



The James

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

SPRING | 2011

# frontiers

TURNING CANCER DISCOVERIES INTO TREATMENTS



## DRUGS ON CAMPUS

A drug-development pipeline that takes cancer therapies from conception and design to the patient bedside isn't a pipe dream at The Ohio State University—it's under construction.



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

## Reasons to Celebrate

### Quality indicators continue to rise

Last year a panel of NCI experts arrived at the OSUCCC to look under the hood and see how we're doing. I'm pleased to report that they liked what they saw. Following that visit and a review of our core-grant renewal proposal, the NCI rated our program "exceptional," their highest descriptor, and recommended continued funding. The amount will be announced early this year.

The renewal enables Ohio State to retain its status as one of only 40 NCI-designated comprehensive cancer centers, a designation that the University has maintained since 1976. The NCI site review team also stated, "This Center should serve as the model for other matrix university-based Centers."

These remarkable outcomes were, of course, a team effort. They were achieved through the dedication,

cooperation and collaboration of our physicians, nurses, investigators and support staff.

Over the past five years, our NCI grant funding has grown by 96 percent, placing the OSUCCC 14th in annual NCI research funding nationally. Our goal is to break into the top 10. During the same period, our investigator-initiated therapeutic clinical trials jumped 258 percent, to 552, and we produced about 4,000 scientific publications. Half of those publications represent collaborations among disciplines—an amazing statistic that shows our investigators are working together to produce the best results.

Speaking of best results, the Leapfrog Group, a coalition of public and private purchasers of employee health coverage that works to improve healthcare quality, has



**MICHAEL A. CALIGIURI, MD**  
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FOUNDATION CHAIR IN  
CANCER RESEARCH

again included the OSUCCC – James on its list of 65 "top hospitals." The selection comes from the organization's national survey of hospital performance in key areas of patient safety and quality.

Finally, the second annual Pelotonia, our grassroots bicycle tour held in August, generated \$7.8 million exclusively for cancer research at the OSUCCC – James. The event attracted 4,047 riders, nearly double the number who participated in the 2009 inaugural Pelotonia. Together, the two events raised more than \$12 million for cancer research here at home. We truly have reasons to celebrate.

#### THE 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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JamesCare Comprehensive Breast Center opens its doors



ON THE COVER: DRUG PIPELINE BEING CONSTRUCTED

# Dispelling D' Confusion

Dietary reference intakes for vitamin D – the evidence is strongest for bone recommendations



By **STEVEN K. CLINTON, MD, PhD**, director of the Prostate and Genitourinary Oncology Clinic and leader of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program, and a member of the Committee to Review Dietary Reference Intakes for Vitamin D and Calcium

In Dec. 2010 the Institute of Medicine announced new dietary reference intakes for vitamin D and calcium. It was the first change in these recommendations since they were first proposed in 1997. Unfortunately, confusion and misinformation has emerged with the new RDIs, leaving many in the public and even some physicians unsure of the report's actual recommendations.

First, it is worth recalling that

RDIs are public-health guidelines designed to meet the needs of generally healthy Americans—97.5 percent of the population—from birth through old age. They help health officials assess the nutritional status of the U.S. population and physicians counsel patients. They provide information for nutrition labels, and they ensure that school-lunch, nursing-home and other institutional food programs are sufficiently fortified for good health.

I was one of a committee of 14 people that spent two years examining the literature, holding public forums and gathering information. We found that there has been great growth in the scientific literature related to vitamin D and calcium, and we reviewed a lot of intriguing data about the influence of vitamin D, in particular, on health outcomes involving cancer risk, frailty during aging, immune function and neurodegenerative diseases such as multiple sclerosis.

But there were too few high-quality clinical studies, particularly over a range of doses, to determine the quantity of vitamin D needed to achieve a certain outcome—except in one instance. There is sufficient clinical trials data to show that vitamin D and calcium play key roles in bone health, and to define the vitamin D DRI. This was the committee's most important finding.

Based on bone health, recommended dietary allowances (RDAs) for calcium range from 700 to 1300 mg per day for healthy individuals age one year and older. RDAs for vitamin D range from 600 international units (IUs) for ages 1 to 70 years, and 800 IUs for those age 71 and older. This corresponds to blood levels of 20 ng/ml of 25-

hydroxy vitamin D, a serum marker of vitamin D status. Other findings include the following:

- The majority of Americans and Canadians, with few exceptions, receive adequate amounts of both vitamin D and calcium through their diet and sun exposure. Exceptions include those with poor nutrition, those living at northerly latitudes or in institutions, or those with dark skin pigmentation.
- 4,000 IUs is an adequate upper limit for dietary of intake, which is double the previous amount. Higher levels can lead to health problems. Since the main function of vitamin is helping the body absorb calcium, the principle risk of high-dose vitamin D intake is hypercalcemia.
- Some human observational studies suggest that use of high-dose vitamin D over months or years is associated with higher mortality or other negative outcomes, such as an increased risk of pancreatic cancer at the highest levels.
- There was no evidence of benefit associated with high-dose vitamin D.

With no evidence of benefit, and with trends toward potential risk, the committee chose against recom-

mending higher limits of vitamin D beyond the RDI.

Physicians treating patients with osteoporosis can continue prescribing pharmacologic preparations of 50,000 IUs per week for a number of weeks and then recheck the blood levels. This will help people who are truly deficient. But ingesting those levels every week for life might increase the risk of a negative outcome.

For a good summary of the 2011 report on dietary requirements for vitamin D and calcium, see "The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know." Ross AC, Manson JE, Abrams SA, et al. *J. Clin. Endocrinol. Metab.* 2011 Jan; 96(1):53-8. 

# BREAKTHROUGH

The Frontiers of Cancer Research

## ▶ MULTIPLE MYELOMA

# MOLECULAR MATCHUPS

## Study Identifies Key Molecules in Multiple Myeloma

Research led by scientists at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) links three molecules to a tumor-suppressor gene that is often turned off in multiple myeloma.

The silenced molecules – miR-192, miR-194 and miR-215 – are microRNAs, a class of molecules discovered about a decade ago that are master regulators of many cell processes. This study suggests that reactivating these three molecules triggers expression of the *P53* tumor-suppressor gene, which in turn slows the growth and leads to the death of myeloma cells, possibly presenting a new strategy for treating this disease.

“Our findings provide a rationale for the further exploration of these microRNAs as a treatment for multiple myeloma, which has few therapeutic options,” says principal investigator **CARLO CROCE, MD**, professor and chair of Molecular Virology, Immunology and Medical Genetics, and director of the Human Cancer Genetics Program.

Multiple myeloma begins as a benign condition called monoclonal gammopathy of undetermined significance (MGUS). Individuals



### THE RESEARCHER

**CARLO CROCE, MD**,  
professor and chair of  
Molecular Virology,  
Immunology and Medical  
Genetics

with MGUS can live many years without treatment, but for unknown reasons this condition can evolve into myeloma. Studies have shown a relationship between *P53* and a gene called *MDM2*. They have also shown that myeloma cells often have unmutated *P53* genes but very little *P53* protein. *P53* protein levels are restored, however, when *MDM2*

expression is blocked.

Croce says the OSUCCC – James study, which examined the role of microRNA in regulating the *P53* pathway in myeloma cells, provides the basis for developing a microRNA-based therapy for this disease.



Published in the journal *Cell*.

## ▶▶ CANCER GENETICS

# BACKGROUND CHECK

## Normal Genetics May Influence Cancer Growth

A person's genetic background – the array of inherited genetic variations – may contribute to DNA changes that occur in tumor cells as cancer develops, an OSUCCC – James study suggests.

Comparing multiple independent tumors from people with squamous cell carcinoma (SCC) for DNA losses and gains in tumor cells, scientists found that the pattern of changes is quite similar in tumors from the same person but quite different in tumors from different individuals. The findings could help identify individuals at greater risk for developing cancer.

“Our data strongly support the idea that an individual's normal genetic constitution can strongly influence genetic changes that occur when he or she develops cancer,” says study leader **AMANDA TOLAND, PHD**, of the Molecular Biology and Cancer Genetics Program at the OSUCCC – James. “They may also provide another strategy for identifying genetic variations within healthy individuals that increase their odds of developing cancer.”

Toland and collaborators analyzed 222 SCC tumors from 135 organ transplant recipients, who as a group are 65 to 250 times more likely to develop SCC than people in the general population. The researchers examined three or more separate tumors from 25 of these individuals.



When they compared the genetic profiles of tumors from the same individual with those from other individuals for DNA copy number changes, they found that the changes in SCCs from the same patient were statistically similar but were significantly different when compared with other patients. They also found that, in some cases, a particular kind of genetic change is preferentially selected in tumors from the same individual.

“Overall,” Toland says, “our findings provide strong evidence that an individual's genetic background plays a key role in driving the changes that occur in tumors during cancer development.”

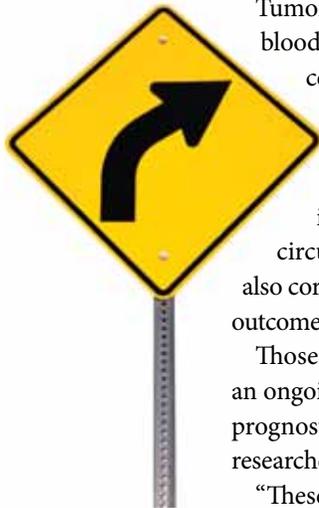
 Published in the journal *Public Library of Science Genetics*.

