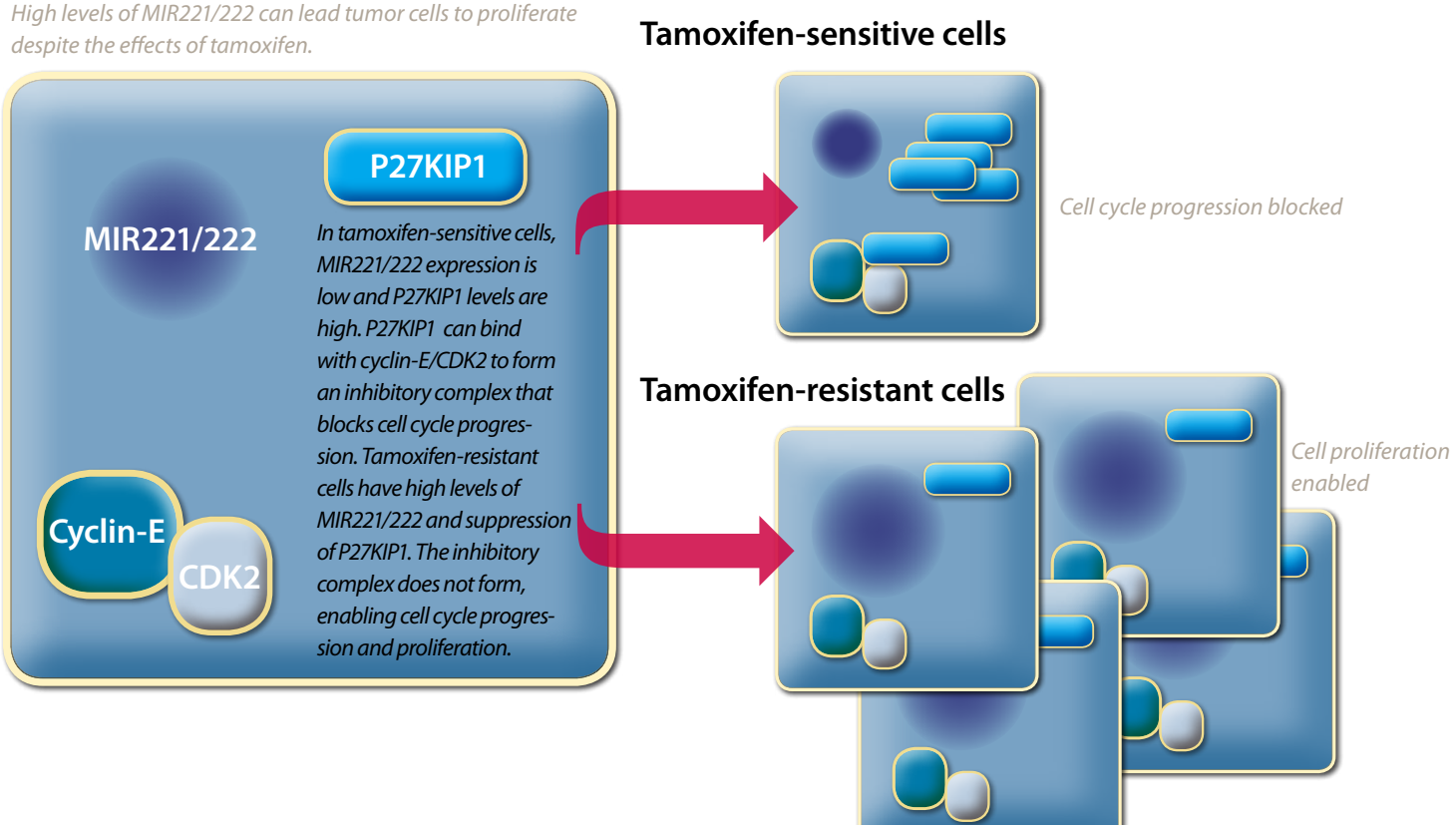
Majumder, Jacob and their colleagues compared microRNA levels in tamoxifen-resistant and tamoxifen-sensitive breast cancer cells. The cancer cells represented estrogen-receptor positive, postmenopausal breast cancer. Eight microRNAs showed unusually high expression levels in the resistant cells, with MIR221 and MIR222 having the highest levels.

It was already known that the two microRNAs regulate levels of P27KIP1 in the cell. And, as expected, the tamoxifen-resistant cells had high levels of MIR221 and MIR222 and low levels of P27KIP1. When the researchers boosted the amount of the P27KIP1 in the drug-resistant cells, many of the cells then died when exposed to tamoxifen, indicating an increase in drug sensitivity and providing strong evidence that high levels of the two molecules contribute to tamoxifen resistance.

Published in the Oct. 31, 2008, issue of the Journal of Biological Chemistry.

THE miR, CRACK'D

High levels of MIR221/222 can lead tumor cells to proliferate despite the effects of tamoxifen.



LEUKEMIA

RULING CLASS

WHO publishes new leukemia classifications

Ohio State University leukemia researcher **CLARA D. BLOOMFIELD, MD,** is among a small group of cancer clinicians who helped revise the World Health Organization's classification of leukemias and lymphomas.

The recently published *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* includes the use of molecular and genetic markers in leukemia cells to determine patient prognosis and treatment to a much greater degree than the previous classification.

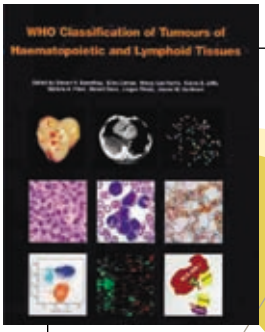
Bloomfield, an internationally renowned acute-leukemia specialist at The Ohio State University Comprehensive Cancer Center, chaired the clinical advisory committee for the section on myeloid tumors. She was one of only a few clinicians among the 130 authors from 22 countries who were invited to help write the new guide.

"The new acute myeloid leukemia (AML) classification is much more heavily based on chromosomal and molecular findings in patients' leukemia cells," says Bloomfield, who has led research that has identified many key cytogenetic and molecular markers in AML. "Over two-thirds of AML cases are now diagnosed based on genetic findings, as compared with about one-third of cases before this."

This change has important clinical significance, she says. "It enables us to identify patients who require different therapies for cure or improved survival and to categorize patients who can be treated using molecularly targeted therapies."

THE RESEARCHER

CLARA D. BLOOMFIELD, MD
Distinguished University Professor and the William G. Pace III Professor in Cancer Research



HIGHLIGHTS OF THE NEW EDITION

AML is now divided into six major subgroups—previously there were five. The new classifications are much more heavily based on genetic findings.

1. AML with recurrent genetic abnormalities

This largest subgroup, which represents about 55 percent of adult AML cases, is now divided into seven subtypes, rather than the previous four. In addition, there are two provisional subtypes identified solely using molecular markers, "AML with a mutated *NPM1* gene," and "AML with a mutated *CEBPA* gene."

2. AML with myelodysplasia-related changes (acute leukemia with ≥ 20 percent blasts in blood or marrow)

3. Therapy-related myeloid neoplasms

4. AML not otherwise specified (AML cases not fulfilling criteria for inclusion in the three prior AML groups)

5. Myeloid sarcoma (a tumor mass consisting of myeloid blasts occurring at a site other than bone marrow)

6. Down Syndrome-related myeloid proliferations

Separated as a distinct subgroup for the first time

GREGORY OTTERSON, MD
Medical oncologist and lung cancer specialist

MIGUEL VILLALONA, MD
Specialist in lung cancer therapy and drug development

where there's

NO smoke

A greater proportion of lung cancer patients are never-smokers. It's a different disease and may require different therapy.

BY BOB HECKER
PHOTOGRAPH BY ROMAN SAPECKI

If 85 to 90 percent of lung cancer cases in the United States are linked to smoking tobacco, what's behind the 10 to 15 percent of cases involving people who never smoked?

Medical scientists aren't sure, but what they do know is that lung cancer in never-smokers is a biologically distinct disease from lung cancer in smokers, and one that sometimes can be treated differently with therapy targeting specific gene mutations.

"In the past decade, researchers have begun studying subtle biological differences in the lung tumors of smokers and of those who have never smoked," says Gregory Otterson, MD, a medical oncologist and lung cancer specialist at The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute (OSUCCC-James). Otterson says carcinogens in cigarette smoke cause gene mutations that are often different from those found in lung tumors of people who have never smoked.

Miguel Villalona, MD, a lung cancer specialist and an expert in drug development at the OSUCCC-James, expects smoking-related lung cancer to remain a difficult disease to treat because tobacco carcinogens cause multiple gene alterations that are hard to target. Scientists have validated two mutations that drive lung tumors in never-smokers, he notes, and an effective frontline treatment is available that targets one of those mutations, although patients eventually relapse.

Some never-smoking patients have neither of the two validated mutations, and a rare few have both, Villalona says, and other mutations may still be found in these tumors. But he believes that ultimately lung cancer in never-smokers will prove easier to treat with targeted therapy because it involves fewer mutations than smoking-related lung cancer.

ONE IN FIVE WOMEN AND **ONE IN 12** MEN DIAGNOSED WITH LUNG CANCER ARE NEVER-SMOKERS, ACCORDING TO DATA FROM THE LUNG CANCER ALLIANCE.

HISTORICAL PERSPECTIVE

Lung cancer is the leading cause of cancer death among both men and women in the United States. The National Cancer Institute (NCI) expected 215,000 new cases and nearly 162,000 deaths from this disease in 2008. The Lung Cancer Alliance (LCA), a national nonprofit organization dedicated to patient support and advocacy, says the disease kills an average of 439 people a day, or one in three cancer deaths overall. But it wasn't always this way.

