



The James

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

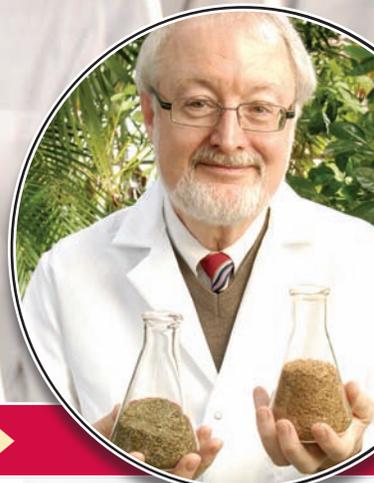
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frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

Shedding new Light

HPV and
Oropharyngeal Cancer



NCI
CCC

A Comprehensive Cancer
Center Designated by the
National Cancer Institute

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OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER—JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

UPFRONT

The Director's Perspective

Role Change

Providing an opportunity for leaders to experience life with cancer

Cancer still kills more than 560,000 Americans every year. Progress against this deadly disease is linked hand-in-glove with funding for cancer research. Higher funding levels are needed, and that requires the support of the public and of state and federal legislative leaders.

One of my initiatives as president of the American Association of Cancer Institutes is to promote an advocacy program called Project Cancer Education. Developed here at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James), this two-hour curriculum offers legislative and opinion leaders an opportunity to experience life as

a cancer patient or caregiver. They also gain a greater understanding of translational research, the relationship between research and patient care, and the need for clinical trials access and additional cancer research funding. For information about Project Cancer Education, write to us at Frontiers@osumc.edu.

I am pleased to report that the OSUCCC-James leukemia program achieved distinction this summer when the National Cancer Institute (NCI) awarded a five-year, \$11.5 million Specialized Program of Research Excellence (SPORE) grant to principal investigator John C. Byrd, MD, and co-principal investigators Clara D. Bloomfield, MD, and Guido Marcucci, MD. This is only the second SPORE grant to be directed at leukemia research. This



MICHAEL A. CALIGIURI, MD
DIRECTOR,
COMPREHENSIVE
CANCER CENTER
CHIEF EXECUTIVE
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HOSPITAL AND SOLOVE
RESEARCH INSTITUTE
THE OHIO STATE
UNIVERSITY, JOHN L.
MARAKAS NATIONWIDE
INSURANCE ENTERPRISE
CHAIR IN CANCER
RESEARCH

issue of *Frontiers* as information about the outstanding research this grant supports.

This issue's cover story describes the work of Maura Gillison, MD, PhD, an OSUCCC-James researcher who has done much to establish the link between oral human papillomavirus and oropharyngeal cancer.

Finally, travel to a Borneo rainforest, then back to The Ohio State University laboratory of A. Douglas Kinghorn, PhD, DSc, to follow the discovery of a natural product that shows unique antileukemic activity.

We hope you enjoy reading this issue of *Frontiers* as much as we enjoy presenting the research it describes.

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

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Chief Executive Officer, James Cancer
Hospital and Solove Research Institute
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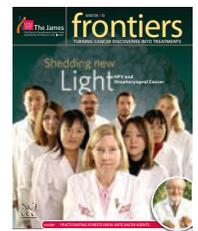
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ON THE COVER: MAURA GILLISON, MD, PhD, AND HER RESEARCH TEAM PHOTOGRAPHED BY ROMAN SAPECKI

Direct-To-Consumer Genomics

“What should I do now, doctor?”



By **AMY STURM, MS, CGC**
*Clinical Assistant Professor
Division of Human Genetics
The Ohio State University Medical
Center*

It is difficult to watch television these days without seeing advertisements for pharmaceuticals. Recently, companies began marketing another type of healthcare product directly to consumers: genetic testing.

In the healthcare setting, genetic testing—the analysis of DNA to detect genetic alterations—is a valuable tool for disease diagnosis, estimating disease risk and predicting the response to certain therapies.

Direct-to-consumer (DTC) marketing of genetic testing involves two separate but related issues. The first is DTC marketing of genetic tests such as those for the *BRCA1* and *BRCA2* cancer susceptibility

genes associated with the hereditary breast and ovarian cancer syndrome. Testing is ordered by a healthcare provider and results are provided back to the healthcare provider for provision to the patient. Previous DTC advertisements for breast and ovarian cancer genetic testing have increased demand for these tests, particularly among individuals with a relatively low risk of having a genetic mutation, many of whom are not appropriate candidates for testing.

The second issue is DTC marketing of a new wave of genetic tests that consumers can use at home. This type of testing is ordered by the consumer over the Internet, or by phone or mail. Results are returned directly to the consumer, and involvement of a healthcare provider is not required. As of May 2009, the Genetics and Public Policy Center identified at least 39 companies that offered such DTC testing for purposes ranging from

determining ancestry to predicting athletic performance, hair loss or susceptibility to diseases such as cancer or mental illness.

The direct marketing and availability of these products raises multiple concerns that intersect at the levels of the consumer, the medical community, legislators and for-profit companies. Unlike pharmaceutical advertisements that include long lists of potential risks and side effects, advertisements for genetic testing tend to overstate the benefits and fail to adequately address the risks and limitations.

Currently, most DTC genetic testing companies offer genome-wide scans for panels of single nucleotide polymorphisms, or SNPs. Most of these SNPs are weak predictors of risk, accounting for only a fraction of the overall heritability of a trait or disease (the relative risk conferred by most SNPs is less than 2).

Experts in genetics and other areas of medicine have raised



concerns regarding the clinical validity and utility of such testing. For example, does the test provide clinically significant information? Will the results affect medical decision-making? Does the test provide better information than simpler tests or the “gold standard” of family history?

As research improves our understanding of complex gene-gene and gene-environment interactions, risk level information will change and require updating. This may produce contradictory risk information over time that is likely to confuse consumers. However, proponents of DTC efforts contend that it may allow for greater consumer awareness and access to genetic tests, and allow consumers to take a more proactive role in their healthcare.

In 2008, the American College of Medical Genetics issued guidelines on DTC genetic testing and proposed the following minimum requirements:

- A knowledgeable professional should be involved in ordering and interpreting a genetic test;
- The consumer should be fully informed regarding what the test can and cannot say about his or her health;
- The scientific evidence on which a test is based should be clearly stated;
- The clinical testing laboratory must be accredited by the Clinical Laboratory Improvement Amendments (CLIA), the state or other applicable accrediting agencies;
- Privacy concerns must be addressed.

Currently, federal oversight of DTC genetic testing is limited, and no uniform or comprehensive system exists for assessing the validity of tests before they are made available to the public. According to a survey by the Genetics and Public Policy Center, 25 states and the District of Columbia permit DTC testing of different types without restriction, 13 states prohibit DTC testing, and 12 states permit only specified categories of tests and tend to exclude genetic tests.

What does all this mean for healthcare professionals? Physicians may find more of their patients requesting certain genetic tests and arriving at their office with genetic test results in hand—perhaps a 25-page report with complex findings

for multiple diseases. How does the busy healthcare provider manage these requests to order and interpret genetic tests?

Multiple resources are available for assistance, including healthcare professionals with specialized training in genetics and genetic counseling who can serve as “genomic consultants.”

To find a genetic counselor in your area, visit the National Society of Genetic Counselors Web site, www.nsgc.org; to locate a certified geneticist, visit the American Board of Medical Genetics Web site, www.abmg.org. Information for the public is also available. The Federal Trade Commission offers a fact sheet on genetic testing for consumers at its Web site, www.ftc.gov, and the National Institutes of Health is developing a Web site for the public about DTC marketed genetic tests.

Genetic testing, combined with appropriate risk assessment, informed consent, education and support, can be a powerful tool that provides essential information regarding health risks to patients and their families, and to the physicians who care for them.

Whether DTC genetic tests will prove helpful to consumers remains to be seen, but many of those who use them are likely to turn to their physicians for help in understanding them. ■

BREAKTHROUGH

The Frontiers of Cancer Research

LEUKEMIA

TRANSLATIONAL TEAMWORK

SPORE Grant Boosts Leukemia Research

The National Cancer Institute (NCI) has awarded The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute a five-year, \$11.5 million Specialized Program of Research Excellence (SPORE) grant to study and treat leukemia.

The SPORE grant represents a milestone for the leukemia program at Ohio State, which is only the second recipient of such an NCI grant directed at leukemia research. Titled “Experimental Therapeutics of Leukemia,” the grant focuses on translational research to improve the understanding of leukemia cause, risk stratification and therapy.

Principal investigator **JOHN BYRD, MD**, and co-principal investigators **CLARA D. BLOOMFIELD, MD**, and **GUIDO MARCUCCI, MD**, helped plan and apply for this award, which encompasses laboratory and clinical investigation in acute myeloid leukemia, acute lymphoid leukemia and chronic lymphocytic leukemia. The grant team includes several prominent senior investigators at Ohio State who have worked together for years to improve prognostic factors and treatments

for acute and chronic leukemias.

“This award will help a team of accomplished cancer researchers engage in bedside and laboratory translational research of adult leukemia with the goal of improving clinical outcomes for patients,” says Michael A. Caligiuri, MD, director of Ohio State’s Comprehensive Cancer Center and CEO of The James. The grant supports five research projects, each led by Ohio State cancer center researchers, including Byrd, Bloomfield, Caligiuri and Marcucci, along with Albert de la Chapelle, MD, PhD, William Blum, MD, Michael Grever, MD, and Robert Lee, PhD.

Accompanying these five projects are five cores that provide a SPORE leukemia tissue bank and services for biostatistics, biomedical informatics, medicinal chemistry and administration and operations. The grant also supports a career development program geared toward young women and minority researchers, and a developmental research program to recruit innovative pilot projects that, if successful, may later become part of the SPORE.



