Recognizing Progress in Cancer Research

The National Cancer Act turns 40, and we present examples of research accomplishments by OSUCCC – James investigators

This Dec. 23rd our nation will celebrate the 40th anniversary of the National Cancer Act. The research done since the act’s passage has led in many cases to cures, to extraordinary new treatments, to earlier detection and to improved quality of life for cancer survivors.

Yet, some 570,000 Americans will die of cancer this year. This issue of Frontiers shows some of what we are doing to reduce that number.

Our cover story offers examples of progress in clinical and translational research that is already making a difference in patients’ lives. Another story looks at how retroviral research is improving our understanding of cancer and read about our skull-base surgery program for a remarkable example of clinical innovations that are improving patients’ quality of life.

In this issue’s Frontline, Peter Shields, MD, internationally renowned physician-scientist and expert in cancer prevention, presents an insightful perspective of cancer prevention research. Peter recently joined Ohio State from Georgetown University as deputy director of the OSUCCC – James.

We’ve successfully worked in the past to improve clinical-trials access. Recently we took another step toward improving the clinical trials process. It is all but impossible to conduct clinical trials evaluating combinations of experimental targeted agents, largely because of intellectual property, commercialization, profit and price issues.

In May, the OSUCCC – James and Friends of Cancer Research organized a Cancer Drug Development Roundtable to begin tackling this complex problem.

The Ohio State Roundtable brought together representatives of academia, government, the pharmaceutical industry, legal services and advocacy groups to address the barriers to co-developing cancer drugs owned by competing interests. Our goal is to bring new cancer treatments more quickly to patients.

Finally, watch for our video icon. Visit Frontiers online and click on it to see OSUCCC – James researchers talking about their work or their views on progress in cancer research.
FROM SATELLITE TO STREET VIEW
Forty years of research reveals cancer to be many diseases requiring individualized care

ENDONASAL SKULL-BASE SURGERY
The OSUCCC – James Comprehensive Skull Base Surgery Center offers an endoscopic approach and comprehensive care for tumors of the skull base, paranasal sinuses, spine and brain.

WHAT CAN BE THE WHY?
Research on retroviruses remains a rich source of insights into how cancer cells work.

FRONTLINE

PETER G. SHIELDS, MD
Prescription for Progress in Cancer Prevention

BREAKTHROUGH

HITTING THE MARK
Targeted Agent Shows Promise in Biliary Cancer

AUSPICIOUS AGENT
Novel Drug Highly Active in CLL Patients

TINY DETECTION
microRNA Findings May Lead to Blood Test for Lung Cancer

TRIPLE TREATMENT
Low-Dose Sorafenib May Improve Therapy for Head and Neck Cancer

PROGNOSTIC PROGRESS
Gene Change Signifies Better Response to Treatment

PRECLINICAL FINDINGS
Component of Chinese Herbal Remedy Might Block Brain Tumor’s Spread

NEED TO KNOW

MODELING HUMAN DISEASE
The Genetically Engineered Mouse Modeling Shared Resource

OFF THE COVER:
SINGLE CANCER CELL (X1, 200, COLOR ENHANCED, LASER SCANNING CONFOCAL MICROGRAPH SHOWING THE NUCLEUS AND FEATURES OF THE CYTOSKELETON).
Although medical science has made great strides in many areas of cancer research and treatment, progress in cancer prevention has been far too slow and somewhat disappointing. Simply put, far too many people still get cancer. We know a lot about the causes of cancer, such as diet, sunlight, tobacco, alcohol and physical inactivity, but we have known about most risk factors for decades. At the same time, new epidemiology studies make only incremental advances, while subsequent intervention studies often do not validate the expected outcomes. Consequently, early detection remains the best, and often the only, option for reducing the cancer burden. This is not good enough.

For real progress in cancer prevention, we need a deeper understanding of cancer’s causes, then we must use that understanding to develop clinically useful markers of cancer risk and evidence-based reasons for choosing a particular intervention or combination of interventions. As we well know, cancer develops from a number of natural cell mechanisms that have gone awry. We need a better understanding of the pivotal nodal points that cause the cascading deregulation of these multiple mechanisms. These nodal points then offer logical targets for intervention.

We can meet these needs using the latest technologies and a three-part prescription for a broader research strategy. It begins with a systems-biology approach that involves multiple ‘omics assessments, e.g., genomics, epigenomics, transcriptomics, proteomics and metabolomics within a single study, and it is guided by experimental studies that follow the continuum from normal cellular function to cancer.

The second part is to take the multiple ‘omics data and vertically integrate them within the experiment studies to see what pathways are affected differently but combine to move the cell toward cancer. These findings are then corroborated across different study designs, using a variety of human cell-culture models, epidemiological studies of healthy subjects and cancer patients, and clinical trials. Thus, the added component in this second part is horizontal integration of the data.

Critical to this process is the identification of how widely people vary (interindividual variation), which provides clues by considering those individuals we usually call the outliers. With this approach, we identify the most promising biomarkers of cancer risk and targets for prevention.

The third part is to validate the importance of these biomarkers by first assessing them in molecular
epidemiology studies and then in cohort and tailored intervention studies. In the future, we should have validated clinical markers that improve predictive capabilities and shift the typical disease timeline toward earlier interventions that will be more effective and will minimize the need for later treatment.

Taking this “nodal” approach should produce findings of high statistical significance, reduce the number of false positive findings, assist in separating out “noise” and downstream effects inherent in ‘omics analysis, and reveal how biological mechanisms interact to make normal cellular mechanisms go awry.

Breast cancer exemplifies both the problem and how this approach might work. Breast cancer is the most common malignancy in women. Incidence rates have risen slowly for the past two decades, and the disease remains the second leading cause of cancer-related death in women.

Of the 209,000 women diagnosed yearly, 80 to 90 percent are sporadic cases (i.e., women without a strong family history of breast cancer). For these women, known risk factors such as age, reproductive or hormonal risk factors, hormone replacement therapy and alcohol consumption account for less than 50 percent of the risk. Given this, we have insufficient methods to predict which individuals in the general population are likely to develop the disease, and therefore we do not do a sufficient job at personalizing cancer prevention.

To prevent breast cancer, we need molecular markers that enable us to identify women at high risk. These women can then work with their physicians to take a proactive, personalized preventive approach, such as behavioral interventions for lifestyle and chemoprevention. They also can have tailored screening methods to shift detection to earlier time points when treatments are most effective. 

In 2010, more than 1.5 million new cases of cancer were diagnosed and 569,490 persons died of cancer in the United States.

- This amounts to more than 1,500 Americans dying each day and makes cancer the second leading cause of death, after heart disease.
- African-Americans are about 33 percent more likely to die of cancer than are whites and more than two times more likely to die of cancer than are Asian or Pacific Islanders, American Indians and Hispanics.
- According to the National Cancer Institute, the estimated total cost of cancer in 2005 in the United States was $209.9 billion.
The experimental agent selumetinib showed promising results in people with advanced biliary cancer in a multi-institutional study led by researchers at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). Findings from this 28-patient phase II study indicate that selumetinib, also known as AZD6244 (ARRY-142886), inhibits the MEK protein, which cancer cells need to proliferate and survive.

The tumor shrank to an undetectable level in one patient, and two patients showed partial tumor shrinkage. In 17 patients, the tumor stopped growing for up to 16 weeks in most cases. On average, patients experienced no cancer progression for a promising 3.7 months, even though nearly 40 percent had prior therapy (such tumors tend to resist further treatment).

“Biliary cancer has no good standard of care,” says principal investigator Tanios Bekaii-Saab, MD, medical director of gastrointestinal oncology at the OSUCCC – James. He notes that most patients present at later stages of the disease, which has a universally poor outcome.

“Our study provides a strong rationale for developing this agent further in larger trials, which we hope will enable us to establish a new standard of care.”

Bekaii-Saab says patients who lacked a target protein called pERK did not seem to respond to the drug. “This suggests that we may be able to identify which patients are most likely to benefit from this agent,” he adds.