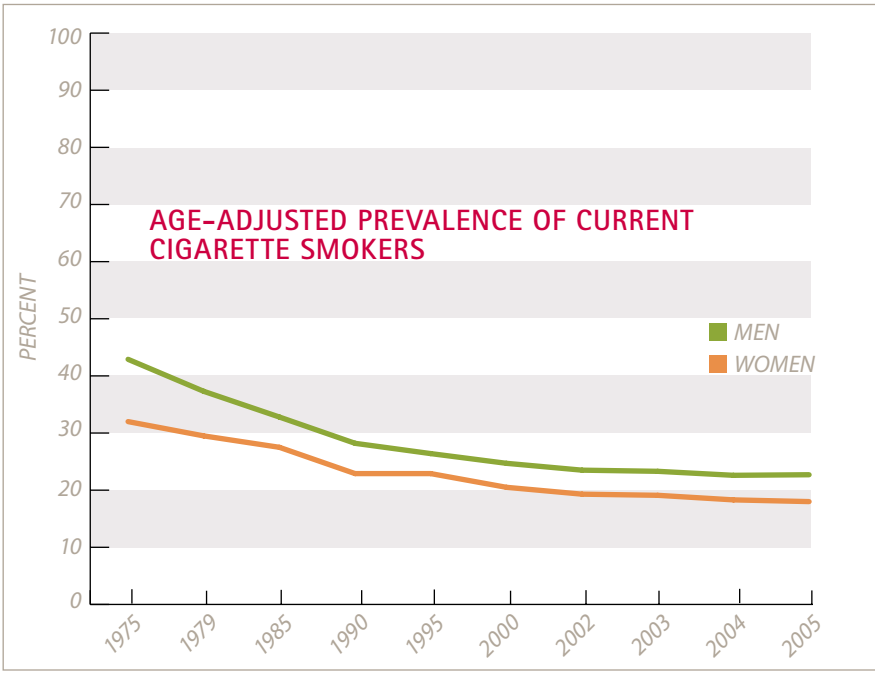
Some 150 years ago, lung cancer was extremely uncommon. For example, it represented only 1 percent of all cancers seen at autopsy at the Institute of Pathology at the University of Dresden in Germany. By 1918, the percentage had risen to almost 10 percent and by 1927 to more than 14 percent.

The growing incidence coincided with a rise in the number of smokers stemming from the mass production of cigarettes beginning in the 1880s. Decades can pass before smokers develop lung cancer, so it wasn't until the 1930s that physicians began noticing a sizable increase in cases.

Not only has lung cancer in smokers evolved into the top cancer killer, but a consumer health report by Harvard Medical School states that if lung cancer in never-smokers alone were classified as a separate disease, it would still rank among the top 10 most lethal cancers.

AN INCREASING PROPORTION

Thanks to highly effective national smoking-cessation efforts, Villalona says, only about 23 percent of American men and 18 percent of women smoke today, compared with an estimated 52 percent of men and 34



percent of women in 1965. Because of this drop in smoking prevalence, a higher percentage of the lung cancer cases seen by physicians today are unrelated to smoking, Villalona says. According to the LCA, more than 60 percent of new cases involve never-smokers or former smokers, many of whom quit decades ago.

Furthermore, non-smoking lung cancer disproportionately affects women. Figures from LCA indicate that one in five women diagnosed with lung cancer are never-smokers compared with only one in 12 men.

"The factors that produce this cancer are not clear," Villalona says. "We don't know, for example, whether a virus or something in the environment is responsible."

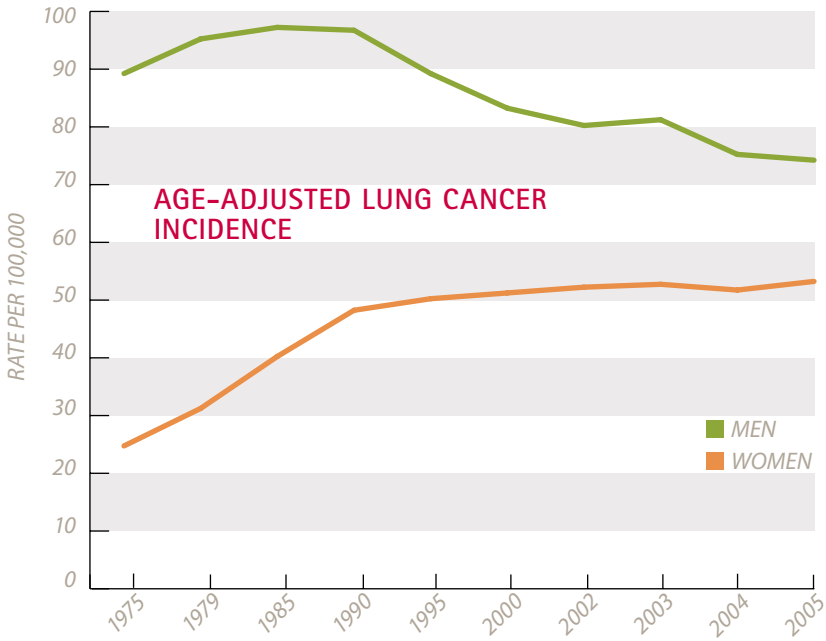
Risk factors for lung cancer other than smoking that are listed by the NCI include exposure to radon gas from rocks and soil, asbestos in homes and buildings, secondhand tobacco smoke, and environmental hazards such as nickel, chromium, arsenic, soot, tar and smog. Age and heredity also may be factors.

Whatever the origin, Otterson says exploring the mechanisms of never-smoking lung cancer is essential. "Our studies of this disease suggest that the proper way to think of lung cancer is not in terms of smoking versus non-smoking forms, but according to the particular molecular and gene defects present in tumor cells. These should define the therapy."

BIOLOGICAL DIFFERENCES

Lung cancer is broadly classed as either non-small-cell (NSCLC), which constitutes some 80 percent of all cases, and small cell.

NSCLC grows and spreads more slowly and has three subtypes: adenocarcinoma, which starts in the interior lining of the lungs and is the most common of all lung cancers; squamous cell carcinoma, which begins in respiratory tract passages; and large cell carcinoma, characterized



YOU WIN SOME...

While the prevalence of smoking has decreased dramatically over the past three decades, the trends in incidences of lung cancer have not been as positive. In 1975, nearly 43 percent of males and 32 percent of females were cigarette smokers. Those numbers dropped to nearly 23 percent for males and 17 percent for females in 2005. During that same time period, 1975 to 2005, the rate of lung cancer incidence in males went from 89 per 100,000 to 74 per 100,000. The incidence of lung cancer in females during that same time period has doubled, increasing from approximately 25 per 100,000 to just over 50 per 100,000.

SOURCES: LEFT, CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL CENTER FOR HEALTH STATISTICS, NATIONAL HEALTH INTERVIEW SURVEY; RIGHT, SURVEILLANCE, EPIDEMIOLOGY, AND ENDS RESULTS (SEER)-9, SURVEILLANCE RESEARCH PROGRAM, NATIONAL CANCER INSTITUTE

by cells that appear large and abnormal under the microscope.

Small-cell lung cancer more quickly reproduces and spreads than NSCLC, and, according to the LCA, it is almost always caused by smoking or secondhand smoke.

Lung cancer in never-smokers is largely adenocarcinoma, Otterson says, whereas lung cancers most associated with smoking are (in order) small cell, squamous cell, large cell and adenocarcinoma. Among all lung cancer cases combined, he says, adenocarcinomas account for about 40 percent, followed by squamous cell at 30 to 35 percent, small cell at 15 percent and large cell at 5 to 10 percent.

Weiqiang Zhao, MD, PhD, co-director of the Pathology Core Facility at Ohio State, leads a team that performs mutation analyses of lung-cancer patients. He has collected data showing that adenocarcinoma occurs in 70 percent of never-smoking lung cancer versus 47 percent of former smoker cases and 40 percent of current smoker lung cancer cases.

Why adenocarcinoma is so common among nonsmoking lung cancers remains unknown.

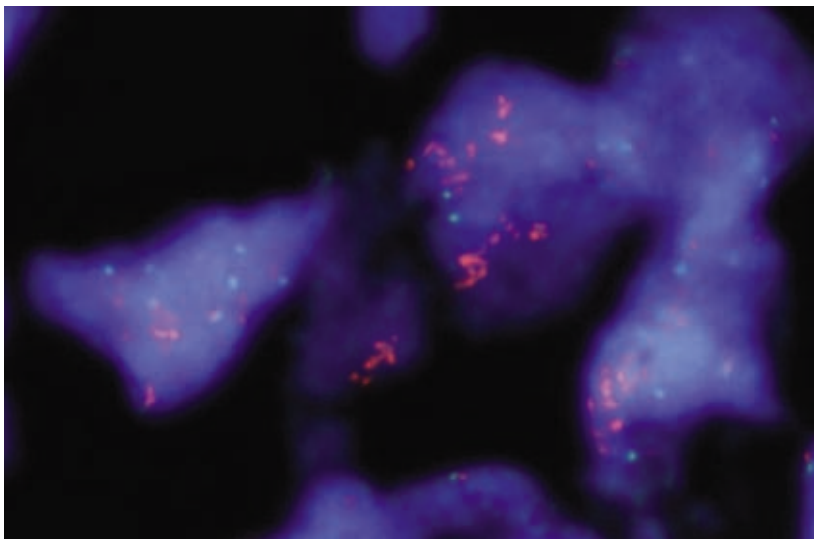
RESEARCH REVELATIONS

"We have been fascinated to find that a good proportion of tumors in never-smokers is driven by alterations in the epidermal growth factor receptor (EGFR)," Villalona says. Mutations in this gene are found in 20 to 30 percent of never-smoker lung cancer. "This is important because it can be targeted by therapy."

When epidermal growth factor (EGF) binds with EGFR, a receptor tyrosine kinase, it activates a signaling pathway that causes cells to grow and multiply. In some lung cancers, EGFR is present either in abnormally high quantities (i.e., it is amplified) or the receptor tyrosine kinase site is extremely sensitive to EGF stimulation (i.e., the gene is mutated), causing excessive cell division. Drugs called tyrosine kinase inhibitors (TKIs), such as erlotinib, are designed to block EGFR tyrosine kinase activation and thwart this aberrant cell division.

Villalona is principal investigator at Ohio State for a national Cancer and Leukemia Group B (CALGB) clinical trial of erlotinib administered with or without standard chemotherapy for never or previous light-smoker (less than 10 lifetime packs) lung cancer patients. "TKIs cannot cure these tumors, but they can produce dramatic long-lasting responses by shrinking them in a good number of these patients," Villalona explains. "Resistance eventually develops, but even with the first generation of these agents, we are seeing improvements in the survival time of many patients."

Zhao and his team in the Pathology Core Facility—accredited by both Clinical Laboratory



This fluorescent in situ hybridization (FISH) shows the EGFR *gene (red dots) is numerous or amplified with fewer* CEP17 *(green—reference for the chromosome 17, to which* EGFR *genes belong). The cell nuclei are stained blue.*

Improvement Amendments and the College of American Pathology—analyze lung tumors for *EGFR* mutations. He notes that patients with *EGFR*-mutant tumors are more likely to be never-smokers and that two types of *EGFR* mutations are often seen in NSCLC. One, an activating mutation in exons 19 and 21, causes high tyrosine kinase activity and cancer cell proliferation. The other is a mutation in exon 20 that is often found in relapsed patients.