THE RESEARCHERS

JOHN BYRD, MD

professor of Internal Medicine, D. Warren Brown Designated Professorship in Leukemia Research and associate director for Translational Research



CLARA D. BLOOMFIELD, MD

Distinguished University Professor, Ohio State University Cancer Scholar and Senior Advisor and William Greenville Pace III Endowed Chair in Cancer Research



GUIDO MARCUCCI, MD

associate professor of Internal Medicine, Division of Hematology Oncology



▶ ORAL CANCER

ACCRUAL UNDER WAY

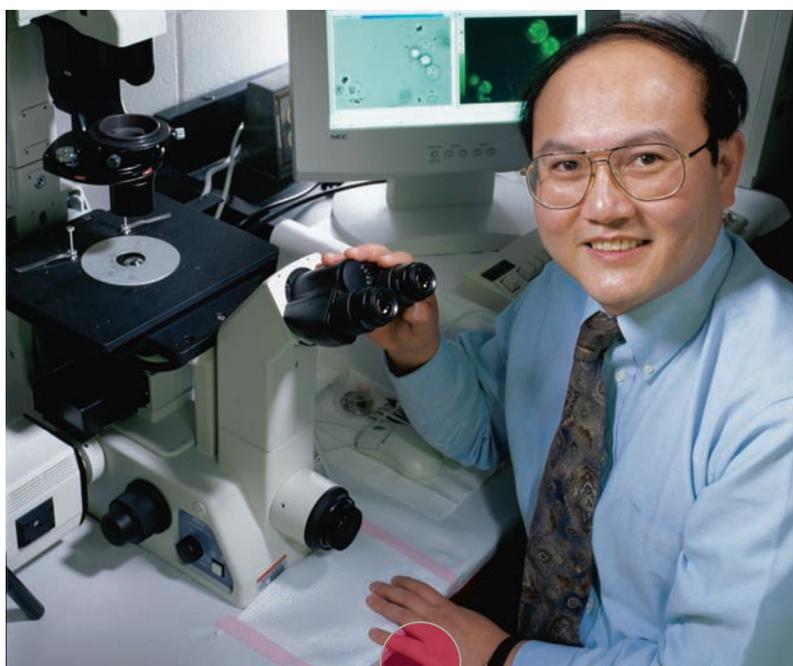
Ohio State Cancer Drug Begins Clinical Testing

A targeted, oral, anticancer drug developed by cancer researchers at The Ohio State University is being tested in a phase I clinical trial to assess its safety and early evidence of activity. The drug, AR-12, has inhibited solid tumors and lymphoma in animal studies.

Patients with advanced or recurrent breast, colon, lung or prostate cancers or lymphoma who have not responded to previous chemotherapy are eligible for the trial, says principal investigator **JAMES THOMAS, MD, PHD**, director of the Clinical Trials Office at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC-James). Ohio State is one of three sites accepting patients to this trial.

Michael A. Caligiuri, MD, director of the OSUCCC and CEO of The James, says Ohio State researchers worked almost a decade to refine this novel treatment mechanism. “This is a ground-breaking achievement for cancer research at Ohio State because it marks the first time a therapeutic drug developed by our scientists will be tested in cancer patients,” says Caligiuri.

OSUCCC-James researcher **CHING-SHIH CHEN, PHD**, worked with cancer and pharmacy colleagues at Ohio State to develop



the small-molecule agent, originally called OSU-03012. The agent is being developed as AR-12 by Arno Therapeutics, Inc., a clinical-stage biopharmaceutical company focused on oncology therapeutics.

“The new agent inhibits PDK-1 and PI3k/Akt pathways, a fundamental signaling point in cancer cells, making AR-12 potentially effective in a wide range of cancer types,” says Chen, a professor of Pharmacy and Internal Medicine.

Chen and colleagues used celecoxib (Celebrex), a nonsteroidal anti-inflammatory drug, to construct AR-12, which triggers

THE RESEARCHER

CHING-SHIH CHEN, PhD,
Lucius A. Wing Chair of Cancer Research and Therapy, professor of Medicinal Chemistry, of Internal Medicine, and of Urology, College of Pharmacy and Comprehensive Cancer Center

cancer cells to self-destruct. In 2004, the agent was accepted by the National Cancer Institute’s Rapid Access to Intervention and Development program, which facilitates the development of promising experimental drugs.

BY THE NUMBERS

Mathematics taking guesswork out of tissue transfer

Plastic surgeons at The Ohio State University are turning to mathematics to ensure that live tissue selected to restore damaged body parts has enough blood and oxygen to survive the surgical transfer.

In the world's first published mathematical model of tissue transfer, mathematicians have used differential equations to determine which tissue segments selected for transfer from one part of the body to another will receive enough oxygen to survive.

The most common transfers are used to restore body parts destroyed by cancer and trauma. Researchers say reliable mathematical modeling of the blood supply and oxygen in tissue segments will reduce failures

in reconstructive surgery.

To obtain tissue for reconstructive surgery, surgeons cut away a tissue flap fed by a set of perforator vessels – an artery and vein that travel through underlying muscle to support skin and fat. Surgeons generally agree that vessels at least 1.5 millimeters in diameter are required to sustain oxygen flow in the flap.

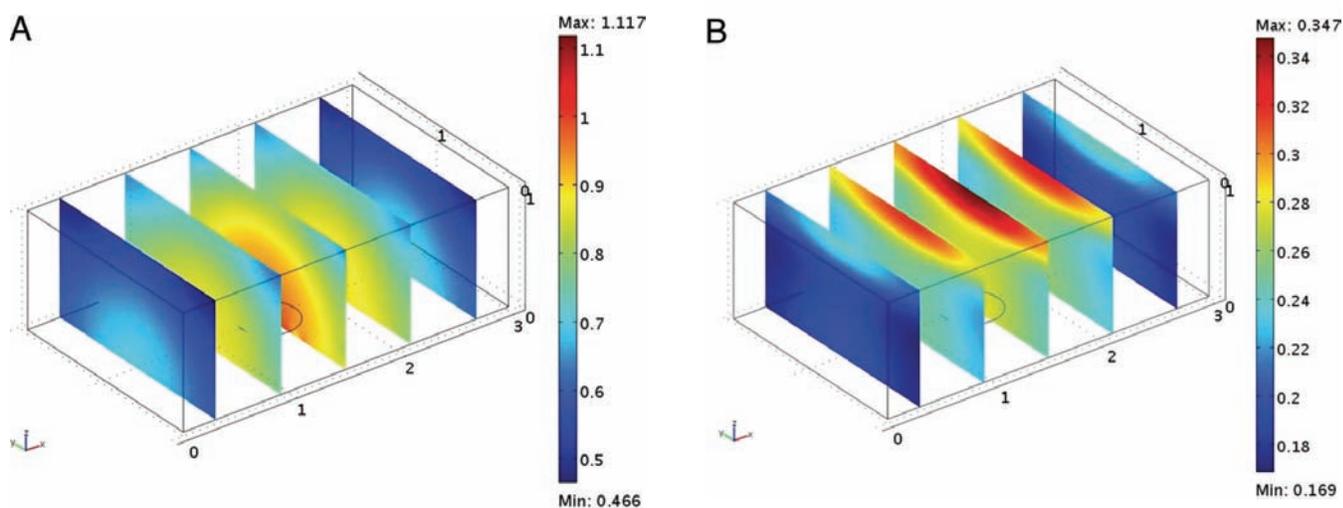
“That guideline is based on experience, trial and error. We need a more precise ability to determine the necessary blood vessel size,” says **MICHAEL MILLER, MD**, professor of Surgery CCC-James and director of the Division of Plastic Surgery at Ohio State. “I’m convinced there’s a relationship that’s probably very predictive between diameter and blood

flow in the vessel and the ability of the tissue to survive based on that.”

The mathematicians have shown that, under certain relationships between flap size and perforator vessel diameter, the oxygen level in the flap remains above 15 percent of normal, ensuring a successful transfer.

“This is still just a concept, but this initial system of five differential equations gives us a range between flap size and the required diameter of the supporting artery that would ensure survival,” says **AVNER FRIEDMAN, PHD**, a Distinguished University Professor of Mathematical and Physical Sciences at Ohio State.

 Published in the July 21, 2009 issue of the Proceedings of the National Academy of Sciences.



Oxygen distribution in artery blood (A) and in tissue (B) after 4 hours of tissue reperfusion in the case of the small tissue flap (dimensions: $3\text{ cm} \times \frac{15}{8}\text{ cm} \times 1\text{ cm}$). In this case, the perforator artery is successful in oxygenating the flap, as no fat necrosis develops.

▶▶ BREAST CANCER

UNDER THE INFLUENCE

Normal cells aid tumor progression

A study led by Ohio State University cancer researchers is the first to show that gene alterations in stromal fibroblasts can foster tumor growth. This work provides the first mouse model that accurately represents the tumor microenvironment found in human breast cancer.

Co-principal investigators **MICHAEL OSTROWSKI, PHD**, and **GUSTAVO LEONE, PHD**, both of The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, and their colleagues eliminated the *Pten* tumor suppressor gene from stromal fibroblasts present in a mouse epithelial mammary tumor.

Pten is a key regulator of cell metabolism that is lost in the malignant cells of many human cancers, this study revealed that it also influences the tumor microenvironment.

The loss of *Pten* led to over-expression of a second fibroblast gene, *Ets2*. That resulted in gene expression changes and led to extensive remodeling of the extracellular matrix, as well as increased inflammation and angiogenesis, all of which favor tumor growth.

Remarkably, altering the *Pten-Ets2* alignment in the mouse model accurately mimicked histological and molecular changes that occur in human breast cancer.

The findings demonstrate that

stromal fibroblasts play an important role in suppressing cancer development and may explain why some human breast cancer patients respond to a standard therapy while others with apparently identical disease don't.

In addition, the studies identify new stromal-specific biomarkers that may help guide treatment and identify molecular targets for developing new therapies aimed at tumor stromal cells. They could also improve the understanding of other pathological conditions that are influenced by the tissue microenvironment, such as autoimmune disease, lung fibrosis and neurodegenerative diseases.



Published in the Oct. 22, 2009, issue of *Nature*

▶▶ SKIN CANCER

VIRAL VEXATION

Virus linked to common skin cancer

A virus discovered in a rare skin cancer also has been found in people with the second most common form of skin cancer among Americans.

Researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute examined tissue samples from 58 people with squamous cell carcinoma (SCC) and identified the virus in more than a third of them and in 15 percent of the tumors tested. All of the virus in tumor cells had a mutation that could enable viral DNA to integrate into host cell DNA.

“This is indirect evidence that

the virus might play a role in causing some cases of SCC,” says principal investigator **AMANDA TOLAND, PHD**, an OSUCCC-James researcher.

The virus was first discovered in patients with Merkel cell carcinoma, a rare, aggressive skin cancer that occurs mainly in the elderly and people with suppressed immune systems. “Originally we thought this virus caused only this rare skin cancer, but our findings indicate it is more prevalent than that,” Toland says.

To learn if people with SCC harbored the virus, Toland and colleagues examined DNA samples

from SCC tumors, normal skin adjacent to the tumor, white blood cells and cells washed from the mouth.

They detected the virus in 26 of 177 SCC samples, 11 of 63 skin samples, and one mouthwash sample. They found no viral DNA in blood samples from 57 patients. In all, 36 percent of SCC patients tested positive for the virus. Sequencing viral DNA from 31 samples revealed that the same mutation was present in all the viruses from tumors and in 60 percent of the viruses from adjacent healthy-looking tissue.



Published in the June 25, 2009 issue of the *Journal of Investigative Dermatology*.

RECEPTOR ROLE REVEALED

Scientists Discover Key Event in Prostate Cancer Progression

A study led by researchers at The Ohio State University Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute (OSUCCC-James), and Dana-Farber Cancer Institute, reveals how malignant prostate tumors gain the ability to progress in the absence of androgen.

The onset of hormone-independent growth marks an advanced and currently incurable stage of prostate cancer.

