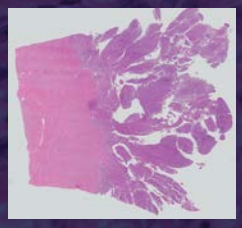
TURNING CANCER DISCOVERIES INTO TREATMENTS

FRONTIERS

WINTER | 2018

PATHOLOGY FROM THE COCKPIT

Bidding adieu (largely) to glass slides



The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

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

UPFRONT

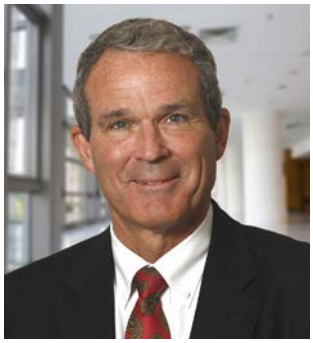
The Director's Perspective

Changing of the Guard

With the changing of the year comes a changing of the guard at The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James).

While we are saddened by the impending departure of former OSUCCC Director and James CEO Michael A. Caligiuri, MD, who in February will embark on a new career opportunity in California, we are also honored to have been chosen to guide Ohio State's cancer program in pursuit of our shared vision of a cancer-free world.

The OSUCCC – James flourished under Dr. Caligiuri's leadership, enjoying record financial performance, earning the highest possible descriptor of "exceptional" during our two most recent NCI surveys, receiving patient-satisfaction scores that rank among the nation's highest, and gaining a reputation as one of the most translational cancer hospitals in the country as we readily convert laboratory discoveries into innovative cancer care and prevention strategies.



WILLIAM FARRAR, MD
Interim CEO, James Cancer Hospital

RAPHAEL POLLOCK, MD, PhD
Director, The Ohio State University Comprehensive Cancer Center

Through the combined efforts of our dedicated faculty, staff and volunteers, we intend to build upon the outstanding reputation of the OSUCCC – James as a transformational cancer hospital that provides compassionate cancer care to the patients and families who turn to us for help.

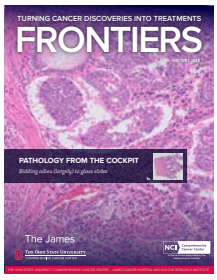
We offer evidence of our commitment in this issue of *Frontiers*. Here you can gain insight into the *RAS* oncogene—which when mutated drives some of the deadliest forms of cancer—and our researchers' efforts to discover an effective inhibitor to blunt its oncogenic effects. You can also read about our recently launched Digital Pathology Program that will fully digitize our anatomical pathology services over the next 10 years.

Excitement is mounting at the OSUCCC – James, and we thank you for sharing in it by taking time to peruse this edition of *Frontiers*.

FRONTIERS

WINTER | 2018

FEATURES



ON THE COVER:
Digital Pathology.
Scanned uterine tumor section enlarged to 400x. See page 14.

MOVING PRECISION CANCER MEDICINE INTO THE CLINIC

BY SAMEEK ROYCHOWDHURY, MD, PHD,
assistant professor in the Division of Medical Oncology at Ohio State and a member of the OSUCCC – James Translational Therapeutics Program

This is an amazing time to be an oncologist. Cancer medicine is in the midst of an exciting transition, shifting away from the organ-based practice that we've known for decades and toward precision cancer medicine (PCM)—the use of genomics to identify genes in patient tumors that we can target with therapy.

Nurturing this evolution is the federal Cancer Moonshot Initiative, which seeks to make a decade's worth of progress in five years. Key concepts that underlie the Moonshot effort include "big data," "data sharing" and "innovation."

At the OSUCCC – James, we are making progress in all three areas in our attempts to help move PCM into the clinic.

INTERPRETING BIG DATA

Interpreting large sets of genetic data is part and parcel of precision cancer medicine. The ultimate purpose for analyzing big data is to identify the most effective therapy for our patients.

Recent research has shown that the presence in tumor cells of an alteration called microsatellite instability has important treatment implications. Microsatellites are short strings of repeated DNA bases. If the number of repeats in malignant cells differs from that of nearby healthy cells, the tumor is said to show microsatellite instability (MSI).