"The exon 19 and 21 mutations enable cancer cells to survive and proliferate in an independent manner even without the presence of EGF because of the intrinsic tyrosine kinase activity of the mutant EGFR," Zhao says. "When we inhibit the kinase with small molecule drugs, it triggers apoptosis. Hence, tyrosine kinases have become popular targets for drug development."

The exon 20 mutation, he says, often emerges following the use of TKIs. It changes the structure of the TKI-EGFR binding site to prevent effective TKI interaction, causing patients to relapse. Zhao's team is working to understand mechanisms of TKI drug resistance.

A second mechanism of TKI resistance involves amplification of *c-MET*, a tyrosine kinase receptor that is activated by hepatocyte growth factor (HGF). "The binding of HGF to c-MET activates downstream signaling pathways that regulate cancer cell growth, angiogenesis, invasion and metastasis," Zhao says.

He describes a recent study involving a lung cancer cell line that developed TKI resistance as a result of *c-MET* amplification. Inhibiting c-MET signaling in these cells restored their sensitivity to the drug. "The status of the *c-MET* gene can be checked by fluorescent in situ hybridization (FISH) or real-time polymerase chain reaction (PCR) techniques," Zhao says. "Our laboratory has developed a FISH probe that will soon be placed into clinical practice."

Another gene alteration that has been validated as a tumor driver in never-smoking lung tumors is a mutated *KRAS*. "These mutations once were thought to occur only in lung cancer patients who smoke, but they also occur in about 15 percent of patients who never smoked," Villalona says. "Lung tumors with *KRAS* mutations tend to be resistant to EGFR TKIs, rendering the agents ineffective against this type of tumor.

"We have no targeted therapy for patients with *KRAS* mutations; we can offer them only standard chemotherapy," Villalona says. However, he is working with Roger Briesewitz, PhD, of the OSUCCC's Experimental Therapeutics Program, to develop a series of agents that targets KRAS.

"The challenge with *KRAS* is in finding ways to disrupt the protein-protein interactions that this mutated oncogene establishes," Briesewitz says. "Mutated *KRAS* provides a strong signaling pathway that gets 'stuck' in an 'on' position and leads to proliferation of cancer cells. We are trying to develop a drug that disrupts interactions between *KRAS* and the signaling proteins that bind to it."

Their idea, he explains, is to generalize the mechanism of two small natural molecules, FK206 and rapamycin, to thwart interactions between the *KRAS* oncogene and KRAS effector proteins, thus stopping cell proliferation and inducing cell death. Briesewitz and his lab are collaborating with Dehua Pei, PhD, professor of Chemistry at Ohio State, who synthesizes the molecules and does the initial testing. Pei's lab studies the catalytic mechanisms of enzymes and designs inhibitors as research tools and potential therapeutic agents.

Villalona is also the principal investigator for an Ohio State trial for never-smoker lung cancer patients with recurrent disease who receive oral applications of another TKI, sorafenib, as a second-line therapy that indirectly targets *KRAS* mutations.

FUTURE PROMISE

A clinical trial opened in spring 2009 to examine the effects of an oncovirus called reolysin, plus chemotherapy, in lung cancer patients with *EGFR* or *KRAS* mutations. The study holds promise, especially for patients with the *KRAS* mutation, Briesewitz says.

Other important treatment-related questions also remain, Zhao says. "For example, how do we treat patients who are non-smokers but have no activating mutations in *EGFR*, or patients who have neither or both the *EGFR* and *KRAS* mutations? What about patients who have relapsed and for whom TKIs are no longer effective? To face these challenges, we hope that a large-scale, randomized clinical trial will help modernize our view of this disease."

Although much work remains, the investigators are excited about global progress in developing targeted cancer therapies.

"In the past decade there has been an explosion of targeted therapeutics based on our improved understanding of the molecular defects that give rise to cancer," Briesewitz says, noting the discovery of imatinib against chronic myelogenous leukemia and erlotinib against lung cancer. "Erlotinib is a breakthrough drug in lung cancer; patients with *EGFR* mutations often respond dramatically to it. My hope is that many more imatinibs and erlotinibs will arise from our research to better understand the genetic defects that cause lung cancer."

The work of these investigators also has important implications for personalized health care. "The term 'lung cancer' is not meaningful unless we think of each case in terms of its molecular and genetic distinctions," Otterson says. "Only then can we best apply all of our resources for treating it."

RUN FOR YOUR LIFE

The family of Jack Roth, a never-smoker who died of lung cancer, turned their tragedy into a triumph for researchers with an annual fundraiser benefiting lung cancer research.

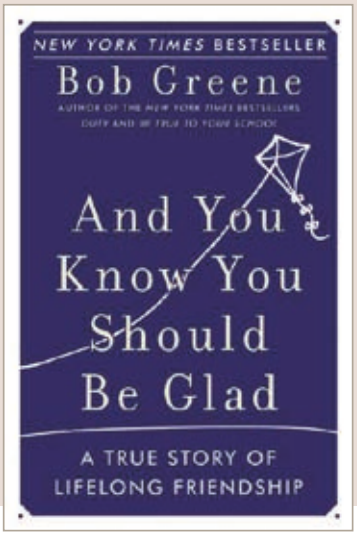
The diagnosis was a deadly surprise for Jack Roth and his family. Roth, 56, was a runner who had never been seriously ill and who routinely received six-month physical exams that confirmed his good health. What's more, he had never been a smoker.

And now—what?—his doctor said he had lung cancer?

"He was one of the healthiest people I knew," says his daughter, Maren Roth. "But he had been feeling a little run down and thought he might have a virus. He was trying to diagnose himself by doing research on the Internet. Eventually my mother found him unresponsive on the floor. He'd had a seizure from a brain tumor."

Tests showed that the tumor was a metastasis of stage four lung cancer. Doctors told Roth he probably had two years to live.

Roth, of Bexley, Ohio, survived for nine months. "He was sick for such a short time, but in that time he had so many friends and visitors around him," Maren says. "It was inspiring to see such amazing friendship."



Noted author Bob Greene, who had known Roth since kindergarten and graduated with him in the Bexley High School Class of 1964, was among Roth's many visitors. In 2006 Greene published a book titled *And You Know You Should Be Glad—A True Story of Lifelong Friendship*.

"Bob Greene's book was a fitting tribute to the kind of man my dad was—a kind, gentle, selfless person who was always helping others," Maren says.

Roth's death prompted his wife and daughter to take action by establishing the Jack Roth 5-K Rock N' Run/Walk, an annual fundraiser for lung cancer research at the OSUCCC.

To date, the event has raised $106,000, including $71,000 for the Jack Roth Memorial Fund at the OSUCCC-James and $35,000 to support research by James medical oncologist Miguel Villalona, MD, into genetic mechanisms of this disease.

The fourth annual Rock 'N Run/Walk will be Sunday, May 31, starting at 9 a.m. at Bexley High School. For information, visit the race Web site at *jackrothfund.org* or *premierraces.com*.

playing by miR

microRNA research is bringing new insights into cancer pathogenesis. Will it also lead to new strategies for treating cancer? The possibilities are excellent.

BY DARRELL E. WARD

PHOTOGRAPH BY ROMAN SAPECKI

It was 2001 and Carlo M. Croce and his colleagues had searched seven years for a tumor suppressor gene that they were convinced lay at 13q14. That genomic address locates a deletion in chromosome 13 that occurs in more than half of B-cell chronic lymphocytic leukemia (CLL) cases, about half of mantle cell lymphoma cases, 16 to 40 percent of multiple myeloma cases and 60 percent of prostate cancers.

"It is often the only chromosomal abnormality present in CLL, which strongly suggests it is the site of an important tumor suppressor gene," says Croce, MD, now a researcher at Ohio State University Comprehensive Cancer Center (OSUCCC) and director of OSU's Human Cancer Genetics program.

Laboratories around the world had looked too, and although eight new genes were identified in the region, there was no evidence linking any of them to cancer.

Most CLL patients have an indolent form of the disease and survive 10 to 20 years; the rest have aggressive disease that requires immediate therapy and can be fatal in three years, Croce says. Patients with the deletion tend to have the indolent form, but there was no way to know for certain which CLL an individual has at diagnosis.

Croce and his group were stymied in their hunt for the tumor suppressor gene, until autumn 2001 when the journal *Science* published three back-to-back papers showing that microRNA (miRNA)—a novel family of RNA molecules that arise from junk DNA and are far too small to code for a protein—is widely found in worms, flies and humans.