**THE RESEARCHER**

**AMANDA TOLAND, PhD,**  
*Molecular Biology and Cancer  
Genetics Program*

# CIRCULATION SIGNPOSTS

## Uncovering Prognostic Clues in Head and Neck Cancer



Tumor cells in the circulating blood of patients with squamous cell carcinoma (SCC) of the head and neck may predict disease recurrence and reduced survival. An increased number of circulating tumor cells (CTCs) also correlates with a worse outcome.

Those are the early findings from an ongoing prospective study of the prognostic importance of CTCs by researchers at the OSUCCC – James.

“These findings suggest the presence of CTCs in the blood is correlated with reduced disease-free survival,” says co-first author **KRIS**

**JATANA, MD**, assistant professor of Otolaryngology – Head and Neck Surgery at Ohio State and Nationwide Children’s Hospital. “If these results are supported with continued prospective follow-up, CTCs would be used as a prognostic marker to help further individualize therapy.”

Currently, no prognostic blood test exists for this malignancy.

To identify CTCs, the researchers first removed normal cells so that only abnormal (cancer) cells remained, a method called negative depletion. They eliminated all of the normal red blood cells by rupturing them, then removed normal white blood cells by labeling them with

magnetic nanoparticles and using a magnetic field to pull them out of each sample. After that, they stained and manually counted the abnormal cells.

The study involves 48 patients who underwent surgical intervention for SCC of the head and neck. To date, no instances of cancer recurrence or disease-related mortality have occurred in patients with no CTCs, but the study has found a correlation between an increasing number of CTCs and a worse prognosis.

 Published in the international journal of *Archive of Otolaryngology, Head and Neck Surgery*.

# BACTERIAL BOOSTER

## Virus May Battle Brain Tumors Better With Bacterial Enzymes

OSUCCC – James researchers have shown that oncolytic viruses, which are engineered to destroy cancer cells, might be more effective against brain malignancies if equipped with an enzyme that helps them penetrate the tumor.

The enzyme, called chondroitinase, helps the virus work its way through thickets of protein molecules that fill spaces between cells. When tested in animals transplanted with a human glioblastoma, the most common and deadly form of brain cancer, the enzyme-armed virus improved survival by 52 percent compared with controls, and in some cases it eliminated the tumor.

“Our results show for the first

time that an oncolytic virus with this enzyme can spread more effectively through the tumor, underscoring the potential for using chondroitinases to enhance the capacity of oncolytic viruses to destroy cancer cells,” says study leader **BALVEEN KAUR, PhD**, of the OSUCCC – James’ Viral Oncology Program.

Derived from the intestinal bacterium *Proteus vulgaris*, the enzyme removes sugar chains that branch from proteoglycans that fill the “narrow spaces between cells. Cutting away these branches helps the virus spread through the tumor.

In this study, Kaur and collaborators injected human glioblastoma

cells under the skin of eight mice. They treated the resulting tumors with the enzyme-armed virus. These mice survived an average of 28 days, with two animals remaining tumor-free after 80 days. Control animals, treated with a virus that lacked the enzyme, survived an average of 16 days.

In another experiment, mice with human glioblastomas transplanted into the brain survived 32 days versus 21 days for control animals, an improvement of 52 percent. Again, two animals lived more than 80 days and showed no trace of the tumor afterward.

 Published in the journal *Clinical Cancer Research*

## ▶▶ BRAIN CANCER

# CANCER CULPRIT

## Loss of Gene Promotes Brain Tumor Development

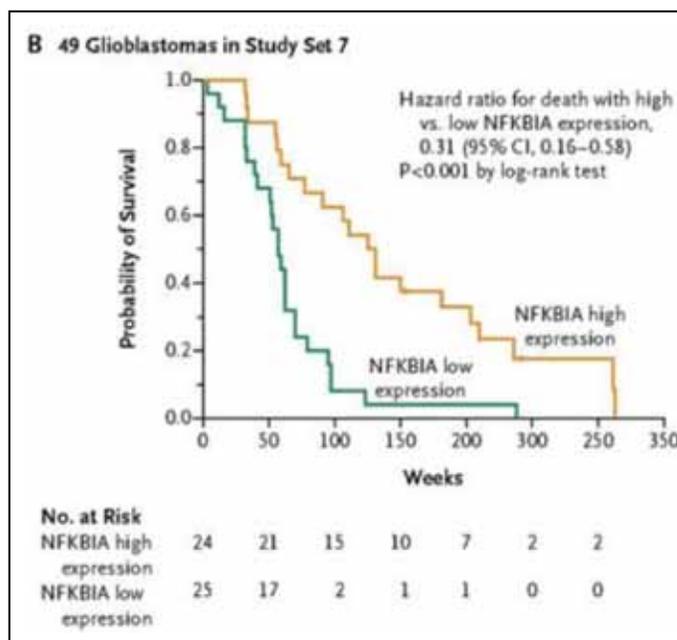
Research at the OSUCCC – James shows that loss of the *NFKBIA* gene promotes glioblastoma multiforme, the most common and deadly form of brain cancer. The study, published in the *New England Journal of Medicine*, also suggests therapies that stabilize this gene may improve survival for certain patients.

“We show that *NFKBIA* status may be an independent predictor of survival in certain patients with glioblastoma,” says senior co-author **ARNAB CHAKRAVARTI, MD**, professor and chair of Radiation Oncology and co-director of the Brain Tumor Program. “We also show that this gene plays a key role in glioblastoma behavior and could be useful for predicting treatment outcomes.”

An estimated 18,500 new cases of glioblastoma occur annually among Americans and result in 12,760 deaths.

Most cases are driven by overexpression of the *EGFR* gene, but this study shows that loss of the *NFKBIA* gene is equally potent in driving glioblastoma development, and that glioblastomas generally show either abnormally high levels of *EGFR* or loss of *NFKBIA*, but not both.

In addition, Chakravarti was principal investigator for an OSUCCC – James study suggesting that certain patients with spinal cord tumors have better long-term survival than others following radiation therapy. This study



also indicates that photon-based radiotherapy results in better survival than proton-beam therapy for these tumors.

The researchers say this is the first study to report long-term outcomes of spinal-cord tumor patients treated by modern radiotherapy techniques.

“Our findings need to be verified in a larger number of patients, but they suggest that individuals younger than 54, those with ependymomas and those treated with photon-based versus proton-beam therapy have better overall survival,” Chakravarti says. “Perhaps



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

most surprising is that the subset treated by protons appears to do worse, even though these patients have more favorable pretreatment demographics.”

 Published in the *International Journal of Radiation Oncology, Biology, Physics*.

# TARGETED ATTACK

## Molecular Rationale for Combining Agents Against Breast Cancer

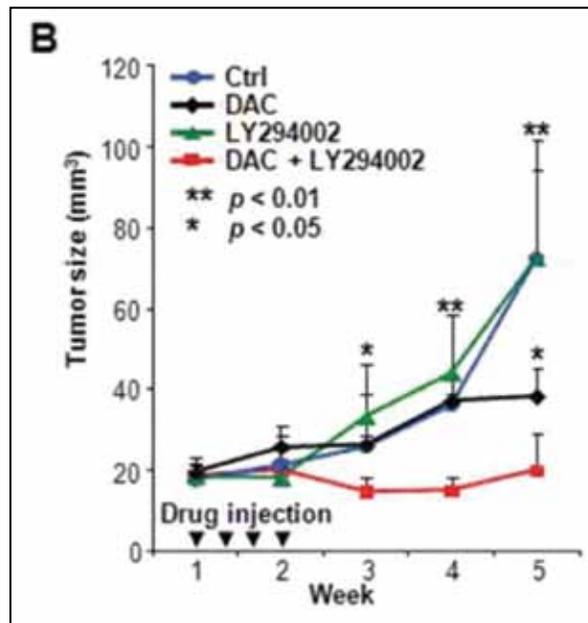
A study by researchers at the OSUCCC – James presents a rationale for treating breast cancer using two targeted agents: one that inhibits an overactive, cancer-causing pathway in cancer cells, and one that reactivates silenced tumor suppressor genes. Both types of agents are currently being evaluated individually in clinical trials.

The laboratory and animal study found that abnormal activation of the PI3K/AKT signaling pathway leads to the silencing of a number of tumor-suppressor genes that regulate cell proliferation, survival and motility, and angiogenesis.

The study also showed that tumor growth is slowed by combining an agent that inhibits PI3K with a drug that reverses the epigenetic changes that cause gene silencing.

“The link we have uncovered between PI3K/AKT signaling and epigenetic silencing offers a new therapeutic strategy for breast cancer that combines a PI3K/AKT inhibitor and agents that target epigenetic changes,” says study leader **TIM H-M HUANG, PhD**, of the OSUCCC – James’ Molecular Biology and Cancer Genetics Program.

The activation of one or more oncogenes and the silencing of tumor-suppressor genes are usually considered separate events that together lead to cancer.



But this and earlier studies led by Huang show that the two events are sometimes linked.