In hormone-dependent disease, androgen receptors regulate an early phase of the cell cycle. In hormone-independent prostate cancer, the research shows, epigenetic changes

reprogram the receptors to selectively regulate genes involved in mitosis.

One of those upregulated genes is *UBE2C*. This causes the cell to skip a mitotic check point, and it accelerates cell division.

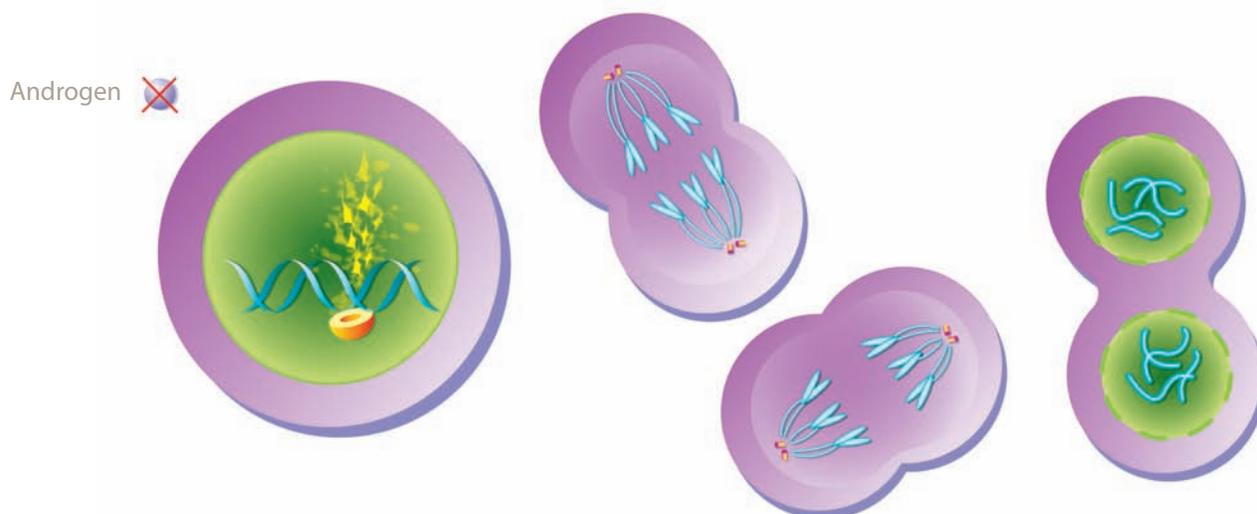
“Some late-phase prostate cancers do not require androgen hormones for tumor growth, but they do require androgen receptors,” says first author and co-corresponding author Qianben Wang, PhD, assistant professor of Molecular and Cellular Biochemistry and a researcher with the OSUCCC-James. “Our study reveals that androgen-independent cancer cells aren’t directing androgen-dependent gene expression without

androgen, but rather that they activate an entirely different pathway that results in androgen-independent growth.”

Wang, working with corresponding author Myles Brown, MD, professor of Medicine at Harvard Medical School and Dana-Farber Cancer Institute, and colleagues conducted the study using prostate cancer cell lines, gene expression data and human tumor tissue.

Wang says the findings could identify new therapeutic targets and lead to new treatments for this lethal stage of the disease.

 Published in the July 24, 2009, issue of the journal *Cell*.



*In androgen-dependent prostate cancer, androgen binds to androgen receptors (AR), resulting in the regulation of G1-S phase of the cell cycle and normal mitosis. In androgen-independent disease (above), epigenetic changes cause AR to selectively upregulate genes involved in mitosis, such as *UBE2C*. Dividing cells skip a mitotic check point, and this accelerates cell division.*

OF NOTE

*Recent Recognitions of
OSUCCC-James Physicians
and Researchers*

AWARDS AND RECOGNITIONS

RICHARD BURRY, director of the OSUCCC Microscopy shared resource and the Campus Microscopy and Imaging Facility, **has received the Carpenter-Rasch Award from The Histochemical Society.** Burry (standing left) was recognized for his years of service and his pioneering work to establish the Society's, *Journal of Histo-chemistry and Cytochemistry* online.



JOHN BYRD, MD, D. Warren Brown Designated Professorship in Leukemia Research and associate director for Translational Research for the OSUCCC, **has been awarded the 2009 Michalee C. Christian Oncology Development Lectureship and Award from the National Cancer Institute's Cancer Therapy Evaluation Program.** The award recognizes the contributions of individuals, particularly those in mid-career, to the development of novel agents for cancer therapy.

A. DOUGLAS KINGHORN, PHD, DSC, the Jack L. Beal Professor and Chair in the Division of Medicinal Chemistry and Pharmacognosy, **has received the 2010 Norman R. Farnsworth Research Achievement Award from the American Society of Pharmacognosy.** The competitive award recognizes lifetime contributions to natural products research.

THE OSUCCC-JAMES caGRID KNOWLEDGE CENTER TEAM has received the NCI's caBIG Award for Collaboration, which recognizes teamwork for achievements based on multiple

contributions from individuals or groups. The caGrid Knowledge Center involves the collaboration of The Ohio State University, where it is based, Emory University in Atlanta and the University of Chicago. The Ohio State team includes director **STEPHEN LANGELLA**; co-director **MICHAEL CALIGIURI, MD**; and operation manager **JUSTIN PERMAR.**

HEATHER HAMPEL, MS, CGC, a cancer genetic counselor and clinical associate director of the Division of Human Genetics, **has been re-elected for a second term as president of the American Board of Genetic Counseling.** The ABGC is the credentialing organization for the genetic counseling profession in North America, and it is responsible for the accreditation of graduate programs in genetic counseling.

REBECCA NAGY, MS, CGC, a genetic counselor and OSUCCC-James researcher, **has begun a two-year term as secretary/treasurer elect of the National Society of Genetic Counselors for 2010.**

MARK BLOOMSTON, MD, FACS, assistant professor of Surgery and director of the Surgical Oncology Fellowship Program, **is one of five recipients worldwide of a 2009 traveling fellowship from the James IV Association of Surgeons based in Edinburgh, Scotland.** The association – named in honor of the fourth Stuart king of Scotland, who was fascinated with science – was formed to strengthen ties between surgeons of the United States and the United Kingdom. Bloomston traveled to Scotland, Switzerland, Italy, Germany, France, Hong Kong and Australia, visiting renowned physicians in liver and pancreas surgery.



GRANTS

MICHAEL A. CALIGIURI, MD, director of The OSUCCC and CEO of The James, received a **\$5.5 million, six-year, National Cancer Institute (NCI) grant** for Cancer and Leukemia Group B (CALGB) correlative sciences studies to better understand leukemia heterogeneity.

ARNAB CHAKRAVARTI, MD, chair and professor of Radiation Oncology and co-director of the Brain Tumor Program, will lead a **two-year, \$2.05 million, multiple-principal-investigator, NCI Challenge grant** awarded to the American College of Radiology. The grant is a collaboration between the OSUCCC-James, M.D. Anderson Cancer Center and the American College of Radiology. The research is designed to improve the classification and treatment of glioblastoma.

CLARA D. BLOOMFIELD, MD, cancer scholar and senior adviser to the OSUCCC-James received a **\$3.2 million, six-year, NCI grant** for continued support of the Cancer and Leukemia Group B (CALGB) activities at the OSUCCC-James.

ALBERT DE LA CHAPELLE, MD, PHD, professor of Molecular Virology, Immunology and Medical Genetics and the Leonard J. Immke, Jr., and Charlotte L. Immke Chair in Cancer Research, received a **\$2.4 million, five-year, NCI grant** to support postdoctoral training in cancer genetics.

CARLO M. CROCE, MD, professor of Molecular Virology, Immunology and Medical Genetics, John W. Wolfe Chair in Human Cancer Genetics, and director of the Human Cancer Genetics program, received a **\$2 million, two-year, NCI grant** for the Loss of miR-29s as Predictor of Response to Demethylating Agents.

TIM HUANG, PHD, professor of Medical Virology, Immunology and Medical Genetics, received a **\$1.8 million, five-year grant** from the NIH Common Fund/Roadmap initiative for a study titled Epigenomics of bisphenol-A exposure and disease risk.

JEFFREY PARVIN, MD, PHD, professor (center); **KUN HUANG, PHD**, assistant professor, in the Department of Biomedical Informatics, and **UMIT CATALYUREK, PHD**, associate professor, received a **\$2.3 million, five-year, NCI grant** to develop a new framework for discovery of genes involved in breast carcinogenesis.



FACULTY AND STAFF

MARK BLOOMSTON, MD, FACS, assistant professor of Surgery and director of the Surgical Oncology Fellowship Program, has been appointed as a **cadre member of the GI surgery sub-committee for CALGB**.

SUSAN BROWN, RN, MSN, has been named **chief nursing officer for the OSUCCC-James**. Brown comes from the Virginia G. Piper Cancer Center in Scottsdale, Ariz., where she served as associate vice president for oncology services and director of the center for the past 12 years. Prior to this, Brown served as administrative director of oncology services for Anne Arundel Medical Center in Annapolis, Md.



STEPHEN CHAYKOWSKI has been named **OSUCCC-James executive director of Development**.

NAGLA ABDEL KARIM, MBBCH, has joined the cancer program as an **assistant professor of Medicine in the Division of Hematology and Oncology**. Her clinical interest is lung cancer.

EDMUND S. KASSIS, MD, has joined the cancer program as an **assistant professor of Surgery**. His clinical and research interests are in thoracic oncology, with a focus on lung and esophageal cancers.



JEFFREY S. ROSE, MD, has joined the cancer program as an **assistant professor in the Division of Hematology and Oncology**. His clinical interests include hepatocellular, gastric and esophageal cancer, and his research interests include localized therapies for unresectable hepatocellular carcinoma.

ROBERT TAYLOR, MD, medical director and fellowship director of the Center for Palliative Care at the OSUCCC-James, has been chosen to serve on an **Ohio Health Care Coverage and Quality Council task force** on "Informed and Activated Patients and Individuals." Taylor says the task force will address medical ethics and care at the end of life and other issues.



PROGRAMS

As part of a Third Frontier Program Award, the The Ohio State University has granted a **subcontract of \$1.4 million to PreCellon Inc.** to help Ohio State and the Cleveland Clinic develop cell

separation and enrichment technology to benefit cancer patients. The money is part of a larger \$3.5 million grant package from the Ohio Department of Development that was awarded in

July 2006 to principal investigator **JEFFREY CHALMERS, PHD**, a professor of Chemical and Biomolecular Engineering at Ohio State, an OSUCCC-James researcher and director of the OSUCCC's Analytic Cytometry Shared Resource.

Shedding new Light

MAURA GILLISON, MD, PhD, Medical oncologist, head and neck cancer specialist and the Jeg Coughlin Chair in Cancer Research with her team (left to right). Hebin Song, MB, PhD; Tatevik Broutian, MS; Zhen-yue Tong, MD, PhD; Michael Koluder; Robert Pickard, MPH, EdM; Esther Kim, MS; Weihong Xiao, MD; Andrea Inman.