Published in the Journal of Clinical Oncology.

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

Underlining and indicate more information online at http://cancer.osu.edu/Frontiers.
An interim analysis of a phase II clinical trial indicates that an experimental agent for chronic lymphocytic leukemia (CLL) is highly active and well tolerated both in previously treated patients and in those who have relapsed and are resistant to other therapy.

The agent, PCI-32765, is the first drug designed to target Bruton’s tyrosine kinase, a molecule essential for CLL-cell survival and proliferation.

Study leader John C. Byrd, MD, director of the Division of Hematology at Ohio State, presented the findings at the 2011 American Society of Clinical Oncology (ASCO) annual meeting in Chicago.

The trial involves 78 patients with previously untreated or relapsed and refractory CLL or small lymphocytic leukemia. This analysis involved the first 21 cases in the untreated-patient group and the first 27 individuals in the relapsed/refractory-patient group. One patient in each group had a complete remission, while 13 patients in the previously untreated group and 12 patients in the relapsed group had partial remissions.

“These are early findings, so patients with partial remissions could improve to complete remissions with further observation,” Byrd says.

Amy Johnson, PhD, co-led pre-clinical CLL work on PCI-32765 at Ohio State, along with Byrd. Those findings, published in the journal Blood, showed that the agent targets B lymphocytes and spares T lymphocytes. If the agent behaves the same way in humans, “It could dramatically improve outcomes for CLL patients,” Byrd says.

Published in the journal Blood.

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

## TINY DETECTION

**microRNA Findings May Lead to Blood Test for Lung Cancer**

OSUCCC – James researchers have identified characteristic patterns of microRNA molecules (miRNA) in the blood of lung cancer patients that might reveal the presence and aggressiveness of the disease, and perhaps who is at risk of developing it.

These patterns may be detectable up to two years before the tumor is found by computed tomography (CT) scans. The findings could lead to a blood test for lung cancer, according to principal investigator Carlo Croce, MD, director of the Human Cancer Genetics Program at Ohio State.

Croce and his collaborators identified the molecular patterns in tissue and blood samples collected from patients participating in a clinical trial examining the use of spiral CT scans to screen for lung cancer. The trial involved 1,035 individuals aged 50 years or older who had smoked at least a pack of cigarettes a day for 20 years or more.

“It might be possible to use these patterns of abnormal microRNAs in the plasma to detect lung cancer in people with the disease,” Croce says. “The abnormal microRNAs were also present in blood serum well before the tumors were detected by a sensitive method such as spiral CT scan, suggesting the possibility of identifying high-risk patients on the basis of miRNA profiling.”

*Published in the journal* Proceedings of the National Academy of Sciences.

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**HEAD AND NECK CANCER**

## TRIPLE TREATMENT

**Low-Dose Sorafenib May Improve Therapy for Head and Neck Cancer**

Adding low doses of the targeted agent sorafenib to the chemotherapy and radiation now often used to treat head and neck cancer might significantly improve patient care and quality of life, a preclinical study at the OSUCCC – James suggests.

The findings indicate that adding sorafenib would maintain treatment efficacy while permitting lower doses of chemotherapy and radiation, thus decreasing harsh side effects. The triple combination was well-tolerated in an animal model.

About 49,200 new cases of head and neck cancer are expected in the United States this year, and 11,500 people are expected to die from it. Treatment is often unsuccessful because the tumors become resistant to both chemotherapy and radiation therapy.

“This preclinical study suggests that using low-dose sorafenib plus chemotherapy and radiation could have significantly milder side effects while maintaining effectiveness,” says principal investigator Pawan Kumar, PhD. “Our findings provide a scientific rationale to evaluate this combination strategy through a clinical trial.”

“Our results suggest a potentially novel strategy in which sorafenib combined with low doses of chemotherapy, radiation therapy or both is as effective in treating head and neck cancer as much higher doses used in existing treatment,” says study co-author Theodoros Teknos, MD, who directs the Division of Head and Neck Surgery at Ohio State.

*Published in the journal* Molecular Cancer Therapeutics.

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Underlining and indicate more information online at http://cancer.osu.edu/Frontiers.
New research proves that a change in the MGMT gene can identify which patients with glioblastoma will respond better to treatment. Testing for this gene can distinguish patients with a more- or less-aggressive form of this disease – the most common and deadliest type of primary brain cancer – and help guide therapy.

Examining the MGMT gene in tumors removed from 833 patients with glioblastoma, the researchers found that when the gene promoter is altered by a chemical change called methylation, patients respond better to treatment.

“We show that MGMT methylation represents a new genetic test that can predict clinical outcomes in glioblastoma patients treated with radiation combined with the chemotherapeutic drug temozolomide,” says co-author Arnab Chakravarti, MD, chair of Radiation Oncology and co-director of the Brain Tumor Program at the OSUCCC – James.

“Glioblastomas are a collection of different molecular and genetic entities that behave uniquely and require personalized treatment,” adds Chakravarti, who is the translational-research study chair for the study.

The findings were presented in June at the 2011 American Society of Clinical Oncology (ASCO) meeting.

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

THE RESEARCHER
ARNAB CHAKRAVARTI, MD,
Chair and professor of Radiation Oncology, co-director of the Brain Tumor Program, member of the Experimental Therapeutics Program and the Max Morehouse Chair in Cancer Research
The active ingredient in a traditional Chinese herbal remedy might help treat deadly brain tumors, according to a study by OSUCCC – James researchers.

The laboratory and animal study suggests that a substance called indirubin blocks both the migration of glioblastoma cells, preventing their spread to other areas of the brain, and the migration of endothelial cells, inhibiting the formation of tumor blood vessels.

“We have pretty good methods to stop glioblastoma from growing in the human brain, but these therapies fail because tumor cells migrate from the original site and grow elsewhere in the brain,” says co-principal investigator E. Antonio Chiocca, MD, PhD, professor and chair of neurological surgery and co-leader of the OSUCCC – James Viral Oncology Program.

“Our findings suggest that indirubins offer a novel therapeutic strategy for these tumors that simultaneously targets tumor invasion and angiogenesis,” he says.

Indirubin is derived from the indigo plant. It is the active ingredient in the Chinese herbal remedy called Dang Gui Long Hui Wan, which is used to treat chronic myeloid leukemia. However, little is known about the form or dose used, or its effectiveness, side effects or drug interactions.

“Although indirubin looks promising in animal models, it has not yet been tested in humans, and it is not approved by the U.S. Food and Drug Administration,” Chiocca cautions.

For other work on glioblastoma cell motility by Chiocca, see Researchers Discover Brain Tumor’s “Grow-or-Go” Switch.
OF NOTE

Recent Recognitions of OSUCCC – James Physicians and Researchers

AWARDS AND RECOGNITIONS

**CLARA D. BLOOMFIELD, MD**, a Distinguished University Professor at Ohio State and cancer scholar and senior adviser to the OSUCCC – James, has been elected to the American Academy of Arts and Sciences, one of the nation’s oldest and most prestigious honorary societies.

**KATHLEEN BORIS-LAWRIE, PHD**, professor of veterinary biosciences and member of the Viral Oncology Program of the OSUCCC – James, and **LARRY SCHLESINGER, MD**, chair of the Department of Microbial Infection and Immunity and member of the Innate Immunity Program, have been elected to fellowship in the American Academy of Microbiology.

The Department of Pharmacy at The Ohio State University Medical Center and the OSUCCC – James have received the **American Pharmacists Association Foundation's Pinnacle Award** for their Medication Assistance Program.

**JOANNE LESTER, PHD, CRNP, ANP-BC, AOCN**, a research scientist and oncology nurse practitioner, has received a two-year, $150,000 Young Investigator Award from the National Comprehensive Cancer Network Foundation. This is the first year for these awards, five of which were issued nationally. Lester’s grant will fund a study entitled, “Effect of survivorship care planning on distress: a randomized control trial with leukemia and breast cancer survivors.”

