SPRING/SUMMER | 10

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

frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS

$timulating Research

As part of the nation's economic stimulus package, four OSUCCC-James researchers receive a 'grand opportunity' to spur research on cancer prevention, prediction and targeted therapies.

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

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

UPFRONT

The Director's Perspective

Forward Moves

New administrative leadership, two new divisions and a new division director

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

I have several exciting developments to share with you.

First, we are pleased to announce that Jeff Walker is returning to The Ohio State University to become the first executive director of our cancer program, effective June 1. Jeff will oversee all administrative, operational and fiscal functions for the OSUCCC-James, both clinical and research.

Jeff served as associate director for administration at Ohio State's Comprehensive Cancer Center from 2001 to 2007. He then joined Roswell Park Cancer Institute in Buffalo, which, like our own James Cancer Hospital and Solove Research Institute, is a free-standing, PPS-exempt cancer hospital. As executive vice president, he oversaw the cancer center's clinical and research operations.

Jeff's experience and unique perspective will help move us toward our goal of becoming one of the nation's top ten cancer programs.

In another exciting development, Ohio State's Department of Internal Medicine has replaced the former Division of Hematology and Medical Oncology with an independent Division of Medical Oncology and an independent Division of Hematology. Having two distinct divisions will ensure the highest quality of patient care, education and research.

I am also pleased to announce that Miguel Villalona, MD, an outstanding leader from within our own ranks, was chosen to direct the new Division of Medical Oncology. He will also continue to direct our solid-tumor experimental therapeutics program.

A native of the Dominican Republic, Miguel is internationally recognized for his work in experimental therapeutics and lung cancer. He is an NCI-funded scholar and a member of the NCI investigational drug steering committee. He is an outstanding mentor, and as a member of the American Association for Cancer Research Council on Minorities in Cancer Research, and in other ways, he works to enhance minority scientist career development.

I hope you enjoy this issue of *Frontiers* and its stories about oncolytic virus therapy, how stimulus grants are furthering cancer research and the value of translational research. Read it as you travel to the American Society of Clinical Oncology meeting June 4-8 in Chicago.

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

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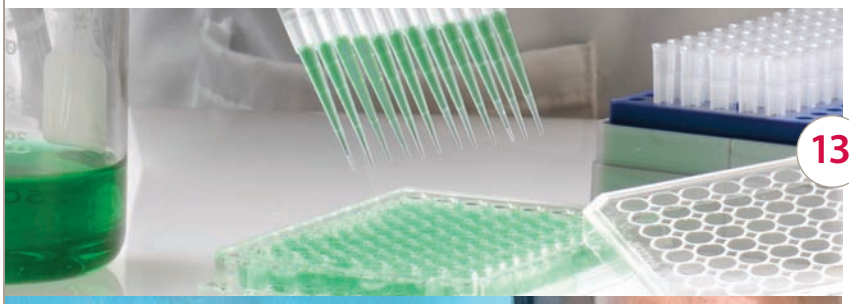

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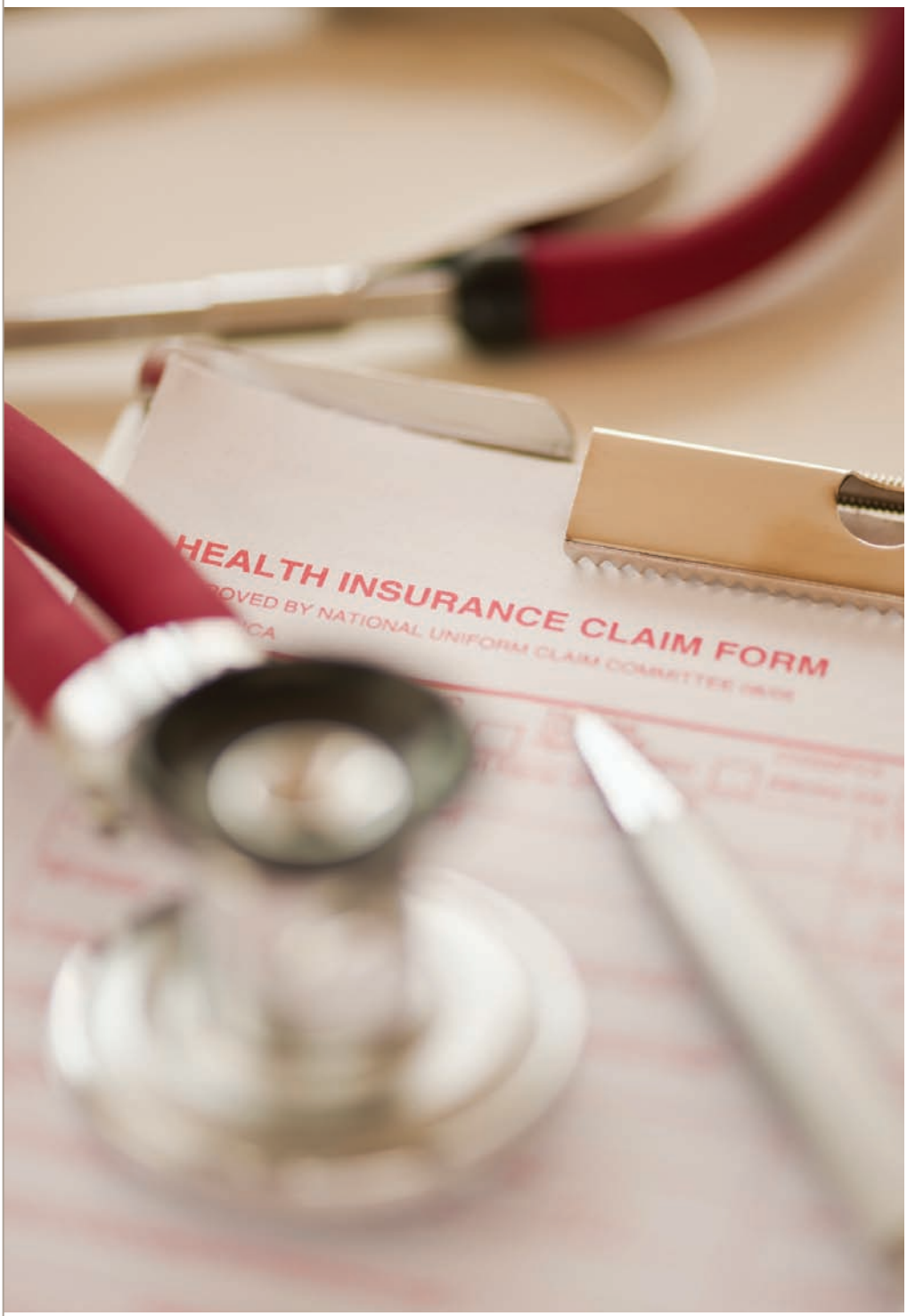


A NEED MET

Federal healthcare legislation addresses routine care during clinical trials

By **JENNIFER CARLSON**
Assistant Vice President for Government Affairs, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

In March, President Obama signed into law a historic bill that extends healthcare coverage to millions of Americans who previously could not afford to purchase it. Included in the legislation is a provision ensuring coverage for individuals who participate in approved clinical trials. The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) was instrumental in adding that component of the bill,

which was modeled after a clinical trials bill passed by the Ohio legislature in 2008.

Clinical trials are the cornerstone of cancer research. They lead to better treatments, improve patient survival and have a positive effect on the nation's economy as well as on the local economy.

Without clinical trials we cannot discover new cancer drugs and better treatments, and without volunteers we cannot conduct trials.

But running a clinical trial from start to finish is complicated and expensive. While the nation's cancer centers, represented by the Association of American Cancer Institutes, work to untangle red tape and other factors that can derail trials, a serious obstacle has remained largely beyond their control—the cost to patients of participating in trials.

This is why the language about clinical trial coverage, sponsored by Senators Sherrod Brown (D-Ohio) and Kay Bailey Hutchison (R-Texas), was so important to include in the federal healthcare reform act.

Commercial health insurers often refuse to pay the cost of routine care that is associated with a clinical trial, arguing that the trial is "experimental" and thus optional or unnecessary. Consequently, many patients experience financial difficulties that prevent them from participating in trials. That, in turn, negatively affects the clinical study and patients' ability to receive promising treatments that are available only through trials, and it slows the development of new cancer therapies.

Routine costs associated with clinical trials include physician visits, blood work, hospital stays and X-rays. These costs would usually be reimbursed by the insurer if the patient were not participating in a clinical trial. The experimental portion of the trial—usually a new drug—is provided at no charge to the patient or the insurer.

About 30 percent of the insured volunteers participating in clinical trials at the OSUCCC-James experience such insurance claim denials of payment for routine care. Denials tend to occur with Medicare Advantage, HMO and PPO plans, and with insurance plans that are based outside the state where the trial is conducted.

Since 1994, 27 states and the District of Columbia have passed laws requiring insurance coverage for routine patient-care costs when patients participate in clinical trials. Another five states have established cooperative agreements with insurers to do so. However, beyond the patchwork nature of such coverage, some of these laws do not necessarily require insurers to cover all cancer patients, such as those in phase I or II clinical trials, or those with employer self-insured plans, in which a large company self-insures its employees.

Clearly, only a federal policy can guarantee that someone will be there to pay for the routine costs for cancer patients who enroll in a potentially life-saving clinical trial.

With no more than 5 percent of adult cancer patients participating in clinical trials, attracting volunteers to trials has been a long-standing struggle for cancer researchers. And yet, thanks in large part to advances realized through clinical trials, two-thirds of cancer patients now survive at least five years after diagnosis, compared with only half of patients a generation ago.

By 2020, the country will be in the midst of a massive demographic shift that will double the number of Americans age 65, moving 78 million people into the age group at highest risk for cancer. Fortunately, we are now in a better position to increase participation in clinical trials and prevent more cancer deaths.

OVERALL CANCER

AMISH ADVANTAGE

Study Shows Clean Living May Lower Cancer Rates

When Ohio State researchers began studying a sect of Amish living in Ohio, they theorized they would find higher incidence rates of cancer, mainly because Amish religious beliefs and traditions limit contact with mainstream society, and intermarriage within their relatively small population could increase cancer-related gene mutations.

But they found just the opposite, says **JUDITH WESTMAN, MD,** clinical director of the Division of Human Genetics in The Ohio State University College of Medicine. Westman says the Amish study suggests that clean living can lead to a healthier life.

Overall cancer rates in this population were 60 percent of the age-adjusted rate for Ohio and 56 percent of the national rate. The incidence of tobacco-related cancers among Amish adults was 37 percent of the rate for Ohio adults, and the incidence of non-tobacco-related cancer was 72 percent.

"The Amish are at an increased risk for a number of genetic disorders, but they probably have protection against many types of cancer both through their lifestyle and through genes that may reduce their susceptibility to cancer," says Westman, who co-authored the study with **AMY FERKETICH, PhD**, a researcher with the OSUCCC-James' Cancer Control Program.

The study, which spanned 1996-2003 and is the first of its kind, looked at the incidence of 24 types of cancer among the Amish. Of those 24, the incidence of seven of them – cervical, laryngeal, lung, oral cavity/pharyngeal, melanoma, breast and prostate – was low enough compared with the Ohio rate to be statistically significant.

Westman and Ferketich say the low cancer incidence in the Ohio Amish may be partially explained by lifestyle factors such as limited tobacco and alcohol consumption, lack of sexual promiscuity, active or labor-intensive lifestyles, and proper dress for avoiding sunlight exposure when working outdoors.

Published January 2010 in Cancer Causes & Control.