MSI is a surrogate marker for the silencing of key DNA repair mechanisms. MSI testing is commonly done when screening for Lynch syndrome, an inherited cancer syndrome that increases the lifetime risk for colorectal and other cancers. But MSI also occurs in spontaneous cancers, and strong evidence suggests that up to 80 percent of patients with MSI-positive tumors might respond well to immunotherapy.

There is little data available for the prevalence of MSI in most types of spontaneous tumors. At the same time, the growing use of next-generation sequencing (NGS) is making data available for tumor types not usually tested for MSI.

This raises the need for tools that can quickly and accurately analyze this data in multiple cancer types.

Fortunately, such tools are available. MANTIS (Microsatellite Analysis for Normal Tumor InStability) is a new algorithm designed to classify samples by MSI status utilizing existing NGS data.

Our team published a study in the journal *Oncotarget* showing that MANTIS had the highest overall sensitivity and specificity for detection of MSI status across six different tumor types. It also required less memory and had faster run times. Next, we will apply this to data from the Oncology Research Information Exchange Network to identify additional patients with MSI, which could lead to a novel immunotherapy for these patients.

DATA SHARING

Our ability to identify the gene mutations, or cancer variants, that drive tumor growth and progression lies at the heart of precision cancer medicine. But

"Through three active clinical trials at the OSUCCC – James, we are studying how patients respond to novel FGFR inhibitors."

doing so requires a common language, standardized terminology and a level of description that facilitates their use in research and their ready interpretation in clinical practice.

Currently, genomic information collected by many databases is described and shared differently, which can create discrepancies, inconsistencies and information gaps that make the clinical or research use of variants difficult. For example, different terminology is often used to classify germline and somatic variants (see box).

Fortunately, progress is underway here, too. We contribute to the team effort of the Clinical Genome Resource (ClinGen), a national NIH initiative that represents 75 institutions.

Recently, ClinGen published guidelines in the journal *Genome Medicine* that attempt to standardize information about cancer variants that is collected and shared so that everyone is speaking the same language.

The guidelines suggest the use of at least 16 discrete data elements to define a mutation. Standardizing these elements creates a common language for uniformly describing mutations and what they mean for patients.

INNOVATION

Ultimately, we use NGS and analyze big data to determine the best therapy for our patients. That relates to another Moonshot goal: developing ways to overcome cancer's resistance to therapy.

Several OSUCCC – James researchers are working on the problems of drug and radiation resistance. Our team recently led a study published in the journal *Molecular Cancer Therapeutics* that demonstrated a mechanism by which lung and bladder cancer cells develop resistance to a new class of drugs called fibroblast growth factor receptor (FGFR) inhibitors.

Our findings in a laboratory model provide insights into how clinical trials for these agents could be further developed to prevent or overcome drug resistance, and how the information could be useful for developing innovative therapies. Through three active clinical trials at the OSUCCC – James, we are studying how patients respond to novel FGFR inhibitors.

Clearly, there is no routine cancer. Each patient is different, and each needs molecular testing. The Cancer Moonshot will focus our research efforts in ways that hasten the transition to precision cancer medicine, and that should produce better outcomes for all cancer patients.

COMPARISON OF GERMLINE AND SOMATIC VARIANT TERMINOLOGY

Germline Variants
- Pathogenic
- Likely pathogenic
- Variant of unknown significance
- Likely benign
- Benign

Evidence
- Very strong
- Strong
- Moderate
- Supporting

Somatic Variants
- Diagnostic
- Prognostic
- Predictive

Evidence
- Prospective trials
- Retrospective trials
- FDA approval
- Expert opinion
- Case reports
- Preclinical
- Inferential

Different terminology is often used to classify germline and somatic gene variations. Germline variants may be classified according to levels of pathogenicity, while somatic variants are classified into biomarker categories. The supporting evidence also is different for each. Evidence of pathogenicity for a germline variant may be based on published reports of high penetrance and be considered "very strong," while supporting evidence for a predictive somatic variant could come from a large randomized trial or from preclinical laboratory data. The ClinGen initiative is working to reduce such inconsistencies in variant terminology.