**TANIOS BEKAIII-SAAB, MD**, medical director of the Gastrointestinal Oncology Program, has received a **Cancer Clinical Investigator Team Leadership Award** for 2010 from the National Cancer Institute (NCI). The award recognizes exceptional contributions to the advancement of new therapies through collaborative team science at NCI-designated cancer centers. The two-year awards include $50,000 in funding.
**FACULTY AND PROGRAMS**

**PETER SHIELDS, MD**, has joined the cancer program as deputy director of the OSUCCC – James. He comes to Ohio State from Georgetown University.

**RICARDO CARRAU, MD**, has joined the cancer program as a professor of Otolaryngology and co-director of the Skull Base Surgery Program. His clinical interests include endoscopic and external skull-base surgery, head and neck oncologic surgery, airway reconstruction, and diagnosis and management of swallowing disorders. His research interests include surgical simulators, telemedicine, clinical outcome studies and development of endonasal reconstructive techniques.

**DAVID E. COHN, MD**, professor of Obstetrics and Gynecology, has been appointed director of the Division of Gynecologic Oncology at the OSUCCC – James.

**VINCENT DANIEL, MD**, has joined the cancer program as an assistant professor of Surgery. His clinical interests include: lung, tracheal and esophageal cancer; esophageal motility disorders and minimally invasive thoracic surgery. His research interests include: molecular markers of lung and esophageal cancer.

**WILLIAM FARRAR, MD**, professor of Surgery, has been named director of the new four-story JamesCare Comprehensive Breast Center, the first of its kind in the Midwest to offer the full spectrum of care at one location.

**JEFFREY FOWLER, MD**, professor of Obstetrics and Gynecology, has been appointed vice-chair of the Department of Obstetrics and Gynecology. Fowler, a physician-scientist at the OSUCCC – James, holds the John G. Boutselis Chair of Gynecologic Oncology and co-directs Ohio State’s Center for Advanced Robotic Surgery.

**DELIANG GUO, PHD**, has joined the cancer program as an assistant professor of Radiation Oncology. His research focuses on EGFR/RTKs/PI3K/Akt and Ras/MEK/ERK signaling transduction and cancer metabolism.

**LARRY SCHLESINGER, MD**, professor and member of the OSUCCC – James Innate Immunity Program, has been named chair of the College of Medicine’s new Department of Microbial Infection and Immunity.

The OSUCCC – James is now a full member of the Radiation Therapy Oncology Group (RTOG), one of the nation’s largest clinical cooperative groups. Fewer than 40 U.S. institutions have full RTOG member status.

**LEADERSHIP ACTIVITIES AND APPOINTMENTS**

**WILLIAM CARSON III, MD**, professor of Surgery and associate director for clinical research for the OSUCCC – James, has been elected the next vice-chair of the Southwest Oncology Group (SWOG) Melanoma Committee. Carson will succeed Dr. Lawrence Flaherty of the Karmanos Cancer Institute in Detroit.

**THERESA DINARDO BROWN,** chief communications officer for the OSUCCC – James, has been elected to a two-year term on the steering committee of the National Cancer Institute Public Affairs & Marketing Network, a professional group of public affairs, marketing and communications officers at the nation’s leading cancer centers.
Cancer cell from a fibroblast tumor cell line. Data from new technologies provide a detailed, molecular, view of cancer.
Progress in cancer research has delivered a molecular view of malignancy that reveals cancer to be many diseases requiring personalized care.

BY BOB HECKER

When President Nixon signed the National Cancer Act in 1971, he made the conquest of cancer a national crusade. It soon came to be called the “War on Cancer,” a name that promotes cancer as a single disease that affects many parts of the body.

That idea was supported by the relatively limited technology then available, which gave more of a satellite view of cancer. Just as one city looks similar to another from an orbiting satellite, breast cancer cells in one woman looked similar to those in another under the microscope. Yet, while breast cancer was considered one disease, patients often responded differently when given the same treatment, and no one knew why.

Today, new tools and technologies, together with an explosion in computing power, have given science a street-level, molecular view of cancer. Breast cancer, it turns out, is at least five distinct diseases, each marked by a distinct genetic profile. That knowledge helps identify optimal treatments and pinpoint new drug targets.

“Doctors can better predict how a particular breast cancer will respond to different treatment based on molecular subtypes,” says Charles Shapiro, MD, director of breast medical oncology at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James).

“In the past, chemotherapy was a ‘one size fits all’ treatment for breast cancer. And while chemotherapy is useful against this disease, it often is not selective enough,” Shapiro says. “Research tells us that certain breast cancers, based on their level of gene expression, are more or less responsive to chemotherapy. The more we can target therapies to cancer-cell characteristics, the more effective the therapies will be.”

To the National Cancer Institute (NCI), a greater biological understanding of cancer is a measure of progress, the soil from which new and more effective therapies emerge.

In a report to the president and Congress on The Nation’s Investment in Cancer Research: 2012, NCI Director Harold Varmus, MD, says the document “reflects on a 40-year history of investigation that has brought about profound change… in our understanding of cancer as a complex set of diseases that will require many different lines of investigation about prevention, diagnosis and treatment.”

“When I began to study animal models of cancer in the early 1970s, the collective understanding of (its) origins and progression was negligible; now, we can describe such events in minute detail at the molecular level,” he writes in the Afterword, adding that this knowledge has led to improvements in controlling an increasing number of cancers.

Varmus contends in the NCI’s Cancer Trends Progress Report – 2009-2010 Update that the continued decline in the incidence and mortality rates of lung, prostate, breast and colorectal cancers – the four most common types – is evidence of the nation’s gains against malignancy. The report includes a graph that tracks the incidence of these cancers from 1975-2007.

Yet, nearly 1.53 million Americans were expected to develop some form of cancer in 2010, and 569,000 of them were expected to die from it. Progress in cancer diagnosis, treatment and prevention is hard-won and ongoing. Here are examples of progress in cancer research by OSUCCC – James investigators.

ACUTE LEUKEMIA

Research led by Clara D. Bloomfield, MD, over her 40-year research career has greatly improved the treatment of patients with acute myeloid leukemia (AML).

“In the 1960s, we didn’t cure anyone with AML. There wasn’t even an intent to treat patients for a cure; AML wasn’t considered a curable disease,” says Bloomfield,
a Distinguished University Professor at Ohio State who also serves as cancer scholar and senior adviser to the OSUCCC – James. “Today, we cure about a third of these patients overall, and in some patient groups we cure 70 to 90 percent.”

Early work by Bloomfield showed that the chromosomal abnormalities often seen in AML cells could distinguish patients likely to be cured by standard therapy from those likely to relapse. Since arriving at Ohio State in 1997, one of the many things Bloomfield has worked on is the identification of molecular markers in patients with cytogenetically normal AML (CN-AML), which occurs in 40–45 percent of AML patients and lacks the chromosomal abnormalities that guide therapy in other AML patients.

Molecular markers identified by Bloomfield and her collaborators now help determine prognosis and guide therapy in patients, as well as define CN-AML subgroups and subtypes. Examples of that work include:

- Discovering the first genetic abnormality in CN-AML, the MLL PTD mutation, in 1994, and that the mutation predicts a poor prognosis; then in 2007, showing that autologous stem cell transplant greatly improves the chance for a cure.
- Discovering that high ERG expression signals poorer survival, even when accompanied by favorable gene markers such as normal FLT3 and mutated NPM1. In 2011, she and her colleagues showed that CN-AML patients with TET2 mutations may need aggressive therapy.
- Helping to revise the World Health Organization (WHO) classification of AML in 2001 and again in 2008. Formerly considered one disease, AML now has six subgroups, the largest of which has seven subtypes plus two provisional subtypes, according to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.
- Serving as senior author on the new internationally accepted European LeukemiaNet Guidelines published in the journal Blood in 2010. This report recommends using cytogenetic and molecular markers from the WHO 2008 reclassification.
- More examples of OSUCCC – James AML research are available here.