PROSTATE CANCER

PROSTATE PROGNOSTICATION

Blood-vessel viewing may predict tumor behavior

A prostate cancer diagnosis raises an important question for physicians and their patients: Will the tumor grow quickly, requiring continuous treatment, or slowly, allowing therapy and its risks to be safely delayed?

The answer may lie in the size and shape of blood vessels within the tumor, according to research led by The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC-James) in collaboration with the Harvard School of Public Health.

A study of 572 men with localized prostate cancer indicates that aggressive tumors tend to have blood vessels that are small, irregular and primitive in cross-section, while vessels in indolent tumors look more normal.

"It's as if aggressive prostate cancers grow faster, and their blood vessels never fully mature," says study leader **STEVEN CLINTON, MD, PhD,** a prostate cancer specialist and researcher at the OSUCCC-James. "Prostate cancer is heterogeneous, and we need better tools to predict whether a patient has a form that is aggressive, fairly average or indolent so we can better define a course of treatment – surgery, chemotherapy, radiotherapy, hormonal therapy, or potentially new drugs that target blood vessels – that is specific for each person's type of cancer."

THE RESEARCHER

STEVEN CLINTON, MD, PhD,
professor of Internal Medicine, and a prostate cancer specialist at the OSUCCC-James

After an average follow-up of 10 years, 44 of the 572 men in this study had developed metastatic cancer or died of their cancer. Men whose tumors had smaller vessel diameters were six times more likely to have aggressive tumors and die of their disease, and those with the most irregularly shaped vessels were 17 times more likely to develop lethal prostate cancer.

The findings, which were independent of Gleason score and prostate specific antigen (PSA) level, apply to men with local disease, whose PSA is only modestly elevated, and who are younger and more likely to choose surgery. "If our findings are validated by larger studies, the measurement of tumor blood vessel architecture might help determine choice of therapy," Clinton says.

Published Nov. 20, 2009, in the Journal of Clinical Oncology.

STEM CELLS

ROLE REVERSAL

Stem cell activators switch function, repress mature cells

THE RESEARCHER

GUSTAVO LEONE, PhD,
associate professor of Molecular Virology, Immunology and Medical Genetics at the OSUCCC-James.

In a developing animal, stem cells proliferate and differentiate to form organs. A new study shows how a crucial step in this process happens and how a reversal of that step contributes to cancer.

The study, led by researchers at the OSUCCC-James, shows for the first time that three proteins – E2f1, E2f2 and E2f3 – play a key role in the transition that stem cells make to their final differentiated state.

These proteins stimulate stem cells to proliferate, but once the cells begin to differentiate into their final type, the proteins switch function and stop them from dividing.

The research also shows how these proteins can switch course yet again in cells that have mutations in the retinoblastoma (*Rb*) gene. Mutated *Rb* genes occur in many cancers, suggesting that E2f proteins might offer a safe therapeutic target in these tumors. "We show that these E2fs are gene activators in stem cells but then switch to gene repressors when stem cells begin differentiating," says study leader **GUSTAVO LEONE, PhD**. "This is a very important step in differentiation. As organs form, there comes a time when their growth must stop because an organ needs only a certain number of cells. The switch by these proteins from activators to repressors is essential."

Before, no one suspected that these regulatory proteins had any role in differentiated cells, Leone says. "It was thought they were important only in proliferating cells like stem cells. But that's not true."

Leone and colleagues show the function of the proteins in differentiation in mouse embryos, retinas, lenses and intestines. They also show how the three proteins could revert back to gene activators in cancer cells and promote tumor growth in cancers with *Rb* mutations.

Published Dec. 17, 2009, in back-to-back papers in Nature.

LEUKEMIA

WHEN BAD IS BETTER

Mutated gene a good sign for older leukemia patients too

Almost half of people younger than 60 with acute myeloid leukemia (AML) may be cured, but that number plunges to 5-16 percent for people 60 and older.

A study at the OSUCCC-James indicates that some older AML patients whose cancer cells have *NPM1* gene mutations respond better to therapy and survive longer.

Mutations in this gene signal a favorable prognosis in younger patients with AML; this new study indicates that the same is true for older patients, suggesting that they should be offered stronger therapy.

"These findings were completely unexpected," says study leader **CLARA D. BLOOMFIELD, MD**, a Distinguished University Professor who serves as cancer scholar and senior adviser to the OSUCCC-James. "Even patients over 70 who have *NPM1* mutations do better than those with the normal gene. This study supports the importance of understanding and thinking positively about what we can do for older people with leukemia."

Bloomfield and colleagues examined the outcomes of 148 AML patients 60 and older with normal cytogenetics, a feature seen in more than half of adults with AML. All of the patients had been treated through one of two national clinical trials sponsored by the Cancer and Leukemia Group B (CALGB).

Overall, 83 patients (56 percent) had *NPM1* mutations. Of those, 84 percent had a complete remission, compared with 48 percent of patients whose cancer cells had a normal *NPM1* gene. Patients with the mutated gene also had a significantly higher three-year survival rate: 35 percent compared with 8 percent.

"The favorable response of patients with *NPM1* mutations suggests these mutations may represent a marker that can be used to stratify older patients with cytogenetically normal AML to intensive chemotherapy, which is often avoided in older patients," says co-author Guido Marcucci, MD.

Published Feb. 1, 2010, in the Journal of Clinical Oncology.

MATHEMATICAL MODEL

Curing cervical cancer cases may be in the numbers

Cervical cancer is curable when caught early, but in a third of cases the tumor either responds poorly to therapy or recurs later, when it is more difficult to cure.

Quicker identification of non-responding tumors may be possible using a new mathematical model developed by researchers at the OSUCCC-James. The model uses information from MRI scans taken before, during and after therapy to monitor changes in tumor size. That information is plugged into the model to predict much earlier whether a case is responding well to treatment. If not, the patient can sooner be offered a more aggressive or experimental therapy.

The study used MRI scans and outcome information from 80 cervical cancer patients receiving a standard curative course of radiation. "The model enables us to better interpret clinical data and predict treatment outcomes for individual patients," says principal investigator and radiation physicist **JIAN WANG, PhD.**

"The outcome predictions presented in this paper were based solely on changes in tumor volume as derived from MRI scans, which can be easily accessed," Wang says. "The model is very robust and can provide a prediction accuracy of 90 percent for local tumor control and recurrence."

A strength of the model, says first author **ZHIBIN HUANG, PhD**, is its use of MRI data to estimate three factors that play key roles in tumor shrinkage and that vary among patients: the proportion of tumor cells that survive radiation exposure; the speed at which the body removes dead cells from the tumor; and the growth rate of surviving tumor cells.

The model is applicable to all cervical cancer patients, and the investigators are developing a model that can be applied to other cancer sites, Wang says.

Published Jan. 15, 2010, in Cancer Research.

TARGETING T CELLS

Multicenter study reduces transplant risk in AML patients

THE RESEARCHER

STEVEN DEVINE, MD,
director of the Blood and Marrow Transplant Program

Patients with acute myeloid leukemia (AML) who were treated as part of a multicenter study by the Blood and Marrow Transplant Clinical Trials Network had excellent survival and a low risk of graft-vs.-host disease, the major complication of transplantation.

STEVEN DEVINE, MD, director of the Blood and Marrow Transplant Program at the OSUCCC-James, was co-chair and first author of the study.

During the three-year study at eight centers, 44 AML patients received allogeneic stem cell transplants from related donors whose immune system markers were identical to those of the patients. This type of transplant is the most effective means of preventing relapse in AML patients who are in complete remission but at high risk for relapse.

Graft-vs.-host disease occurs in 30-40 percent of patients who receive transplants from related donors, limiting the use of this otherwise curative procedure. The disease is most effectively prevented by removing the T cells that cause it from the donor graft via T-cell depletion. However, Devine says T-cell depletion is not often used because there is no FDA-approved method for it.

"We designed a clinical trial for adult AML patients that used a single processing method for depleting T cells that did not require post-transplant graft-vs.-host disease prophylaxis," Devine says. Since the T cells were removed ahead of time, none of the patients had to be on drugs to prevent rejection or graft-vs.-host disease.

After six months, 81 percent of patients in the study had achieved disease-free survival, and 64 percent maintained disease-free survival at one year. The results are close to what is observed using other current transplant procedures, but with fewer complications related to graft-vs.-host disease. Devine says the study confirms the feasibility of using a uniform method of T-cell depletion.

Presented at the 51st Annual Meeting of the American Society of Hematology, December 2009.

LEUKEMIA

PROTEIN PICKOFF

Targeted agent prolongs survival in chronic leukemia model

Current therapies for human chronic lymphocytic leukemia (CLL) often damage the immune system, leading to infections that are the primary cause of death for these patients.

But an experimental oral agent called 17-DMAG may help overcome this problem, according to a study by researchers at the OSUCCC-James.

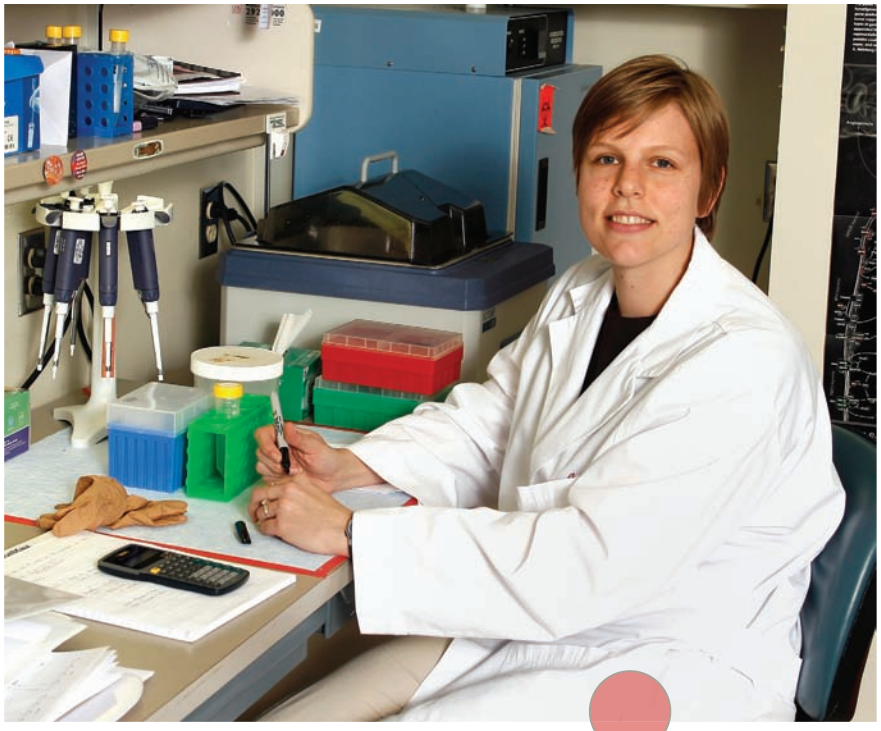
The laboratory and animal findings indicate that this agent is highly selective for CLL cells and has minimal effect on normal immune cells, suggesting that it may leave a patient's immune system healthy, the researchers say.

"This agent turns off multiple proteins that cancer cells need to survive, and we show that this activity occurs both in CLL cells from patients and in a CLL mouse model," says study leader **AMY JOHNSON, PhD**. "Our findings strongly support testing this agent in CLL patients in a phase I clinical trial."

The research showed that the drug significantly prolonged survival in a CLL mouse model. Animals treated with the agent survived an average of 75 days, compared with 66 days for animals that didn't receive it.