LYMPHOMA |

CAR-T Immunotherapy Approved for Certain Adult Lymphoma Patients

SAMANTHA JAGLOWSKI, MD, MPH
hematologist at the OSUCCC – James

The Food and Drug Administration (FDA) has approved a breakthrough cancer therapy known as CAR-T for use in adults with advanced lymphoma. The therapy uses a patient's own white blood cells, which are modified in a lab and re-trained to recognize specific markers on the surface of the cell and then target and kill only those cancerous cells.

"This is truly a living therapy. It's a patient's own cells that are reinfused and go to work fighting cancer," says Samantha Jaglowski, MD, MPH, a hematologist at the OSUCCC – James, who tested the therapy in clinical trials. "This is really the epitome of personalized medicine."

Clinical trial data showed that more than half of patients who had failed at least two rounds of chemotherapy or a stem cell treatment responded to CAR-T treatment.

"For these patients, the rate of success in the next line of treatment is about 26 percent, and the average overall survival is about six months," says Jaglowski. "But with CAR-T, the response rate is nearly 60 percent, and the average survival rate of those patients is yet to be seen. Patients who have success with this therapy tend to stay in remission."

Jaglowski notes that CAR-T tends to work quickly, with many patients achieving complete remission within a few months and often with fewer side effects than traditional cancer treatments such as chemotherapy and radiation.

The OSUCCC – James is one of only a handful of centers across the country currently offering CAR-T therapy. The therapy is also FDA-approved for a rare type of treatment-resistant childhood leukemia.

To learn more about CAR-T and clinical trials at the OSUCCC – James, visit cancer.osu.edu/cart.

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

GLIOBLASTOMA

Onalespib may be an Effective Treatment for Glioblastoma

The targeted therapy onalespib has shown effectiveness in preclinical studies of glioblastoma by researchers at the OSUCCC – James. The findings suggest that the targeted inhibitor is long-lasting, crosses the blood-brain barrier and is more effective when combined with temozolomide, a chemotherapy drug used for brain-tumor treatment.

Onalespib inhibits a protein called HSP90, a molecule that helps newly made protein molecules fold into their functional form. A large number of receptor and DNA-damage-response proteins require HSP90 to achieve functional conformation. In cancer cells, HSP90 expression can be 10 times higher than in normal cells.

This study showed that onalespib blocked HSP90 activity, which reduced expression of cell-survival proteins such as AKT and endothelial growth factor receptor in glioma cell lines and in glioma stem cells obtained from patient tumors. This, in turn, reduced cancer cell survival, proliferation, invasion and migration.

In animal models of glioblastoma (GBM), the agent crossed the blood-brain barrier and was most effective at improving survival in combination with temozolomide.

"Our findings suggest that onalespib can efficiently breach the blood-brain barrier better than other HSP90 inhibitors, and that, in combination with chemotherapeutic temozolomide, could be an exciting new therapy for GBM," says principal investigator Vinay Puduvalli, MBBS, professor and director of the Division of Neuro-Oncology at Ohio State and a clinician-researcher at the OSUCCC – James.

"Based on the results of this study, we have generated a clinical trial that will determine whether onalespib in combination with standard therapy is safe and effective in patients with newly diagnosed glioblastoma," he says.

Glioblastoma is the most common form of brain cancer, with more than 12,000 new cases expected in 2017. It remains incurable, with overall survival averaging 16-18 months.

Published in the journal Clinical Cancer Research

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

VINAY PUDUVALLI, MBBS, *professor and director of the Division of Neuro-Oncology at Ohio State and a clinician-researcher at the OSUCCC – James.*

LIVER CANCER |

A microRNA With Macro Implications

miR-122 expression might predict survival of liver-cancer patients

KALPANA GHOSHAL, PHD
associate professor of pathology

A molecule called microRNA-122 (miR-122) is critical for regulating liver-cell metabolism and for suppressing liver-cancer development. A study led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and at Rockefeller University's Howard Hughes Medical Institute shows that miR-122 interacts with thousands of genes in liver cells. Levels of this molecule often drop during liver-cancer development, and the study also found that when this happens, the expression of certain cancer-promoting genes goes up.

The findings could one day help doctors better predict survival in liver cancer patients and help determine whether miR-122 should be developed as an anticancer drug.