**CHRONIC LEUKEMIA**

The drugs used to treat chronic lymphocytic leukemia (CLL) over the past 40 years have shown degrees of benefit in patients, but the disease remains incurable despite the number of drugs used to treat it. To help relieve the problem, scientists at the OSUCCC – James are studying novel agents that target specific genetic abnormalities.

“If we can find several agents that strike different targets in CLL cells, they might in combination increase the number of patients who have durable remissions,” says John C. Byrd, MD, director of the Division of Hematology and of the Hematologic Malignancies Program.

Fludarabine is the standard chemotherapy for CLL, but drug resistance often occurs and patients relapse. The only FDA-approved therapy for fludarabine-resistant CLL is alemtuzumab, which can cause a serious drop in white blood cell counts and an increased risk of infections. Byrd, with collaborator Michael Grever, MD, who co-leads the Experimental Therapeutics Program at the OSUCCC – James, is studying several promising possibilities:

- Interim analysis of a 2011 phase II clinical trial led by Byrd indicated that the experimental agent PCI-32765 is highly active and well tolerated in both newly diagnosed and relapsed, drug-resistant CLL patients. The agent is the first to target Bruton’s tyrosine kinase, a protein essential for CLL-cell survival.
- A 2011 multi-institutional study led by Byrd of 104 CLL patients showed that treating CLL patients with the targeted agents rituximab and fludarabine produces remissions lasting 10 years or more in some patients without
A 2009 study showed that a gene called FOX3 is silenced by epigenetic changes early in CLL development, and that therapy to reverse this silencing might delay or prevent CLL progression.

More examples of OSUCCC – James research in chronic leukemia are available here.

**HEAD AND NECK CANCER**

In 2000, Maura Gillison, MD, PhD, was first author on a seminal study that strongly linked oral human papillomavirus (HPV) infection and oropharyngeal cancer. A quarter of the tumors analyzed were HPV-positive, and 90 percent of those were positive for HPV16, the cause of cervical cancer. Investigators also found that the HPV-positive patients had about half the risk of death from cancer compared with their HPV-negative counterparts.

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

Gillison says those findings revealed a newly recognized oral cancer caused by a major new risk factor: sexually transmitted HPV. Previously, head and neck cancer was thought to be caused largely by tobacco and alcohol.

In a 2010 study published in the *New England Journal of Medicine*, Gillison and her collaborators determined that the presence of HPV in oropharyngeal tumors is the most important predictor of patient survival. The study showed that HPV in tumors accounts for a better response to therapy, rather than other favorable factors such as young age and small tumors. It suggested that HPV status, along with smoking history and cancer stage, could be used to determine aggressiveness of therapy.

“Previous studies indicated a relationship between HPV in oropharyngeal cancers and patient survival, but they couldn’t determine if other favorable factors were responsible for better outcomes,” Gillison says. “Our findings closed the door on these questions and are allowing the field to move forward with clinical trials to determine how we should use molecular and behavioral factors to personalize therapy.”

More examples of OSUCCC – James research in head and neck cancer are available [here](http://cancer.osu.edu/Frontiers).

**TRANSLATIONAL RESEARCH**

Carlo Croce, MD, director of Ohio State’s Human Cancer Genetics Program, was the first, in 2002, to link microRNA (miRNA) to human cancer. As well as identifying the role of miRNA in cancer, he and his colleagues explore how these small regulatory RNA molecules might be used prognostically, diagnostically and therapeutically. His work ranges over chronic and acute leukemia, multiple myeloma, and thyroid, breast, lung and other human cancers.

- Croce co-led a study that identified patterns of abnormal miRNAs in the plasma of lung cancer patients. The findings could lead to a blood test for lung cancer.
- Croce’s lab has linked three miRNAs – miR-192, miR-194 and miR-215 – to reactivation of the P53 tumor-suppressor gene and to slowing the growth of multiple myeloma cells. The findings provide a rationale for further study of these microRNAs as a treatment for the disease, which has few therapeutic options.
- In a 2005 *New England Journal of Medicine* paper, Croce and
his colleagues showed that they could distinguish between the indolent and aggressive forms of CLL by evaluating the expression pattern of 13 miRNA genes. “It’s vital for oncologists to know which kind patients have so they can properly treat the disease,” Croce says.

- Visit here for more examples of OSUCCC – James microRNA research.

**GLIOBLASTOMA**

Glioblastoma multiforme is the most common and deadly form of brain cancer, with a median survival of 11 months after diagnosis. Arnab Chakravarti, MD, chair of Radiation Oncology and co-director of the OSUCCC – James Brain Tumor Program, is one of several Ohio State cancer investigators working to improve glioblastoma treatment.

- A prospective study of 833 glioblastoma patients reported at the 2011 American Society for Clinical Oncology meeting proves that when a gene called *MGMT* in tumors is methylated, patients respond better to treatment, says Chakravarti, a coauthor of the study. Overall survival for patients with the methylated gene was 21 months versus 14 months for those with the unmethylated gene. “Testing for *MGMT* methylation can predict clinical outcomes in glioblastoma patients treated with radiation plus temozolamide,” says Chakravarti, who was the project’s translational-research study chair.

  - Glioblastoma is often driven by overexpression of *EGFR*, but research led by Chakravarti and Markus Bredel, MD, PhD, at the University of Freiburg in Germany, shows that loss of the *NFKBIA* gene is another important promoter of glioblastoma development. Published in the *New England Journal of Medicine*, the study found that glioblastomas generally show either normally high levels of *EGFR* or loss of *NFKBIA*, but not both. “*NFKBIA* status may be an important predictor of survival and perhaps of treatment outcomes in some glioblastoma patients,” Chakravarti says.

  - More examples of OSUCCC – James research in glioblastoma are available here.

Chakravarti notes that gliomas are among the most treatment-resistant of all human tumors. He is working to understand the molecular mechanisms of radiation resistance and to use this knowledge to develop novel therapies.

“Glioblastomas vary in their molecular and genetic makeup and as a result behave differently and require personalized treatment,” Chakravarti says. Pursuing new treatments based on tumor biology will lead to further progress against cancer, he adds. “As science continues to reveal the true nature of cancer as not one but many diseases that affect individuals differently,” Chakravarti says, “we steadily increase our chances of controlling these malignies and improving the lives of patients.”

**Glioblastoma**

*2010, USA*

**INCIDENCE:** 18,500

**MORTALITY:** 12,760

More at cancer.osu.edu/about/publications/frontiers/
The OSUCCC – James Comprehensive Skull Base Surgery Center offers an endoscopic approach and comprehensive care for tumors of the skull base, paranasal sinuses, spine and brain.
Tumors of the skull base are rare, but when they arise, they occupy an area of the body that few people know exists—the area inside the head that forms the floor of the cranium and the roof of the sinus cavities. It is an anatomical terrain that is dense, complex and delicate.

“Skull-base anatomy presents a complicated network of nerves and blood vessels residing in a tricky landscape of depressions, prominences and irregularities,” says Ted Teknos, MD, director of Head and Neck Oncologic Surgery at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). “The optic nerves, facial, olfactory, auditory and other small nerves leave the brain from the skull base, and the carotid arteries are always close by.”

Skull-base neoplasms include pituitary gland tumors, meningiomas, chordomas, and sinus and olfactory endothelium tumors. Most are diagnosed at an advanced stage, when they press on adjacent structures or obstruct respiration. To treat these difficult lesions, the OSUCCC – James earlier this year began a Comprehensive Cranial Base Surgery Program spearheaded by the recruitment of two internationally renowned leaders in the field: otolaryngologist Ricardo Carrau, MD, and neurosurgeon Daniel Prevedello, MD. Working together, Prevedello and Carrau played a leading role in revolutionizing the surgical treatment of skull-base tumors. They now form a team with Bradley Otto, MD, an otolaryngologist and endoscopic skull base surgeon, and Matthew Old, MD, a head and neck and skull base surgeon.