The agent works by inhibiting the action of protein HSP90, which is active mainly in CLL cells. This protein accompanies and protects other proteins as they are being made by CLL cells.

These other proteins include AKT, RAF and Zap-70, all of which are important for the survival and growth of the cancer cells. Blocking the protective protein leads to destruction of the other proteins.



In addition, the agent reactivates a gene called *FOXD3*. This same research group showed in previous work that *FOXD3* is silenced early during human CLL development, a change that likely plays an important role in CLL progression.

Presented at the 51st Annual Meeting of the American Society of Hematology, December 2009.

THE RESEARCHER

AMY JOHNSON, PhD, *assistant professor in the Division of Hematology and Oncology and a researcher with the OSUCCC-James*

OF NOTE

Recent Recognitions of OSUCCC-James Physicians and Researchers

GRANTS

MARY ELLEN WEWERS, PhD, MPH, *professor of Health Behavior and Health Promotion, College of Public Health, and co-leader of the Cancer Control Program,* **has received a five-year, $2,974,000 grant from the NCI** *for a study titled Tobacco Cessation Interventions with Ohio Appalachian Smokers.*

AMANDA EWART TOLAND, PhD, *assistant professor of Molecular Virology, Immunology and Medical Genetics and a member of the Human Cancer Genetics Program,* **has received a three-year, $1,245,000 grant from the NCI** *for a study titled Genetic Interactions in Colorectal Cancer Susceptibility.*

GARY STONER, PhD, *faculty emeritus of Hematology and Oncology, and professor of Pathology and of Human Nutrition,* **has received a four-year, $1,762,000 grant from the NCI** *for a study titled Prevention of Esophageal Cancer with Berries.*

AWARDS AND HONORS

MICHAEL GREVER, MD, *professor and chair of the Department of Internal Medicine and co-leader of the OSUCCC-James Experimental Therapeutics Program,* **has been elected to the Association of American Physicians**, *an organization closely allied with the American Society for Clinical Investigation. William Osler was a founding member of the organization, which today includes Nobel Laureates and members of the National Academy of Sciences and the Institute of Medicine.*

The **DIVISION OF PLASTIC SURGERY** **has received two awards from the American Society of Reconstructive Microsurgery, one for "Best Case of the Year" and the other for "Best Save of the Year."** **MICHAEL MILLER, MD,** *professor and division director, says the awards are particularly noteworthy because the University has never before participated in this competition, and no university has ever won both awards at the same meeting.*

PROGRAMS

SUSAN GEYER, PhD, *has joined the cancer program as an* **associate professor in the Division of Hematology and Oncology** *and as a* **senior biostatistical scientist in the Center for Biostatistics**. *Formerly, Geyer was an associate senior scientist at the National Academy of Sciences, working with the Radiation Effects Research Foundation in Hiroshima, Japan. Her research interests include evaluating high dimensional and potentially correlated data (e.g., complete immune function data and imaging data), longitudinal data analysis and clinical trial designs for targeted therapy.*

The U.S. Food and Drug Administration has approved a phase I clinical trial *for an agent designed and synthesized in the laboratory of OSUCCC-James researcher* **CHING-SHIH CHEN, PhD,** *professor of Medicinal Chemistry, of Internal Medicine and of Urology. The agent, AR-42 (OSU-HDAC42), is a histone deacetylase inhibitor that shows promise in leukemia, multiple myeloma, lymphoma and prostate cancer. Chen's lab also designed and synthesized an earlier drug, AR-12 (OSU-0312), which in preclinical models inhibited solid tumors and lymphoma and is now in phase I testing.*

LEADERSHIP

Research from the lab of **MAURA GILLISON, MD, PhD,** *medical oncologist and head and neck cancer specialist,* **has been highlighted for the third consecutive year by the American Society of Clinical Oncology (ASCO)** *in its annual report of important clinical advances.*

SCOTT JEWELL, PhD, *associate director for biorepository and biospecimen resources at the OSUCCC-James,* **has been elected as president-elect of the International Society for Biological and Environmental Repositories (ISBER) for 2010-11.**

MICHAEL LAIRMORE, DVM, PhD, *associate director for basic sciences at the OSUCCC-James,* **has been elected president of the American College of Veterinary Pathologists.** *The College fosters excellence in veterinary pathology to protect and improve animal, human and environmental health to benefit society.*

CLAY MARSH, MD, *executive director of the Center for Personalized Health Care and director of the Center for Critical Care at The Ohio State University Medical Center,* **has been named to the Personalized Medicine Coalition's (PMC) board of directors.** *The PMC is an educational and advocacy group comprising pharmaceutical, biotechnology, diagnostics and information technology companies, as well as major academic institutions and governmental agencies.*

CARLO CROCE, MD, *who leads the Human Cancer Genetics Program at Ohio State,* **is included in the list of the world's "12 Hottest Researchers" for 2009** *compiled by Thomson Reuters Science Watch. Researchers on the list have published the most "hot papers" in the last two years as derived from Thomson Reuters' Web of Science℠ database. Croce was also named in the 2008 list.*

$timulating Research

Four OSUCCC-James researchers receive 'grand opportunity' grants to spur research on cancer prevention, prediction and targeted therapies.

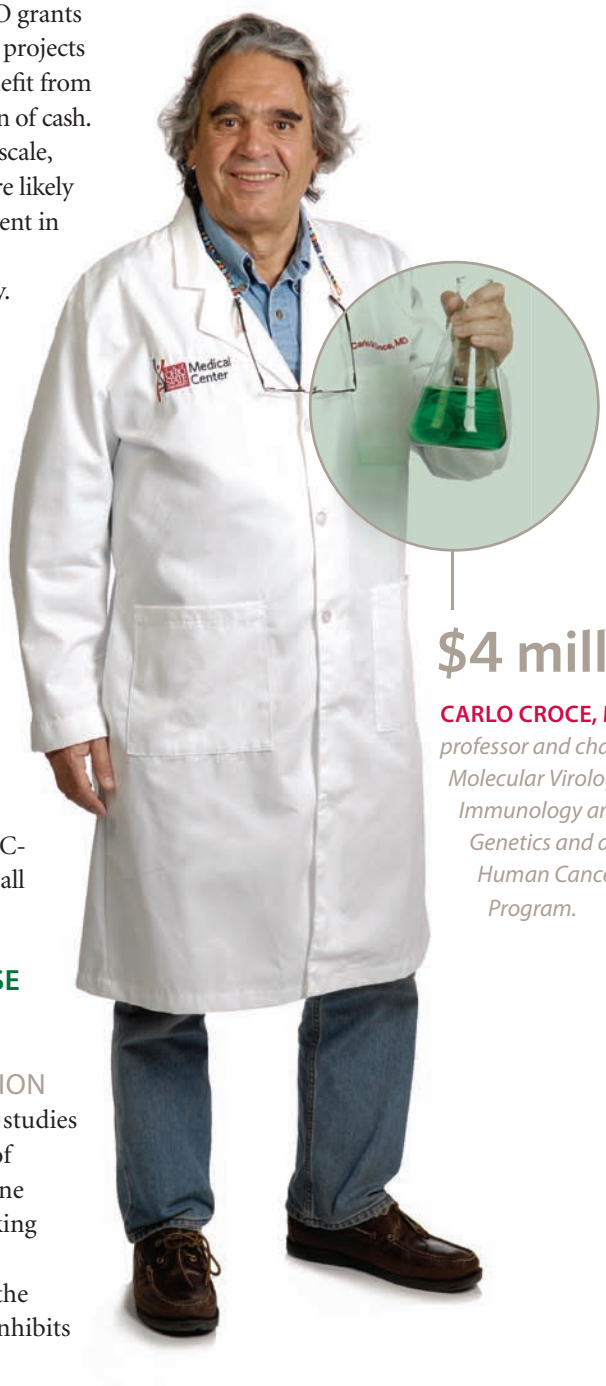
BY KENDALL POWELL
PHOTOGRAPHY BY ROMAN SAPECKI

When President Barack Obama signed the American Recovery and Reinvestment Act (ARRA) into law on February 17, 2009, it meant an influx of $787 billion to stimulate the U.S. economy. It included $8.2 billion to fund new biomedical research projects, and $1 billion for building new laboratory facilities through the National Institutes of Health.

The NIH designated the ARRA money to fund projects that would stimulate the economy, create new jobs or retain existing jobs, and that had the potential to make scientific progress within two years. To date, Ohio State University researchers have been awarded 174 grants totaling $82 million from the ARRA funds, with $42 million of that going to 42 researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC-James). The cancer center also received two construction grants from ARRA funds totaling $11.9 million (see "Concrete Results," page 17).

Four cancer center investigators received "Grand Opportunity" grants, also known as GO grants, totaling $7.3 million. In the same way that the total ARRA funds are meant to jump-start the economy with new jobs, construction projects and tax breaks, the NIH GO grants are meant to boost research projects that would significantly benefit from a one-time, two-year infusion of cash.

GO grants support large-scale, high-impact projects that are likely to spur growth and investment in biomedical research, public health or healthcare delivery. They must also be projects that researchers can deploy immediately and that have a budget greater than $500,000 per year for two years. They might be projects that require collaboration across laboratories or institutions, that create new research methods or unique data sets or that partner with industry and small businesses to accelerate the testing of new therapies. The OSUCCC-James GO grants exemplify all of these.



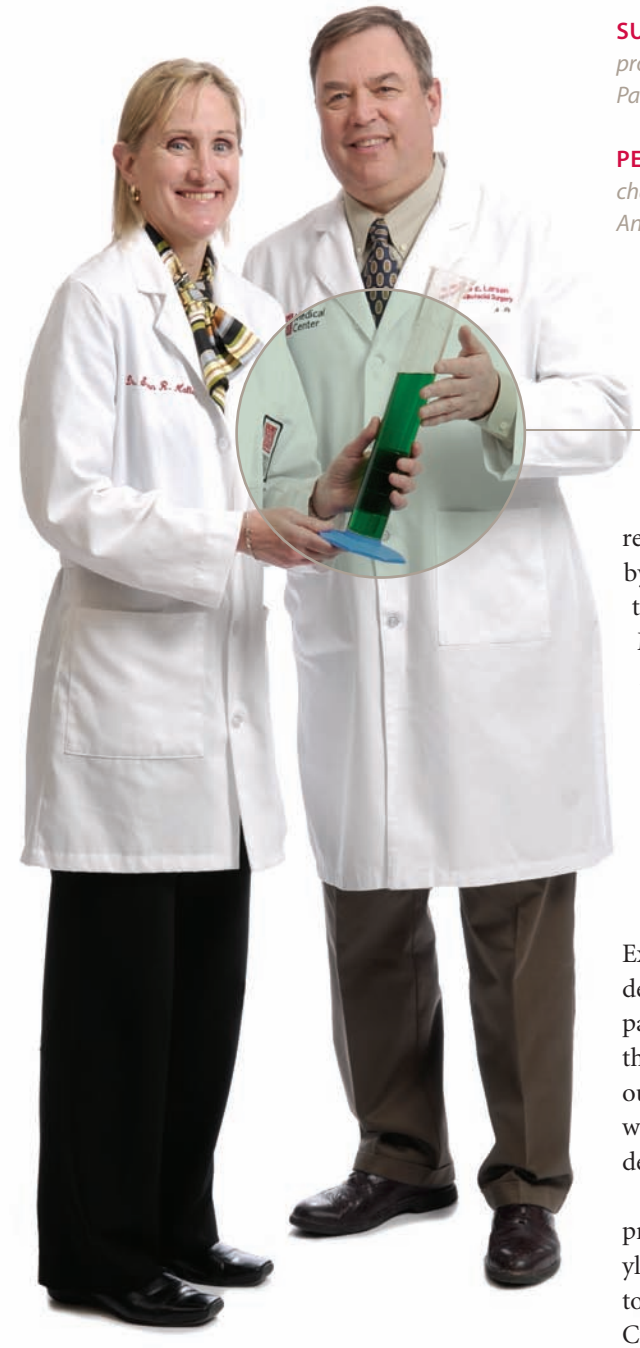
$4 million

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

PREDICTING RESPONSE TO THERAPY WITH microRNA

TOTAL GRANT: $4 MILLION

Carlo Croce's laboratory studies microRNA, a large family of molecules that regulates gene expression usually by blocking translation. Croce and his colleagues discovered that the microRNA called miR-29 inhibits



SUSAN MALLERY, DDS, PhD,
professor, Division of Oral Surgery, Pathology and Anesthesia

PETER LARSEN, DDS,
chair of Oral and Maxillofacial Surgery, Anesthesiology and Pathology

$1.3 million

DNA methyl transferases (DNMTs), enzymes that aberrantly methylate DNA and silence tumor-suppressor genes in cancer cells. The investigators also found that when mutations shut down miR-29, tumor-suppressor genes are also silenced, facilitating tumor progression.