BY DARRELL E. WARD

PHOTOGRAPHY BY ROMAN SAPECKI



The throat seemed an odd site for a virus linked to cervical cancer, yet several small studies published in the 1990s reported finding human papillomavirus (HPV) in squamous cell carcinomas of the oropharynx.

Those early findings intrigued Maura L. Gillison, MD, PhD, a medical oncologist, head and neck cancer specialist and a world authority on HPV-associated oral

positive for the virus, and 90 percent of those were HPV16, the cause of cervical cancer. HPV33 turned up in three cases, one of which was coinfecting with HPV31 and one with HPV18. All three of these are high-risk cancer viruses. One case was positive for the low-risk HPV11.

Of the virus-positive tumors, 57 percent developed in the

negative counterparts.

“Our findings strongly suggested that this was a distinct type of head and neck cancer that affected people who did not necessarily smoke and drink, whose tumors were largely poorly differentiated and located mainly in the oropharynx, and had a better prognosis,” Gillison says.

MAURA GILLISON, MD, PHD ▶▶

“The CDC estimates that at least 50 percent of women will have an HPV infection by age 60, and that is likely an underestimate because it does not account for infection at other sites, such as oral or anal infection.”

cancer now at The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. In the mid-’90s, however, she was an oncology fellow at The Johns Hopkins University School of Medicine.

By 2000, Gillison was first author on a seminal study showing a strong association between HPV and oropharyngeal cancer. The research, led by Keerti V. Shah, MD, Dr. PH, and published in the *Journal of the National Cancer Institute (JNCI)*, analyzed tumors from 253 patients with head and neck squamous cell carcinoma (HNSCC), screening them for more than 30 types of HPV.

One fourth of the tumors were

oropharynx—the area of the throat that encompasses the base of the tongue and the tonsils—and the great majority of those arose in the tonsils. The tumors also showed a high viral copy number and tumor-specific viral clones, indicating that they originated from a single infected cell.

The real surprise for the investigators came when they calculated the estimated survival: It was more than 91 months for patients with HPV-positive tumors and 76 months for those with HPV-negative tumors. After the investigators adjusted for age, lymph node status, alcohol consumption and *TP53* mutations, they found that the HPV-positive group had about half the risk of death from cancer than their HPV-

DEFINING THE PROBLEM

“Those findings shook the field,” Gillison says. “We thought head and neck cancer was caused largely by alcohol and tobacco, but here was a major new risk factor.”

The Centers for Disease Control and Prevention (CDC) estimates that HPV is the most common sexually transmitted infection in the United States. A 2007 National Health and Nutrition Examination Survey (NHANES) study reported HPV prevalence rates of 24.5 percent in women age 14 to 19, and 44.8 percent in young women age 20 to 25. Combining the two age groups yields an overall prevalence of 33.8 percent, which corresponds to 7.8 million infected young women.

“The CDC estimates that at least 50 percent of women will have an HPV infection by age 60, and that is likely an underestimate because it does not account for infection at other sites, such as oral or anal infection,” Gillison says.

Cervical cancer is the most common and best known HPV-related cancer. But while the incidence of cervical cancer is decreasing in the United States, the rate of HPV-related oral cancer is rising, particularly among men.

“We now need to track this infection over time to learn which infected individuals are at greatest risk of developing cancer, how best to treat those who develop the disease and whether HPV vaccines can prevent the infections that promote development of a malignancy.”

TIGHTENING THE CAUSAL LINK

Gillison was convinced of the association between HPV and oral cancer as early as 1998. As the data accumulated for the *JNCI* paper, she began preparing for follow-up studies. She reviewed the literature to learn all she could about the role of HPV and lower genital tract infections and used this as a framework for planning investigations of HPV and oral cancer.

Her initial work included studying how to collect and process oral HPV samples to ensure that they were reproducible and to maximize detection. One study looked at the effect of HPV DNA purification on

oral samples. “We found it could be huge, and we were surprised by that,” Gillison says.

In 1998, Gillison and her colleagues planned a case-control study that would help build a causal association between HPV and oropharyngeal cancer and guide future prevention efforts, such as a vaccination program.

The study examined 100 cases of oropharyngeal cancer and 200 control patients. *The New England Journal of Medicine (NEJM)* published the findings in 2007. The disease was significantly associated with HPV16, which they found in 72 of the 100 tumor specimens, and this was true whether subjects had a history of heavy tobacco and alcohol use or not.

However, tobacco and alcohol were associated mainly with HPV-negative tumors, while having six or more oral sex partners or a high lifetime number of vaginal sex partners—26 or more—tripled the odds of developing oropharyngeal cancer.

HPV AND ORAL CANCER INCIDENCE

These findings caused Gillison to wonder what influence HPV infection might be having on oral cancer incidence generally, particularly since behavioral studies were showing that oral sexual practices were widespread among adolescents.

Teaming up with colleagues at the National Cancer Institute (NCI), the investigators used data

from the NCI’s Surveillance, Epidemiology, and End Results (SEER) program to estimate HPV-associated oral cancer incidence trends over three decades.

Using SEER data, they tabulated oral squamous cell carcinoma cases from 1973 through 2004. Next, they used disease classification codes to divide the cases into anatomic sites that were potentially HPV-related and sites that were probably HPV-unrelated. The former included tumors of the tonsils, oropharynx and tongue base (17,625 cases); the latter included cancers of the tongue, gum, palate and floor of mouth (28,144 cases).

Their findings, published in the *Journal of Clinical Oncology (JCO)* in 2008, showed that the incidence of potentially HPV-related oral SCC increased significantly over the time period, while the HPV-unrelated cancers decreased over that period. (They also learned that potentially virus-related cancers were diagnosed earlier, age 61 vs. age 63, than virus-unrelated cancers.)

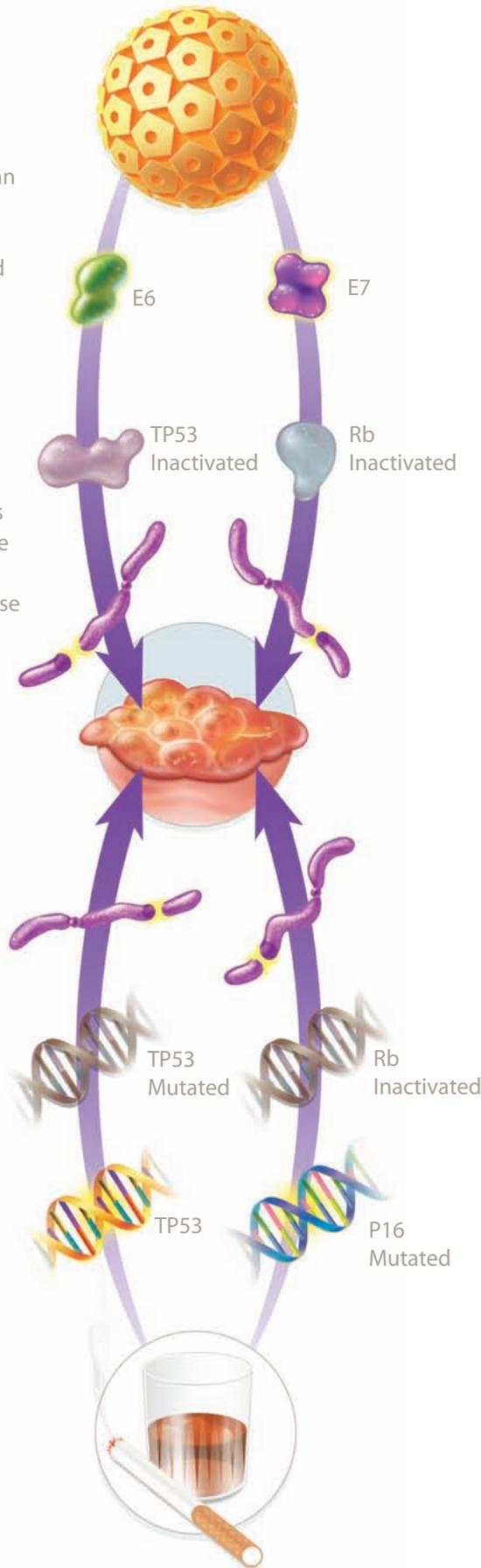
Furthermore, the investigators learned that people born after 1930 had a higher incidence rate of potentially HPV-related cancers than people born before that year, and that the risk grew with every birth cohort thereafter.

“This suggests that a societal change was behind the rising incidence of potentially HPV-related cancers,” Gillison says. A likely societal change that could influence the incidence of sexually transmitted

PATHWAYS TO OROPHARYNGEAL CANCER

Research by Maura Gillison, MD, PhD, a medical oncologist and specialist in human papillomavirus (HPV)-related oral cancer at Ohio State, and others suggests that oropharyngeal cancer in HPV-positive and HPV-negative tumors develops through different molecular pathways. The same cell regulatory and DNA repair pathways are inactivated in both cases, but the inactivation happens in different ways.

HPV-positive tumors are driven by proteins produced by carcinogenic strains of HPV, particularly HPV16, that silence the p53 and Rb tumor suppressor genes. (top half of illustration). Tobacco and alcohol use tend to drive HPV-negative tumors. They also silence p53 and Rb, but directly, through mutations (lower half of illustration).



HPV

1. HPV's E6 protein inactivates the TP53 protein and mediates its degradation, effectively silencing the action of the *TP53* tumor-suppressor gene.
2. HPV's E7 protein inactivates the Rb protein, silencing the *Rb* tumor-suppressor gene.
3. Inactivation of *TP53* and *Rb* leads to chromosome instability, breakage and loss, which contributes to tumor progression.

OROPHARYNGEAL CANCER

3. Mutational damage leads to chromosome instability, breakage and loss, which contributes to tumor progression.
2. Tobacco carcinogens cause mutations that inactivate the *P16* gene, which lies upstream of the *Rb* tumor suppressor gene. The silencing of *P16* inactivates *Rb*.
1. Tobacco carcinogens, abetted by alcohol use, cause mutations that silence the *TP53* tumor-suppressor gene.

TOBACCO AND ALCOHOL

MAURA GILLISON, MD, PHD ▶▶

“The single greatest risk factor for HPV infection is sexual contact with someone who has HPV infection. The greater the number of partners you have, the higher the probability that one of those partners is HPV-positive.”

infections was the sexual revolution of the 1950s and '60s, particularly the greater acceptance of more partners, she says.

“The single greatest risk factor for HPV infection is sexual contact with someone who has HPV infection,” she says. “The greater the number of partners you have, the higher the probability that one of those partners is HPV-positive.”

In addition, the researchers found a 23-percent improvement in two-year survival for HPV-related cancers during 1993-2004, but not for HPV-unrelated cancers, which they concluded might be due to the underlying shift in the etiology of these cancers and an inherent radiation sensitivity among HPV-related cancers, rather than improvements in therapy over time.