“This is high-price real estate; the anatomy is dense—there are no parts to spare,” says Carrau, a head and neck surgeon and director of the Cranial Base Surgery Program of the Otolaryngology-Head and Neck Surgery Department. “We want to save critical blood vessels and nerves; the trick is doing the surgery without producing a problem that is worse than the tumor itself.”

**A NEW STRATEGY**

Typically, skull base tumor surgery involves an “upstairs-downstairs” approach. A neurosurgeon performs a craniotomy and comes at the tumor from above, and an otolaryngologist comes in from below, through facial incisions.

In the 1990s, Carrau was at the University of Pittsburgh, where he and a small group of physicians developed a less invasive, endoscopic means of removing skull base lesions. Prevedello also joined the group and has become one of the premier endoscopic neurosurgeons in the world. The “endoscopic endonasal approach” they developed removes tumors through the nose, a technique that has several important advantages for patients:

- It avoids the need for a craniotomy and retracting the brain to reach the tumor, which reduces the risk of tissue swelling and of cognitive or personality changes that sometimes follow skull base traditional surgery.
- Patients typically recover faster and have shorter hospital stays. Also, the endoscope’s light and high-definition camera, which can angulate to look around corners, offers a better view of the tumor and surrounding tissue than is usually possible during open-field surgery. The camera’s images are displayed on a monitor in the operating room, enabling close inspection of the surgical area. “Our visualization enables us to better distinguish tumor from normal tissues, allowing us to preserve normal tissue to a higher degree,” Teknos notes.

**EXPERIENCE AND TEAMWORK**

“Skull base anatomy presents a complicated network of nerves and blood vessels, and it takes incredible knowledge of the anatomy to cut around a structure such as a tumor,” Teknos says, “Drs. Prevedello and Carrau have tremendous experience in that area.”

The two surgeons, recruited to the OSUCCC – James from the University of Pittsburgh, joined Otto, who also trained in endoscopic skull base surgery at that University, to bring a unique perspective and skill set to the endoscopic procedure and place...
Ohio State at the forefront of endoscopic endonasal surgery worldwide. “There’s a lot of teamwork involved,” Prevedello says. “The neurosurgeon has the expertise to work around and inside the brain, while the head and neck surgeon has the expertise to work in the sinuses and skull base itself. We really complement, and learn from, each other.”

Often, the otolaryngologist first creates a space in the nasal cavity for two surgeons to work. Then together the otolaryngologist and neurosurgeon expose the skull base lesion. The neurosurgeon removes the tumor that is adjacent to the brain or on its dural covering. Tumors larger than the nasal cavity are either collapsed or removed piecemeal. If a patient’s eye is involved, the team will include a third surgeon, an ophthalmologist.

COMPREHENSIVE CARE

Carrau estimates that fewer than 10 centers in the United States provide comprehensive care for skull base tumors.

“One of the advantages here at the OSUCCC – James is that everyone on the skull base team—surgeons, nurses, therapists and support staff—is trained in both the traditional and endoscopic approaches,” Carrau notes. “We can treat any tumor and meet any need a patient may have. We have expertise in open and endoscopic procedures and have recently incorporated robotic surgery in our armamentarium. Through an international cooperation with surgeons from Rosario, Argentina, our team has pioneered reconstructive techniques that are now used throughout the world.”

Core members of the team are housed in one location. Patients can see their head and neck surgeon, neurosurgeon, reconstructive surgeon, and nurse practitioners, as well as endocrinologists, ophthalmologists, speech and swallowing therapists, and prosthetic experts if needed. A concierge service is available to arrange housing and other services for out-of-town and international patients. Ideally, Prevedello says, patients meet with their lead physicians on the same day to avoid multiple appointments.

Carrau says that the center’s surgeons have linked with Don Stredney, a research scientist in Biomedical Applications at the Ohio Supercomputer Center, to develop a realistic surgical simulation program that will help surgeons train for these intricate surgeries.

“Developing your skills requires doing many procedures, and these tumors are rare, so it’s not easy to acquire the needed practice in a timely fashion,” explains Carrau. “We’d like to create a simulation program that mimics the procedures we perform in the operating room—it would be like a souped-up video game that gives a surgeon the same sensory feeling that he or she would experience when cutting through tissue or bone with real instruments.”
RESEARCH

The center draws patients from across the country and around the world, offering the opportunity for research to improve the procedures and post-surgical care—such as reducing the risk of swallowing problems that often follow skull base surgery—and to study the molecular events that drive these malignancies.

Otto, Old, Carrau and Prevedello are tracking patient outcomes to better define the tumor types and stages that the technique is best suited to treat. “We still need to prove that minimal-access surgery is as good as, if not better, than traditional surgery,” Carrau says.

Little is known about the genetic mutations and other molecular changes that fuel their growth, or how they might be treated with drugs in addition to surgery. “Acquiring enough tissue to study these tumors can be difficult,” Teknos says. “But with the center, we are building a bank of tumor tissue that will allow us to investigate potential therapies based on a tumor’s individual genetic characteristics.”

This research has already begun. OSUCCC - James cancer biologist Quintin Pan, PhD, research director for the Head and Neck Oncology Program, has shown that certain tongue and oropharyngeal cancers overexpress protein kinase C epsilon (PKC epsilon), a molecule important for tumor growth and metastasis. Pan and Teknos are investigating whether PKC epsilon plays a role in skull base olfactory-nerve tumors called esthesioneuroblastomas. The team eventually wants to test a PKC-epsilon inhibitor developed by Pan as a potential treatment for esthesioneuroblastomas.

“There’s been little basic science done on these rare tumors,” says Pan. “We expect that the OSUCCC-James center will naturally attract these patients and provide tumor samples, which would enable us to produce cell lines and really look in depth to understand the genetic alterations that drive this tumor type.”

Carrau, Prevedello, Old and Otto look to robotic technology to raise skull-base surgery to the next level. Using robotic-assisted surgery, surgeons can execute fine movements that are impossible for human hands alone. “This means less collateral damage to healthy surrounding tissues,” Prevedello says.

Current robotic devices, however, use two or more arms that are too unwieldy for endonasal skull base surgery. “We will be working to develop a single-arm robot that is compatible with the endoscope and skull base characteristics,” he says.

Prevedello and Carrau both say that the commitment of the OSUCCC – James to a skull-base center of excellence drew them to Columbus. “Leadership at the University is fantastic,” Carrau says. “They are trying to provide the best care, with the best physicians available, supported by research to advance that care. Academically, professionally and philosophically, this matches my interests.”

To refer a patient, please call The James Line New Patient Referral Center toll free: 1-800-293-5066.
What Can Be The Why Can Be What
Research on retroviruses has revolutionized our understanding of cancer and remains a rich source of insights into how cancer cells work.
Few situations are more exasperating to the inquirer than to watch a tiny nodule form on a rabbit’s skin at a spot from which the chemical agent inducing it has long since been gone, and to follow the nodule as it grows, and only too often becomes a destructive epidermal cancer. What can be the why for these happenings?

— PAYTON ROUS, NOBEL PRIZE LECTURE, DECEMBER 13, 1966

BY DARRELL E. WARD

In the early 1990s, Kathleen Boris-Lawrie, PhD, was working in the laboratory of Nobel Prize laureate Howard Temin at the University of Wisconsin. She’d constructed a simpler form of bovine leukemia virus (BLV) as a step toward developing a retrovirus vaccine against infectious cancers and AIDS.

Boris-Lawrie, who today is a professor of veterinary biosciences and a researcher with The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), had modified the BLV genome in several ways.

To prevent replication in host cells, she stripped out two critical regulatory genes, tax and rex. She also removed the tax and rex response elements, which are sequences of bases in the viral RNA. The Tax and Rex proteins bind to these response elements and induce efficient transcription, transport and translation of viral RNA which are required for viral replication. Boris-Lawrie replaced the deleted BLV material with sequences from the genetically simpler spleen ne-crosis virus.