"We speculated that we can reactivate these tumor suppressors by reintroducing miR-29s into cells that had lost them," says Croce, MD, professor and chair of Molecular Virology, Immunology and Medical Genetics and director of the Human Cancer Genetics Program. His group showed that was true in cell culture.

Targeted agents already exist that work by demethylating tumor-suppressor genes. Examples include 5-azacytidine and decitabine. Croce reasoned that if patients had lost the miR-29s, then their DNMTs were operating without regulation, and these patients would more likely respond to demethylating agents.

Using a test for miR-29, "We can predict the response to the demethylating agents, who should respond to the drugs and who will not," says Croce. "These are very toxic drugs, so you don't want to treat a patient with a harmful drug if the patient will not respond to it."

Croce's GO grant will fund three small clinical trials to test this idea in three cancer types: acute myelogenous leukemia, lung cancer and the aggressive form of chronic lymphocytic leukemia. Croce says this is critical to find better ways to "stratify" patients as cancer treatments become increasingly targeted to specific genetic problems. This work will also lay the foundation for developing a targeted therapy that would deliver miR-29s to patients whose tumor cells have lost them. "We know how to do this in mice and rats, but not yet how to deliver them to humans," says Croce.

A BIOADHESIVE BERRY GEL FOR ORAL CANCER

TOTAL GRANT: $1.3 MILLION

As an oral pathologist, Susan Mallery spends much of her time peering down a microscope at the precancerous and cancerous lesions removed from patients' mouths. It frustrates her that these lesions return in about one-third of patients, and that one-third of these recurring lesions progress to oral squamous cell carcinoma, a malignancy that affects 35,000 Americans per year.

Mallery, DDS, PhD, professor in the Division of Oral Surgery, Pathology and Anesthesia, and her colleague, oral surgeon Peter Larsen, DDS, chair of Oral and Maxillofacial Surgery, Anesthesiology and Pathology, have seen firsthand how debilitating this recurrent disease and its treatment can be. Repeated surgery in the highly sensitive areas of the tongue, lips and floor of the mouth is often necessary. It can be disfiguring, and recovery can be painful.

They would like to offer patients a chemopreventive agent that prevents these lesions from progressing or recurring. Gary Stoner, PhD, an emeritus professor in the College of

Medicine, studies natural products that are potential chemopreventive agents. He found that black raspberries contained high levels of four anthocyanins, natural compounds that are antioxidants and have anticancer properties. When he fed the berries to rats as 10 percent of their diet, it inhibited esophageal cancer.

But the investigators knew that patients are unlikely to eat that quantity of berries, and that anthocyanins are absorbed poorly from the digestive tract. They chose a method that delivers a higher dose of the treatment directly to the precancerous cells in the mouth.

"Gary's very promising animal studies, my interest in local delivery formulation, and Pete's observations on our patients all came together and we decided on a bioadhesive gel," says Mallery.

The team developed a gel that is 10 percent freeze-dried black raspberries and tested it in a pilot phase I clinical trial on a small group of patients that included 10 healthy controls and 20 with premalignant lesions. The patients applied the gel four times a day—after meals and before bed—for six weeks. That initial test showed that the gel decreased some genetic markers of progression for some patients.

The GO grant will allow the team to test the gel in a larger, more complex phase I/II trial that will also include the University of Louisville and the University of North Carolina Chapel Hill. That trial will compare the gel's effects against a placebo, and it will test how patients respond to and metabolize the gel.

"We had some patients with higher-grade lesions who responded extremely well," says Mallery. "We even had patients where the lesions clinically disappeared." But some patients seemed to be refractory to the treatment, and she'd like to know what controls those different responses.

"Quality of life for our citizens is worth a lot of money," says Mallery. "If we find an effective way to prevent progression or induce regression of this cancer, then we'll have that many more citizens in the workforce, getting more pleasure from life and not facing another surgery on their mouth."

A VACCINE FOR EBV LYMPHOMA

TOTAL GRANT: $1 MILLION

Even though 95 percent of Americans are infected with the Epstein-Barr virus (EBV), the virus that causes mononucleosis, for most of us it amounts to little more than a nuisance infection during our college years. "Patients with intact immune systems can fight it off, and it doesn't give them as much grief," explains Robert Baiocchi, MD, PhD, assistant professor in the Division of Hematology and Oncology.

But for Baiocchi's HIV patients with compromised immune systems, the virus can lead to deadly lymphoma. The good news, he explains, "is that EBV-caused lymphomas are in theory preventable, if we can boost the patient's immune response."

Toward that goal, Baiocchi's group is designing an EBV vaccine including multiple full-length viral proteins that will present multiple antigens. "We believe this will evoke a much more robust immune response," Baiocchi says.

EBV has more than 90 proteins that could be used in a vaccine. Baiocchi and his colleagues have already identified one protein, called BZLF1, that when detected by a lymphoma patient's immune system correlates with survival and tumor regression. They are incorporating it into a vaccine that will be tested in a phase I safety trial.

His team will use the GO grant to generate four or five more EBV proteins for use as vaccine components that can be tested in clinical trials. Ultimately, Baiocchi believes it will take a vaccine with multiple components, including viral proteins and adjuvants, to prevent these lymphomas. Funding from the Leukemia & Lymphoma Society of America supported his group as they took the BZLF1 vaccine from the lab to animal models and finally to testing in patients. The GO grant "allows us to discover new targets and put them into that same pathway of development that already exists," he says.

His group will partner with local biotechnology companies that can produce the different vaccine components. Each viral protein they verify in the lab as immune-boosting will need to be grown, purified, tested for toxicity and manufactured into a vaccine that can be tested in a phase I trial. "Even if we just discover two or three target viral proteins that are attractive, each will need to go into the next phase of development. This is a strategy that needs to be

ROBERT BAIOCCHI, MD, PhD,
assistant professor in the Division of Hematology and Oncology.

$1.3 million

tried because these are preventable cancers."

SORTING MOLECULAR MARKERS FOR GLIOBLASTOMAS

TOTAL GRANT: $2.5 MILLION, OSU SUBCONTRACT IS $1 MILLION

In the 1990s the Radiation Therapy Oncology Group (RTOG), an international oncology cooperative, developed a system for categorizing glioblastoma—one of the most devastating of human tumors—into six prognostic groups, from best to worst survival times. This model, called a recursive partitioning analysis, was largely based on the clinical features of patient tumors and on patient demographics.

But Arnab Chakravarti, MD, professor and chair of Radiation Oncology and co-director of the Brain Tumor Program, wants to update that model, largely because of two recent advances. First, research has uncovered molecular, genetic and epigenetic traits that are important for glioblastoma progression or that play a key role in treatment resistance. Second, the standard of care for these tumors has evolved to include not only surgery and radiation, but also the chemotherapy drug temozolomide (TMZ) during and after radiation treatment, explains Chakravarti, who is also chair of the RTOG Brain Tumor Translational Research Group.

Because of this, Chakravarti and the RTOG believe that including new variables about the particular molecular signatures of each patient's tumor and their response to radiation-plus-TMZ or other treatments will greatly improve the prognostic model.

In one study, for example, patients whose tumor cells had a methylation mark that silences a DNA repair gene called *MGMT* had improved outcomes with TMZ treatment. "Patients without this methylation did not appear to reap any extra benefit from the addition of TMZ," says Chakravarti. In other words, TMZ is more effective when the *MGMT* gene is not expressed. Certain other molecules, such as a mutated version of the epidermal growth factor receptor, permit cancer cells to resist the effects of radiation and chemotherapy.

Charting these molecular signatures will improve doctors' ability to stratify patients. It will help determine which current or experimental therapies will most benefit individual patients, and it will guide the development of new molecular-based therapies.

To refine the classification model, Chakravarti and his collaborators at MD Anderson Cancer Center in Houston, Texas, will use the GO grant to analyze tissue samples taken from about 2,000 glioblastoma patients from North America, Europe and Asia. The team will assess the samples for a panel of about 30 key molecular, genetic and epigenetic markers and correlate them with patient responses to radiation-plus-TMZ treatments and patient outcomes.

"Our ultimate objective is to identify molecular markers for treatment resistance mechanisms in cancer cells, then take those

back to the lab and find ways to overcome those mechanisms," says Chakravarti. To accomplish this and move potential therapies into the clinic, at the end of the two-year GO grant Chakravarti and the RTOG plan to apply to the NIH for a Specialized Programs of Research Excellence (SPORE) grant to continue this work. At $2.5 million per year for five years, SPORE grants are among the largest grants awarded by the NIH.

A BOON FOR OHIO AND THE NATION

For these OSUCCC-James researchers, calling these "stimulus grants" means something slightly different for each investigator.

Baiocchi sees his grant leading to partnerships with local biotechnology companies and to the workforce needed to support all the steps necessary to produce and test the new vaccines against EBV. Chakravarti's effort to profile almost 2,000 cases of glioblastoma—the largest data set to date for brain tumors—will bring many new employment opportunities for scientists.

"This could be a huge benefit to the economy both of Ohio and nationwide. These findings will likely lead to diagnostic and prognostic platforms for brain tumor patients, and that will require hands on deck to manufacture these platforms and get them out to the medical community at large," he says.

Recently, while discussing experiments, one of Mallery's postdoctoral fellows slipped in the comment, "I know you don't like to waste money." Mallery took the moment to point out that it is the taxpayer money from the cashiers at the local store, from schoolteachers and other workers that ultimately funds medical research.

"They are entrusting their money to us, and we need to use it wisely," she told her postdoc. "If we can improve just 10 people's lives, how cool is that? We are lucky to be able to try to do that."

CONCRETE RESULTS

In addition to research grants, ARRA grants are improving the infrastructure of the OSUCCC-James. An $8 million construction grant will support finishing the fourth floor of Ohio State's Biomedical Research Tower (BMT) to provide a home base for the Experimental Therapeutics Program. Another construction grant for $3.9 million will fund the renovation of an 8,776-square-foot space within the Goss Laboratory building that houses a group of highly collaborative viral oncology researchers.

Michael Grever, MD, professor and chair of the Department of Internal Medicine and co-leader of the Experimental Therapeutics Program, says, "The OSUCCC-James is one of a limited number of institutions in the country that has National Cancer Institute funding for both phase I and II studies of new drugs."