The researchers sought to biochemically (rather than computationally) define all miR-122 target sites in the liver and hepatocellular carcinoma (HCC), the most common form of liver cancer, and to learn which target genes were critical for liver-cancer development or progression. miR-122 is found almost exclusively in liver cells, where its role includes regulating cholesterol and lipid metabolism.

"We want to understand how miR-122 regulates liver metabolism and suppresses cancer development, and to identify common targets in humans and mice that may be involved in HCC development," says co-principal investigator and OSUCCC – James researcher Kalpana Ghoshal, PhD, associate professor of pathology. "That knowledge is critical for determining whether this molecule should be developed as a possible therapeutic agent for liver cancer."

Ghoshal and her colleagues conducted their study using a mouse model that lacked miR-122, along with normal mice; liver cancer tissues and normal liver tissues from nine HCC patients; and data from 373 HCC patients in The Cancer Genome Atlas Liver Hepatocellular Carcinoma dataset.

The findings significantly extend the number of miR-122 binding sites identified by earlier studies because the methods used by the investigators identified sites that other techniques miss, Ghoshal adds. (Note: One gene can have multiple microRNA target sites.)

Published in the journal Molecular Cell

ENDOMETRIAL CANCER

NSAIDs Implicated

Long-term anti-inflammatory drug use may increase cancer-related deaths for certain patients

Regular use of over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen is associated with greater risk of dying in patients diagnosed with type 1 endometrial cancers, according to a new population-based study led by researchers at the OSUCCC – James.

In this observational study, a multi-institutional team of cancer researchers sought to understand the association of regular NSAID use and the risk of dying from endometrial cancer among a cohort of more than 4,000 patients. They found that regular NSAID use was associated with a 66-percent increased risk of dying among women with type 1 endometrial cancer, a typically less-aggressive form of the disease.

The association was statistically significant among patients who reported past or current NSAID use at the time of diagnosis, but it was strongest among patients who had used NSAIDs for more than 10 years in the past and had ceased use prior to diagnosis. NSAID use was not associated with mortality from typically more aggressive type 2 cancers.

"There is increasing evidence that chronic inflammation is involved in endometrial cancer risk and progression, and recent data suggests that inhibition of inflammation through NSAID use plays a role in that process," says Theodore Brasky, PhD, co-lead author of the study and a cancer epidemiologist with the OSUCCC – James.

"This study identifies a clear association that merits additional research to help us fully understand the biologic mechanisms behind this phenomenon," Brasky adds. "Our finding was surprising because it goes against previous studies that suggest NSAIDs can be used to reduce inflammation and reduce the risk of developing or dying from certain cancers, like colorectal cancer."

Researchers point out that information about specific dosages and NSAID use after surgery was not available in the current study, which represents a significant limitation.

Published in the Journal of the National Cancer Institute

THEODORE BRASKY, PHD,
co-lead author of the study and a cancer epidemiologist with the OSUCCC – James

"There is increasing evidence that chronic inflammation is involved in endometrial cancer risk and progression, and recent data suggests that inhibition of inflammation through NSAID use plays a role in that process."

Updated AML Guidelines

Advances prompt release of new recommendations for diagnosis, management of adult AML

CLARA D. BLOOMFIELD, MD,
Distinguished University Professor at Ohio State; cancer scholar and senior adviser for the OSUCCC – James

"These guidelines are an important update of the current and widely used recommendations for managing AML, for constructing clinical trials and for predicting outcomes of AML patients."

An international panel of experts has released updated evidence-based and expert-opinion-based recommendations for the diagnosis and treatment of acute myeloid leukemia (AML) in adults.

The recommendations were issued by the European LeukemiaNet (ELN) and published in the journal *Blood.* The paper's senior author was Clara D. Bloomfield, MD, a Distinguished University Professor at Ohio State who also serves as cancer scholar and senior adviser for the OSUCCC – James.

"These guidelines are an important update of the current and widely used recommendations for managing AML, for constructing clinical trials and for predicting outcomes of AML patients," says Bloomfield, who co-chaired the panel. "They will be the new standard of care and will replace the 2010 ELN recommendations for managing AML patients and designing clinical trials."