She put her model to the test and published the 1995 study in the Journal of Virology. The findings noted that, rather than being unable to replicate, the hybrid BLV remained remarkably fecund. The question was, Why?

Peyton Rous initiated the use of tumor-causing viruses in cancer research 100 years ago when, in 1911, he discovered that a “filterable element” extracted from tumors in one chicken quickly produced tumors in another chicken. “It was the first example of a cancer-causing infectious agent,” Boris-Lawrie says. That agent was later named the Rous sarcoma virus (RSV), and ultimately its study led to the anticancer drug, Gleevec.

Renato Dulbecco at the California Institute of Technology, along with students Harry Rubin and Howard Temin, gave new life to RSV research in the 1950s. Rubin added RSV particles to normal chicken fibroblasts and found that they induced morphologic and behavioral changes characteristic of cancer cells. Suddenly, scientists realized they could study cancer-cell transformation in a Petri dish.

Temin wanted to know why the virus’s RNA genome could persist in tumor cells. He arrived at a radical explanation: RSV and related viruses copied their RNA genome into DNA. This “backward” flow of information earned these infectious agents the name “retroviruses.”

David Baltimore at the Massachusetts Institute of Technology, working independently of Temin and Dulbecco, also discovered reverse transcriptase. The three researchers shared the 1975 Nobel Prize in Physiology or Medicine.

J. Michael Bishop and Harold E. Varmus, now director of the National Cancer Institute and former director of the National Institutes of Health, quickly put RSV reverse transcriptase to work. They discovered the first oncogene, SRC (pronounced “sarc”), and explained how RSV transformed cells, dramatically advancing the understanding of cancer.

Using reverse transcriptase, Bishop and Varmus made a single-stranded DNA copy of the wild-type RSV RNA genome. They fragmented the DNA copy, then hybridized the pieces to the RNA genome of tumor-causing RSV. Some fragments remained unbound, however, and they used these leftovers to probe the host genome. From this they learned that the viral src was a shortened version of a gene found naturally in the host genome.

“We learned to our surprise that a cellular protein—not a viral protein—was modulating this effect.”

KATHLEEN BORIS-LAWRIE, PHD OSUCCC – James Researcher

Temin wanted to know why the virus’s RNA genome could persist in tumor cells. He arrived at a radical explanation: RSV and related viruses copied their RNA genome into DNA after entering host cells. Until then, genetic information was thought to move from DNA to RNA and never the reverse. But Temin, working with Dulbecco, discovered reverse transcriptase, a viral enzyme that enables RSV and similar viruses to copy their RNA genome into DNA. This “backward” flow of information earned these infectious agents the name “retroviruses.”

Underlining and indicate more information online at http://cancer.osu.edu/Frontiers.
Bishop and Varmus won the 1989 Nobel Prize in Physiology or Medicine for discovering the cellular origin of retroviral oncogenes. “Cells with the mutant src, which is found in the virus, make a truncated tyrosine kinase receptor that is constantly active,” Boris-Lawrie says. “In addition, src can have another mutation that makes it even more active, producing strong growth signals that push cells to proliferate.”

Boris-Lawrie was finishing the BLV study when Temin, a lifelong nonsmoker, died of lung cancer in 1994. She moved to Ohio State, set up her lab and began investigating how spleen necrosis virus endows the castrated BLV with the ability to replicate. First, she and her collaborators discovered that unspliced spleen necrosis virus RNA contains an element that boosts protein production 20,000-fold. They described this “post-transcriptional control element” in a 1999 Journal of Virology paper.

“We learned to our surprise that a cellular protein—not a viral protein—was modulating this effect,” Boris-Lawrie says. They speculated that host cells probably also use this protein to enhance translation. “We believed that if we identified the protein, we could use the retrovirus as a model system to learn something important about RNA translation,” she says.

Next, the researchers discovered

**PROGRAM PROJECT GRANT**

**Using Retrovirus Models to Understand Cancer**

Retrovirus research at Ohio State is supported in part by a five-year, $10.9 million Program Project Grant (PPG) from the National Cancer Institute. Patrick Green, PhD, professor of Veterinary Biosciences at Ohio State’s College of Veterinary Medicine, and co-leader of the OSUCCC – James Viral Oncology Program, assumed leadership of the PPG after the original principal investigator, Michael Lairmore, DVM, PhD, professor of Veterinary Biosciences, transitioned from Ohio State to become dean of the University of California Davis School of Veterinary Medicine in October 2011. The goal of the PPG is to identify new therapeutic targets against retroviral-induced lymphoma and associated syndromes, such as hypercalcemia.

The PPG has five interrelated projects, each with a principal investigator:

**Project 1:** Stefan Niewiesk, DVM, PhD, associate professor of Veterinary Biosciences, and Mamuka Kvistahelia, PhD, associate professor of Pharmaceutics, are investigating the role of accessory proteins in the human T-lymphotropic virus type 1 (HTLV-1), which causes an aggressive lymphoma and leukemia and a number of immune system disorders.

**Project 2:** Patrick Green, PhD, is defining novel post-transcriptional mechanisms of HTLV, particularly the p28 protein and its contribution to viral replication and cellular transformation.

**Project 3:** Kathleen Boris-Lawrie, PhD, is investigating translational control mechanisms in retroviruses and host-cell growth-control genes that involve RNA helicase A.

**Project 4:** Katherine Weilbaecher, MD, of Washington University, St. Louis, and Thomas Rosol, PhD, of Ohio State, are studying the bone microenvironment in osteolytic and osteoblastic tumor models.

**Project 5:** Lee Ratner, MD, of Washington University, St. Louis, is examining the role of inflammation in tax-mediated carcinogenesis using transgenic mouse models that express HTLV-1 tax.
that the post-transcriptional control element was a specialized structure on viral RNA consisting of two stem-like configurations topped with a loop—like golf tees each with a ball in profile. They described this 2003 finding in the Journal of Virology.

The breakthrough came three years later. The elusive protein was RNA helicase A (RHA), an enzyme involved in transporting mRNA from the nucleus to the cytoplasm and in initiating translation. When RHA was knocked out, the retrovirus no longer made several vital proteins.

In addition, Boris-Lawrie and her colleagues showed that an important cell growth-control gene that is lost in many cancers, junD, produces an unspliced mRNA and interacts with RHA.

RHA binds to the post-transcriptional control element on junD mRNA, allowing translation. If RHA is missing, the protein isn’t made.

“Retroviruses seem to use RHA to enhance production of their own proteins, and cells use it to control the amount of particular proteins they make, many of which are involved in growth control,” says Boris-Lawrie. Nature Structural and Molecular Biology featured the study on the cover of the June 2006 issue.

“These findings provided important insights into how cells regulate certain growth proteins, many of which play an important role in cancer, along with showing how viruses use cell mechanisms to establish an infection,” Boris-Lawrie says.

That the retrovirus needs RHA to make these essential proteins suggests that the enzyme is a potential target for antiretroviral therapy and for blocking cancer-cell growth, Boris-Lawrie says.

When Jeffrey Parvin, MD, PhD, professor of biomedical informatics, came to Ohio State from Harvard, he’d already discovered that RHA interacts with BRCA1, a tumor-suppressor gene involved in DNA repair. Research by others has shown that mutations in RHA can prevent its proper interaction with BRCA1, causing a failure of BRCA1-associated DNA repair.

“Studies of breast-cancer patients show that RHA mutations can occur independently of BRCA1 mutations,” Boris-Lawrie says. “Other studies show that patients with the BRCA1 phenotype but without BRCA1 mutations had mutations in RHA. This could explain why patients without BRCA1 mutations can have the BRCA1 cancer phenotype,” Boris-Lawrie says.

“We are now assessing breast-cancer cohorts to see if RHA is deregulated in breast cancer,” she continues.