Currently, investigators in the Experimental Therapeutics Program are spread out across various departments on campus.

Although the new floor of the BMT will not house all members of the program, it will bring together biologists, chemists, translational scientists and clinicians to develop new therapeutic strategies for cancer, says Grever. The construction

ARNAB CHAKRAVARTI, MD,
professor and chair of Radiation Oncology and co-director of the Brain Tumor Program

$2.5 million

MICHAEL LAIRMORE, DVM, PhD,
associate dean of research , College of Veterinary Medicine

$3.9 million

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

$8 million

project will create lab and office space for about 16 investigators and their groups—part of a plan to accelerate the recruitment of more faculty to the program. In addition, the 24,000-square-foot space will hold core laboratory facilities for medicinal chemists to synthesize new molecules, for pharmacokinetics studies to measure how drugs get distributed in the body, and for pharmacodynamics studies to measure how well drugs hit the targeted tumor cells.

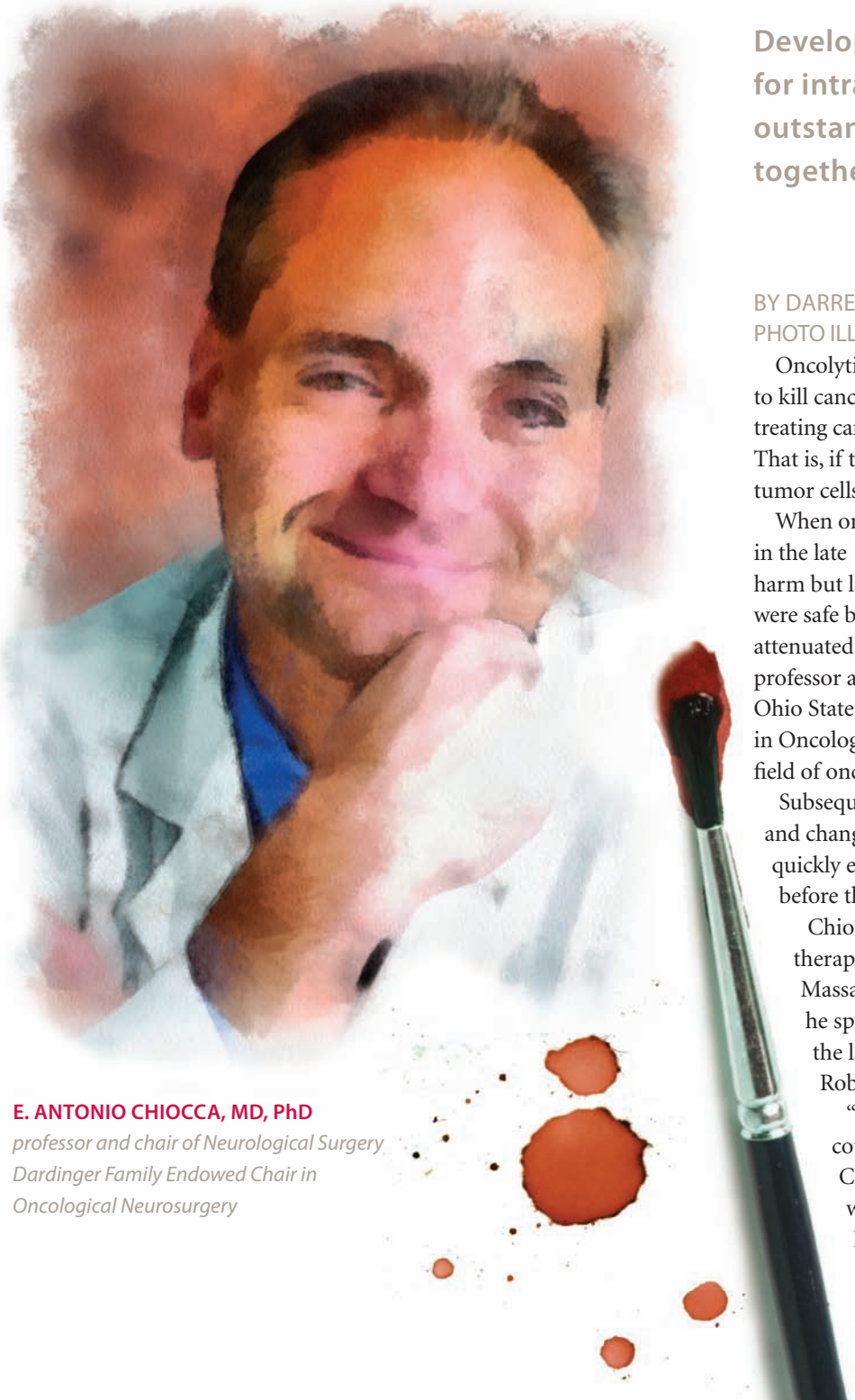
When the Goss Laboratory building was built in 1961, the laboratory spaces were isolated from one another. The renovation will gut the space and install open laboratory benches and office space.

"This allows us to design a modern, interactive space for researchers doing similar things," says Michael Lairmore, DVM, PhD, associate dean of research for the College of Veterinary Medicine. The new space will house four investigators who have large laboratory groups and collaborate on an NIH Program Project Grant using retroviruses to understand the biology of cancer cells.

The space will also include tissue culture hoods for working with infectious viruses and a state-of-the-art facility for performing necropsies on infected animals. "These facilities, designed around a theme of our groups' research and equipment we share in common, will provide a real opportunity for us to accelerate our research," Lairmore notes.

Both the Goss Laboratory and Biomedical Research Tower renovations are expected to begin in spring and summer of 2011. The BRT renovation alone is expected to create 40 new construction jobs and space for 16 new faculty, and produce a demand for 100 support personnel.

The Fine Art of Collaboration



E. ANTONIO CHIOCCA, MD, PhD
professor and chair of Neurological Surgery
Dardinger Family Endowed Chair in
Oncological Neurosurgery

Developing new treatments for intractable cancers requires outstanding minds working together toward a common goal

BY DARRELL E. WARD
PHOTO ILLUSTRATION BY ROMAN SAPECKI

Oncolytic viruses—viruses that are engineered to kill cancer cells—offer a promising strategy for treating cancers that remain steadfastly incurable. That is, if the virus can get a toehold in enough tumor cells to work.

When oncolytic viruses entered clinical testing in the late 1990s, they showed no evidence of harm but little evidence of good. "The viruses were safe but ineffective. They were too attenuated," says E. Antonio Chiocca, MD, PhD, professor and chair of Neurological Surgery at Ohio State, Dardinger Family Endowed Chair in Oncological Neurosurgery and a leader in the field of oncolytic virus therapy for brain tumors.

Subsequent research showed that host defenses and changes in the tumor microenvironment quickly eliminated the emasculated viruses before they had a chance to kill tumor cells.

Chiocca's interest in oncolytic virus therapy began during his residency at Massachusetts General Hospital, where he spent two and a half years working in the laboratory of his mentor, Harvard's Robert L. Martuza, MD, FACS.

"Bob was trying to learn if viruses could be used to kill cancer cells," Chiocca says. "We began collaborating with the herpes virus group at Harvard, and then I was hooked."

CHIOCCA IS CURRENTLY CONDUCTING AN INDUSTRY-SPONSORED PHASE I TRIAL OF AN ONCOLYTIC RETROVIRUS FOR GLIOMAS MADE BY ONCOLYTIC BIOTECH.

Chiocca, who is co-leader of the OSUCCC-James Viral Oncology Program, specializes in malignant gliomas, particularly glioblastoma multiforme, which has a median survival of about 15 months. These tumors, with their multiple extensions into the surrounding gray matter, are difficult to cure even with surgery, chemotherapy and radiation, Chiocca says. But they are excellent candidates for oncolytic virus therapy.

Since arriving at Ohio State in 2004, Chiocca's research has focused on developing oncolytic viruses based on herpes simplex virus type 1 (HSV-1) that are more potent and more selective for tumors of the brain, and on understanding the host responses that limit or impede the virus's ability to destroy the tumor.

To ask the right questions and generate imaginative hypotheses related to tumor targeting, intracellular antiviral defenses, inflammatory and innate immune responses, angiogenic changes and extracellular matrix alterations, requires talented collaborators.

"Science has become more complex," Chiocca says. "Work such as ours requires people with different insights, skills, ideas, points of view and expertise… collaboration can make research more relevant."

Chiocca works with a number of accomplished collaborators, and together they form an oncolytic virus group.

JOSEPH C. GLORIOSO III, PhD
herpes virus specialist, University of Pittsburgh School of Medicine

rQNestin34.5

Working with these colleagues, Chiocca has developed several oncolytic herpes strains, two of which—MGH2 and rQNestin34.5—he hopes to test soon in phase I trials. "Both are more potent and more selective for tumor cells, as well as being safe," Chiocca says.

The rQNestin34.5 oncolytic virus exemplifies Chiocca's progress. This oncolytic virus is attenuated in two ways. First, the gene encoding viral ribonucleotide reductase is deleted from the viral genome, leaving the virus unable to replicate without an outside source of the enzyme. That outside source is provided by tumor cells with defects in the *p16* tumor-suppressor pathway. These cells, even when quiescent, overexpress the enzyme and so enable viral replication.

The second novel attenuation involves the viral ICP34.5 neurovirulence protein, which normally blocks a defense mechanism that pushes infected cells into apoptosis. Wild type HSV-1 has two copies of the gene, both of which were deleted from early HSV-1 oncolytic virus mutants to ensure safety.

To improve potency in the rQNestin34.1, Chiocca and his colleagues restored one of the two *ICP34.5* genes. To maintain safety, the researchers coupled the viral gene to a glioma-specific promoter. The promoter comes from the gene for the protein nestin, an intermediate filament in embryonal brain cells.

Chiocca and colleagues showed in a 2005 study published in the journal *Cancer Research* that nestin is expressed in malignant adult glioma cells but not in healthy adult astrocytes.

Furthermore, their *in vitro* studies suggested that combining the nestin promoter with *ICP34.5* improved tumor specificity by enabling viral replication in glioma cells but not in healthy astrocytes, and it made the virus more cytotoxic to glioma cells. In mice with established gliomas, the nestin virus increased long-term survival by 50 percent when administered early as therapy, and it significantly increased survival even in symptomatic animals.

TIMOTHY P. CRIPE, MD, PhD
pediatric oncologist, Cincinnati Children's Hospital Medical Center

More recently, Chiocca has identified a population of tumor-initiating cells that is resistant to his HSV vectors. Working with Chiocca, herpes virus specialist Joseph C. Glorioso III, PhD, at the University of Pittsburgh School of Medicine, is developing vectors with tumor-specific receptors that target those resistant cells. Glorioso and his laboratory also grow and purify the vectors needed by Chiocca for preclinical studies that use human brain tumors in animal models. Of major interest are the creation of vectors that target epidermal growth factor receptor found on glioblastoma and tumor stem cells, and the engineering of oncolytic HSV that depends on the differential expression of microRNAs for selective replication in brain tumors.

While Chiocca prepares the rQNestin34.5 virus as therapy for adults with brain tumors, one of his collaborators, pediatric oncologist Timothy P. Cripe, MD, PhD, at Cincinnati Children's Hospital Medical Center, is studying its potential for treating neuroblastoma in children.

"We have developed some very good therapies for these tumors over the years, but we are unable to cure the majority of patients with metastatic disease, so there is still a large unmet medical need," Cripe says.