Huang and colleagues are planning a clinical trial that will investigate the use of combined targeted drugs in metastatic breast cancer.

*Published in the journal Cancer Research*



**TIM H-M HUANG, PhD,**  
Molecular Biology  
and Cancer  
Genetics Program

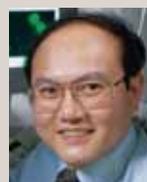
# OF NOTE

*Recent Recognitions of  
OSUCCC – James Physicians  
and Researchers*

## GRANTS



**DENIS GUTTRIDGE, PhD**, a member of the OSUCCC's Molecular Biology and Cancer Genetics Program, **has been awarded a \$1.6 million grant** from the National Cancer Institute (NCI) for a study titled "Elucidating the Role of NF- $\kappa$ B in Rhabdomyosarcoma."



**CHING-SHIH CHEN, PhD**, a member of the OSUCCC's Molecular Carcinogenesis and Chemoprevention Program, **has been awarded a \$1.35 million grant** from the NCI for a study titled "Novel Energy Restriction-Mimetic Agents for Prostate Cancer Prevention."

## AWARDS AND HONORS



**KATHLEEN BORIS-LAWRIE, PhD**, and **MICHAEL LAIRMORE, DVM, PHD**, both professors of Veterinary Biosciences and members of the OSUCCC – James Viral Oncology Program, **have been elected as Fellows of the American**



**Academy of Microbiology**, the honorific leadership group within the American Society for Microbiology.

**CHIARA BRACONI, MD, PhD**, a postdoctoral researcher with the OSUCCC – James, is **one of 25 oncology trainees from around the world to receive an American Society of Clinical Oncology (ASCO) Cancer Foundation Merit Award** for important contributions to gastrointestinal cancer research. The awards are designed to promote clinical cancer research by young investigators.



**ROBERT BRUEGGEMEIER, PhD**, dean of Ohio State's College of Pharmacy, and a member of the OSUCCC – James Molecular Carcinogenesis and Chemoprevention Program, **was named the 2011 Outstanding Dean** by the American Pharmacists Association Academy of Student Pharmacists.



**EHUD MENDEL, MD, FACS**, professor of Neurological Surgery, of Medicine, of Orthopaedics and of Engineering, and director of the Spine Program, **has been listed among the 100 best spine surgeons and specialists in America** by Becker's Orthopedic & Spine Review.



**ELECTRA PASKETT, PhD**, associate director of Population Sciences at the OSUCCC – James, **has been recognized by the American Society of Preventive Oncology**. For her achievements as president of the organization, ASPO has established the Electra Paskett Scholarship Award, to be given annually to a trainee to attend the society's annual meeting.



**ROBERT TAYLOR, MD**, medical director of the Center for Palliative Care at the OSUCCC – James, **has been named a fellow of the American Academy of Hospice and Palliative Medicine**. Taylor, an associate professor of Neurology at Ohio State, received fellowship status for his commitment to scholarship in hospice and palliative medicine. Taylor, a medical ethicist, specializes in pain and symptom management in patients with life-limiting diseases.

## FACULTY AND PROGRAMS



**MICHAEL LAIRMORE, DVM, PhD**, professor of Veterinary Biosciences and member of the OSUCCC – James Viral Oncology Program, **has been appointed associate director for Shared Resources at the OSUCCC – James**. He oversees 16 specialized services, or core facilities that help investigators conduct cancer research through expert leadership and training; clinical, administrative and technical support; and state-of-the-art instrumentation.



**GUSTAVO LEONE, PhD**, associate professor of Medicine and member of the Molecular Biology and Cancer Genetics Program, **has been appointed associate director for basic research at the OSUCCC – James**. He will oversee laboratory-based efforts of some 275 investigators representing 11 colleges at Ohio State and work to recruit additional investigators in breast, genitourinary, gastrointestinal and thoracic cancer.



**GUIDO MARCUCCI, MD**, director of the Myeloid Malignancy Program and holder of the John B. and Jane T. McCoy Chair in Cancer Research, **has been appointed associate director of translational research at the OSUCCC – James**. In this role, Marcucci will work to accelerate translational research throughout the Ohio State cancer program.



**THOMAS D. SCHMITTGEN, PhD**, chair of Pharmaceuticals in the College of Pharmacy, and member of the OSUCCC – James Experimental Therapeutics Program, **coauthored a paper identified by ScienceWatch.com as the most cited paper in the last decade across 22 fields and 20 countries**. Using data from journals indexed by Thomson Reuters, the website determined that the 2001 paper by Kenneth J. Livak and Schmittgen was cited over 9,200 times between January 2000 and August 31, 2010. The paper describes the initial equations and methods to perform calculations for quantitative PCR. (A paper from the Netherlands with 7,405 citations came in second.)

**OSUCCC – JAMES Leads GU Trial Accrual for five years straight**, the OSUCCC – James has been the leading institution in accruals to genitourinary oncology clinical trials conducted by the Cancer and Leukemia Group B (CALGB), a national clinical research group sponsored by the NCI.

## NATIONAL LEADERSHIP



**ELECTRA PASKETT, PhD**, associate director of Population Sciences, leader of the Cancer Control Program at the OSUCCC – James and president of the American Society of Preventive Oncology **led this year's annual meeting of ASPO**, an organization that promotes research in cancer prevention, control and survivorship.



The OSUCCC – James has presented **BRUCE A. CHABNER, MD**, director of clinical research at the Massachusetts General Hospital Cancer Center, **the 18th annual Herbert and Maxine Block Memorial Lectureship Award for Achievement in Cancer**. The prize, which includes \$25,000, was established by the Block family of Columbus to honor their parents, Maxine and Herbert J. Block, who both died of cancer. Chabner, a professor of Medicine at Harvard Medical School, presented a lecture entitled "Cancer as a Rare Disease: Revolutionizing Drug Development." The Lectureship is funded by proceeds from the Herbert J. Block Memorial Tournament, an annual golf outing established by the Block family.



# DRUGS ON CAMPUS

A drug-development pipeline that takes cancer therapies from conception and design to the patient bedside isn't a pipe dream at The Ohio State University—it's under construction.

BY KENDALL POWELL  
ILLUSTRATIONS BY RICHARD  
LILLASH

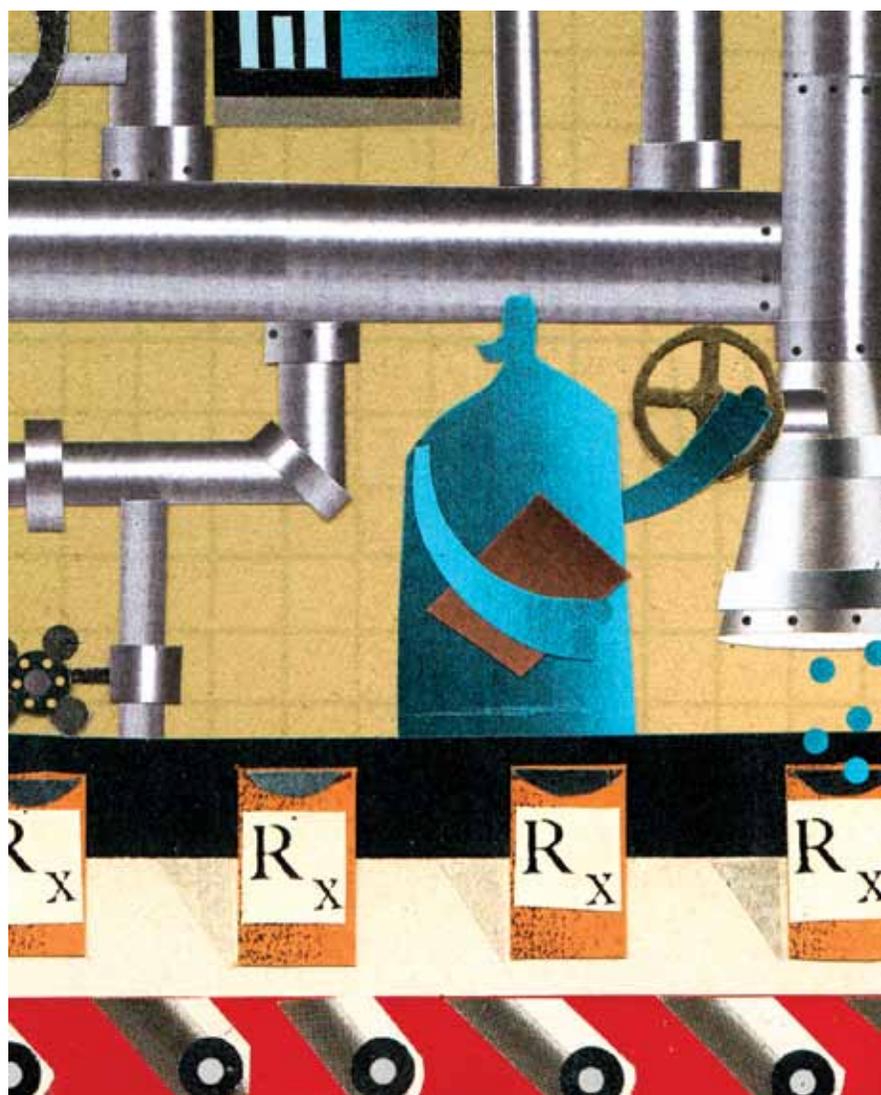
In 2003, a casual conversation between a chemist with a knack for designing new molecules and a physician-scientist treating leukemia patients sparked the development of a potential new cancer therapeutic. The physician, John Byrd, MD, director of the Division of Hematology, was running a clinical trial of a new class of anticancer drugs, called histone deacetylase, or HDAC, inhibitors. He pondered out loud to his colleague Ching-Shih Chen, PhD, professor of Medicinal Chemistry, of Internal Medicine, and of Urology, whether it would be possible to design a more potent version of a well-known HDAC inhibitor, valproic acid, which has a long record as a safe antiseizure medication. Chen took up the question as a challenge and seven years later, the compound he designed, known as AR-42 began being tested in cancer patients with hematologic malignancies (blood or bone marrow cancers) at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

Chen, with the help of his clinical colleagues and support of the OSU College of Pharmacy and the OSUCCC – James Experimental Therapeutics Program, has ushered, not one, but two anticancer compounds into Phase I clinical trials. His success shows that the early stages of drug discovery and

development can be executed within an academic campus setting, literally moving an idea from the laboratory bench to a pill in a patient’s hand. Leaders at OSU hope to capitalize on the unique resources and expertise available on campus and nearby to create a drug development pipeline that would propel discoveries into the clinic even more efficiently.