CLARIFYING RISK FACTORS

Gillison learned more about the risk factors for HPV-positive oral cancer by leading a hospital-based case-control study that involved 240 patients with cancer of oropharynx, larynx or with an unknown primary of the head and neck. Ninety-two of the tumors were HPV-positive.

Each case was matched with two control subjects. All participants were asked to self-report on sexual behaviors such as the number of vaginal and oral sex partners, participation in casual sex and use of

barriers during sexual activity, and on their use of tobacco, alcohol and marijuana.

She planned the study in 1998; *JNCI* published the findings in 2008. The HPV-positive cases were associated with sexual behaviors and frequency of marijuana use, but not with tobacco and heavy alcohol use. HPV-negative cases, on the other hand, were associated with cigarette smoking, heavy alcohol use and the number of teeth lost (a marker of oral hygiene), but not with sexual practices or marijuana use.

This provided further evidence that HPV-positive and HPV-negative were different diseases, and it suggested that oral cancers can develop through at least two pathways, one initiated by HPV infection, the other by tobacco and alcohol use (see sidebar).

TREATMENT

So if HPV-positive and HPV-negative oral cancers are different diseases, do patients respond differently to therapy? In 1998, Gillison and her colleagues began exploring this question prospectively by adding a correlative study of survival outcomes and treatment response to an Eastern Cooperative Oncology Group (ECOG) phase II trial then under design.

The study involved 96 patients with stage III and IV oropharyngeal

or laryngeal cancer were treated with chemotherapy and radiation. The two-year survival for HPV-positive and HPV-negative patients was 95 percent and 62 percent respectively after a median follow-up of 39 months. The findings, published in *JNCI* in February 2008, clearly suggested a strong association between HPV status and survival of oral cancer patients.

This was confirmed by another study led by Gillison of 206 HPV-positive and 117 HPV-negative patients and presented at the 2009 American Society of Clinical Oncology meeting.

At two years, 88 percent of HPV-positive patients were still alive, compared with 66 percent of HPV-negative patients, and progression-free survival was 72 percent and 50 percent, respectively. The incidence of second primary cancers among HPV-positive patients was less than half that of HPV-negative patients at five years: 90 percent vs. 18.5 percent.

Given that these are two separate diseases, the most important question now is whether patients with HPV-positive cancers should receive different therapy. “We don’t know,” Gillison says. “Currently, the standard of care for these patients is the same as it is for head and neck cancer generally.”

Mounting evidence—much of

MAURA GILLISON, MD, PHD ▶▶

“We need to understand the possible role of HPV vaccines in preventing oral HPV infections that lead to oropharyngeal cancer. It may offer the means to reverse the rapidly increasing incidence rates for oropharyngeal cancer. We need clinical trials to answer the question.”

it from Gillison’s studies—shows that HPV-positive oral cancers have a better prognosis. Some physicians and patients are using that information alone to determine treatment, and this makes Gillison uneasy.

“It is inappropriate to make treatment decisions based on a prognostic marker alone, at least not until there is clinical trials data upon which to base treatment decisions,” she says.

Those clinical trials need to be done soon, she adds.

“Overall, the literature consistently suggests that HPV is an important prognostic factor for head and neck cancer,” Gillison says. “But it also says that the reasons for that improved survival are probably multifactorial, and the extent to which they depend upon the patient’s treatment is unclear. At this point it appears that the survival difference between the HPV-positive and HPV-negative patient is independent of therapeutic choice, as long as the therapy is based on some standard of care. The question now is ...which therapy is the best choice for each group?”

In Scandinavia, for example, the standard treatment for tonsillar cancer is radiation alone, Gillison says, noting that HPV-positive and

HPV-negative patients have a five-year survival of 85 percent and 45 percent, respectively.

In Italy, tonsillar cancer is treated with surgery followed by radiation if pathology indicates it. A retrospective analysis showed the five-year survival for surgically treated HPV-positive and HPV-negative patients to be 80 to 85 percent and 40 to 45 percent, respectively.

“People will tell me that HPV-positive patients do well with surgery alone,” Gillison says. “I get patients referred to me who have been treated with surgery alone and were told that they were fine and don’t need radiation therapy.”

Others believe just the opposite, she says. “One person said to me, ‘Patients want survival. Survival is their ultimate goal, not minimizing toxicity. So we have to give them intensive therapy.’ But we don’t know if intensive therapy determines the outcome or not for HPV-positive patients.

“We don’t know how to make these decisions because there is insufficient data,” she says. “We need clinical trials to answer these questions. And even that will be tricky. How do we determine the best therapy for patients who seem to do very well with any modality

we use? It requires huge sample sizes.”

It is a challenge she hopes to overcome at Ohio State. “I have found a lot of flexibility here to do what I want to do, and I think the institution cares and wants people to succeed,” Gillison says. She hopes to take advantage of the wide-ranging resources available at Ohio State, where cancer center members come from 13 different colleges within the University. Already she has begun an epidemiologic study of oral HPV infection in healthy Americans through NHANES. She is also working with colleagues in national clinical cooperative groups to design therapeutic trials specific for HPV-positive or HPV-negative patients, and she is involved in studies that will assess the effectiveness of HPV vaccines for the prevention of these cancers.

“Because HPV infection is so prevalent,” Gillison says, “we need to understand the possible role of HPV vaccines in preventing oral HPV infections that lead to oropharyngeal cancer. It may offer the means to reverse the rapidly increasing incidence rates for oropharyngeal cancer. All we need are clinical trials to answer the question.” 

Fractionating Forests

Discovering promising anticancer agents requires experience and the science of pharmacognosy.

DOUGLAS KINGHORN, PHD, DSC

Jack Beal Professor and Chair of Natural Products Chemistry and Pharmacognosy in the College of Pharmacy

BY DARRELL E. WARD

PHOTOGRAPHY BY

ROMAN SAPECKI

In August 2000, Drs. Soedarsono Riswan and Leonardus B.S. Kardono, both of the Indonesian Institute of Science, led a small crew into a remote rainforest of Indonesian Borneo on a plant-collecting expedition for a U.S. National Cooperative Drug Discovery Group (NCDDG) project. The team made their way through thick undergrowth, ignoring heat, humidity, insects and rain, as they gathered twigs, leaves, roots, fruits and flowers from selected plants.

They took careful notes, recorded each plant's global positioning coordinates, photographed the leaves and flowers and preserved reference specimens in herbarium paper. They packed the samples in porous sacks, dried the material in the sun, then shipped it to the NCDDG, based then at the University of Illinois, Chicago.

The project was headed by A. Douglas Kinghorn, PhD, DSc, who in 2004 joined Ohio State as the

Jack Beal Professor and Chair of Natural Products Chemistry and Pharmacognosy in the College of Pharmacy, and as a researcher with The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James).

Kinghorn and his laboratory are internationally recognized in the field of natural product drug discovery. He has isolated more than 250 natural product compounds that show potential anticancer or chemopreventive activity, with more than 50 having a novel structure. They include aromatase inhibitors and pervilleines A-F, potent inhibitors of the drug-resistance protein, P-glycoprotein.

His laboratory evaluates some 400 plant samples per year for promising “lead compounds,” molecules with biological activity and interesting structures. They may investigate a

dozen or more plants at a time.

For 15 years he has been editor-in-chief of the *Journal of Natural Products*, the leading journal in his field. He is series-editor-in-chief of the book series *Progress in the Chemistry of Organic Natural Products*, and he chairs the Dietary Supplements – Botanicals Expert Committee of the U.S. Pharmacopeia.

Today, Kinghorn directs a \$7 million, five-year, National Cancer Institute (NCI) program project grant, titled *Discovery of Anticancer Agents of Diverse Natural Origin*, which funds the collection and analysis of tropical rainforest plants, and of cyanobacteria and fungi. His collaborators include researchers at the University of Illinois, Chicago; University of North Carolina-Greensboro; and Bristol-Myers Squibb (see sidebar).

That same team was involved in the NCDDG grant and the Borneo collection, which, as it turned out,

THE HOLLOW-FIBER ASSAY

Economic in vivo testing

In the mid-1990s, Michael R. Grever, MD, now co-director of the OSUCCC-James Experimental Therapeutics program, was associate director of Developmental Therapeutics at the National Cancer Institute (NCI). He needed a more rapid *in vivo* method to evaluate new agents produced by the NCI Cancer Drug Screen, one that required a small amount of each novel agent.

Work by Melissa Hollingshead, DVM, PhD, presented an interesting opportunity. To study protein production by the human immunodeficiency virus, she was placing viral-infected cells into hollow plastic fibers, then implanting the fibers in experimental animals.

After recruiting Hollingshead to the NCI, Grever and

his colleagues worked with her to turn the idea into today's screening assay for possible anticancer agents. Tumor cells are grown in fine polyvinylidene fluoride fibers that are implanted in immune-deficient mice. The mice are treated with an experimental agent, which enters the fibers through small pores in the plastic. The fibers are then removed and the effects on cell-growth determined by optical density. Implanting fibers in both the peritoneal cavity and subcutaneously provides a “two-compartment” test that estimates an agent's ability to withstand systemic circulation. Results are usually available much sooner than with typical *in vivo* models, which facilitates the advancement of exciting new agents into more detailed animal studies.

would yield an extraordinarily interesting compound from a tree in the mahogany family, *Aglaia foveolata*. Kinghorn named the new substance silvestrol.

Natural products—substances made by living organisms that often have pharmacological activity—have historically been an important source of anticancer drugs. Taxol is one example. According to a recent study, of 155 antineoplastic agents marketed in Western countries and Japan since the 1940s, 47 percent were either unmodified natural products or semi-synthetic derivatives of natural products.

These plant-derived anticancer agents fall into four structural classes: the vinca alkaloids (vinblastine, vincristine, vinorelbine), the epipodophylotoxins (etoposide, etoposide phosphate, teniposide), the taxanes (paclitaxel and docetaxel), and the camptothecin derivatives (irinotecan and topotecan). Silvestrol may add yet another.

HOOKED ON PHARMACOGNOSY

Kinghorn came to his career reluctantly. As a teenager in the United Kingdom, he planned to enter medical school. Then his father, a pharmacist, became seriously ill. He called Kinghorn, the oldest of five children, to his bedside. Concerned that he might die, the father wanted his son to attend pharmacy school so he could look after the family.

Kinghorn enrolled in the pharmacy program at the University of Bradford. There, pharmacognosy—the study of drugs or substances of natural origin, and the search for new drugs from natural sources—captured his imagination. He went

above and beyond, completing a literature review of hallucinogens, a microscopic study of parsley, and a gas chromatography analysis of a fixed oil. He graduated with special honors.

“I was hooked,” Kinghorn says. He focused on drug discovery and searching for biologically active compounds in graduate school. “I’ve been faithful to that throughout my career,” he says.