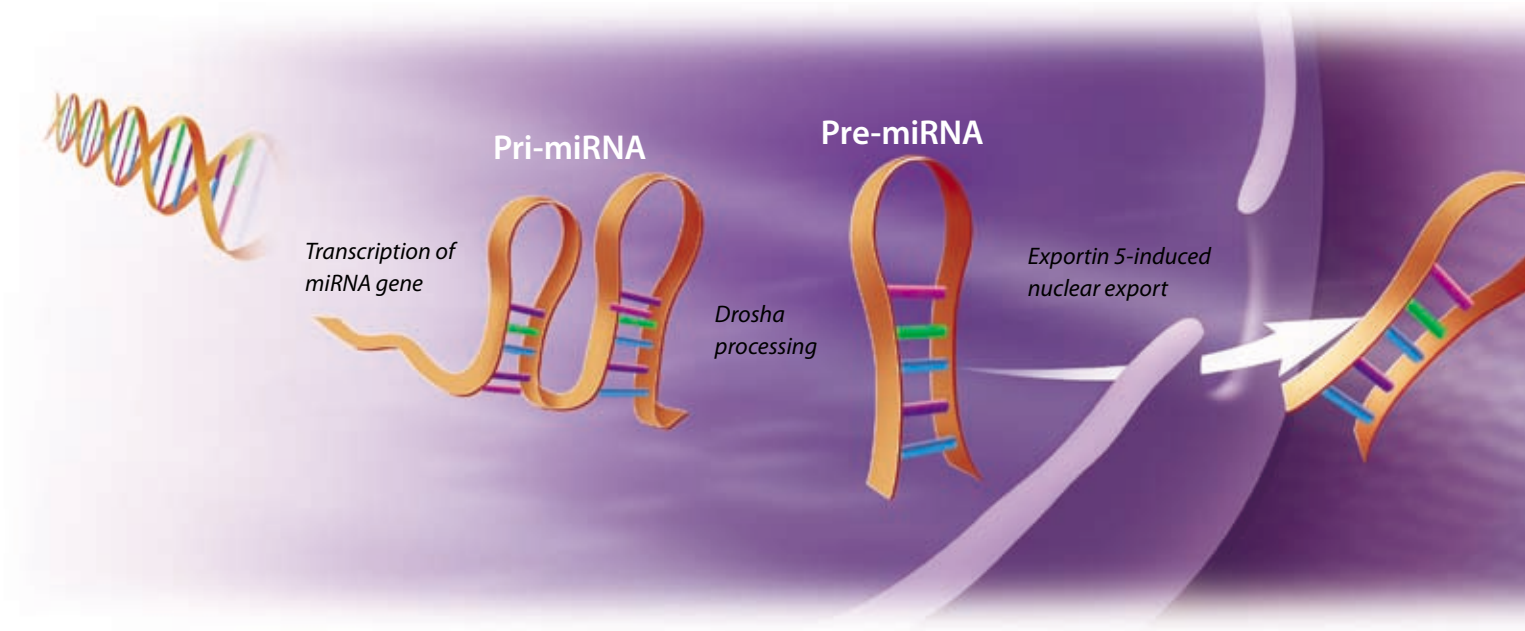
Croce and his colleagues quickly looked again at the region of the deletion, and in a fragment of that fragment they discovered genes for miRNA-15a (MIR15A) and miRNA-16-1 (MIR16-1). "We then looked at CLL cells from 60 patients and found that both these miRNA genes were lost in 68 percent of them," says Croce, who is also the John W. Wolfe Chair in Human Cancer Genetics.

The finding, published in the *Proceedings of the National Academy of Sciences* (PNAS) in 2002, was the first to link miRNA to cancer,

THE FIRST TIME miRNA WAS LINKED TO CANCER WAS IN A STUDY LED BY CROCE AND PUBLISHED IN THE *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES* IN 2002.

CARLO CROCE, MD

The John W. Wolfe Chair in Human Genetics, professor and chair of Molecular Virology, Immunology and Medical Genetics, director of OSU's Human Cancer Genetics Program



and it changed science's perception of the disease.

"Until then, we thought of cancer as a disease caused by alterations in protein-coding genes," he says. "But there were no protein-coding genes in this very small region that is deleted in CLL—only two miRNA genes. That gave us the first clue that miRNA could be involved in cancer."

miR POTENTIAL

Research by OSUCCC investigators and others has shown that miRNAs act as tumor suppressor genes and as oncogenes, with the same miR sometimes serving as a tumor suppressor in one tissue and as an oncogene in another.

"This is an exciting field because there is a good possibility we can use miRNAs or anti-miRNAs for therapy," Croce says. "Their small size means that they can be readily synthesized in the laboratory and taken up by cells."

MicroRNA research at Ohio State brings together basic and clinical investigators at the OSUCCC and the College of Medicine with investigators in Pharmacy, Veterinary Medicine and Chemistry.

Their studies include the molecular mechanisms and pathways involved in microRNA gene changes in cancer, the basic chemistry and biochemistry of miRNA molecules, and the pharmacology and formulation of miRNA agents for preclinical and pharmacologic studies of formulations of miRNA agents for preclinical and clinical studies of miRNA in diagnosis and cancer therapy.

CANCER LINKS GROW

Croce's 2002 study also showed that MIR15A and MIR16-1 are highly expressed in normal B cells, indicating their importance for maintaining cell health. In a genome-wide bioinformatics search for miRNA genes in 2004, Croce and his colleagues found that about half of the 186 human microRNA genes known at the time lay in regions frequently involved in cancer—fragile sites, break points, and areas that are often amplified or show loss of heterozygosity—further evidence of the molecules' pathogenic role.

The same year, Croce and his colleagues developed a microarray with 245 human and mouse precursor and mature miRNA probes. They used the array to discover that miRNA expression changes correlated with the gene changes that clinically predict CLL progression (e.g., *ZAP70* expression, 13q14 deletions), suggesting that miRNA expression patterns influence CLL biology and behavior.

In a *New England Journal of Medicine* paper in 2005, the researchers identified a signature of 13 miRNAs that reliably distinguished between indolent and aggressive CLL.

"If verified, this signature could determine whether a CLL patient needs very aggressive treatment or not."

Importantly, Croce adds, "for the first time, we found mutations in miRNA genes, both germline and somatic. The germline mutations could be involved in initiation."

They may also offer a new mechanism for cancer predisposition and an explanation for the 10 to 20 percent of familial CLL and other cancer cases for which no predisposing mutations have been found in protein-coding genes, he says.

The researchers found the mutations after sequencing 42 miRNA genes from 75 CLL patients. They identified five mutations in 11 of the patients. "This was fascinating because the mutations are not in the mature miRNA, which is only 21 to 22 nucleotides in length; they are in the precursor, and they probably alter how the precursor is processed."

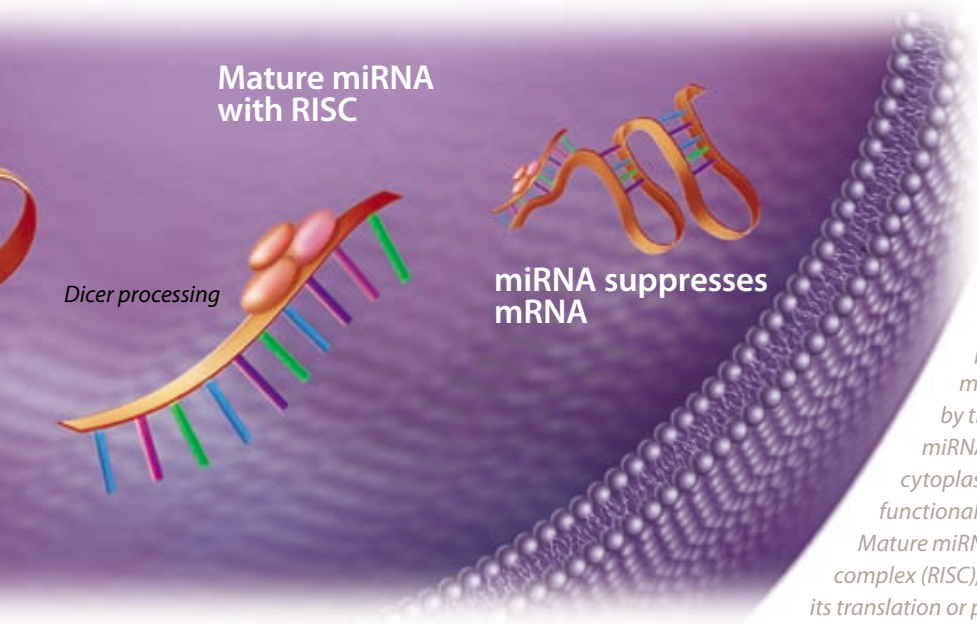


ILLUSTRATION BY THOMAS GRAVES

PRI- BEFORE PRE-

MiRNA is first expressed as a gene transcript called primary miRNA (pri-miRNA). These hairpin-loop molecules remain in the nucleus where they are cleaved by the Drosha complex to form double-stranded precursor miRNA (pre-miRNA). Pre-miRNA is transported to the cytoplasm where it is cleaved by the Dicer complex to form functional, mature miRNA that are about 22 nucleotides long. Mature miRNA first bind with the RNA interference silencing complex (RISC), then with the target messenger RNA (mRNA), blocking its translation or prompting its degradation.

Two patients had germline mutations located at the same site in *MIR15A* and *MIR16-1*. Cheek cells in the patients had both the normal gene and the abnormal gene, but their leukemia cells had only the abnormal gene. "That is a strong indication that these miRNAs are tumor suppressor genes, and that miRNA mutations may be a predisposing factor in CLL," Croce says.

In another 2005 study, Croce and his collaborators determined that MIR15A and MIR16-1 target *BCL2*, a gene that inhibits apoptosis. Low levels of the two miRs correspond to high levels of BCL2. "*BCL2* is over-expressed in most B-cell CLLs," Croce says, "so restoring these miRs may provide a way of treating CLL cases in which *BCL2* is over-expressed."

MIR29

MIR29 occurs in two gene clusters, one on chromosome 1, the other at chromosome 7q32. "We felt the 7q cluster to be particularly important because it is consistently lost in some acute myeloid leukemias," Croce says. *MIR29* is also lost in prostate cancer, lung cancer and a subset of breast cancers.

The cluster consists of three subtypes, *MIR29A*, *MIR29B* and *MIR29C*, which arise through different editing of the same pre-miRNA, he says.

Croce's lab and others had shown that the *MIR29* cluster is down-regulated in non-small-cell lung cancer (NSCLC). The miRs were predicted to target two key DNA methylation enzymes, DNA methyl transferase-3A and -3B, which are often over-expressed in lung cancer and associated with a poor prognosis.

A 2007 study led by Croce showed that expression of the two enzymes in cell lines and NSCLC tissues is inversely correlated with *MIR29* expression, and that the miRs directly target the two methylation enzymes, inhibit cell growth and induce apoptosis.

The researchers showed that forced expression of *MIR29A*, *MIR29B* and *MIR29C* leads to the re-expression of tumor suppressor genes such as *WWOX* and *FHIT* and triggers cell death by apoptosis in lung cancer cell lines, and reduces the size of engrafted tumors by 56 to 94 percent compared with controls.