“At OSU, we have a really outstanding College of Pharmacy,

College of Medicine, College of Veterinary Medicine, College of Math and Physical Sciences, along with the OSUCCC – James. And we are right across the street from Battelle Memorial Institute,” an international leader in preclinical therapeutic research including pharmacology and toxicology studies, notes Michael Grever, M.D. chairman of the Department of Internal Medicine and co-leader of the OSUCCC – James Experimental



Therapeutics Program. “We started talking and thought there would be some value in putting together a more formal drug development program here.”

### A TALE OF TWO COMPOUNDS

Both of the anticancer compounds designed by Chen’s laboratory started with key information about drugs already on the market. AR-42 began as a search to make a structure similar to the short-chain fatty acid

valproic acid that would have a more potent HDAC inhibiting activity.

After the conversation with Byrd, Chen’s group started with a scaffold similar to valproic acid and then performed structure-based drug design to arrive at AR-42, which proved to be about four or five times more potent than the leading HDAC inhibitor drugs already in clinical testing. In addition, the new compound had some other advantages, such as inhibiting not just HDAC, but also AKT, an enzyme that helps cancer cells evade programmed cell death.

“I often say that basic scientists have to work closely with clinicians because they can provide us with a good perspective into clinical medicine,” Chen says, who is known for being a very engaged collaborator.

Similarly, the idea for the second compound, called AR-12, started from the observation that patients taking daily doses of the pain medicine celecoxib (Celebrex) may have a generally lower incidence of cancer. Celecoxib’s pain relief is related to its inhibition of the COX2 enzyme, and Chen wondered if the anticancer effect was due to this inhibition or to something else altogether. His laboratory began by dissecting that question and found that the cancer prevention was instead related to celecoxib’s secondary inhibition of PDK1, a kinase that acted upstream of AKT.

“AKT is a holy grail for cancer-drug discovery because it is key for cancer cells to survive and proliferate,” Chen says. “As soon as that was identified as the target

[of celecoxib], we jumped on this problem.”

His group began designing a molecule that would remove the COX2-inhibiting activity (which is now known to have negative cardiac side effects) and enhance PDK1 inhibition. The result, AR-12, potently inhibited PDK1 kinase and when tested against a panel of cancer cell lines, successfully inhibited many of them, including breast and prostate cancer cell lines.

With encouragement from Grever, Chen submitted applications for both compounds to the National Cancer Institute’s (NCI) Rapid Access to Intervention Development (RAID) program. This program sponsors the pre-clinical testing of compounds developed in academia, specifically the pharmacology and toxicology studies needed to submit an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA). An IND application typically requires toxicology and pharmacokinetic data from testing in two different animal models as well as evidence of the drug’s in-vivo efficacy.

RAID-program support was essential for the continued development of both AR-12 and AR-42, Chen says, since OSU lacks the resources and facilities to perform the toxicology studies and to manufacture a drug in the quantities and quality needed for first-in-human studies. But it also came with a substantial load of paperwork and was a long process since the NCI must identify a subcontract laboratory to



handle the testing. (NCI has since discontinued the RAID program and replaced it with a new program called NExT, for NCI Experimental Therapeutics Program.)

Once Chen was ready to publish his team's findings on the new compounds, he sent an invention disclosure, along with the manuscripts, to Jane New, associate director of Ohio State's Office of Technology, Licensing, and Commercialization. Her office filed patent applications to protect the intellectual property rights for the agents, then worked to secure an appropriate industrial partner to license the technology for further development. By the end of 2007, a deal was signed with Parsippany, New Jersey-based Arno Therapeutics, a biopharmaceutical company with expertise in cancer therapies.

"The RAID-sponsored studies put a stamp of approval on our work because it is a very vigorous review process, and it generated a substantial amount of data for the IND application," Chen says. "That saves a partnering company a lot of time and money when filing the IND," Chen says.

In 2009, AR-12 began being tested in a phase-I clinical trial in patients with advanced or recurrent breast, colon, lung or prostate cancers or lymphoma who had failed previous chemotherapy treatments. AR-42 began phase-I testing in the fall of 2010 in hematological cancer patients, specifically multiple myeloma, chronic lymphocytic

leukemia (CLL), and lymphoma patients whose cancer has progressed after standard therapies.

Craig Hofmeister, M.D., assistant professor of medicine and a myeloma specialist, is overseeing the trial of AR-42 which will determine the proper dosing regimen of the drug including monitoring safety, side effects, and feasibility. Hofmeister notes that HDAC inhibitors as a class have a history of causing heartbeat irregularities, fatigue, and stomach upset, but so far he isn't seeing those issues in the patients taking AR-42.

Because the protocol for this trial was designed by Ohio State investigators (and funded by an NCI grant to Grever and Byrd), Hofmeister explains that it will go a step beyond safety and also monitor patient responses or resistance to the drug.

"This trial is especially unusual because it is investigator-initiated, meaning the protocol was developed at Ohio State and has correlative studies attached to it that involve collecting patients samples and investigating the drug's mechanism of action," Hofmeister says.

That means that six months later, researchers will have the blood or bone marrow biopsy samples from all patients given AR-42 to perhaps determine why some patients responded to the drug and others did not. Both the myeloma patients and the CLL patients, Hofmeister explains, exhibit easily trackable biomarkers that show whether their cancers are progressing, stable, or

regressing at a given point in time. This data can be used to decide early on which types of patients might benefit the most from the drug.

"People often think that drug discovery takes a tremendous amount of resources that are only available in industry," Chen says. "But our success in developing these two drugs from design to clinical trials shows that drug discovery is doable in the academic setting."

#### A SPEEDIER PIPELINE

Grever and Chen both envision a drug-development process in the future that takes even greater advantage of local resources and collaboration with Ohio State's colleges and Battelle.

Battelle is the world's largest, independent research and development organization and manages seven national laboratories. It has facilities that cover all parts of the drug discovery and development pipeline, including pre-IND toxicology, pharmacology, and safety research. In addition, Grever points out that the dean of Ohio State's Fisher College of Business, Christine Poon, is a former executive who most recently managed the pharmaceutical businesses of Johnson & Johnson. "Between Battelle and the resources on campus, we are in a unique position to move things through the pipeline more rapidly, which would be a tremendous value to our patients," says Grever. Several planning meetings including scientists from both Ohio State

and Battelle are exploring the feasibility of this exciting scientific collaboration.

Grever expects that such a facilitated pipeline on campus, with less bureaucratic red tape and more local interactions, would potentially shave one to two years off the pre-clinical development process. “That is important to investors, who don’t want to lose those years of patent life,” he notes. “Furthermore, it is most important to our cancer patients who want to try an investigational therapy in an attempt to help their condition.”

Such a pipeline program would first focus on Ohio State’s strengths in the development of anti-cancer agents. Grever expects that the OSUCCC – James would work closely with Dean Poon to develop a business model to help secure the financial resources needed to fund drug discovery and development. These efforts would also capitalize on the decades of experience the OSUCCC – James has in running phase-I and II trials.

“With our large phase-I program in place, we have many patients who need access to new, experimental drugs,” says Grever.

Compounds likely to move forward through such a pipeline would be completely novel chemical structures or biological molecules. When a research team has worked out the mechanism of action of a novel compound and knows it is hitting a targeted pathway in cancer or overcoming a known mechanism of drug resistance, then it should

move ahead to be tested in both healthy and tumor-bearing animals. If the drug’s delivery and absorption in animals seems straightforward, then that would bode well for a compound moving into the much more expensive and detailed studies required for the IND application—studies that can cost \$800,000 to \$1 million.

At that point, the Office of Technology, Licensing, and Commercialization would step in to facilitate the partnership with a company that would invest that money to complete the IND. New says a stronger commitment to drug development on campus would attract more industry partners.

“When it comes to pharmaceuticals, the more development [a university] can do, the more things to move it along the pathway, the easier it makes it on a company to better pick up something and move it to a commercial, FDA launch,” says New. “The more hurdles we can overcome, means reducing the risk for the company and increasing the return to the university. Especially, if we can manage to do it quicker.”