**REX, TAX AND HBZ**

Twenty years ago, Patrick Green, PhD, professor of Veterinary Biosciences and of Molecular Virology, Immunology, and Medical Genetics, and co-leader of the OSUCCC – James Viral Oncology Program, experienced a “why” moment that guided his research for a decade.

Green was drawn to the retrovirus human T-cell lymphotropic virus type 1 (HTLV-1) and its close relative HTLV-2 early on. HTLV-1 causes adult T-cell leukemia/lymphoma and the demyelinating disease, tropical spastic paraparesis. HTLV-2 is not clearly associated with any disease.

Using gel electrophoresis to separate HTLV-2 proteins into bands for identification, he noticed that a key regulatory protein called Rex formed two bands on the gel, whereas the HTLV-1 Rex protein formed only one. (Improvements in technology would later show that HTLV-1 Rex also segregates into two close bands.)

“I spent about ten years working to understand why Rex from HTLV-2 showed two bands—we thought it might be an important difference between the two viruses,” Green says.

He learned that one of the bands represents the active, phosphorylated form of the Rex protein while the other is the inactive, dephosphorylated form.

Phosphorylation, which adds an energy-laden phosphate group to certain molecules, had changed the shape of the activated Rex, resulting in a second band.

Rex helps transport unspliced viral RNA from the nucleus to the cytoplasm, Green notes. “Interestingly, we found the active form in the nucleus and the inactive form in the cytoplasm. We proposed that
active, phosphorylated Rex binds with the target RNA in the nucleus and exports it to the cytoplasm. There, Rex is dephosphorylated, drops its RNA payload and relocates to the nucleus."

This mechanism enables the virus to stockpile inactive Rex in the cytoplasm that would be immediately available for viral replication, he says. “In short order the protein could be activated, move to the nucleus and start exporting viral RNA. This could happen really quickly because the protein doesn’t have to be made from scratch.”

Green then focused on Tax, an HTLV regulatory protein that increases the transcription of viral proteins. Using a complex recombinant virus model, he and his colleagues showed that Tax is critical for malignant transformation of host cells. "Without Tax, cell transformation doesn't happen and the virus is essentially dead," Green says.

They also learned how Tax transforms host cells: The protein activates NFkB, a master regulator of gene transcription. "Without NFkB activation, transformation doesn't occur," Green says.

But this presented a quandary. Many ATL cells stop making Tax, yet NFkB is constitutively active. "Something else was picking up what Tax was no longer there to do," Green says. He believes the culprit is a viral protein called Hbz, which is present in almost all ATL tumor cells and also plays a role in NFkB signaling. Hbz was discovered relatively recently, and interest in it has grown over the last decade, Green says. “We hypothesize that Tax, along with Hbz, is ultimately required for malignant transformation, and that the two may work in concert, or that Hbz substitutes for various Tax functions,” he says.

"We provided the first evidence that this protein is directly involved in proliferation of both infected cells and tumor cells."

PATRICK GREEN, PHD
Co-leader, OSUCCC – James
Viral Oncology Program

"Our lab focuses on how viral proteins interact with host cells. We try to address questions using natural target cells and physiological levels of gene expression, and we have a variety of infectious proviral clones in which we can manipulate RNA and protein expression.”

This enabled his lab to quickly answer important questions about Hbz. "We provided the first evidence that this protein is directly involved in proliferation of both infected cells and tumor cells," Green says. "It is likely expressed early in replication, suggesting that infected cells require it to survive—perhaps to suppress innate immunity—or to stimulate growth. We're looking at that now.

"Once we understand these virus-host interactions, we might be able to use small molecular inhibitors to disrupt them."

Green has collaborated with colleagues in Japan to produce transgenic mice that express Hbz and develop tumors. “This boosts our original hypothesis that Hbz is a transforming factor, along with Tax,” he says. “Overall, our evidence suggests that HTLV-1 tumorigenesis involves multiple oncogenes, with Tax as the initiator and Hbz providing infected cell persistence and tumor maintenance,” he says. “There is no published data yet to determine whether targeting Hbz will benefit patients, but that is forthcoming. It’s the holy grail for us at this point.”

Laboratory research lays the groundwork for new rational therapies for cancer, Green says. "You first have to identify the pathways involved and learn how they work and what they lead to. Then you can define how to inhibit, regulate or disrupt what the viral protein is doing to that pathway."

"The basic-research side feeds into the preclinical-research side, which feeds the development of clinical trials that evaluate novel agents in patients,” he says.

Peyton Rous’ filterable elements continue to contribute to science’s understanding of cancer beyond what might be expected. That and the determination to answer, "What can be the why?"
2011 PELOTONIA FELLOWSHIPS SUPPORT STUDENT-PROPOSED CANCER RESEARCH AT OHIO STATE

Grants fund research by undergraduate, graduate, medical and postdoctoral students

Each year, Pelotonia – a bicycling event that raises money for cancer research at The Ohio State University – funds fellowship grants for undergraduate, graduate, medical school and postdoctoral students who want to help cure cancer at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. As of August 2011, more than $3 million raised through Pelotonia has been committed to fund fellowship grants.

2011 funding for the Pelotonia Fellowship Program is supporting 43 cancer research projects that range from biology and engineering physics to exercise science and mathematics.

“Last year’s second annual Pelotonia grassroots cycling tour raised $7.8 million, and those Pelotonia dollars are funding vital cancer research at Ohio State, helping our youngest and brightest cancer investigators to bridge the gap until they may qualify for federal research funding,” says Michael Caligiuri, MD, director of The Ohio State University Comprehensive Cancer Center and CEO of The James Cancer Hospital and Solove Research Institute. “Student researchers play a crucial role in making new discoveries that may one day lead to a cancer-free world.”

Gustavo Leone, PhD, director of the Pelotonia Fellowship Program, adds that the program fosters collaboration between students and highly accomplished researchers at Ohio State.

In 2011, $2 million has been dedicated to the Pelotonia Fellowship Program. As of August, those funds are supporting four categories of grants, with additional categories to be announced this autumn:

• 27 undergraduate fellowships, which provide up to $12,000 for projects that last up to one year.
• 10 graduate fellowships for up to two years and pay a competitive annual stipend of up to $25,000 plus fees and tuition.
• One one-year medical school fellowship, which pays a competitive annual stipend of $25,000.
• Five postdoctoral fellowships, which pay a competitive annual stipend based on NIH guidelines for up to two years.

For more information about Pelotonia, visit http://www.pelotonia.org.
USE OF FUNCTIONAL CONFECTIONS IN PROMOTING ORAL HEALTH IN MEN AND WOMEN

HYPOTHESIS: A strawberry concentrate incorporated into a gummy-type confection will deliver bioactive phytochemicals to the oral mucosa, and these phytonutrients will induce expression of critical genes and proteins associated with key biological pathways that may foster good oral health. Data from this trial is crucial for planning future prevention trials for people at high risk for or who have early-stage oral cancer.

RATIONALE: An estimated 80 percent of the U.S. population is affected with gum disease, and 30,000 individuals are newly diagnosed with oral cancer annually. Studies indicate that diets high in fruit intake can reduce oral-cancer risk by 20 to 80 percent, an effect attributed to the many phytonutrients found in fruit. Phytonutrients in strawberries show particular promise in preventing oral disease, but these compounds are readily broken down by gastrointestinal microflora and eliminated with little systemic absorption.

A more effective and palatable system to deliver phytonutrients to the oral mucosa is needed. This six-week, phase I/II, placebo-controlled clinical trial for healthy smokers and non-smokers evaluates the topical application of phytochemicals using a strawberry gummy confection.

The trial investigates whether short-term administration of the strawberry concentrate will transfer measurable amounts of phytonutrients to oral tissues and modulate genes associated with oxidation and inflammation, without significant adverse affects. The study also investigates the effects of smoking on these parameters.