His father? He survived the illness. “He was a fellow of the Royal Pharmaceutical Society of Great Britain, and I became one too, just before he died,” says Kinghorn. “We were the only father and son with the same name to ever be fellows together, and that meant a tremendous amount to him.”

As a postgraduate, Kinghorn studied plant-derived anticancer agents with Norman R. Farnsworth at the University of Illinois, Chicago. In subsequent independent work on identifying sweet plant substances, a review of ancient Mexican botanical literature turned up a 16th century monograph that led Kinghorn to the Aztec sweet herb, *Lippia dulcis*. From that, he isolated hernandulcin, an oil 1,000 times sweeter than table sugar.

“I got very lucky with that,” he says. “It really was a major discovery among sweeteners.” *Science* published the findings in 1985.

After discovering several novel sweet substances, Kinghorn—who remains a recognized world authority on phytochemical sweeteners—changed his focus to natural product anticancer agents.

“It’s all drug discovery,” he says. “The trick is to recognize really great leads and dump the not-so-promising

stuff. It’s a skill that comes with experience.”

In 1992, Kinghorn became principal investigator on an NCDDG award, and it was that grant which funded the 2000 plant-collecting trip to Indonesian Borneo.

CUTTING THROUGH THICKETS

Kinghorn and his colleagues chose the Borneo site because his former graduate student, Leonardus Kardono, could help arrange and coordinate the formal plant collection agreement with Indonesia.

To plan collections, the researchers check NAPRALERT, a natural products research database, to identify plants in the area that are under-investigated. They also give the local collectors a botanical manual indicating which genera to sample. Flowers and fruits are of special interest. “Someone may have to climb 250 feet up to reach them, so it’s not always possible,” Kinghorn says. “A lot depends on how well you can motivate the people out in the field.”



THE UNUSUAL SIDE CHAIN THAT CHARACTERIZES SILVESTROL INCREASES THE COMPOUND'S ACTIVITY BY **1,000** TIMES.

A given plant may produce some 5,000 to 10,000 individual compounds, which can be separated into “primary” and “secondary” metabolites.

Primary metabolites include nucleic acids, amino acids, fatty acids, sugars and other materials required for growth.

Plants produce secondary metabolites, or simply “natural products,” for physiological and ecological reasons. They include the chlorophylls and carotenoids, as well as specialized compounds such as silvestrol that are made by only a restricted group of plants. Secondary metabolites that influence human cells *in vitro* are potential drugs.

Kinghorn’s search for such bioactive compounds begins with powdered plant samples, which are usually prepared by colleagues at the University of Illinois, Chicago. A pound or two of material will usually yield 100 mg of purified compound, enough for *in vitro* and initial *in vivo* testing.

For silvestrol, Kinghorn’s lab made aqueous and chloroform extracts from powdered twigs and fruit and tested them against several cancer cell lines and rapid *in vitro* assays that provide mechanistic data.

“Crude extracts can contain factors that inhibit or accentuate activity,” Kinghorn explains, “but our screening assays quickly provide large amounts of biological information. If there is something there, we will see it in 90 percent of cases.”

Only the chloroform extract showed cytotoxic activity. Using column chromatography, they divided that portion into eight fractions, then evaporated each of

those down and tested the residue against a panel of cancer cells. Fraction five showed the strongest activity, so it was divided into six sub-fractions. Of those, sub-fraction two showed the greatest activity. Continued fractionation yielded pure silvestrol.

In all, Kinghorn’s lab purified two new cytotoxic compounds: silvestrol, a white powder, and episilvestrol, a yellowish gum. Tested against a panel of cancer cell lines, silvestrol had three times the cytotoxicity of episilvestrol, which itself had cytotoxicity comparable to paclitaxel (Taxol).

IN VIVO TESTING

Silvestrol was both potent and promising. “But we don’t get enthusiastic about a compound until we test it in an animal system,” Kinghorn says.

First is the hollow-fiber assay. Developed at the NCI in the mid-1990s by Melinda G. Hollingshead, DVM, PhD, and Michael Grever, MD, now the Charles Austin Doan Chair of Medicine and co-director of the OSUCCC Experimental Therapeutics program, it uses human tumor cells growing in hollow plastic fibers that are implanted into test animals (see sidebar).

“We rely heavily on this assay,” Kinghorn says. “It requires only up to about 25 mg of the compound versus perhaps 100 mg for an average xenograft study.”

Tested at four doses, silvestrol inhibited the growth of a lung cancer cell line by 15 to 82 percent. “The outcome of the hollow-fiber assay was beautiful. Silvestrol came up trumps,” Kinghorn says.

Finally, the compound was tested in a mouse lymphocytic leukemia model, where it increased survival by 150 and 129 percent over controls, depending on the route of administration.

By then, Kinghorn and his group had worked out the compound’s structure and stereochemistry using nuclear magnetic resonance spectroscopy and X-ray crystallography.

They published the characteristics of the agent in the *Journal of Organic Chemistry* in 2004. “Our findings suggested that silvestrol should be investigated further as a potential new cancer chemotherapeutic agent,” he says.

INTERESTED CLINICIAN WANTED

Kinghorn had taken silvestrol as far as he could. “We can get a new agent to a certain level,” Kinghorn says, “then a physician-researcher must take it on and foster it.”

He found that physician in Ohio State’s Michael Grever, who also heads the OSUCCC-James Phase I Clinical Trials Program.

“Dr. Grever is one reason I came to Ohio State, and I’m so glad I did,” he says. “Physicians at Ohio State are very open to collaboration. This is part of the whole overall philosophy from top to bottom here. People are actively trying to find collaborations. It’s wonderful.”

Grever was intrigued by silvestrol’s structure and activity. Furthermore, studies by his research associate, David Lucas, PhD, examining silvestrol’s activity in special chronic lymphocytic leukemia (CLL) cell lines and an acute lymphoblastic leukemia mouse model suggested that the agent was more active

against B cells than T cells. Those 2009 findings were published in the journal *Blood* (see also The Right Collaboration, page 24).

To ensure that Grever and Lucas had an adequate supply of silvestrol for their work, Kinghorn organized a recollection of the plant's bark in 2005.

Purifying larger amounts of a compound from a recollection is a tedious, months-long effort that falls to post-doctoral students, Kinghorn says. "It's not very interesting and there are few prospects for getting a publication, but it requires care and detailed documentation of the spectroscopy to ensure purity." Kinghorn becomes part psychologist and part cheerleader to move the work along.

Silvestrol's development received an important boost when, in 2007, the NCI advanced it to Drug Development Group IIA status. The NCI would examine the agent in xenografts, perform range-finding toxicology studies and develop a clinical formulation. It was an important step toward a phase I clinical trial.

More compound was needed. Dr. Soedarsono Riswan returned to the original collection site and shipped back about 50 kg of dried stem bark, bringing many members of Kinghorn's NCI drug development grant team into play. The dried material was sent to Dr. Doel Soejarto, a taxonomist at the University of Illinois, Chicago, and a methanol extract was prepared at the University of Illinois Pharmacognosy Field Station, in Downers Grove, Illinois.

The laboratory of Dr. Jimmy Orjala, one of the grant's project

leaders at the University of Illinois, Chicago, concentrated the extract to a residue and shipped most of it to Dr. David Newman, chief of the NCI's Natural Products Branch in Frederick, Maryland. Newman worked with Thomas McCloud, head of the isolation group at the NCI's SAIC-Frederick research center, and they produced two grams of 97 percent pure silvestrol for further biological testing.

"Our work is highly multidisciplinary," Kinghorn says.

The American Cancer Society estimates that more than 1.4 million Americans will be diagnosed with cancer and that 562,300 people will die of cancer in 2009. Most will succumb to recurrent or advanced disease that lacks effective therapy. "We need new agents that have novel mechanisms of action and don't overlap with drugs currently in use," Kinghorn says.

Parsing plants for anticancer agents has its challenges. Active compounds tend to occur in low concentration, and they are often chemically unstable or have solubility problems. Political unrest in the nation of origin can delay recollection, and even with recollection, the compound may be missing due to biological variation.

On the other hand, "Because natural products are made by living things, they offer unique molecular scaffolds that are unlikely to arise in synthetic drug-discovery laboratories," Kinghorn says.

"Natural products research offers a very real opportunity to discover chemical entities that may cure some of our most threatening diseases." 

THE HUNT IS ON

Grant to fund the discovery of novel bioactive compounds

When A. Douglas Kinghorn, the Jack L. Beal Professor and Chair in Natural Products Chemistry and Pharmacognosy in the College of Pharmacy, arrived at Ohio State in 2004, he directed an NCI-funded, multi-institutional National Cooperative Drug Discovery Group (NCDDG) project aimed at discovering new anticancer agents from tropical plants. Kinghorn headed that program for 15 years and oversaw the collection of more than 2,600 plant acquisitions.

The NCDDG grant was succeeded in 2007 by a \$7 million, five-year, NCI program project grant awarded to Kinghorn titled Discovery of Anticancer Agents of Diverse Natural Origin. The new grant funds the collecting and sampling of tropical rainforest plants, blue-green algae, and filamentous fungi for novel bioactive compounds.

The research involves the collaboration of two academic centers, a nonprofit organization, a pharmaceutical company and a biotechnology company, listed here with their areas of responsibility:

The Ohio State University

Tropical Plants
Biological testing
Project administration, biostatistics

University of Illinois, Chicago

Aquatic cyanobacteria
Collecting tropical plants
Biological testing

Research Triangle Institute

Filamentous fungi
Biological testing

Bristol-Myers Squibb, Inc.

Biological testing
Pharmaceutical development

Mycosynthetix, Inc.

Maintains a library of 55,000 filamentous fungi from targeted ecosystems around the world

The Right Collaboration

Improving the clinical outcome of CLL patients.

BY BOB HECKER

PHOTOGRAPHY BY ROMAN SAPECKI

Patients with chronic lymphocytic leukemia (CLL), the most common leukemia among adults in the United States, have few therapeutic alternatives despite decades of research.

“Drugs developed over the past 30 years for treating CLL have shown responses in patients, but the disease remains incurable, so we just can’t rest on what we’ve done so far,” says Michael Grever, MD, professor and chair of the Department of Internal Medicine, and co-leader of the Experimental Therapeutics Program at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James).

“We will probably never find one drug that cures CLL,” adds Grever, a specialist in hematologic malignancies, “but if we can find several that act against it, they may ultimately work in combination to increase the number of patients who have durable remissions.”