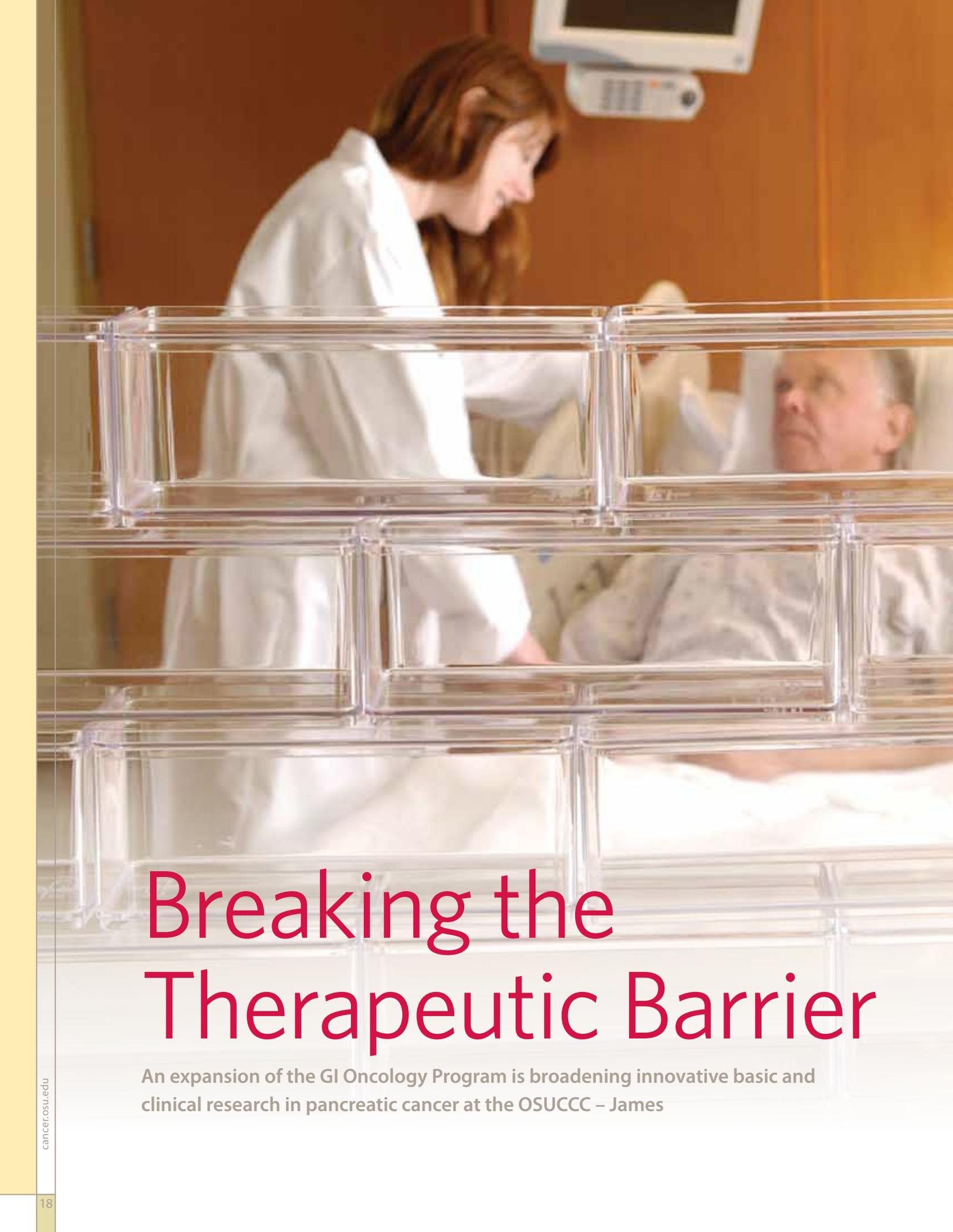
Dean Robert Brueggemeier of the College of Pharmacy has been a major supporter of Chen’s research from the start. He notes that Chen’s collaborative, cross-campus approach is a hallmark of both the College and the OSUCCC – James. “A number of critical faculty in each of the colleges working together on a problem come up with novel solutions that they wouldn’t have come up with individually. The College of

Pharmacy supports and facilitates that team-science approach.”

Ohio State has the advantage of having chemists in the College of Pharmacy who specialize in early drug discovery and development, clinician-scientists at the OSUCCC – James who specialize in oncology treatment and running clinical trials, and resources such as the Pharmaceutical Analysis Shared Resource (PHASR), which can measure the concentration of drugs in a patient’s blood or urine sample in real-time. In addition, the key things OSU lacks — such as toxicology experts and a GMP facility to produce drugs suitable for use in humans — can be found nextdoor at Battelle.

“We have a very unique opportunity here in central Ohio,” says Brueggemeier. “Strengthening the partnership between OSU and Battelle will be really critical for putting together a drug development pipeline here.”

Grever concurs, noting that the confluence of local expertise is key not only for moving potential new therapies along in development, but also for the initial conversations — such as the one between Byrd and Chen — that generate the seeds of drug discovery in the first place: “Through the Experimental Therapeutics Program, we have the ability for chemists, biologists, and physicians to get together and have these collaborative discussions. We’re lucky that we’re all on one campus and not split up.” ■



# Breaking the Therapeutic Barrier

An expansion of the GI Oncology Program is broadening innovative basic and clinical research in pancreatic cancer at the OSUCCC – James

BY BOB HECKER  
PHOTOGRAPHY BY ROMAN SAPECKI

A national “call to action” against pancreatic cancer—one of the world’s deadliest malignancies—is being well-served by an ongoing expansion of the Gastrointestinal (GI) Oncology Program at The Ohio State University.

Driving the expansion is a rising volume of patients with cancer of the pancreas, esophagus, liver and bile duct, malignancies that cry out for more research to foster better therapies.

“Although progress has been made in some gastrointestinal cancers, such as colorectal cancer, very little has been made in others—especially pancreatic, which is the only major cancer with a single-digit five-year survival rate for all stages combined (less than 6 percent),” says Tanios Bekaii-Saab, MD, medical director of the GI Oncology Program at Ohio State’s Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James).

“With our science-based treatments attracting more patients, along with the need for better therapies to serve our growing caseload, we are recruiting more medical professionals to our multidisciplinary program,” Bekaii-Saab says. He notes that the program will soon move to larger

quarters in a new Gastrointestinal Comprehensive Cancer Center near Ohio State’s main campus.

“Our team of GI oncologists, surgeons, radiation oncologists, interventional radiologists and geneticists will be consolidated in one location designed to absorb our growth,” he adds. “We’ll offer the full spectrum of scans, blood draws, chemotherapy and radiation therapy, colonoscopies, upper endoscopies, etc., for treating patients with all forms of GI cancer.

“Our program sees about 1,000 new patients per year, and annually we have between 12,000 and 15,000 patient visits. Our goal in the next year or two is to increase patient volume by 10 to 20 percent.”

### ENGAGING THE ENEMY

Bekaii-Saab believes the expansion will help the OSUCCC – James take more strides against pancreatic cancer, which is the fourth-leading cause of cancer death in the United States despite ranking 10th in incidence.

The American Cancer Society estimated that more than 43,000 Americans were diagnosed with the disease in 2010 and projected that nearly 37,000 would die from it that year. For those diagnosed in earlier stages, 20-30 percent survive



**DENIS GUTTRIDGE, PhD,**  
*associate professor of Medicine*

five years, but less than 5 percent survive that long if they have later-stage disease. Most patients are diagnosed in later stages since there is no standard screening method, and symptoms typically do not present until the disease has advanced.

“It usually shows up late, tends to be resistant to current therapies, and often recurs despite surgery and chemotherapy,” Bekaii-Saab says. “In absolute numbers, the incidence and mortality rates are almost the same, which means that almost every patient with pancreatic cancer dies from it, and many die within six months to a year.”

In 2007, the National Cancer Institute (NCI) brought together researchers, clinicians, patient advocates and pharmaceutical industry representatives to produce a consensus report on developing and testing treatments for pancreatic cancer over the next few years. It appeared online on Oct. 26, 2009, in the *Journal of Clinical Oncology*.

In a subsequent article in the *NCI Cancer Bulletin*, the report’s lead author, Philip A. Philip, MD, of the Barbara Ann Karmanos Cancer Institute in Detroit, described it as a “call to action” that cites a need for “better clinical trials based on solid

science” and for greater patient participation in those studies in order to improve outcomes.

The *Bulletin* stated that the report recommends designing “pilot studies that test potential treatments in smaller groups before proceeding to the kinds of large trials that have yielded disappointing results in the past.” It also said decisions about molecular targets and potential drugs should be based on scientific evidence that includes preclinical and animal studies that better represent pancreatic cancer in humans. “A challenge,” the article added, “is to develop treatments when knowledge of pancreatic

cancer biology is still limited.”

Bekaii-Saab says the OSUCCC – James’ GI Oncology Program is addressing the report’s concerns through both basic molecular studies and innovative clinical trials. On the clinical side, he says, “We’re pioneering the report’s recommendation for smaller targeted studies by leading NCI-sponsored trials involving novel therapeutic agents.”