A total of 36 healthy men and women will be stratified into three age groups, with six active smokers and non-smokers in each group. Subjects will visit Ohio State’s Clinical Research Center five times during the six-week period.

Ohio State’s Department of Food Science and Technology developed the six-gram, gummy confection so that it can easily be cradled in the oral vestibule even by individuals with significant tooth loss, oral sores and other oral maladies. The gummies, prepared by Ohio State’s Food Industries Center Gould Food Pilot Plant, contain 45 percent freeze-dried fruit. Used as directed, they deliver the equivalent of one cup of whole strawberries daily. Placebo gummies have no freeze-dried fruit.

The study has three main objectives:
- To measure compliance with consumption of the strawberry gummies.
- To quantify the absorption and excretion patterns of strawberry polyphenols in smoking and non-smoking participants.
- To determine if consumption of the strawberry gummy compared with placebo has a greater effect on salivary inflammatory markers and modulates the expression of genes that promote oral health following short-term exposure.

The benefits to the subject related to strawberry polyphenol bioavailability and oral health are unknown. Participants receive parking or bus vouchers to assist with their travel, and gift certificates to compensate for time and effort.

AT A GLANCE
Use of Functional Confections in Promoting Oral Health in Men and Women

PI: YAEL VODOVOTZ, PHD, associate professor, Department of Food Science and Technology and a member of the Molecular Carcinogenesis and Chemoprevention Program

Phone: 614-247-7696

Email: Vodovotz.1@osu.edu

Eligibility: Age 18 to 70; Smoker or non-smoker; Agree to a cotinine urine test to determine smoking status; Agree to consume a standardized vitamin and mineral supplement; No history of metabolic disorders; Body mass index between 18 and 30 kg/m2; Abstain from foods with significant anthocyanins and polyphenols; Agree to avoid all commercial and homemade mouthwashes.
NEED TO KNOW
Resources for Professional Development

SHARED RESOURCES

MODELING HUMAN DISEASE
The Genetically Engineered Mouse Modeling Shared Resource

Mouse modeling is a powerful, highly effective tool for understanding cancer etiology and investigating novel experimental therapeutics. The OSUCCC – James Genetically Engineered Mouse Modeling Shared Resource is available to all Ohio State investigators who work or intend to work with mouse models of human diseases.

Director Vincenzo Coppola, MD, is a former scientist with the NCI’s Mouse Cancer Genetics Program. He and his staff are particularly interested in helping investigators with minimal experience who would like to start using mouse models to complement and strengthen their in vivo studies or grant proposals.

The facility has extensive experience generating and maintaining genetically engineered mouse lines, including classical transgenic lines by pronuclear injection and targeted lines (knock-out, knock-in, conditional) by embryonic stem cell technology. The facility also offers sperm or embryo cryopreservation, rederivation and in vitro fertilization (IVF) services.

VINCENZO COPPOLA, MD, director of the Genetically Engineered Mouse Modeling Shared Resource and a member of the Molecular Biology and Cancer Genetics Program

Conference Calendar

MULTIDISCIPLINARY MANAGEMENT OF NEUROENDOCRINE CANCERS: FROM STANDARD OF CARE TO CUTTING-EDGE THERAPIES
December 3, 2011

FOCUS: This symposium will review the latest evidence-based information on the diagnosis and management of neuroendocrine cancers. The meeting will focus on the needs and practice gaps in physician practice to improve patient outcomes by promoting multidisciplinary teams to address clinical and patient issues.

For more information, contact Nancy Jones at (614) 293-3688 or visit http://cancer.osu.edu/neuroendo.

CENTER FOR RETROVIRUS RESEARCH AWARD ANNOUNCED
April 5, 2012

Ohio State’s Center for Retrovirus Research in the College of Veterinary Medicine will award its 2012 Distinguished Research Career Award to Warner Greene, MD PhD, director of the Gladstone Institute of Virology and Immunology at University of California, San Francisco. Green focuses on the HIV-1 and HTLV-I retroviruses, which cause contrasting diseases: Acquired Immune Deficiency Syndrome (AIDS) with HIV-1, and the Adult T-cell Leukemia with HTLV-1.
RADIATION THERAPY TAKES WING AT THE OSUCCC – JAMES

RT Now Available at JamesCare Comprehensive Breast Center

The JamesCare Comprehensive Breast Center, which opened in April, now has its own TrueBeam linear accelerator and began offering radiation therapy for breast cancer patients in July. The OSUCCC – James Comprehensive Breast Center is the first of its kind in the Midwest to offer the full spectrum of breast cancer treatment – surgery, radiation therapy and chemotherapy – along with all-inclusive prevention, detection and survivorship services in one location.

Second Floor, Please
When the new James Cancer Hospital and Solove Research Institute opens in 2014, patients arriving for radiation therapy will head to the Second Floor, rather than Ground Level, which is the typical location for a radiation oncology department.

“The new James Cancer Hospital will have one of the few radiation oncology departments that is located above ground,” says Arnab Chakravarti, MD, chair of Radiation Oncology at the OSUCCC – James.

The 64,400 sq. ft. space will include:
- Seven treatment vaults, plus brachytherapy areas;
- 24 examination rooms and three consultation rooms;
- Separate registration areas for new patients and on-treatment patients;
- Waiting areas with natural light and interior rooms with more meditative designs;
- More spacious treatment vaults with storage to hide immobilization and treatment masks.

“We are putting a lot of thought into creating a calming, friendly environment to offer our patients the very best in personalized care in Radiation Oncology,” Chakravarti says.

TOP The new TrueBeam linear accelerator at the OSUCCC – James Comprehensive Breast Center.
ABOVE The Department of Radiation Oncology will be located on the second floor of the new Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, which is expected to open in 2014.
USNWR Ranks OSUCCC – James 20th in Nation

For the 13th consecutive year, the OSUCCC – James earned a place on U.S. News and World Report’s top 50 list of “America’s Best Hospitals” for cancer care. This year, Ohio State’s cancer program was ranked 20th in the nation by U.S. News, a significant jump from last year’s impressive ranking of 26th. The OSUCCC – James first made the list in 1999, less than a decade after the hospital opened in July 1990, and has remained there ever since.

This ranking follows an “exceptional” rating of the OSUCCC – James by the National Cancer Institute earlier this year. “Exceptional” is the highest rating that the NCI gives to cancer centers around the country.


Pelotonia Riders Reap Dollars for Cancer Research

Almost 5,000 riders and some 1,700 volunteers joined forces to ensure the success of Pelotonia ’11, the annual bicycling tour to raise money for cancer research at the OSUCCC – James. As of early September, the Aug. 20 weekend-long ride between Columbus and Athens, Ohio, had raised nearly $9.4 million.

The event attracted riders from 38 states and four nations. More than 1,000 riders constituted Team Buckeye, the official Ohio State University super peloton (riding group).

Fundraising for Pelotonia ’11 will continue through Oct. 21, but revenue from this year’s ride is expected to push the overall three-year total to more than $21 million. Last year’s tour generated $7.8 million, and the 2009 inaugural Pelotonia raised $4.5 million.

Some of the money raised supports the Pelotonia Fellowship Program, which has provided 120 students with money to pursue innovative ideas in cancer research. To learn about some of the 2011 Pelotonia Fellowship recipients, see page 28.

For more information about Pelotonia, visit http://www.pelotonia.org/.

IN THE NEXT ISSUE OF frontiers...

CANCER SURVIVORSHIP 2012
Life as a cancer survivor today is dramatically different from what it was in 1971, the year the National Cancer Act was signed. This story explores how advances in cancer diagnosis, treatment and supportive care are enabling more people to live disease-free for longer periods and what the future holds.

THE MYSTERY OF METASTASIS
Roughly nine in 10 cancer deaths are caused not by growth of the primary tumor but by metastatic tumors that arise at distant sites. Yet, the process of metastasis remains poorly understood. Researchers at the OSUCCC – James are focused on the particularly debilitating and painful spread of cancer to bone and are working to prevent the problem.