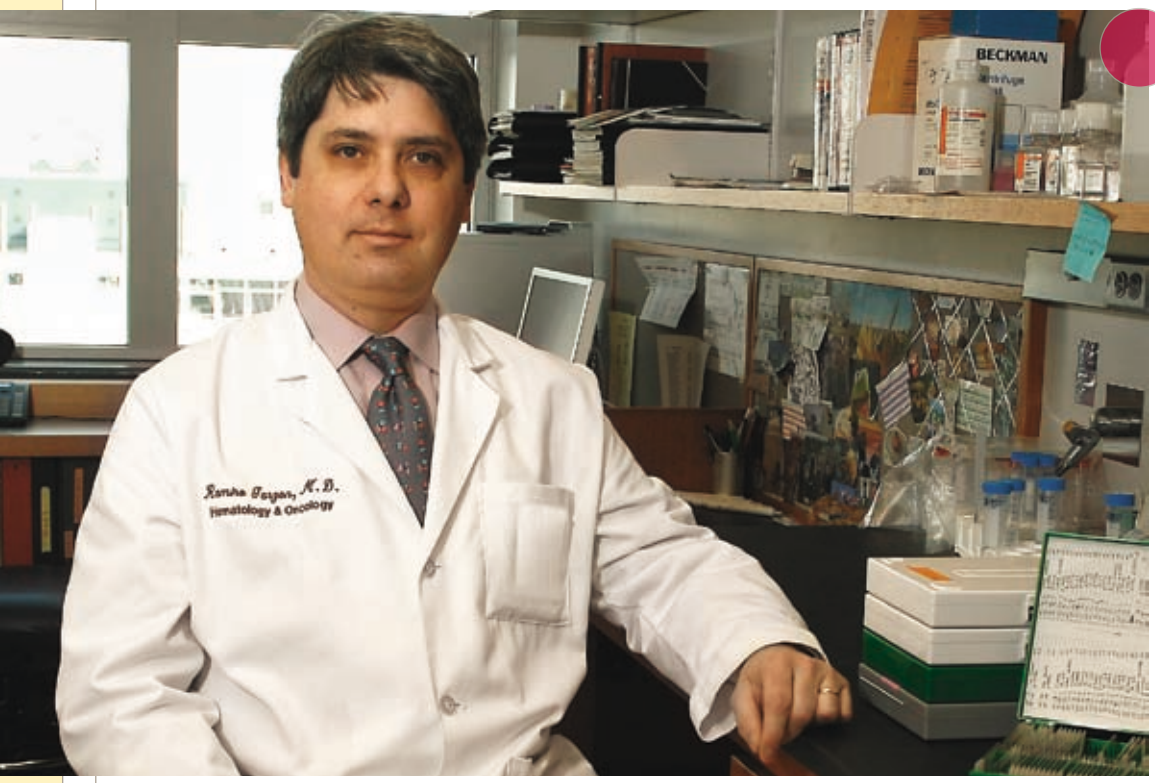
"This showed a new mechanism through which microRNA regulates gene expression," says Muller Fabbri, MD, a researcher in Croce's lab and first author of the *PNAS* paper. "It also showed how miRNA expression can have indirect anti-tumoral effects and why *MIR29* might offer a new therapy for cancer."

THE RESEARCHER

DENIS C. GUTTRIDGE, PhD
OSUCCC Molecular Biology and Cancer Genetics Program

MIR29 AND MUSCLE

One floor below Croce's lab in Ohio State's new Biomedical Research Tower is the laboratory of OSUCCC researcher Denis C.



THE RESEARCHER

RAMIRO GARZON, MD
Hematologist and Oncologist and OSUCCC researcher

Guttridge, PhD, who studies muscle-cell changes in cancer wasting and other diseases and the role of the transcription factor NF-κB in muscle cell differentiation.

Guttridge and his research fellow Huating Wang, PhD, in collaboration with Croce's laboratory, had shown that NF-κB works in conjunction with a protein called YY1 to epigenetically silence a set of muscle-specific genes.

Guttridge and Wang next learned that NF-κB, in conjunction with YY1, also epigenetically silences *MIR29* in immature muscle cells, and that *MIR29* promotes muscle cell differentiation.

"At that point Carlo and his lab joined us and took the study to a new level," Guttridge says. "We then asked if MIR29 functions as a tumor suppressor in muscle."

Guttridge turned to the nearby Research Institute at Nationwide Children's Hospital, which has the nation's only recognized rhabdomyosarcoma (RMS) tumor bank. The Ohio State investigators screened several RMS cell lines and ten RMS tumors and found that *MIR29B* expression was down by 90 percent or more in both compared with controls. When they forced the expression of *MIR29B* in an RMS cell line, cell growth slowed more than two-fold, and the cells began forming multinucleated myotubes.

"Our study indicated that *MIR29B* is a tumor suppressor in rhabdomyosarcoma, but that, in skeletal muscle, it functions by promoting differentiation rather than by causing cell death," Guttridge says.

"It also suggests that inhibiting NF-κB or intervening at the microRNA level might offer new therapeutic approaches for rhabdomyosarcoma."

AML

Early in 2009, OSUCCC investigators Guido Marcucci, MD, associate professor of Internal Medicine; Clara D. Bloomfield, MD, Distinguished University Professor; Croce and Ramiro Garzon, MD, assistant professor, reported findings showing that MIR29B not only targets DNA methyltrasferase-3a and -3b in AML, but also DNA methyltransferase 1 (*DNMT1*).

"We showed for the first time in leukemia cell lines and patient samples that over-expressing *MIR29B* decreases DNA methylation, re-expresses the tumor suppressor genes p15 and *ESR1* and induces blast-cell differentiation," Garzon says.

A second study explored how MIR29B functions as a tumor suppressor, showing that restoring *MIR29* expression causes apoptotic cell death. "We learned that MIR29B targets four major pathways that are affected in leukemia, those involved in apoptosis, cell death, proliferation and epigenetic silencing of tumor suppressor genes," Garzon says.

miRNA AS THERAPY

Studies of synthetic MIR29B and MIR16-1, and an anti-miRNA (or antagomir) as agents for the treatment of CLL, AML, NSCLC and hormone-resistant breast cancer are being done by a group of OSUCCC clinical and translational researchers, and drug development specialists.

"It's a challenge to deliver miRNAs into cells," says drug delivery specialist Robert J. Lee, PhD, associate professor of Pharmaceutics and a researcher in the OSUCCC Experimental Therapeutics Program. "We've developed nanoparticle formulations that seem to work, but it's too early to say that we've found the best delivery system."

Lee and his colleagues work closely with Ohio State's Nanotechnology Center to package synthetic MIR29B in nanoparticles that carry an antibody or ligand on their surface that targets tumor cells and

triggers their uptake by endocytosis (see illustration).

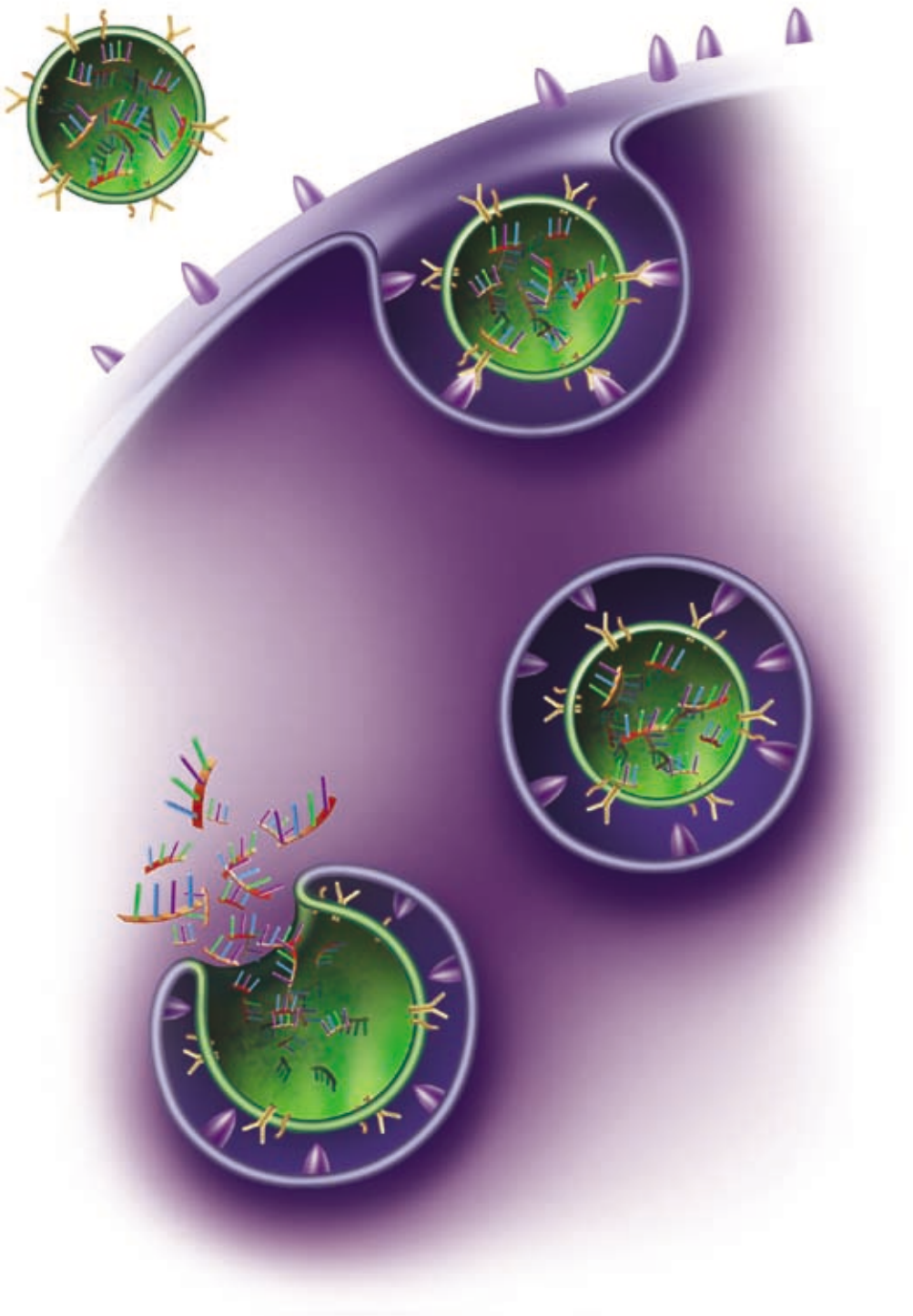
Pharmacokineticist Kenneth K. Chan, PhD, professor of Pharmaceutics and of Internal Medicine and a researcher in the OSUCCC Experimental Therapeutics Program, conducts pharmacokinetic studies of the prospective agents. He developed a method called hybridization-based fluorescent ELISA for measuring exogenous miRNAs in cell lysate and circulating blood at picomolar levels.

"Because miRNAs will likely be used in combination with other drugs or with other miRNAs, we have also developed methods that allow us to measure an individual miRNA in a mixture of several miRNAs," Chan says.