One is a randomized, multi-institutional, phase II study led by Bekaii-Saab to assess progression-free survival in patients with recurrent or metastatic pancreatic cancer who receive the oncolytic virus Reolysin® in combination with standard chemotherapeutic drugs paclitaxel and carboplatin, relative to those who receive paclitaxel and carboplatin alone. The NCI’s Cancer Therapy Evaluation Program (CTEP) is sponsoring the trial, and Oncolytics Biotech Inc. is providing the virus.

Reolysin® is a naturally occurring human reovirus. While reovirus infection in humans is generally mild and limited to the “upper respiratory and gastrointestinal tracts, the virus replicates in, and is cytotoxic to, cells with mutations that activate the RAS gene signaling pathway.

He points out that RAS mutations are found in some 30 percent of all human cancers, including close to 90 percent of pancreatic ductal adenocarcinomas, making the RAS pathway a prime therapeutic target.

“The chemotherapy drugs, combined with the virus, will do two things: help destroy tumor cells and suppress the body’s immune response to the virus, allowing it to reach its target and have its effect,” Bekaii-Saab says.

Seventy patients will be accrued to the study, which also is being conducted at Memorial Sloan-Kettering Cancer Center and at Georgetown University.

In addition, the OSUCCC – James is accruing patients to an NCI-sponsored phase I dose-escalation clinical trial that examines the use of 3-AP (Triapine®) plus radiotherapy in patients with unresectable stage III nonmetastatic pancreatic cancer. The goals are to determine the maximum tolerated dose of this agent when used with radiotherapy, and to gauge the therapeutic response rate.

Twenty-four patients will be accrued to this study, which is available only at the OSUCCC – James. “In our first nine patients, we’re already seeing some promising responses that wouldn’t be attributable to the radiation alone,” says Bekaii-Saab, principal investigator.

These two studies are among several clinical trials at the OSUCCC – James designed for patients with all stages of pancreatic cancer.

“We can treat patients along the entire continuum of care, from prior to surgery all the way to second-line treatment in metastatic cancer,” Bekaii-Saab says. “We

also have an active basic research program for studying molecular biomarkers, genetic pathways, tumor microenvironment and other biological aspects that may help us better understand, detect and treat this disease.”

## OTHER INROADS

An important basic science finding came recently from the lab of Mark Bloomston, MD, a surgical oncologist whose team identified a microRNA profile that could distinguish pancreatic cancer tissue from nearby normal tissue and from chronic pancreatitis. Published in the *Journal of the American Medical Association*, the finding suggests that microRNAs might help detect this disease sooner and predict how patients will fare.

“Such correlations with survival are lacking in pancreatic cancer,” Bloomston says, noting that this finding was “just a starting point. We and others need to validate the role of these molecules in pancreatic cancer. We’re looking at how the tumor microenvironment interacts with tumor cells to alter the expression of microRNAs.”

Bloomston’s group also is starting a project to test the effectiveness of optical coherence tomography (OCT) for early detection of precancerous pancreatic lesions that previously were difficult to find due to limitations in imaging.

With the aid of an “idea grant” from Pelotonia, an annual

grassroots bicycle tour that raises millions of dollars for cancer research at the OSUCCC – James, Bloomston and colleagues will build an OCT device at Ohio State in collaboration with Case Western Reserve University physicist Zhilin Hu, PhD, who developed the technology.

“Optical coherence tomography is an endoscopic procedure,” Bloomston says. “The probe is a fiber that can be inserted into the pancreatic duct to provide 3D images at the microscopic level, allowing detection of abnormal cells not visible with current technology.” He says the OCT device initially will be used in the operating room to image pancreatic tissue removed from patients undergoing surgical resection for suspected precancerous lesions, after which the OCT images will be compared with microscope images.

“Over the two years of this project, we expect to detect occult cancers in six to eight of the 30 to 40 patients who will be having surgery here,” Bloomston says. “Once the reliability of the OCT device is confirmed, we’ll undertake a larger project to presurgically image the pancreas of patients at high risk for pancreatic cancer. We hope eventually to make treatment decisions based on OCT images.”

He adds that the OCT device also will be equipped to deliver radiation, “which opens the possibility for treating precancerous pancreatic lesions without radical surgery – a potentially revolutionary step in early detection and prevention.”

## DRUG DISCOVERY

Of vital importance in pancreatic cancer research is the development of promising molecules that may lead to new therapies.

“Patients with advanced or metastatic pancreatic cancer often are treated with gemcitabine (the current standard) to gain modest survival benefit,” says Ching-Shih Chen, PhD, a medicinal chemist at the OSUCCC – James. “Part of our drug discovery effort targets enzymes that promote development of drug-resistant properties or metastatic behavior in pancreatic cancer cells.”

Chen says that an energy restriction-mimetic agent his team recently developed shows a unique ability to downregulate the expression of two enzymes—ribonucleotide reductase and thymidylate synthase—that contribute to chemoresistance to gemcitabine.

He says investigators also will test the efficacy of a newly developed integrin-linked kinase inhibitor that eradicates cancer cells expressing aldehyde dehydrogenase, which marks pancreatic cancer cells that have stem cell and mesenchymal features.

## NF-κB AND CANCER CACHEXIA

Combating the devastating effects of pancreatic cancer, such as cachexia, is another aspect of helping patients with this disease at the OSUCCC – James.

Denis Guttridge, PhD, associate professor of medicine, and his lab study the NF-κB family of transcription factors and their role in cell growth and differentiation.

Strong evidence indicates that the NF-κB signaling pathway is also involved in tumor progression and in limiting the ability of skeletal muscle to regenerate, which may be a factor in muscular dystrophy and cancer cachexia.

“Our research on skeletal muscle suggests that NF-κB could be relevant in several wasting disorders,” Guttridge says. “Cachexia is prevalent in aggressive cancers such as those in the GI region, so we’re trying to understand how NF-κB promotes it.”

“There is evidence that activating NF-κB in skeletal muscle leads to its breakdown and to muscle loss,” he explains. “Our work with muscular dystrophy shows that, in that disease, NF-κB can inhibit skeletal muscle regeneration. We want to know whether there are common mechanisms in how NF-κB regulates degeneration in muscular dystrophy versus how it may promote muscle wasting in cancer cachexia.”

Guttridge says clinicians have seen pancreatic cancer patients lose up to 20 percent of their body weight due to skeletal muscle degeneration. He points out that weight is a prime predictor of prognosis: Patients who lose a lot are more difficult to treat aggressively with radiation and chemotherapy.

Guttridge and Chen also recently received a Pelotonia “idea grant” to study NF-κB inhibition cancer therapy. They plan to design an agent that targets this protein and that, if successful in preclinical studies, could be developed for treating breast and hematologic



**TANIOS BEKAII-SAAB, MD,**  
*medical director of GI the Oncology Program*

**MARK BLOOMSTON, MD,**  
*Surgical Oncologist*

malignancies.

“This study will involve cell lines, human tissue and potential mouse models of leukemia and breast cancer,” Guttridge says. “We chose these cancers because we have animal models that are already accepted, and because two of our experts in these disciplines—Gustavo Leone, PhD, and John Byrd, MD—can critically analyze the results for us.”

He says the agent could later be applied to other cancers, including pancreatic.

### GLIMMERS OF HOPE

Despite what Bekaii-Saab calls a historically “pathetic and baffling” lack of research funding for pancreatic cancer compared with other cancers, he believes the NCI “call to action” will help.

“Work being done now by us and others suggests there are ways to break through the therapeutic barriers,” he says. “At Ohio State and other academic medical centers we have the advantage of multidisciplinary care backed by the presence of multiple clinical trials. As more programs

around the nation become similarly comprehensive, I believe we’ll get to a day when this cancer is as treatable as some other forms are now.”

“From a research standpoint, we can learn here from every patient, and we have clinical trials for patients at every stage of this disease,” Bloomston adds. “We are starting to see longer survival periods. In my career, I’ve gone from seeing patients typically survive less than a year to many who are living two to four years—not necessarily cured, but living longer with a good quality of life. And that’s the first step.” 

# Extended Benefits

NCIT32 training grants enable Ohio State to attract talented doctoral and postdoctoral students into research labs today and to mentor them as the cancer scientists of tomorrow.





BY DARRELL E. WARD

PHOTOGRAPHY BY ROMAN SAPECKI

Nadine Bowden is a young veterinarian working her way through a doctoral program at Ohio State to pursue her dream job: collaborating on preclinical studies of promising anticancer agents in transgenic mouse models. She is preparing to assess experimental agents for efficacy, antitumor effects and associated pathologies during preclinical testing, and to contribute to human risk assessments prior to phase I testing of agents.

Bowden's specialized, interdisciplinary training is made possible by T32 grants, a National Institutes of Health funding mechanism that supports the training of doctoral and post-doctoral students for two to three years. Congress created these grants in 1974 to ensure that the nation has an adequate number of biomedical-research scientists.

A year into her pathology residency program, Bowden applied for a slot on the Oncology Training Grant, directed by Michael A. Caligiuri, MD, director of The Ohio State University Comprehensive Cancer Center and CEO of the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). She spent two years on the grant interacting with young physicians on the grant, attending a journal club and discussing clinical oncology research and cancer therapeutics.