"Our collaboration with Dr. Chiocca has been very fruitful. We have found that the nestin protein is upregulated in neuroblastoma, suggesting that this tumor may be another target for the rQNestin virus," he says.

"We're also exploring the addition of cyclophosphamide to suppress the immune response to oncolytic virus infection, something that Dr. Chiocca pioneered," Cripe says.

That finding came from a 2006 study led by Chiocca and published in the journal *Proceedings of the National Academy of Sciences*. The researchers showed that high numbers of innate immune cells—natural killer (NK) cells, macrophages and microglia—are drawn to the tumor within six hours of injecting an oncolytic virus.

They found that the drug cyclophosphamide briefly dampens this immune cell activity, giving the oncolytic virus more opportunity to disperse through the tumor and kill cancer cells. Animals given the drug and an oncolytic virus showed a 50-percent increase in the number of tumor macrophages, for example, compared with a three-fold increase in animals given the virus and no drug.

"Cyclophosphamide seems to temporarily inhibit just this early immune response, making it unnecessary to totally suppress the immune system during treatment," says Chiocca.

The agent inhibits the innate immune response at least in part by inhibiting production of interferon gamma (IFN-γ) by NK cells, according to the findings of work reported in the same paper and led by Michael A. Caligiuri, MD, an authority in NK cell biology, director of Ohio State's Comprehensive Cancer Center and CEO of the James Cancer Hospital and Solove Research Institute.

IFN-γ attracts immune cells to an infection site, which could intensify the immune response against the anticancer virus. In rats with brain tumors that were treated with the virus alone, IFN-γ levels rose by a factor of 10 after six hours, and by more than 120 times after 72 hours. However, IFN-γ levels rose only slightly in animals treated with the virus plus cyclophosphamide.

Overall, the study suggests that cyclophosphamide can improve oncolytic virus therapy by delaying the activity of NK cells and other innate immune cells.

Seeking NK details

NK cells have both antiviral and antitumor properties, so it is crucial to understand how they interact with tumors infected with an oncolytic virus. Christopher A. Alvarez-Breckenridge, a student in Ohio State's combined MD/PhD degree program and a member of Chiocca's lab, is identifying the signals

IN MARCH, CHRISTOPHER ALVAREZ-BRECKENRIDGE RECEIVED A 2010 AMERICAN MEDICAL ASSOCIATION FOUNDATION JUNIOR-INVESTIGATOR "SEED GRANT" AWARD TO CONDUCT BASIC OR CLINICAL RESEARCH

exchanged between NK cells and infected versus uninfected tumors.

"Our preliminary findings indicate that NK cells are moderately activated by uninfected brain tumors in an animal model but highly activated by virus-infected tumors," says Alvarez-Breckenridge, who works closely with the Caligiuri laboratory. "And if we culture NK cells together with uninfected and infected tumors, they preferentially clear viral infected tumors."

Overall, Alvarez-Breckenridge says, his findings suggest that suppressing

CHRISTOPHER ALVAREZ-BRECKENRIDGE
MD/PhD student

the immune system for 72 hours, perhaps less, might give the virus sufficient time to replicate and spread. "At that point, the immune system might actually aid the virus and help clear the tumor," he says.

Inhibiting angiogenesis

Chiocca collaborator and cancer center member Balveen Kaur, PhD, associate professor of Neurological Surgery, studies how the tumor microenvironment impedes oncolytic virus therapy for gliomas.

An animal study led by Kaur found that, three days after an oncolytic virus is injected into a tumor, tumor blood vessels become leaky, immune cells infiltrate the site, and IFN-γ expression rises. Administering one dose of the angiogenesis inhibitor cRGD (cyclic peptide of arginine-glycine-aspartic) prior to viral treatment, however, reduced vessel permeability, immune cell infiltration and IFN-γ expression.

In addition, rats treated with the agent had higher viral titers and significantly lower tumor vasculature (28 vessels versus 62 in control animals per area of viewing field), and the treated animals showed a 23-percent increase in survival.

"The survival increase was significant because these are very aggressive tumors," Kaur says. "This work suggests that antiangiogenic agents can reduce virus-induced inflammation in brain-tumor tissue and improve the efficacy of oncolytic virus therapy by slowing the immune system's ability to clear the virus." The 2007 study was published in the *Journal of the National Cancer Institute*.

The following year, Kaur and her colleagues found that, as oncolytic viruses destroy glioma cells, the cells release proteins that stimulate tumor angiogenesis. The study, published in the journal *Molecular Therapy,* found that virus-treated tumors had roughly five times more blood vessels than untreated tumors. These vessels facilitate the innate immune response that eliminates the virus, and they support re-growth of residual tumor cells.

Probing further, Kaur and her colleagues identified three genes linked to blood-vessel growth that were overexpressed, in particular. Of those, the gene called *CYR61* was nine times more active in virus-treated tumor cells than in uninfected tumor cells, and the activity increased in a dose-dependent manner.

"This change in gene activity may represent a general host response to the viral infection," says Kaur.

The investigators are now studying whether expression of this gene might serve as a biomarker reflecting patients' response to oncolytic virus therapy. "Measuring a patient's response to viral infection is currently not feasible," Kaur says, "so if this were to work, it would be a significant advance."

RAMBO

Kaur's findings have led her and her colleagues to modify the oncolytic virus by adding a gene for a natural, brain-specific angiogenesis inhibitor called vasculostatin. They called the new virus RAMBO, for Rapid Antiangiogenesis Mediated By Oncolytic virus.

The researchers tested the new virus in six animals with dermal xenografts of human glioblastomas. RAMBO-treated animals survived an average of 54 days, and three mice were tumor-free at the end of the experiment. Control animals, treated with a virus that lacked vasculostatin, survived an average of 26 days, and none were tumor-free.

When they treated five animals with a human glioblastoma in the brain, the animals survived 54 days, with one remaining tumor-free for more than 120 days.

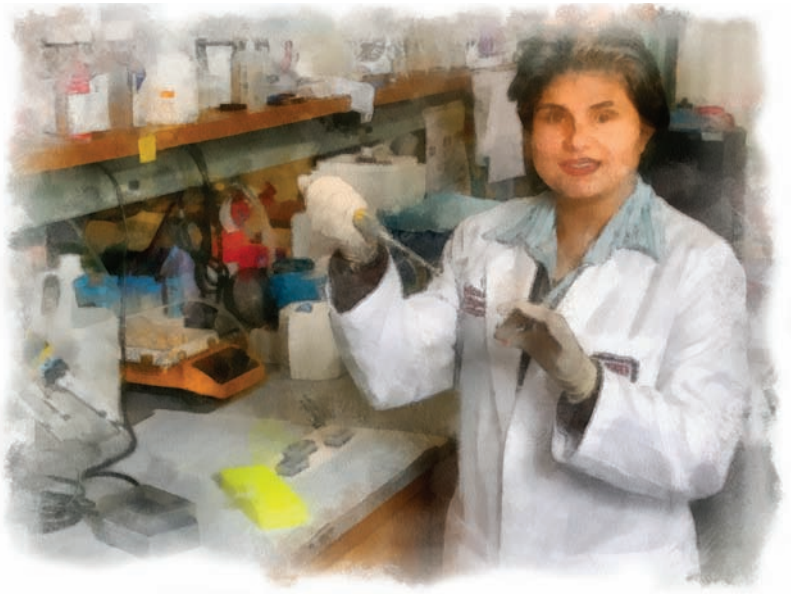
A time-course study showed that, after an initial period of shrinkage, implanted brain tumors began regrowing about day 13 in control animals, but not until about day 39 in RAMBO-treated animals.

The study, published in *Molecular Therapy* in 2010, "shows a significant antitumor effect and supports further development of this novel virus as a possible cancer treatment," Kaur says.

Chiocca's rQNestin34.5 and MGH2.1 oncolytic viruses, both second-generation agents, are undergoing preclinical testing in preparation for possible phase I trials in people with malignant brain tumors. Meanwhile, he and his colleagues are moving forward with third-generation viruses such as RAMBO and the development of oncolytic virus therapy for children.

"The atmosphere here at Ohio State encourages cooperative research," says Chiocca. "People check their egos at the door for the common good. Having a first-rate team of investigators allows us to do stronger work, write better papers and higher quality proposals, compete for higher quality journals and obtain better funding."

Outstanding minds coming together toward a common goal can offer real hope to people with an intractable cancer. It is hope born of collaboration.



BALVEEN KAUR, PhD,
associate professor of Neurological Surgery

AN ONCOLYTIC MEASLES VIRUS

Corey Raffel, MD, PhD, professor of Neurosurgery at Nationwide Children's Hospital in Columbus, a close collaborator of E. Antonio Chiocca, is developing oncolytic virus therapy for children with meduloblastoma using a modified measles virus. About 350 meduloblastoma cases occur annually in the United States. The malignancy has about a 70-percent survival rate. "The problem is that curing the tumor requires radiation therapy, which is not good for a child's brain, so the kids who survive often do poorly," Raffel says. "We are trying to find ways of curing them without the devastating effects related to radiation therapy." He is studying the use of an oncolytic measles virus with a receptor that is aberrantly upregulated on meduloblastoma cells, enabling the virus to target and enter the tumor cells. The altered measles virus has been tested in adults but not in pediatric tumors. Raffel began his oncolytic virus work about five years ago while still at the Mayo Clinic. One of the two animal models he has developed enables him to study disseminated meduloblastoma, which occurs when the tumor spreads through the cerebrospinal fluid to another location in the central nervous system. Raffel attends many of Chiocca's weekly lab meetings to exchange information, discuss data and suggest ways to improve experiments and overcome problems. "We work with different viruses, but these meetings offer valuable opportunities to show your work to others and receive comments and suggestions," Raffel says.

Found in TRANSLATION

A new approach to research speeds the flow of data between basic-science bench and patient bedside

BY BOB HECKER
PHOTOGRAPHY BY ROMAN SAPECKI

THE RESEARCHERS

PRAVIN KAUMAYA, PHD,
professor of Obstetrics and Gynecology, director of the Division of Vaccine Development and of the Peptide and Protein Engineering Laboratory, Department of Obstetrics and Gynecology

WILLIAM CARSON III, MD,
professor of Surgery, associate director for Clinical Research and co-leader of the Innate Immunity research program

In August 2009, cancer researchers at The Ohio State University began recruiting patients to a landmark phase I clinical trial for an experimental agent called AR-12, which inhibited solid tumors and lymphoma in preclinical studies.

"That trial marked the first time a therapeutic drug developed by Ohio State cancer researchers entered clinical testing in cancer patients," says John Byrd, MD, associate director for translational research at Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James).

AR-12 was discovered in the laboratory of Ching-Shih Chen, PhD, of the OSUCCC-James Molecular Carcinogenesis and Chemoprevention program, and its development involved a nearly decade-long collaboration among Ohio State researchers who refined its novel mechanism of action.

"We were very excited about the trial," Chen says. "As bench scientists, our goal is to see our research translated into the clinic."

A second agent designed and developed in Chen's laboratory, AR-42, will enter clinical testing in mid-2010. And more agents are in the pipeline.

"AR-12 and AR-42 are both fantastic examples of translational research," Byrd says. "A biological target relevant to cancer was identified through basic research, a drug was designed to interfere with it, preclinical validation was performed, and efforts were transitioned to the National Cancer Institute (NCI) to bring a new class of drugs into the clinic."

Translational research is a process of scientific investigation in which research findings cyclically move from laboratory bench to clinical application and back to the laboratory bench. "The goal is to rapidly and efficiently move the most promising scientific discoveries from the basic-science laboratory into early-phase clinical testing, and to improve that therapy through research back in the laboratory," Byrd says.