MiRNAs present fascinating questions. "MiRs seem part of a major puzzle that we are just starting to decipher," Fabbri says. "We still lack the whole picture of the miRNA pattern in a tumor. We don't know, for instance, if they interact with each other, or if they require certain conditions to interact with a target that are present in some tumors and not in others."

This could explain the cancer-specific differences in miRNA behavior, and why computationally and biostatistically predicted miRNA targets can be experimentally validated only part of the time, he notes.

Among the most important questions is whether miRNA agents offer safe, effective therapies. "We are doing studies now to learn if synthetic MIR29B can achieve therapeutic concentrations and effectively down-regulate target genes in animals," Garzon says. "Perhaps then we can begin human trials."



GOOD THINGS IN SMALL PACKAGES

OSUCCC investigator Robert J. Lee, who specializes in receptor-targeted drug delivery systems, is testing the use of nanoparticles to carry therapeutic MIR29B to acute myeloid leukemia (AML) cells. A lipid-polymer shell encloses the microRNA and displays CD33, a monoclonal antibody specific for AML cells. Binding of the antibody with the cell receptor triggers the endocytotic uptake of the particle and the intracellular release of the miRNA.

ILLUSTRATION BY THOMAS GRAVES

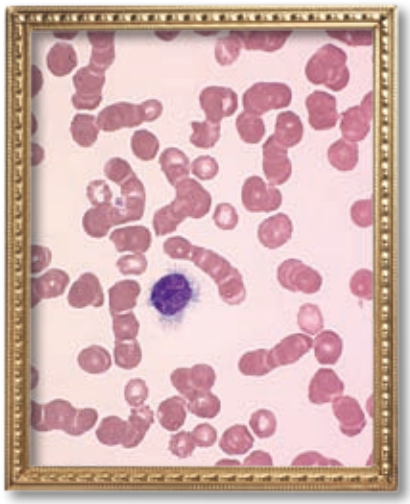
ERIC H. KRAUT, MD
Professor of Internal Medicine, hematologist-oncologist and researcher with the OSUCCC Experimental Therapeutics Program

BERTHA A. BOURONCLE, MD
Professor emeritus of Internal Medicine

MICHAEL R. GREVER, MD
Chair of Internal Medicine, hematologist-oncologist and co-leader of the OSUCCC Experimental Therapeutics Program

hairy cell godmother

Fifty years ago, Bertha A. Bouroncle, MD, published a landmark paper on hairy cell leukemia. A triumph of cancer research followed, but recurrence remains a problem for some.



BY DARRELL E. WARD

PHOTOGRAPH BY ROMAN SAPECKI

The year 2008 marked the 50th anniversary of the discovery by Ohio State hematologist Bertha A. Bouroncle, MD, of a relatively rare and formerly fatal form of leukemia.

In her landmark 1958 paper in the journal *Blood*, Bouroncle and coauthors Bruce K. Wiseman, MD, and Charles A. Doan, MD, two famous hematologists, called the disease leukemic reticuloendotheliosis because of the atypical cells then called reticulocytes in the blood and bone marrow.

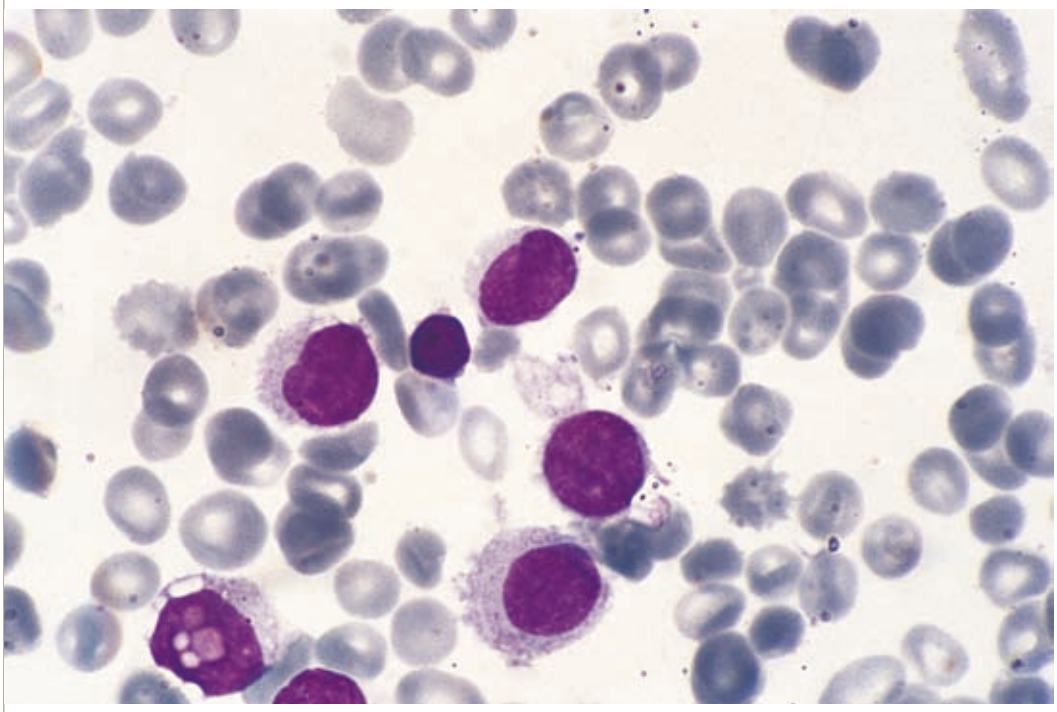
Then, probably in the mid-1960s, the ragged edge of the malignant cells, which display fine, hair-like projections under the phase contrast microscope, earned the disease the name hairy cell leukemia (HCL).

Bouroncle's report was a highly detailed description of 26 cases, the most in one place up to that time, that identified the condition as an independent hematologic and pathologic entity. "Dr. Bouroncle's paper represents a substantial accomplishment in the field of clinical research," wrote David Golden and Mark Weiss of Memorial Sloan-Kettering Cancer Center in a 2000 historical perspective on HCL.

The most common physical symptoms of the 26 adult patients, 21 of whom were male, were an enlarged spleen, followed by an enlarged liver and lymphadenopathy. Sixteen of the patients had died. After the onset of symptoms, their survival had ranged from less than one year in four patients, to nearly 16 years in one patient. Pneumonia or other infections and hemorrhage were often the cause of death.

"The paper was talked about across the country because it provided the first comprehensive description of the disease," says Michael R. Grever, MD, chair of Internal Medicine and co-leader of the Ohio State University Comprehensive Cancer Center (OSUCCC) Experimental Therapeutics Program. "Many hematologists and oncologists had seen one or two of these cases during their career, and this report helped them understand what it was."

CHARLES A. DOAN, THE FIFTH PRESIDENT OF THE AMERICAN SOCIETY OF HEMATOLOGY, BECAME DEAN OF OHIO STATE'S COLLEGE OF MEDICINE AND BUILT IT INTO A NATIONAL MEDICAL CENTER.



Hairy cell leukemia gets its name from the ragged edge of the malignant cells, which display fine, hair-like projections under a phase contrast microscope.

How to manage the disease and identifying the cell of origin became the subject of many meetings. Into the 1970s, the disease was linked to, or misdiagnosed as, acute leukemia and treated as such. "The standard chemotherapy of the day made patients worse," says Grever, who worked with Bouroncle, first as a hematology fellow then as a junior faculty member in the late 1970s.

Splenectomy was the only therapy for 25 years. "About 80 percent of HCL patients have enlargement of the spleen," Grever says. "Some became massive and involved the entire abdomen." Removing the spleen raised blood counts and eased symptoms for a time but did nothing to eliminate the malignant hairy cells from the blood or bone marrow.

Then, in the span of several years in the 1980s, three therapies for this disease emerged and remain the primary treatments for HCL today. Grever, working with Eric H. Kraut, MD, then also a junior Ohio State faculty member, largely developed one of the most important of those, the purine analogue deoxycoformycin, or pentostatin, as therapy for HCL.

The other drugs were interferon alpha (IFN-α) and a second purine analogue, 2-chlorodeoxyadenosine (2-CDA). These therapies have improved survival and have reduced splenectomy to a minor role in HCL management.

"This has been a remarkable success story," Grever says. "We've gone from a disease that wasn't treatable, other than removing the spleen, to now trying to determine how best to keep people in complete remission," Grever says. "We changed the natural history of this disease in our lifetime."

"Unfortunately, our success has led many to believe that HCL is no longer a problem, yet, 40 percent of patients still experience recurrence," Grever says. "It's like taking the ball down to the five-yard line and not trying to score the touchdown."

Hardly ready to quit, Grever is rallying the team.

TREATMENTS EMERGE

About 500 cases of HCL are diagnosed yearly in the U.S., accounting for about 2 percent of all leukemias. In 1974, evidence emerged that it was a B cell malignancy, and diagnosis improved with identification of characteristic surface markers, including CD25, the interleukin-2 receptor.

The first treatment breakthrough for the disease came with a January 1984 paper in the *New England Journal of Medicine* showing that IFN-α improved the blood counts in about 80 percent of the patients studied. However, only about 10 percent of patients enter complete remission with interferon and, if the therapy is discontinued, patients relapse.

"Nothing had been effective until then, except removing the spleen, which helped only for a while, so this paper was of great interest and Dr. Bouroncle was very excited about it," Grever recalls.

In the early 1970s, research showed that loss of the enzyme adenosine deaminase (ADA) caused severe combined immunodeficiency syndrome in children. Research also linked the lymphopenia associated with the condition to the intracellular accumulation of deoxyadenosine triphosphate (dATP), which caused the cells to die by apoptosis. This knowledge gave rise to the idea that a drug that inhibited ADA might kill malignant cells in patients with lymphoid malignancies, although there was a real concern that such an agent might also lead to overwhelming immune suppression.

Pentostatin was known to be a potent ADA inhibitor that was being tested in Europe in patients with acute leukemia. Clinical trials, however, raised concerns that the drug was too toxic.

Grever began studying pentostatin in 1979, and showed two years later that the dose needed for acute leukemia exceeded the maximum

tolerated dose. He also showed that lower doses of the drug were well tolerated, and that they were sufficient to achieve complete remission in patients with chronic lymphocytic leukemia (CLL).

The drug proved unsuitable for acute leukemia patients because acute leukemia cells have high levels of ADA, requiring high doses of pentostatin, while chronic leukemia cells have low levels of the enzyme, permitting a safe and effective dose in CLL patients.