Her doctoral research focuses on the human T-lymphotropic virus type 1 (HTLV-1) and its role in the development of adult T-cell lymphoma. Her mentor is HTLV-I specialist Michael Lairmore, DMV, PhD, professor of Veterinary Biosciences and associate director for Shared Resources at the OSUCCC – James.

Bowden is investigating a protein called p30 that the virus produces to escape detection by the immune system. “Our ultimate goal is to find a target that will weaken the virus’s ability to evade the immune system,” Bowden says.

At the same time, she is studying mouse models through a training grant awarded to Lairmore titled *Mouse Pathobiology: Models of Human Disease*.

Bowden notes that one of the most important advantages of working on training grants is the people you meet. “I have interacted with investigators and trainees I probably otherwise would not have met, particularly when I was on the oncology training grant because the majority of those recipients were MDs.”

These grants also provide trainees with a salary and some funds to attend a conference and for research support. “It helps you transition from being a post-doc to having your own laboratory,” she says. Trainees go on to fill faculty positions at other universities or to work for government or industry.

More than 70 percent of T32 grants are awarded to National Cancer Institute (NCI)-designated Comprehensive Cancer Centers, such as Ohio State, which offer a multidisciplinary environment, well-equipped laboratories and faculty with wide-ranging expertise, says Linda Weiss, PhD, director of NCI’s Office of Cancer Centers. “And we want cancer centers training tomorrow’s cancer researchers.”

In 2010, the Cancer Training Branch spent about \$166 million overall for training grants, with the T32 program receiving a little over a third of that, according to Ming Lei, PhD, chief of the Cancer Training Branch in NCI’s Center for Cancer Training.

“The National Research Service Award T32 program is the main NCI institutional training mechanism that supports the training of predoctoral and postdoctoral fellows,” Ming says.

For trainees, the benefits of T32 grants include a structured training environment, didactic courses, and an emphasis on interdisciplinary training and career development training, Ming says. “We encourage mentors to train fellows to manage career goals, to teach them how to obtain grants and progress from one career stage to the next, and to prepare them for an independent biomedical research career.”

“The program is also designed to promote diversity in the workforce among groups that may be under-represented in biomedicine, including the disadvantaged and the disabled,” says Sonia B. Jakowlew, PhD, a program director in the Center for Cancer Training.

### **The soul of a research lab**

Training grants not only prepare the biomedical researchers of tomorrow, they are vital to progress in cancer research today. “T32 training grants are enormously important because they provide an

opportunity to recruit competent young researchers who bring with them new ideas and techniques,” says Albert de la Chapelle, MD, PhD, professor of Medicine and the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research.

A modern biomedical research laboratory typically includes a senior, or principal, investigator who heads the lab and spends most of his or her time writing grant proposals to obtain research funding, reviewing data from current experiments and writing up research findings for publication in a journal, and one to several doctoral or postdoctoral students.

“It is the students who work for the principal investigator who are the drivers of the lab’s research projects,” says de la Chapelle, who also co-leads the OSUCCC – James Molecular Biology and Cancer Genetics research program. “Research ideas may come from the principal investigator, but the actual development and work of doing experiments comes from the doctoral and postdoctoral students. They are the soul of the lab. Every discovery is basically made by a post doc or a graduate student.”

“We want the brightest doctoral and postdoctoral students working in our laboratories today,” Caligiuri says. “They are the ones who are thinking purely science, and they are the ones who make the discoveries. Senior investigators will determine what to do with a discovery, but it’s the students who

## PELOTONIA TRAINING GRANTS

In addition to receiving federally awarded T32 training grants, the OSUCCC – James has established its own in-house training-grant program, which is supported by the Pelotonia bicycling fundraising event held by the Ohio State cancer program each August.

“The goal of the Pelotonia Fellowship Program is to get the best young minds at Ohio State involved in cancer research,” says director Jeff Mason, who notes that Pelotonia fellowships are available to undergraduate, graduate, post-docs in any of Ohio State’s \_\_ colleges, as well as to medical students. In addition, the program is particularly timely because federal funding for training grants has remained flat for several years.

In 2010, its first year, 70 fellowships were awarded: 29 to undergraduates, 22 to graduate students, 18 to post-doctoral students and one medical student. Awardees present their work at the OSUCCC – James annual research symposium (see the back cover).

“There is no other program that I know of like our one-year undergraduate fellowship program,” Mason says. “We are funding cancer-related research by trainees all over campus,

including arts and sciences, communications and world literature in addition to projects in cancer prevention, survivorship, genetics, and population sciences.

Examples of undergraduate research projects include one to “Design Effective Anti-Smoking PSAs Targeting African Americans: A Dynamic Motivational Activation Model” by a Communications student, and “Targeting Protein Arginine Methyltransferase 5 (PRMT5) Overexpression in Glioblastoma Multiforme,” by a Biochemistry major.

“Pelotonia fellowships offer a great opportunity for students and trainees, one that can help launch their career in cancer research,” Mason says, “and they are valuable to the rest of us because they help train the next generation of cancer researchers.”

For more information about the Pelotonia Fellowship Program, visit <http://cancer.osu.edu/research/researcheducation/pelotoniafellowshipprogram/Pages/index.aspx>. For information about riding Pelotonia or working as a volunteer, visit <http://pelotonia.org>.

make the discoveries.”

Caligiuri offers an example from his own laboratory. Aharon “Ronnie” Freud was a doctoral candidate in Ohio State’s medical scientist program who discovered where immune cells called natural killer (NK) cells mature in the human body.

Freud had completed hundreds of hours of flow cytometry of NK cells, and his work revealed a pattern that looked to Caligiuri as if the cells were trafficking to the lymph nodes. “I would never have guessed that,” Caligiuri says. “Ronnie obtained the code, and I

deciphered the message. But the discovery was due to Ronnie’s persistence, energy, creativity and intelligence.” The finding was published in the journal *Immunity* (2005).

Caligiuri notes that training programs are peer reviewed every five years for the progress trainees have made. “There is tremendous pressure to provide a strong program,” he says. “If your trainees don’t succeed, your training program comes to an end. It’s a very good system.”

### From trainee to mentor

William E. Carson III, MD, is a professor of surgery and breast-cancer specialist at the OSUCCC – James, and co-leader of the cancer center’s Immunology Research Program.

In 1991, Carson was a new surgical oncology fellow at Roswell Park Cancer Institute in Buffalo. He had a year of research experience and an interest in immune therapy for cancer, so his mentor encouraged him to apply for a slot in their T32 program.

Doing so would mean spending two years as a research fellow, along

with two years as a clinical fellow. “At first I didn’t think that would be the way to go,” he recalls, “but I did it, and the training helped focus my career on academic surgery and prepared me to set up my own research laboratory. It gave me experience in the lab and data and papers that jump-started my research career. I also wrote a proposal and received a K11 award, which I wouldn’t have been able to do otherwise.” K awards are an NIH funding mechanism designed to help promising young faculty members establish their careers and laboratories.

Today, Carson has his own T32 grant to train postdoctoral students in immune therapy for cancer. Trainees participate in courses and meetings sponsored by the OSUCCC and the Immunology Program, and they are exposed to bioinformatics, human cancer genetics, translational medicine, experimental therapeutics and other related disciplines and receive training in responsible of human research.

“The overall experience helps trainees understand the translational potential of their discoveries, and it helps jumpstart their own research careers,” Carson says. Four students are on the grant at any one time, each working in their own area of interest under a research mentor.

### Two for Translation

Sometimes NCI specifies the design of T32 grants; in other cases, investigators propose a design. The training grant in cancer genetics awarded to de la Chapelle, along with Gustavo Leone, PhD, OSUCCC

– James associate director for Basic Research, and OSUCCC – James researcher Joanna Groden, PhD, professor of medicine, provides two mentors for every trainee. The main mentor is the head of the lab in which a trainee works. The other mentor is, when possible, a clinician who introduces the trainee to clinical thinking, clinical conferences and clinical research, including the role of Institutional Review Boards and ethical issues of human subject research.

“Many doctoral and postdoctoral students have little idea of the intricacies and hard work involved in collecting and storing clinical data and samples,” de la Chapelle explains. “We try to provide this. We bring mentors and students together for a monthly conference to discuss topics related to translational and clinical research. The overall experience gives trainees insights into what is clinically important and what is not.”

Lairmore’s grant, Mouse Pathobiology: Models of Human Disease, recruits trainees from students who have entered the veterinary pathology residency program. It trains veterinarian scientists to understand and evaluate pathophysiologic alterations of murine models of human disease.

Trainees on the grant attend research seminars related to mouse physiology and models, they spend time at a major The Jackson Laboratory, a national center for mouse genetics and receive specialized training in laboratory animal husbandry. “These are also net-working opportunities that connect

trainees together,” Lairmore says.

“Their training leaves them with broad, comprehensive experience with mouse models and the ability to work with and guide medical oncologists on their hypothesis and on the best model to use,” Lairmore says.

They could help an investigator determine which cancer model best mimics the particular human disease they are studying. They could help them design the study, rank lesions and help interpret events during the study, along with others on the team, such as pharmacologists. “Some become comparative pathologists,” he says.