The NCI views translational research as essential for transforming scientific discoveries from laboratory, clinical and population studies into applications that reduce cancer incidence, morbidity and mortality.

Byrd sees another important benefit of translational research. "As medicine becomes more specialized, it's harder for people to be involved in both laboratory-based work and clinical practice. A strong translational research program creates a fertile research environment that helps attract and retain outstanding investigators."

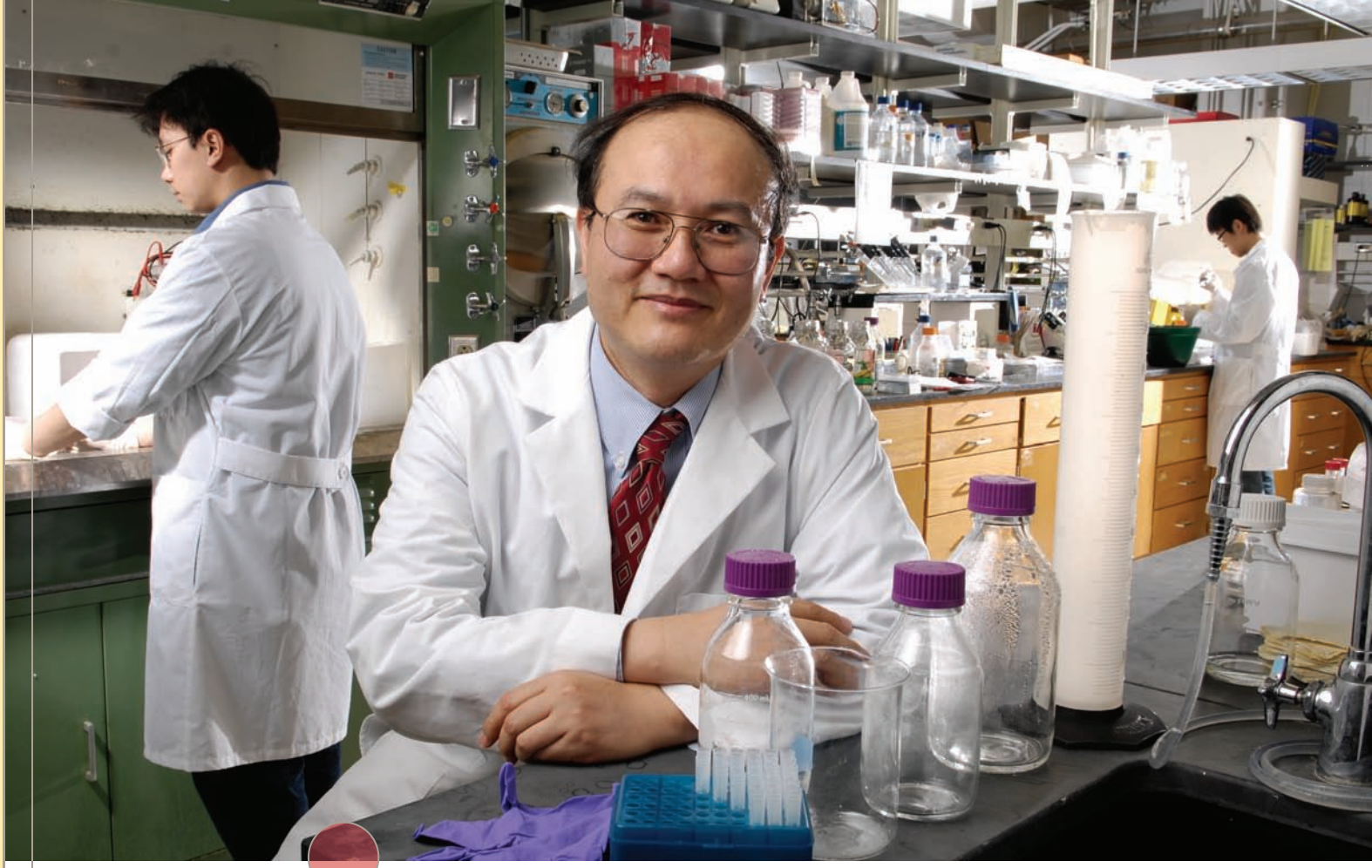
CAREFULLY CONTRIVED COMPOUNDS

Chen and his colleagues used the anti-inflammatory drug celecoxib as a starting point to construct AR-12 (OSU-0312), which is in clinical testing at two other centers as well as at Ohio State.

"AR-12 works by inhibiting the PDK-1 and PI3k/Akt pathways, which are fundamental signaling points in cancer cells, making AR-12 potentially effective in a range of cancer types," says Chen, a professor of Medicinal Chemistry, of Internal Medicine, and of Urology. Patients with advanced or recurrent breast, colon, lung or prostate cancers or lymphoma who haven't responded to chemotherapy are eligible for the trial.

Chen's second drug, AR-42 (OSU-HDAC42) is a histone deacetylase inhibitor, an agent that reactivates silenced tumor-suppressor genes by reversing aberrant epigenetic changes.

In a 2008 transgenic mouse study published in the journal *Cancer Research*, HDAC42 prevented precancerous prostatic intraepithelial neoplasia from progressing to advanced prostate cancer in 100 percent of treated animals compared with 74-percent incidence of poorly differentiated carcinoma that developed in control animals. The drug



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

both kept the animals cancer-free and prolonged their survival.

"This study shows that an agent with a molecular target can dramatically inhibit prostate cancer development in an aggressive model of the disease," says medical oncologist and co-author Steven Clinton, MD, PhD, who leads the Molecular Carcinogenesis and Chemoprevention Program.

The NCI's Rapid Access to Intervention and Development (RAID) Program helped further the development of both agents for clinical testing.

VERGING ON A VACCINE

Translational research is designed to expedite medical advances, but it still takes time. "Translating basic knowledge to the clinic is not a straightforward process; it is a continuous process of rational design and execution using emerging concepts and advances in several scientific fields, such as immunology, protein and structural chemistry, molecular biology and others," says Pravin Kaumaya, PhD, director of the Division of Vaccine Development in the Department of Obstetrics and Gynecology. Kaumaya also directs the OB/GYN Peptide and Protein Engineering Laboratory in Ohio State's College of Medicine.

Kaumaya and colleagues have produced one of Ohio State's first "homegrown" anticancer vaccines to move from the lab to the clinic. "It has taken us two decades to reach this point," he says.

The vaccine targets HER-2, a protein that is aberrantly expressed in about a third of breast cancers and in other cancer types. HER-2 generally signals a poor response to therapy and a high likelihood of recurrence. A phase I trial involving 24 women and men with metastatic or recurrent solid tumors showed that the vaccine was safe, but there was also evidence of effectiveness.

"Six of the patients showed clinical benefit—one had tumor shrinkage and five had stable disease," says Kaumaya, who says this was the first male-female trial involving a vaccine strategy using two B-cell epitopes (published in the *Journal of Clinical Oncology*, November 2008).

The trial also produced a surprise.

"We were developing a vaccine for breast cancer that targets HER-2, but because this was a phase I trial we also enrolled patients with other forms of cancer. As it turned out, only one of the six who showed clinical benefit was HER-2 positive.

Patients who were not HER-2 positive benefited the most," Kaumaya says. "That's because a component of the vaccine also interferes with epithelial growth factor receptor (EGFR). So what we have here is the possibility of a solid tumor universal vaccine that targets both HER-2 and EGFR-overexpressing cancers. I didn't know that when we started."

The findings suggest that the vaccine may be effective in brain, lung, pancreatic, colon and ovarian cancers.

Kaumaya and his students have produced a second-generation vaccine that will begin phase I testing later this year (see sidebar, page 28). Currently, his team has engineered a third-generation combination peptide vaccine and therapy involving HER-2 and vascular endothelial growth factor (VEGF) that have shown synergistic and additive efficacy in preclinical studies in animals.

BEDSIDE TO BENCH

For Carlo Croce, MD, director of Ohio State's Human Cancer Genetics Program, translational research starts with patients.

"The most common view is that research findings in the lab are exploited to develop novel approaches to diagnosis, prognosis and treatment of cancer at the bedside," Croce says. "But I see translational research as the bi-directional flow from observation at the bedside to the lab, where we make discoveries that we can convert to the clinic. It can go both ways, depending on the circumstances, but in my work we always start with bedside samples of the disease and apply basic science to make discoveries for improving patient care."

For example, nearly a decade ago, Croce and colleagues were searching for a tumor-suppressor gene located at 13q14, a chromosome site that is deleted in more than half of B-cell chronic lymphocytic leukemia (CLL) cases. Then they read in the journal *Science* that microRNA—a family of RNA molecules too small to code for a protein—is widely found in worms, flies and humans.

This seemingly unrelated basic finding gave them an idea. "I was convinced there was a gene on 13q14 that is involved in cancer, but no protein-coding genes were found there that could be linked to the disease," Croce says. "So I knew a different kind of gene must be involved. When we heard about microRNA, we wanted to find out if it could be involved in CLL, and it turned out we were right."

Croce and colleagues discovered two microRNA genes at the deletion site. They also analyzed CLL cells from 60 patients and showed that the genes were absent in 68 percent of the cases. Their 2002 findings, published in the journal *Proceedings of the National Academy of Sciences*, made Croce's lab the first to link microRNA to cancer.

His group and others have since shown that microRNAs are involved in all human cancers and can be used to improve diagnosis and prognosis.

"Our next big challenge," Croce says, "will be finding ways to use microRNA and anti-microRNA (antisense molecules) for treating CLL—in short, replacing microRNA genes that are underexpressed, or inserting anti-microRNAs to destroy microRNA genes that are overexpressed. We're doing preclinical toxicology studies now in animals to test the safety of such treatments.

"This is a wonderful example of how you apply observations of disease in the clinic to basic laboratory science that leads to a discovery."

REASON TO HOPE

William Carson III, MD, values translational research because it can lead to clinical options even for patients with advanced, metastatic or recurrent cancer.

"One of the loneliest feelings in the world is talking to a cancer patient and not having a good treatment to offer," says Carson, a surgical oncologist at the OSUCCC-James who also is associate director for clinical research and, with Byrd, co-leads the Innate Immunity research program.

"Advanced or metastatic melanoma is resistant to most chemotherapy drugs, and average survival is about six to nine months, so there is a serious need for new therapies that involve drug combinations," says Carson, whose specialties include this disease.

Carson and his colleagues are refining immune-based treatments that take advantage of the body's strong immunological response to melanoma. They combined interferon-alpha (INF-α) with the targeted agent bortezomib and showed in animal studies that the two agents worked better together than either one alone, prolonging survival and reducing the growth of melanoma xenografts by half.

"The two drugs synergistically

activate complementary cell-death pathways and overcome the usual mechanisms that make melanoma cells resistant to standard therapies," says Greg Lesinski, PhD, a researcher with the Innate Immunity program and first author on a 2008 paper published in the journal *Cancer Research*.

These results led to a phase I clinical trial—the first to test this combination against melanoma—involving 15 patients with metastatic disease who had no other treatment options. The combination was well-tolerated and showed anti-cancer activity, including partial shrinkage of a tumor in one patient and disease stabilization in others, says investigator and melanoma specialist Kari Kendra, MD, PhD.

The question now is whether to pursue a phase II trial or to attempt new phase I trials testing combinations of other agents that Carson and his colleagues are studying. He notes that the translational process often involves intuition along with science.