John Byrd, MD, a professor of Internal Medicine and The D. Warren Brown Designated Professorship in Leukemia Research at the OSUCCC-James, adds that current CLL therapies often suppress the bone marrow and immune system,

lobi
silvestrol

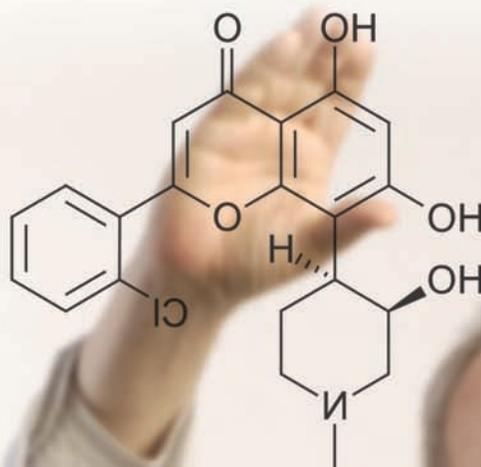
Alamtuzumab

FOXO3

JOHN BYRD, MD, professor of Internal Medicine, and The D. Warren Brown Designated Professorship in Leukemia Research and co-leader of the OSUCCC Innate Immunity Program

MICHAEL GREVER, MD, professor and chair of the Department of Internal Medicine, and co-leader of the OSUCCC Experimental Therapeutics Program

Flavonoid

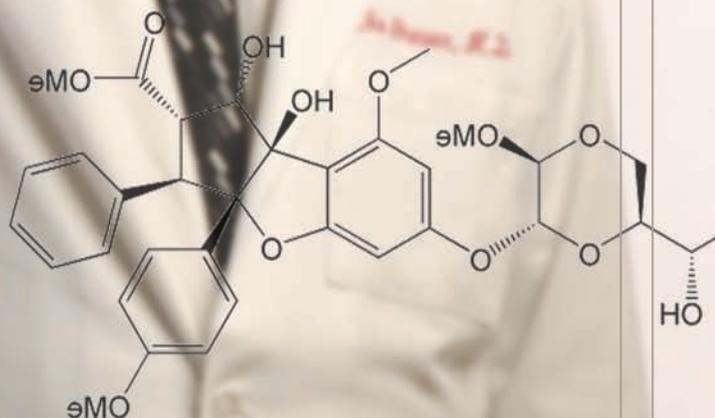


Aglyca foveolata

Rituximab

CD37-2MP

CTL



increase the risk of serious infections and make blood or platelet transfusions necessary.

New agents are needed. To develop them, Grever, Byrd and other top leukemia researchers at the OSUCCC-James are collaborating to translate basic laboratory findings into novel therapies that range from natural products and antibody-like molecules to immune modulators and epigenetic agents.

CLL usually strikes people age 50 or older, though its causes remain unknown. Malignant B lymphocytes accumulate to high levels and lose their ability to recognize antigens and produce antibodies, leaving patients vulnerable to opportunistic pathogens. The clinical course is widely variable. Some patients survive only months while others live 10 years or more.

The standard chemotherapy for CLL is fludarabine. However, as Grever, Byrd and colleagues note in a May 2009 paper in the journal *Blood*, this agent targets not only leukemic B cells but also depletes normal T cells, further eroding immunity and raising infection risk. Even when fludarabine is initially effective, patients eventually develop drug resistance and relapse through such mechanisms as dysfunction of the *TP53* tumor-suppressor pathway. “Although deletion of 17p13.1, the chromosomal site of the *TP53* gene, is uncommon in CLL at diagnosis,” they write, “this abnormality increases in frequency with disease progression.”

Treating fludarabine-resistant CLL is even more difficult. The only FDA-approved therapy is alemtuzumab,

a drug that is also lethal to T cells and can cause a range of dangerous complications, including infections, autoimmune disorders and secondary cancers. The median survival for these patients is just 13 months.

“Alemtuzumab-treated patients face a 55-percent infection rate, and half of these infections are rated as serious or life-threatening,” says David Lucas, PhD, a research scientist who manages Grever’s laboratory. “The fact that alemtuzumab was approved despite these problems indicates the critical need for new therapies for these patients.”

The goal, he says, is to find new agents that kill CLL cells, particularly the drug-resistant type, without damaging T cells or other cells. Investigators at Ohio State are pursuing multiple approaches that involve both natural and synthetic products.

ASSESSING SILVESTROL

Grever notes that nearly 40 percent of all drugs used to treat cancer are derived from natural substances isolated from plants, fungi and soil microbes. A key strategy in drug discovery, he says, is identifying and testing structurally unusual agents that show novel biological activity against human disease.

“We look for products with molecules that don’t exist in humans, that have unique chemical structures and that don’t overlap with drugs already in use,” Grever says. “If we find one of those, and it kills leukemia cells at concentrations that are potentially achievable in patients, we will want to investigate it.”

One of the most promising natural compounds investigated recently

at Ohio State is silvestrol, isolated from the Indonesian plant *Aglaia foveolata* by A. Douglas Kinghorn, PhD, DSc, the Jack Beal Professor and Chair of Natural Products Chemistry and Pharmacognosy in the College of Pharmacy.

The May 2009 *Blood* paper described for the first time silvestrol’s significant preclinical activity against B-cell malignancies. Even more encouraging, the findings from both *in vitro* studies and a mouse model suggest the agent has greater potency against B cells, including CLL cells, relative to T cells. They also demonstrate silvestrol’s effectiveness in tumor samples from patients with *TP53* deletions and its selectivity in blocking translation of the MCL1 survival protein.

“It was immediately apparent that this compound was bioactive,” says Kinghorn, an expert in natural-product drug discovery who was recruited by Grever to Ohio State in 2004. When he arrived, Kinghorn, a professor of medicinal chemistry and pharmacognosy, had already isolated silvestrol, documented its cytotoxic activity and characterized its structure and stereochemistry. The compound, he and his colleagues reported in the *Journal of Organic Chemistry*, possesses a structurally unusual carbon backbone and a side chain that is unprecedented in nature.

But by then a patent for the compound had been obtained by the Malaysian state of Sarawak, prompting the American drug company that had helped Kinghorn study silvestrol to pull out of the project.

“It seemed I was the only person in the world who cared about this compound at the time,” he recalls, explaining that, as a medicinal chemist, he had done all he could with it. “So I was really glad when Drs. Grever and Lucas shared my excitement and agreed to preclinically test silvestrol and its analogs.”

Based in part on data from the paper in *Blood* – for which Kinghorn was a co-author – the National Cancer Institute’s Developmental Therapeutics Program has agreed to further develop silvestrol in anticipation of future clinical testing.

“We then hope to submit an investigational new drug application to the FDA,” Grever says. “If that is approved, we will use the resources of the OSU Phase I program to design and conduct a clinical trial of silvestrol.” (For more about the discovery of silvestrol, see *Fractionating Forests*, page 19.)

KEEPING FLAVOPIRIDOL AFLOAT

Flavopiridol is another agent rescued from oblivion by Ohio State researchers. Grever, Byrd and colleagues consider it one of the most exciting agents ever discovered for the treatment of CLL, primarily because the drug has shown efficacy against fludarabine-resistant disease – particularly in patients with *TP53* deletion – in phase I and II clinical trials at the OSUCCC-James. Grever says it also works against bulky disease (lymph nodes greater than five centimeters in diameter) and doesn’t appear to increase the risk of severe infections as alemtuzumab does.

Flavopiridol was once written off as ineffective against human cancer by the pharmaceutical company investigating it. Grever and Byrd also found that it was ineffective when administered at the recommended dose of 24- to 72-hour

continuous infusions. But when laboratory experiments revealed that a higher dose given over just a four-hour period worked well against CLL cells, they collaborated with pharmacy colleagues to devise a four-hour dosage that maintained a similarly effective drug concentration in patients’ blood.

This led to a clinical trial in which CLL patients received half the weekly dose intravenously in a 30-minute bolus to escalate the drug level, immediately followed by the remaining half in a four-hour continuous infusion. Following this amended schedule, flavopiridol proved extremely active against refractory CLL, producing responses in approximately 40 percent of patients. Confirmation of this success in a subsequent phase II study at Ohio State, with results to be published in the *Journal of Clinical Oncology*, led to an international

FIVE FOR FIVE

SPORE grant supports further leukemia investigations

Over the past four years, a Leukemia & Lymphoma Society Specialized Center of Research Excellence (SCOR) grant has funded much of the CLL research at the OSUCCC-James. While work under this grant will continue, the NCI recently awarded Ohio State an \$11.5-million, five-year Specialized Program of Research Excellence (SPORE) grant that will help some of the cancer program’s top researchers translate basic research findings into better treatments for patients with all types of leukemia.

John Byrd, MD, is program director for the grant, in which three of five projects involve CLL. Clara D. Bloomfield, MD, cancer scholar and senior adviser at

the OSUCCC-James, and Guido Marcucci, MD, a leukemia specialist and OSUCCC-James researcher, are co-program directors. Bloomfield and Marcucci also lead the SPORE investigations of acute myeloid leukemia (AML). “This unites the strengths of the major leukemia translational investigators at Ohio State who already work closely on parallel discoveries that benefit patients with AML and CLL,” Byrd says.

The SPORE’s five projects investigate the following:

- Early predisposing genes and risk stratification for CLL.
- Molecular characterization and risk stratification of AML.
- Lenalidomide as an immune modulating agent for CLL.
- Pre-clinical and clinical investigation of MLL-PTD AML.
- Pre-clinical and clinical development of silvestrol in CLL.

registration study for FDA approval of the therapy that is currently under way.

“It’s like an expanded phase II study to show that other institutions can safely administer this therapy to patients with far-advanced disease and get good results like we have,” Grever explains. As of August 2009, more than 100 patients at more than 20 hospitals had entered the trial worldwide.

PUNCHING OUT PROTEINS

Several agents studied at Ohio State target proteins on CLL cells.

In 2003, Byrd presented to the American Society of Hematology a report from national phase II and III clinical trials in which the monoclonal antibody known as rituximab became the first of any modern therapy to show significant improvement in overall survival for CLL patients. Rituximab targets the CD20 protein on malignant B lymphocytes and spurs apoptosis, or natural cell death.

Investigators found that combining rituximab with fludarabine increased progression-free survival by 22 percent and overall survival by 12 percent compared with fludarabine alone. “The results suggest that rituximab is going to be an extremely important drug in the treatment of CLL,” says Byrd, the national study leader.

Byrd’s lab has also reported promising results from the use of TRU-016, a “small modular immunopharmaceutical” (or SMIP) agent that recognizes the CD37 protein on the surface of CLL cells. This newly engineered drug candidate attaches to CD37 and

triggers an immune response that kills the cell. In a leukemia animal model, this compound worked as well as rituximab.

“This agent is very active against CLL and is currently in phase I studies,” Byrd says, noting that it works “in a manner different from rituximab or other B-cell-directed antibodies.”

Another approach involves knocking out the MCL1 survival protein, which normally keeps immune cells healthy and promotes their development. However, Byrd and his colleagues have found that CLL cells that overexpress MCL1 are more resistant to anticancer drugs such as rituximab. Byrd says these findings, reported in the journal *Clinical Cancer Research*, “give us a rationale for targeting this protein in CLL cells and suggest that reducing MCL1 levels should enhance the action of rituximab or perhaps other agents.”