"When we treated patients with advanced CLL with pentostatin, we saw dramatic improvement," says Grever, who serves as the principal investigator for the phase I clinical trials program at Ohio State.

In about 1984, Kraut was contemplating how to help a patient with progressing hairy cell leukemia who had already had a splenectomy. He wondered if pentostatin might also help his patient. "I consulted with Mike and with the patient," he recalls. "We were concerned about the risk of immune suppression and infection, but we agreed that we should try it. We treated the man on a phase I study after securing approval from the National Cancer Institute, and he significantly improved."

In December 1984, a paper by A.S.D. Spiers and two co-authors appeared in the *Journal of Clinical Oncology* reporting the treatment of three HCL patients with pentostatin, two of whom had advanced, untreated disease.

That paper reported "prompt clearance of hairy cells from the blood, regression of splenomegaly and lymphadenopathy … ." Side effects were tolerable, and both patients achieved complete remission and remained in remission at nine and six months. The third patient was undergoing treatment, with disappearance of splenomegaly and clearance of hairy cells from the blood at 10 weeks.

MICHAEL. R. GREVER, MD

"Now, 25 years after we started the initial trial, most of our patients are still alive…a disease that was deadly for some within three or four years of diagnosis was now often treatable."

"That increased our enthusiasm for our trial," Grever says.

"Not only did my original patient have a good response, but we saw good responses, without severe problems in many other patients," Kraut says. The success of that study led to a phase II trial of the drug in HCL, with Grever, Kraut and Bouroncle collaborating on the study.

When Kraut presented the outcomes of their first eight patients at the Central Society for Clinical Research meeting in Chicago in November 1985, a few found the results too good to believe. In particular, those who favored interferon therapy questioned whether such dramatic results were possible.

"We continued adding patients to our study, and other groups started looking at the drug, and lo and behold, we found that our early results were genuine," he says.

The Ohio State group then reported the outcomes of 10 patients in the November 1986 issue of *Blood*, noting that nine had achieved complete remission. "Low-dose deoxycoformycin administered intravenously every other week represents an extremely effective therapy for hairy cell leukemia," they concluded.

"Now, 25 years after we started the initial trial, most of our patients are still alive," Kraut says. He still sees several of those original patients in clinic.

"This led to this amazing advance, in which a disease that was deadly for some within three or four years of diagnosis was now often treatable."

A THIRD THERAPY EMERGES

The third therapy for HCL was described in an April 1990 issue of the *New England Journal of Medicine*. The paper presented a study showing lasting remissions in 12 HCL patients treated with a new drug, 2-chlorodeoxyadenosine (2-CDA).

"We came to the conclusion that both pentostatin and 2-CDA are highly effective for treating HCL, and that the long-term follow-up is almost identical," Grever says.

In 1999, a recombinant immunotoxin was developed at the National Cancer Institute (NCI) and tested in a phase I trial in a group of patients with hematologic malignancies. Four HCL patients included in the group responded to the therapy, with one experiencing complete remission and

MEN ARE **FOUR TO FIVE** TIMES MORE LIKELY TO DEVELOP HAIRY CELL LEUKEMIA THAN WOMEN.

the other three showing a 98 to 99.9 percent reduction in malignant circulating cells. The patients had lived with the disease for 12 to 17 years and were resistant to 2-CDA, IFN-α and, in one case, pentostatin.

The immunotoxin targets the interleukin-2 receptor, also known as CD25, on the malignant cells. Of the patients in the trial, four had HCL. The study, published in *Blood*, concluded that LMB-2 "may be an effective new therapy for patients with chemotherapy resistant CD25+ HCL."

The agent, which remains in phase II testing, was developed by Robert J. Kreitman, MD, who today is a senior NCI researcher and head of the Clinical Immunotherapy Section, and who received his medical degree at Ohio State.

HCL CONSORTIUM

The 2008 American Society of Hematology (ASH) conference recognized the 50th anniversary of Bouroncle's original *Blood* paper, and Grever and a group of colleagues used the occasion to rally interest in new research on HCL.

"Too many people seem to feel that this disease is no longer a problem," he says, noting that only three abstracts had been submitted to the 2007 ASH conference by people doing research on the disease.

"Yet, 35 to 40 percent of people still relapse," he says. "Those who get HCL at age 70 will probably lead a relatively normal life span, but someone who is 40 may not. We can't simply forget about those patients."

Grever organized a symposium for the 2008 ASH meeting that brought together HCL experts from across the country and from Italy and Great Britain. With the backing of the Rockefeller Foundation, they organized an international consortium for HCL, with representatives from the United States, United Kingdom, Canada, Germany, Italy and Sweden (see *www.hairycell.org*).

An initial goal of the consortium is to identify HCL experts in the U.S., Canada and Europe for patients seeking a second opinion about, for example, when treatment should begin, Grever says.

"We are collectively working on guidelines that help us decide when therapy is indicated and about what therapy to use," he says, "but telling patients that we can watch their disease for a while may make them want a second opinion."

Patients with infections and who need therapy raise additional questions. "We would prefer not to treat people with an active infection, but we can," Grever says.

Combination therapy for HCL is also being studied. "Rituximab is being used in conjunction with 2-CDA or pentostatin, and we think that might be useful," Grever says, "but it needs careful study." Some centers give the two drugs in series, while others use them together.

"No one knows which is more effective," Grever notes. Several clinical trials under way at Ohio State and other centers hope to find the answer.

Other questions include the significance of residual disease. "If we look carefully at the marrow, the majority of patients show signs of residual leukemia. It just stays quiet for years and years.

"We tend to think that those patients will be in that 40 percent who relapse," he says, "but should we wait until they relapse to resume therapy, or would it be better to treat them with rituximab, for example?"

Research on HCL at the molecular level is also needed, he notes, to learn why hairy cells are much more sensitive to these drugs than CLL cells. "This might reveal ways to make CLL more responsive to therapy," Grever says.

Kraut's involvement in the development of pentostatin for HCL impressed upon him the importance of drug development research and fate and timing in life. "I tell the story of HCL to patients who come to me with a disease that is not yet curable or treatable as an example of how things can change pretty quickly, and how miracles can happen," he says.

"The development of pentostatin at Ohio State is an example of the right people being in the right place at the right time. Because Bertha was here, we had enough HCL patients for a clinical trial. Mike Grever had the expertise with pentostatin, and he championed the drug. And I was fortunate to have the patient and the thought at the time to try the drug. It was an example of a tremendous partnership."

"The story of progress in hairy cell leukemia at Ohio State emphasizes something that the people at this university do very well," Grever says. "We work hard to improve therapy for people.

"Ohio State is committed to high quality clinical and translational research, and it has a large patient base. This gives us opportunities to make real breakthroughs."

NEED TO KNOW

Resources for Professional Development

FUNDRAISERS

LIFE CYCLE

Pelotonia, August 28 to 30, 2009, brings Lance Armstrong to Columbus

PELOTONIA

Pelotonia is a new weekend cycling event that promises to raise millions of dollars for cancer research at Ohio State University's Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute. Pelotonia will be held August 28 to 30, with riders choosing one of three options, a 50-mile, 100-mile or 190-mile ride, all of which begin in Columbus. More than 2,000 cyclists—including cycling legend and cancer survivor Lance Armstrong—as well as 1,000 volunteers and other participants, will enjoy a positive three-day experience while raising funds critical to extending cancer research.

The event was established by NetJets, which in March 2008 announced plans to expand its operations in central Ohio and made a $12.5 million gift to establish a unique annual cycling event. The name, Pelotonia, is based on the French word for a pack of riders in a cycling race who benefit from working together as a group. All future proceeds from this event will fund cancer research at the OSUCCC-James.

Pelotonia will attract serious riders, along with emotionally committed neighbors, friends and spectators, for an ambitious weekend of cycling, entertainment and volunteerism to benefit cancer research.

To ride, volunteer or donate, visit www.pelotonia.org.

FOLLOW THE LEADERS

Activities & Appointments of OSUCCC-James Physicians and Researchers

JOHN C. BYRD, MD, *a hematologist and oncologist, OSUCCC associate director for Translational Research and co-leader of the Innate Immunity Program, has been named* **chair of the grants selection committee for the American Society of Clinical Oncology (ASCO).** *In this role, Byrd oversees the criteria the committee chooses to use for candidate applications, funding and administration of awards. The committee reviews applications for the Young Investigator Award and the Clinical Research Career Development Award to determine which applicants are most qualified.*

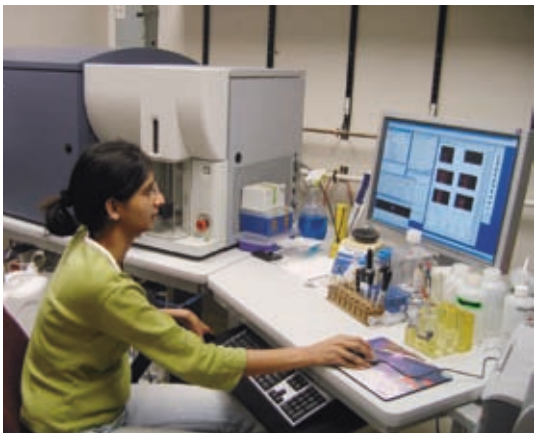
MICHAEL A. CALIGIURI, MD, *director of Ohio State's Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute, accepted an invitation to serve as the* **Baldini Visiting Professor at the Beth Israel Deaconess Medical Center,** *a teaching hospital of Harvard Medical School in Boston. In addition to lecturing at Hematology/Oncology Grand Rounds and at Medical Grand Rounds, he met with selected members of Harvard faculty and reviewed cases with fellows. His lecture topics involved his research on a vaccine to*

NOTABLE NUMBER

The Clinical Treatment Unit in The James has supported **66** *protocols and treated more than* **900** *patients since it opened Jan. 19, 2004.*

ANALYZE THIS

Flow cytometry capabilities expanded



The addition of new instrumentation has expanded the capabilities and capacity of the Analytical Cytometry Shared Resource (ACSR) for OSUCCC-James investigators. The ACSR, one of the cancer center's 17 shared services, provides cell sorting and analysis of cell populations based on selective cell marker expression.

"The new equipment gives us more capacity and a higher-level, more sophisticated analysis for those who need it. It can run more types of analysis per sample," says ACSR Director **JEFFREY CHALMERS, PhD.** "The new equipment is also easier to run and more reliable."