"Clinical observation is also important when making these determinations; knowing what's going on with your patients is key," Carson says. "In a way, deciding to try the INF-α and bortezomib combination was an educated hunch along with a little serendipity."

But he adds, "We don't simply guess at what might work. We pre-test these therapies in the lab and gather experimental evidence indicating a high probability that they will benefit patients. Patients who volunteer for clinical trials can know there's a good chance these therapies will help. The more we can back up our therapies with science, the better it is for patients who are taking a chance with their life."

Translational research is a means to progress, Byrd says.

"We seek to discover new knowledge and apply it to patients. This is a strength of our cancer center. Translational research enables us to leverage our research dollars to maximally use everything we learn," he explains. "Patients with cancer want hope that there is something new and better that might allow them to move on with their lives without illness. We need to develop new medicines to get us there, and the best way to do that is through translational research."

RATIONAL VACCINE DESIGN

Pravin Kaumaya, PhD, and his Ohio State colleagues are using new data about the molecular structure of their original HER-2- and EGFR-targeted anticancer vaccine to develop a second-generation vaccine that could be effective against a range of malignancies, and they may begin phase I testing this autumn.

While the original vaccine was based on predictive models and animal studies, the newer version is based on the crystal structure of HER-2 bound with its antibodies. "It's rationally engineered to mimic the 3-dimensional structure of the HER-2 oncogene, so we hope it will be more efficacious," Kaumaya says.

The National Cancer Institute (NCI) has awarded $750,000, and the OSUCCC-James will contribute $100,000 for the new trial, which Kaumaya hopes to complete in less than a year. Meanwhile, his team is working on a third-generation vaccine.

"We have filed patent applications for a combination vaccine that uses technology relating to our HER-2-targeting drug plus an angiogenesis inhibitor that we designed from scratch," Kaumaya says. "Our preclinical studies have shown that this combination vaccine works." Next, the researchers will apply to the NCI for funding for a phase I trial.

"This could be a major breakthrough that may one day cure patients and not just treat them," he says, noting that it's been an arduous journey involving much time, money and work.

"With translational research, you have to believe in what you're doing and keep at it even if some people don't recognize it as important," Kaumaya says. "It takes unabated perseverance."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

OSU 09120 – Phase I Trial of Vorinostat in the Treatment of Advanced Oropharyngeal Squamous Cell Carcinoma (OPSCC)

HYPOTHESIS: The addition of vorinostat to a standard chemo-radiation therapy protocol for the treatment of unresectable or borderline resectable OPSCC will improve the toxicity of this effective regimen; improve tumor immune surveillance by activating adaptive and innate immune responses, especially in human papilloma virus (HPV)-positive tumors; and improve the methylation status of commonly methylated genes in OPSCC.

STUDY DESIGN: Phase I clinical trial

RATIONALE: Despite aggressive therapy that can include chemotherapy and concurrent chemoradiation, the overall five-year survival rate for advanced-stage OPSCC is less than 50 percent. Better treatment options are needed for this functionally and aesthetically sensitive area.

It has become evident in recent years that there exists an aggressive subtype of OPSCC characterized by female gender, a history of smoking, an anti-apoptotic phenotype and poor survival; and a subtype that is HPV-positive with low EGFR expression that is associated with good treatment response and survival.

In both cases, chemoradiation therapy protocols are very toxic, with radiation-related complications that include soft tissue fibrosis, muscle fibrosis and atrophy, dysphagia, and osteoradionecrosis and chondroradionecrosis. Improving therapeutic efficacy while minimizing toxicity to normal tissues is the overriding rationale for the use of vorinostat in this investigation.

Vorinostat (SAHA) inhibits the enzymatic activity of several histone deacetylases at nanomolar concentrations. These enzymes catalyze the removal of acetyl groups from proteins such as histones and transcription factors, altering gene expression.

Elevated histone deacetylase (HDAC) levels have been observed in head and neck cancer. HDAC inhibitors, such as vorinostat, regulate gene transcription, inhibit growth and induce apoptosis. Evidence indicates that these agents also preferentially induce both intrinsic and extrinsic apoptotic pathways in head and neck squamous cell carcinoma while sparing normal oral mucosa.

These characteristics—along with targeted cell-cycle disruption, inhibition of angiogenesis, inhibition of cell proliferation in tumor cells but not normal cells—is why vorinostat has been shown to sensitize head and neck cancer to radiotherapy while minimizing radiation-related damage. Vorinostat also suppresses the cutaneous radiation syndrome by decreasing production of TNF-alpha and TGF-beta.

Research has shown that vorinostat can be safely combined with platinum-based chemotherapy, and that it may sensitize head and neck cancer to this cytotoxic agent. Finally, evidence from our laboratories suggests that this agent modulates the immune system to better recognize virally induced tumors. Thus, the multiple effects of vorinostat indicate that this agent should improve the response rates of HPV-positive and HPV-negative OPSCC to organ-preservation therapy, while reducing treatment toxicity.

AT A GLANCE

Clinical trial OSU 09120

PI: **THEODOROS N. TEKNOS, MD,** professor of Otolaryngology

Phone: 614-293-8074

Email: *Ted.Teknos@osumc.edu*

Eligibility: Histologically confirmed unresectable or borderline resectable OPSCC; Oropharyngeal sites of tumor include tonsil, soft palate, base of tongue, lateral and posterior pharyngeal wall; Must be AJCC Stage III or Stage IVa and be either unresectable or borderline resectable; No prior therapy for the tumor, including extensive surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy or any other investigational agents; ECOG 0-2; Age greater than 18 years old; Cannot have active peptic ulcer disease; Patients with known active viral hepatitis or known HIV infection are excluded.

SHARED RESOURCES

FROZEN ASSETS

Biorepository and Biospecimen Shared Resource

The Biorepository and Biospecimen Shared Resource (BBSR) collects, stores and distributes biospecimens—tumor tissue, normal tissue, serum, plasma, whole blood, white blood cells, urine samples and other body fluids—obtained during clinical visits or surgery. Standarized best practices are used to process (frozen, fixed and RNA-inhibitor) and store biospecimens as a high-quality collection.

The BBSR obtains patient informed consent for the collection of biospecimens that includes the annotation of their medical and healthcare information in collaboration with The Ohio State University's Information Warehouse. The biospecimens are distributed to members of Ohio State's Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

"Investigators can review the inventory of biospecimens prior to their research and then apply for the use of the biospecimens with assistance from the staff to foster hypothesis-driven cancer research," says BBSR Director Scott Jewell, PhD, associate professor of Pathology.

BIOSPECIMENS COLLECTED

- The BBSR began operation in February 2009. In its first year, 2,500 patients were consented to the program.
- 1,368 patients provided blood specimens—plasma, serum, WBCs—for a total of 9,725 specimen aliquots.
- Cancer tissue has been collected from 569 patients with a total of 2,856 specimen aliquots.
- About 30 anatomic cancer tissue types were donated in the first year.

SHARED RESOURCES

ProjectONE

Ohio State and City of Columbus in ProjectONE Partnership

ProjectONE is The Ohio State University Medical Center's $1 billion expansion that will provide a new home for the James Cancer Hospital and Solove Research Institute and a new site for the care of critically ill patients. The expansion will generate up to 10,000 jobs for Columbus—6,000 at the Medical Center plus 4,000 related to the growth. To help finance the project, the city of Columbus has offered a performance-based tax incentive for a portion of each of the 6,000 new Medical Center jobs.

Ohio State, in turn, will reinvest $10 million in tax incentives from ProjectONE to improve health care and housing on the city's East Side. Exactly how these dollars will be reinvested will be determined through a study of the neighborhood and feedback from residents.

ProjectONE AND CONSTRUCTION REFORM

Ohio law requires that state-funded construction projects award separate contracts for each part of a project, such as contracts for mechanical, electrical and plumbing work.

Last fall, Ohio Gov. Ted Strickland convened a panel to recommend ways to increase the speed and efficiency of public sector construction projects. This resulted in proposed construction reform that would permit new methods of project management that might save the state $330 million annually.

The reform procedures would allow the state to use either the current method of management or one of three other ways that give more control and responsibility to the contractor, architect or both.

ProjectONE has been designated as one of three Construction Reform Demonstration Projects that will test alternative methods of public construction management.

"This kind of construction flexibility on our expansion will allow us to be a better financial steward through what we hope will be a faster and more efficient completion of the project," says Steven Gabbe, MD, OSU senior vice president for Health Sciences and CEO of OSU Medical Center.

Groundbreaking for the new cancer hospital is expected in mid-June. For more information and to follow the expansion, visit www.projectone.osu.edu or http://projectoneblog.osumc.edu.

OSUCCC-James events calendar

PELOTONIA

August 20 to 22, 2010

FOCUS: Pelotonia is a grassroots bike tour to raise money for cancer research at the OSUCCC-James. It is designed for serious and casual riders who are committed to fighting cancer. Every dollar raised goes to research. Riders can choose from several ride options, with routes available for every skill level, from less-demanding shorter rides to a two-day round-trip ride through picturesque Ohio countryside. The 2009 inaugural event involved 2,265 cyclists and more than 1,000 volunteers, and raised nearly $4,512,000.

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

THIRD ANNUAL PERSONALIZED HEALTH CARE NATIONAL CONFERENCE: ADVANCING PREDICTIVE, PREVENTIVE, PERSONALIZED AND PARTICIPATORY MEDICINE

October 14-15

Ohio State's PHC conference is attended by experts and key decision-makers in the emerging field of personalized health care. Topics this year include state-of-the-art developments in genomics medicine and their potential in predicting clinical events; developing and implementing a new model of preventive and prospective care; delivering the promise of pharmacogenomics and targeted therapy in patient care; and engaging and empowering patients and consumers for participatory health care.

For more information and to register, visit http://phc.osumc.edu.

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

TRANSLATIONAL PHILANTHROPY

How private support furthers cancer research

THE CHARLES W. HINSON ENDOWMENT FUND

The Charles W. Hinson Endowment Fund at the OSUCCC-James supported the recruitment of Arnab Chakravarti, MD, professor and chair of Radiation Oncology, co-director of the Brain Tumor Program and holder of The Max Morehouse Chair in Cancer Research.

Chakravarti and his laboratory are working to understand the mechanisms of radiation resistance in cancer cells and to develop strategies for overcoming them, particularly in patients with glioblastoma multiforme, one of the most treatment-refractory of all human tumors.

His research has shown that radiation can alter signal transduction pathways in ways that improve cancer-cell survival. His findings have led to novel therapies that are already being studied in clinical trials, and they have suggested new therapies that will be developed and tested at Ohio State in collaboration with colleagues in the OSUCCC-James Experimental Therapeutics Program, the phase I and II clinical trials program and the Department of Neurological Surgery.

"Our ultimate goal," Chakravarti says, "is to take our basic science findings and apply them to provide optimal and personalized care for all radiation oncology patients."

THE RESEARCHER

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

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

DATA DELUGE
Easier and cheaper genome sequencing enables cancer biologists to ask even more probing questions. It also produces huge, complex data sets that are difficult to analyze. The OSUCCC-James is solving the problem through efforts that bring together basic and physician researchers with bioinformaticians and computational scientists.

PROSTATE CANCER PUSH
Steven K. Clinton, MD, PhD, directs the OSUCCC-James multidisciplinary Prostate and Genitourinary Oncology Clinic, which specializes in high-risk patients and leads the field nationally in clinical trials accrual. His laboratory studies tumor angiogenesis as a prognostic marker and novel chemopreventive agents to delay recurrence.