FOXD3 FINDING

A recent study led by Byrd, and published in *Proceedings of the National Academy of Sciences Early Edition*, found that a gene called *FOXD3* may play a role in CLL development because it is silenced early in the disease, even before symptoms appear, and is followed by the silencing of other genes. The findings suggest that monitoring the expression of certain genes may serve as markers for detecting CLL earlier.

“The silencing of *FOXD3* might represent a very early gene involved in the initiation of CLL that we can target for re-expression with specific drugs,” says Byrd. The

findings occurred in both human CLL cancer cells and in a relatively new animal model, the TCL1 transgenic mouse, which was developed by Ohio State cancer researcher Carlo Croce, MD, and colleagues in 2002. The TCL1 model was the first animal model for CLL and is being used by many groups to help develop new CLL therapies.

“Our data demonstrate strong similarities in gene-silencing patterns in the mouse leukemia and human CLL,” Byrd says. “We know that human CLL involves the silencing of a number of genes, but we can study it only after patients develop the disease. This mouse model allows us to look at events that lead to the disease and to identify markers for early detection and testing new therapies.”

He says *FOXD3* silencing is perhaps “the most exciting finding we have made in the laboratory. We are exploring the efficacy of several therapies that target this co-repressor complex, and we hope that one or more of these will go into the clinic soon.”

Byrd says the body of collaborative, translational work by researchers at Ohio State, as well as at other institutions, is cause for optimism about future therapies for CLL.

“Many of these therapies are directed at targets that are present in leukemia cells and not in normal cells,” he explains. “This assures a very good therapeutic index that allows effective treatment of leukemia in the absence of side effects. That really should get doctors and patients alike very excited about the future.” **f**

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU 08173 – A Randomized, Double-Blind, Multi-Center, Phase III Study of Brivanib Plus Best Supportive Care versus Placebo Plus Best Supportive Care in Subjects with Advanced Hepatocellular Carcinoma (HCC) Who Have Failed or Are Intolerant to Sorafenib: The BRISK PS Study

HYPOTHESIS: The overall survival of patients with advanced HCC who have progressed following sorafenib therapy, or who are intolerant to it, will be superior for those randomized to receive brivanib plus best supportive care as compared with patients who receive placebo plus best supportive care.

STUDY DESIGN: Double-blind, placebo controlled, randomized phase III clinical trial.

RATIONALE: HCC is diagnosed at an advanced stage in more than 80 percent of patients, precluding potentially curative therapy. The prognosis of advanced HCC largely depends on tumor characteristics, the severity of underlying chronic hepatic disease and the patient's general condition.

Systemic chemotherapy, immunotherapy and hormonal therapy have been tested in HCC with little benefit. The use of more aggressive systemic chemotherapy regimens is limited by liver cirrhosis and compromised liver function in these patients, whom clinical studies show have a median overall survival of three to seven months.

Overwhelming evidence indicates that angiogenesis is fundamentally important for the progression and dissemination of HCC. Key drivers of this process are the vascular

endothelial growth factor (VEGF) and fibroblast growth factor (FGF) pathways.

The recent regulatory approval of sorafenib demonstrates that VEGF-receptor inhibition is an effective therapeutic strategy in HCC in patients with advanced disease. However, recent findings indicate that the efficacy of sorafenib, and antibodies such as bevacizumab, is limited by activation of the FGF pathway, an angiogenic rescue mechanism that overcomes VEGF-receptor-mediated angiogenesis inhibition.

Brivanib (BMS-582664) is an oral, investigational, small-molecule inhibitor of both VEGF receptors and FGF receptors.

Preliminary results of the brivanib phase I/II development program indicate potential clinical activity in patients with advanced tumors who have received prior antiangiogenic treatments. Phase II data in advanced HCC support use of brivanib either in the frontline setting or after one prior anti-angiogenic therapy. By exerting a continuous VEGF-receptor inhibition combined with FGF-receptor pathway blockade, brivanib may prolong overall survival in HCC patients with progressive disease or intolerance to sorafenib treatment.

AT A GLANCE

Clinical trial OSU 08173

PI: **TANIOS BEKAI-SAAB, MD**, assistant professor of Internal Medicine, Division of Hematology and Oncology

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Eligibility: Histologically/cytologically confirmed HCC; Advanced disease not eligible for surgery or loco-regional therapy or progression after surgery or loco-regional therapy; Cirrhosis Child-Pugh A or B score of 7; ECOG 0-2; Life expectancy of at least 8 weeks; Cannot have brain metastases or evidence of leptomeningeal disease; No prior immunotherapy for HCC; No prior use of any systemic anticancer chemotherapy or targeted agents for HCC (except sorafenib).



NEED TO KNOW

Resources for Professional Development

▶▶ IN THE NEWS

BREAKING GROUND

ProjectONE plan approved



Architectural rendering of ProjectONE's proposed 17-story tower that will house the new cancer hospital plus a critical care hospital and outpatient and support facilities.

In September, The Ohio State University Board of Trustees approved architecture and construction plans for ProjectONE, a \$1 billion expansion project that will include a 17-story tower to house a new 276-bed James Cancer Hospital and Solove Research Institute spread over seven floors.

The tower also will hold a new five-floor, 144-bed critical care hospital. The remaining five floors

will contain outpatient and support services.

ProjectONE is one of the largest job-generating initiatives in Ohio's history.

"The new configuration and technologically advanced facilities will ease collaborations among researchers, physicians and patients, reshaping hands-on care and making possible transformational discoveries, therapies and treat-

ments," says Ohio State President E. Gordon Gee.

A new hospital is needed because inpatient admissions at The James are expected to grow by 21 percent over the next 10 years. "The James' expansion is critical to those seeking the latest advancements in diagnosis and treatment," says James CEO Michael Caligiuri, MD, who also directs Ohio State's Comprehensive Cancer Center.

"ProjectONE's state-of-the-art facilities will give scientists, researchers and clinicians the environment they need to collaborate and solve critical and complex health-related issues," Caligiuri says.

▶ SHARED RESOURCES

HELPING HANDS

Supporting clinical correlative research

The Clinical Treatment Unit and the Clinical Trials Processing Laboratory (CTU/CTPL) Shared Resources provide support to investigators conducting phase I and phase II clinical translational research studies at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

The CTU is an outpatient, phase I clinical trial unit at The James that treats patients who require intense monitoring or complex correlative sample collection and processing. The CTPL specializes in procuring correlative research specimens from the CTU and from the hospital's

inpatient care areas, and processing, storing and shipping them to outside laboratories.

“By working with the CTU and CTPL, clinical investigators can improve protocol compliance by freeing up research nurses and coordinators to focus on other protocol-related activities,” says director **LARRY J. SCHAAF, PHD**, an adjunct professor in The Ohio State University College of Pharmacy who has more than 20 years experience conducting and analyzing phase I and phase II clinical correlative trials.

“In addition, all of our staff are trained in protocol specimen requirements.”



Between January 2004 and December 2008, the laboratory procured 26,634 specimens. During 2008, the CTU/CTPL activities included the following:

- Supporting 82 therapeutic trials
- Procuring 7,983 specimens
- Shipping 1,108 sample sets, all according to IATA Dangerous Goods and DOT regulations.

OSUCCC-James events calendar

UPDATE IN ROBOTIC SURGERY IN MULTIPLE SPECIALTIES FOR THE PRIMARY CARE PHYSICIAN

February 26, 2010

FOCUS: The conference will update primary care physicians on current robotic applications and additional techniques and applications being pioneered at The Ohio State University Medical Center.

 For more information, contact Nancy Jones 614-293-3688.

13TH ANNUAL MEETING OF THE TRANSLATIONAL RESEARCH CANCER CENTERS CONSORTIUM (TRC 3)

March 1 and 2, 2010

THEME: Immune Suppression and the Tumor Microenvironment 2010
FOCUS: Physicians, surgeons, basic scientists and clinical researchers and other healthcare professionals will gain a greater understanding of how the immune system interacts with the tumor microenvironment

and biologic therapies. Presentations will highlight novel mechanisms by which the host immune system can influence responses to biologic-based cancer therapies; evaluate evidence that cellular immune-system components contribute to cancer development; and identify therapeutic strategies aimed at overcoming immune suppression associated with cancer.



Sarah E. Schmidt, sarah.schmidt@osumc.edu or 614-293-5521.

▶▶ FUNDRAISING

RIDE WRAP UP

Pelotonia '09 Raises more than \$4.5 million for cancer research at the OSUCCC–James



Pelotonia Payoff – Pelotonia representatives present a check for more than \$4.5 million to Ohio State University officials in Ohio Stadium on Oct. 31. The money will support cancer research at Ohio State's Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute. Representing Pelotonia are (from left) Andy Hutter, Kelley Griesmer, Jessica Kinman and Executive Director Tom Lennox. Holding the check are (from left) Ohio State University President E. Gordon Gee, OSUCCC Director and James CEO Michael A. Caligiuri, MD, and Peter Weiler, senior vice president for university development and president of The Ohio State University Foundation.

The 2,265 cyclists who participated in the inaugural Pelotonia bicycling excursion came from 31 states and Canada. The youngest rider was 11 and the oldest was 77, and they included renowned cycling champion and honorary chair Lance Armstrong. Together, they raised \$4,511,868.42, every penny of which is supporting cancer research at the Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute.

Pelotonia's riders were greeted by an outpouring of support along the route between Columbus and Athens in southern Ohio during the weekend of Aug. 28-30. More than 1,000 volunteers assisted the riders along the way.

"The feeling of achievement is incredibly addictive," says Tom Lennox, executive director of Pelotonia. "This was our first Pelotonia, and although we were optimistic about the success of the event, we

are even more pleased with the outcome. We are looking forward to making Pelotonia 10 an even bigger success."

Many riders said they would ride again and bring friends and family to join them in the 2010 Pelotonia, scheduled for Aug. 13-15. Registration opened Dec. 1, 2009.

"Each and every one of us has been affected by cancer in some way, and we all want to take the battle into our own hands," says E. Gordon Gee, president of The Ohio State University. "Pelotonia gives us that chance. The inaugural ride's remarkable success testifies to the tremendous partnership among individuals, communities, corporations, and the University."

Gee noted "the very real ways in which the funds raised enable our physicians and researchers to improve the lives of patients and their families."

"We need a world that's cancer-free," says OSUCCC Director and James CEO Michael A. Caligiuri, MD. "And because of Pelotonia, we have additional, much-needed funding resources that will help prevent, detect, diagnose and treat cancers."

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

STIMULUS PLAN

NIH grants awarded through the American Recovery and Reinvestment Act (ARRA) are designed to stimulate the U.S. economy by advancing scientific research. More than three dozen Ohio State cancer researchers have received ARRA funding, while other ARRA grants are supporting cancer-center growth and improvements.

ATTACK VIRUSES

Malignant brain tumors are among the most devastating human cancers. Oncolytic viruses are a promising therapeutic approach being studied by Ohio State neuro-oncologists in clinical trials, preclinical models and bench investigations of microRNA, immune modulators and angiogenesis inhibitors.