The new i-Cyt Reflection cell sorter and analyzer is supported by the ACSR in conjunction with the College of Veterinary Medicine, where it is housed. It serves more than 60 separate labs, with the majority run by OSUCCC members.

The new instrument is most commonly used for cell sorting and flow cytometry analysis such as multicolor immunophenotyping, analysis of rare populations and functional assays such as proliferation, apoptosis and cell cycle. It is also the only infectious flow sorter on campus. It is housed in an instrument-specific safety hood and is contained within a secure room for safe sorting and analysis of infectious material up to BSL-2 level.

The Flow Cytometry Core Lab was recently upgraded with a FACSAria II cell sorter. It also has a Leica Confocal Scanning Microscope, a BD FACSCalibur multipurpose flow cytometer, a BD LSR II benchtop flow cytometer and a FACSVantage cell sorter.

The BD FACSAria II is the latest fluorescence based cell sorter. In addition to advanced electronics and fiber optic, diode lasers, it has the potential to sort based on at least 10 different colors.

ACTIVITIES AND APPOINTMENTS

NOTABLE NUMBER

More than **800** *OSU cancer researchers attended the 11th OSUCCC Annual Scientific Meeting at the Columbus Convention Center in February. Investigators exchanged information, viewed more than* **220** *posters, and listened to guest speakers address this year's theme, transdisciplinary approaches to understanding cancer health disparities.*

E. ANTONIO CHIOCCA, MD, PhD, *chair of the Department of Neurological Surgery at Ohio State and co-leader of the Viral Oncology Program at the OSU Comprehensive Cancer Center, was elected to the* **board of directors of the Society for Neuro-Oncology.** *With 1,100 members worldwide, the Society focuses on advancing neuro-oncology through multidisciplinary education and research. Chiocca will represent the neurosurgical subspecialty during bimonthly teleconferences. Chiocca and his research team investigate the use of biologic therapies and gene-delivery methods to treat brain tumors and other central nervous system disorders. Chiocca, who holds the Dardinger Family Endowed Chair in Oncological Neurosurgery, recently received a $5.5 million grant over five years from the National Institutes of Health to develop a more potent oncolytic virus for treating brain cancer.*

HEATHER HAMPEL, MS, CGC, *clinical associate director of the Division of Human Genetics at Ohio State's Medical Center and a cancer genetic counselor at Ohio State's James Cancer Hospital and Solove Research Institute, has been elected* **president of the American Board of Genetic Counseling.** *Hampel provides genetic counseling for patients regarding hereditary cancer predisposition syndromes, including hereditary breast-ovarian cancer syndrome, Lynch syndrome (a hereditary predisposition to colorectal and endometrial cancers) and familial adenomatous polyposis. Hampel also coordinates research studies to identify cancer susceptibility genes. The American Board of Genetic Counseling is the credentialing organization for the genetic counseling profession in North America, providing certification and recertification of qualified professionals. It also is responsible for the accreditation of graduate programs in genetic counseling. Hampel also represents The James on the National Comprehensive Cancer Network's Genetic/Familial High-Risk Assessment Panel.*

MICHAEL D. LAIRMORE, DVM, PHD, *professor and chair of Veterinary Biosciences, associate director for Basic Research at the OSUCCC-James and a researcher with the OSUCCC Viral Oncology Program, has been elected* **vice president and president-elect of the American College of Veterinary Pathologists,** *which has more than 1,500 members in 17 countries. Lairmore will be responsible for helping implement the organization's strategic plan. At Ohio State, Lairmore is the associate director for Basic Sciences at the Comprehensive Cancer Center and holds a joint appointment in microbiology and immunology. His clinical research includes veterinary medicine, retrovirology and pathobiology. Lairmore has contributed to more than 150 peer-reviewed publications, is an associate editor for* Retrovirology, *and*

calendar of events

REGIONAL NEURO–ONCOLOGY CONFERENCE

September 8 to 10, 2009

Organized by E. Antonio Chiocca, MD, PhD, co-leader of the OSUCCC Viral Oncology Program.

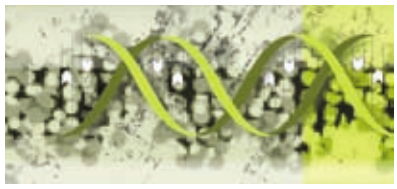
For more information or registration details, contact Nancy Jones at 614-293-3688 or nancy.jones@osumc.edu.

IACRLRD SYMPOSIUM XXIV

October 14 to 16, 2009

The OSUCCC will host the International Association for Comparative Research on Leukemia and Related Diseases (IACRLRD) Symposium XXIV: Molecular Approaches to Leukemia in the 21st Century: Biology, Outcome Prediction and Personalized Therapy from October 14 to 16. Clara D. Bloomfield, MD, a Distinguished University Professor who also serves as cancer scholar and senior adviser to the OSUCCC-James Cancer Hospital and Solove Research Institute, is current president of the IACRLRD. The symposium will feature a distinguished group of internationally renowned presenters and brings together physicians, veterinarians and scientists worldwide. An additional mini-symposium on "Comparative Animal Models of Leukemia" will be held on October 14.

Online registration is available at www.osuccc.osu.edu/iacrlrd/registration.pdf.



REGIONAL EPIGENETICS CONFERENCE: EPIGENETICS AND microRNA IN CANCER

November 12 to 14, 2009

Organized by Carlo M. Croce, MD, director of OSU's Human Cancer Genetics program, and by Samson T. Jacob, PhD, co-director of the OSUCCC Experimental Therapeutics program.

For more information or registration details, contact Nancy Jones at 614-293-3688 or nancy.jones@osumc.edu.

an editorial board member for the journal Virology *and the* Journal of Virology.

ELECTRA PASKETT, PhD, *co-leader of the OSUCCC Cancer Control Program, has been elected* **president-elect of the American Society of Preventive Oncology (ASPO),** *which represents more than 50,000 health professionals and other members. Her two-year term begins in 2011. Paskett was also elected chair of ASPO's new Cancer Forum. The forum will focus on policy issues and work with other ASPO forums, sections and programs to integrate the association's varied cancer-related activities, as well as stimulate cancer prevention research and implement successful prevention strategies.*

STEVEN K. CLINTON, MD, PhD, *leader of the OSUCCC Molecular Carcinogenesis and Chemoprevention Program and director of prostate and genitourinary oncology, has been asked to join a* **national committee to update the Institute of Medicine's Dietary Reference Intakes for vitamin D and calcium.** *He is one of 13 researchers provisionally appointed to the committee, which will meet and prepare a report over the next two years. Clinton also co-directs Ohio State's Center for Advanced Functional Foods Research and Entrepreneurship.*

CLARA D. BLOOMFIELD, MD, *has accepted an invitation to serve as the* **American Society of Clinical Oncology representative on the Scientific Committee** *for the 2009 and 2010 Annual Meetings on Molecular Markers in Cancer. The meeting is co-sponsored by the European Organisation for Research and Treatment of Cancer, the National Cancer Institute and the American Society of Clinical Oncology. Committee members develop the content and structure of the meeting's educational and scientific program.*

PATRICK GREEN, *director of the Center for Retrovirus Research and co-leader of the Viral Oncology Program at the OSUCCC, has been elected as a* **fellow in the American Academy of Microbiology,** *the honorific leadership group within the American Society for Microbiology.*

JENNIFER CARLSON, *director of Government Relations at Ohio State's Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute, has been elected to the* **executive board of Ohio Partners for Cancer Control (OPCC),** *a statewide organization formed in 2000 to reduce the cancer burden in Ohio through a collaborative and comprehensive approach. Carlson's two-year term on the board will extend through 2010.*

OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER–
ARTHUR G. JAMES CANCER HOSPITAL AND
RICHARD J. SOLOVE RESEARCH INSTITUTE
300 W. 10th Avenue
Columbus, OH 43210-1240

OSU-026

NATIONAL RECOGNITION

AAAS ACCLAIM

OSUCCC scientists named fellows

Six members of Ohio State's Comprehensive Cancer Center (OSUCCC) were among 17 OSU faculty elected earlier this month as fellows of the American Association for the Advancement of Science (AAAS), the world's largest scientific organization.

Only one other institution surpassed Ohio State this year in the number of research faculty named as new fellows of the AAAS, a highly regarded recognition for researchers. OSU has been either first or second annually since 2002 in the number of faculty named to this honor and is believed to have the largest contingent of current fellows of any university in the nation. This year's election brings the number of AAAS fellows on the OSU campus to 159. The newly elected AAAS fellows from the OSUCCC, are **STEVEN CLINTON, MD, PhD,** leader of the OSUCCC Molecular Carcinogenesis and Chemoprevention Program; **TSONWIN HAI, PhD,** of the OSUCCC Molecular Biology and Cancer Genetics Program; **RANDALL HARRIS, MD, PhD,** of the OSUCCC Cancer Control Program; **REBECCA JACKSON, MD,** of the OSUCCC Cancer Control Program; and **JOHN F. SHERIDAN, DDS, PhD,** of the OSUCCC Cancer Control Program. Earlier this year, **LAWRENCE SCHLESINGER, PhD,** of the OSUCCC Innate Immunity Program, was elected as an AAAS fellow.

CREDENTIALS

JOINT APPROVAL

The James gains new three-year accreditation

Following a favorable five-day survey by members of the Joint Commission, Ohio State's James Cancer Hospital and Solove Research Institute has earned a new three-year accreditation as an outstanding medical institution.

In his summation to the hospital's executive staff, surveyor John Milazzo, MD, stated that the hospital had done very well and added that he was amazed by the quality of staff and processes in place at The James, as well as the care and dedication shown to patients.

During their visit, two surveyors and an engineer reviewed James facilities, processes, procedures, protocols, documentation and staff.

"This type of success is the result of teamwork, all of us working collectively toward shared patient-care quality and safety goals," says James CEO **MICHAEL CALIGIURI, MD,** who also directs Ohio State's Comprehensive Cancer Center.

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

HPV-RELATED CANCERS

Epidemiological and laboratory research has clearly shown that human papilloma virus (HPV) is a causative agent for a subset of head and neck squamous cell carcinomas (HNSCC). The risk factors for HPV-linked oral cancer are different from those for other HNSCCs, indicating that it is a separate disease entity. Ohio State cancer researchers are investigating effective ways to detect, prevent and treat HPV-associated HNSCC.