“My DVM training gave me a strong understanding of the animal as a whole, and my research training helps me understand the molecular basis of things,” Bowden says

“My particular interest is drug development,” she continues. “If I can understand what the molecular biologists are doing, and I can also understand the laboratory-animal veterinarian’s concerns when testing a particular molecule, then it helps to ease the communication process and hopefully the process of drug development overall.”

The opportunity presented by her training grants, Bowden says, “has absolutely been a beneficial experience. I definitely recommend applying for a T32 if the opportunity presents itself.”



Visit Frontiers online and view a video interview with Nadine Bowden talking about her experience with a T32 grants.

## BENCH TO BEDSIDE

*From the Laboratory to the Pharmacy***OSU-10054 – A Multicenter Phase I/II Study on the Anti-Tumor Activity, Safety and Pharmacology of IPH2101, a Human Monoclonal Anti-KIR, Combined with Lenalidomide in Patients with Multiple Myeloma Experiencing a First Relapse**

**HYPOTHESIS:** The combination of lenalidomide and IPH2101 is safe, and that the agents in combination show clinical activity in patients experiencing a first relapse of multiple myeloma.

**RATIONALE:** Multiple myeloma (MM) is a malignancy of plasma cells. Treatment involves chemotherapy with high-dose corticosteroids or high-dose melphalan with stem cell rescue for selected patients. Targeted drugs, including the immunomodulatory agent lenalidomide, are broadening patients' therapeutic options. Nonetheless, MM remains incurable, with relapses invariably occurring a median of 24 to 30 months following stem cell transplant.

NK cells, large granular lymphocytes that play a crucial role in cellular innate immunity and tumor cell killing, play an important role in controlling MM, but this ability is gradually lost during disease progression. Recent data suggests that lenalidomide can help restore the ability of NK cells to kill MM cells.

Lenalidomide's mechanism of action against MM is not understood, but evidence suggests there are several. The agent may work directly on MM cells by inducing apoptosis or arresting growth. Perhaps more significantly, lenalidomide stimulates T-cell proliferation,

which leads to increased IL-2 and IFN-gamma secretion. These circulating cytokines then boost NK cell number and activity and increased MM cell death.

Cell killing by NK cells is tightly regulated by killer immunoglobulin-like receptors (KIR) displayed on the cell surface. There are both inhibitory and activating KIR. Inhibitory KIR generally outnumber, and bind cellular ligands more readily than, activating KIR, and this can prevent NK-cell killing even when activating signals are present.

IPH2101 is a novel therapy that may reduce this effect. Data suggests that this human monoclonal antibody binds to inhibitory KIR and blocks inhibitory signaling, thereby increasing MM cell killing by NK cells. Clinical studies indicate that the agent is well tolerated by patients.

Collectively, the evidence suggests that IPH2101 and lenalidomide have additive or synergistic mechanisms of action and supports their development as a promising, novel, steroid-sparing combination therapy for patients with MM. Moreover, the effect is specific to the MM tumor cell clone. NK cell cytotoxicity assays of the agents on normal peripheral blood mononuclear cells have shown no increase in killing.

**AT A GLANCE**

Clinical trial OSU-10054

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**Eligibility:** Patients with progressive or relapsed multiple myeloma after one prior therapeutic treatment with response duration of at least six months; prior treatment regimens may have included lenalidomide and thalidomide; if previously treated with lenalidomide, the subject must not have progressed during treatment and must not have discontinued the drug due to intolerance; Measurable disease; ECOG 0,1, or 2; Clinical lab values at screening; FCBP must have negative pregnancy test 10-14 days prior to and again within 24 hours of prescribing lenalidomide and agree to use 2 methods of birth control; must be registered and willing to comply with requirements of RevAssist.



# NEED TO KNOW

Resources for Professional Development

## SHARED RESOURCES

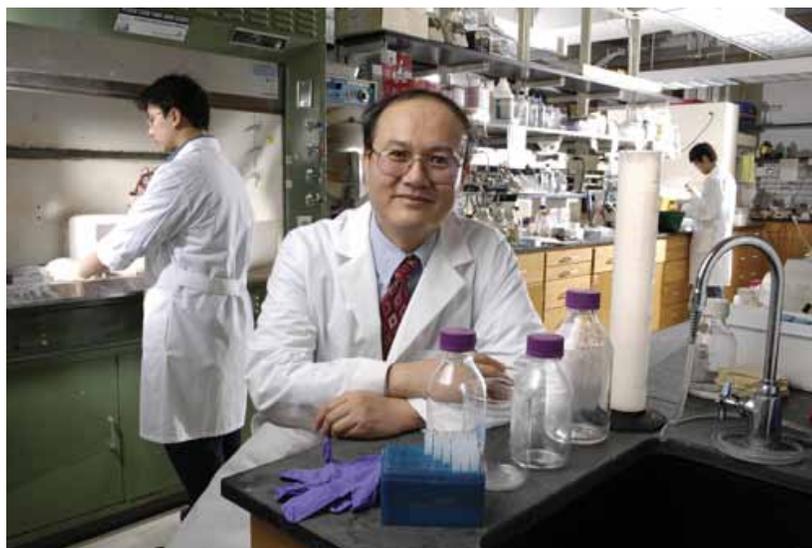
### EXPEDITING TRANSLATION

The Medicinal Chemistry SR analyzes, synthesizes small-molecule agents

The Medicinal Chemistry Shared Resource (MCSR) integrates synthetic and process chemistry, instrumental analysis, molecular pharmacology and other disciplines to provide medicinal chemistry support to investigators at the OSUCCC-James and other academic and commercial institutions.

Services include the following:

- Consultation and general medicinal chemistry. The MCSR can determine the chemical stability, commercial sources, and purity of commercial chemical agents. NMR and mass spectrometric analyses are used to determine the identity or purity of chemical agents. For agents



in tablet form, the MCSR can isolate the active pharmaceutical ingredient (API) with high purity.

- Custom synthesis. The MCSR can synthesize agents that are unavailable from commercial sources, after determining that synthesis is feasible.
- Lead optimization. MCSR will identify strategies for structurally optimizing promising lead agents.

For more information about the Medicinal Chemistry Shared

Resources, call 614-688-4008, e-mail [chen.844@osu.edu](mailto:chen.844@osu.edu), or visit

## Calendar of Events

**PELTONIA: OPENING CEREMONIES**

**AUGUST 19, 2011**

**PELTONIA: THE RIDE**

**AUGUST 20-21, 2011**

For more information and to register as a rider or volunteer, visit <http://www.pelotonia.org>



# FULL-SERVICE BREAST CARE UNDER ONE ROOF

## New OSUCCC – James Comprehensive Breast Center Opens Its Doors

The new JamesCare Comprehensive Breast Center, located near The Ohio State University Medical Center, began welcoming patients in mid-January. The four-story, multidisciplinary center combines all facets of breast care in one location, including annual mammograms, complete diagnostic services, comprehensive breast-cancer treatment, access to clinical trials, reconstructive breast surgery, medical nutrition services, survivorship support, risk counseling, financial counseling, a library and resource center, a meditation room and private and semi-private waiting areas.

The center also houses Hope's Boutique, a shop that offers a full range of products and services designed to help women look and feel their best during and after cancer treatment. The front of the new boutique is a public shopping area, while the back offers privacy and assistance with bra and prosthesis fittings.



» FUNDRAISING

## MEDICAL CENTER, THE JAMES, TO BENEFIT FROM \$100 MILLION GIFT

Ohio State University alumnus and Board of Trustees Chair Leslie Wexner, along with the Limited Brands Foundation, are investing \$100 million in his alma mater.



The majority of the gift – the largest in Ohio State’s history – will be allocated to the Medical Center and the James Cancer Hospital and Solove Research Institute, with additional gifts to the Wexner Center for the Arts and other areas within the University.

“During the past several decades, Les Wexner’s vision, guidance, engagement and generosity have

shaped Ohio State in myriad and lasting ways,” said University President E. Gordon Gee. “This latest gift is nothing short of transformational. It affirms the direction and growing excellence of our programs and underscores the role that this land-grant institution plays in assuring that talented young people can realize their educational aspirations, make their mark, and do good in the world.”-

## EXCEPTIONAL CANCER RESEARCH FROM PATIENT TO POPULATIONS

More than 700 faculty, staff and students attended this year’s OSUCCC – James 13th Annual Scientific Meeting held in February at the University’s Ohio Union. The central purpose of the cancer program’s Scientific Meeting is to foster research collaborations that may lead to new studies and possible breakthroughs. This year’s meeting carried the theme “Exceptional Cancer Research From Patient to Populations,” and it included 268 research posters and four speakers from outside Ohio State.



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

#### **ONE-STOP DRUG-DISCOVERY WORKSHOP**

It is now possible for investigators to design anticancer agents and move them through preclinical testing and into phase I and II clinical trials, all at the OSUCCC - James. It is drug discovery at its most efficient, and it is leading to a complete drug-development pipeline at The Ohio State University.

#### **TARGETING GASTROINTESTINAL CANCERS**

Continuous growth in patient volume over the past few years has prompted the OSUCCC – James to expand and strengthen its Gastrointestinal Oncology Program under the medical direction of Tanios Bekaii-Saab, MD. This expansion has led to promising new studies in GI malignancies, including pancreatic cancer.