Adult AML affects an estimated 21,400 Americans per year and kills 10,600 of them, according to the American Cancer Society.

The updated recommendations include revised ELN genetic categories, a proposed response category based on minimal residual disease status, and a proposed category for progressive disease for clinical trials.

The recommendations also include the newly updated World Health Organization classification of myeloid neoplasms and acute leukemia.

Bloomfield says updating the ELN recommendations was prompted by new insights into the molecular and genomic causes of the disease, by the development of new genetic tests and tests for detecting minimal residual disease, and by the development of novel antileukemic agents.

Published in the journal Blood

PEDIATRIC CANCER

Anticancer Synergy

Two investigational antitumor agents work better together against peripheral nerve sheath tumors and neuroblastoma

Two investigational agents—the aurora A kinase inhibitor alisertib and the oncolytic herpesvirus HSV1716—have separately shown some antitumor efficacy as monotherapies in early clinical trials. However, a new study demonstrates that their use in combination increases antitumor efficacy in models of malignant peripheral nerve sheath tumor (MPNST) and neuroblastoma.

"We investigated this combination in MPNST and neuroblastoma because these are two difficult-to-treat sarcomas that have shown susceptibility to these agents individually," explains senior author Timothy Cripe, MD, PhD, a professor of Pediatrics and a researcher at the OSUCCC – James.

"MPNST is a rare pediatric cancer, but for patients with neurofibromatosis 1, a genetic cancer predisposition disorder, it is the leading cause of death. More importantly, MPNST is resistant to chemotherapy," says Cripe, who also is division chief of Hematology/Oncology and BMT at Nationwide Children's Hospital (NCH) and a principal investigator at the Center for Childhood Cancer and Blood Diseases in The Research Institute at NCH.

Cripe says many mechanisms likely worked synergistically to increase the antitumor effect in this study. Particularly, HSV1716 increased the sensitivity of uninfected cells to alisertib cytotoxicity. Alisertib also increased peak virus production and slowed virus clearance from tumors. The team also found that alisertib inhibited virus-induced accumulation of intratumoral myeloid-derived suppressor cells.

"Our study shows that alisertib helps the infection phase of HSV1716 because innate immunity is impacted," Cripe says. "It's possible that it could inhibit the second phase, the downstream immunotherapeutic effects of the virotherapy, but based on data from other studies, we don't think that's the case."

Published in the journal
OncoTarget

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TIMOTHY CRIPE, MD, PHD,
professor of Pediatrics at Ohio State and a researcher at the OSUCCC – James

"We investigated this combination in MPNST and neuroblastoma because these are two difficult-to-treat sarcomas that have shown susceptibility to these agents individually."

Improving Prognostic Prowess

New prognostic classification may help clinical decision-making in glioblastoma

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

"We believe that incorporating c-MET- and MGMT-protein expression enhances the prognostic classification of glioblastoma patients over and above the traditional clinical variables, and that it will improve clinical decision-making."

New research shows that taking molecular variables into account will improve the prognostic classification of the lethal brain cancer called glioblastoma (GBM).

Led by researchers at the OSUCCC – James, the study found that adding significant molecular biomarkers to the existing GBM classification system improves the prognostic classification of GBM patients who have been treated with radiation and the drug temozolomide.

The current model, used internationally for nearly two decades, is based on clinical variables alone. It was created before the introduction of temozolomide, which along with radiation is the current standard of care for GBM.

The new, refined classification was derived using samples from 452 GBM patients treated with radiation and temozolomide. It includes such key molecular markers as MGMT-protein and c-MET-protein expression, along with such clinical variables as age, performance status, extent of resection and neurological function.

The researchers validated the model in an independent group of 176 patients.

"Our study has established and independently validated a novel molecular classification of glioblastoma, perhaps the most aggressive of all human malignancies," says principal investigator Arnab Chakravarti, MD, professor and chair of the Department of Radiation Oncology at Ohio State and co-director of the Brain Tumor Program. "The revised model offers a more accurate assessment of prognostic groups in GBM patients who have been treated with radiation and temozolomide.

"We believe that incorporating c-MET- and MGMT-protein expression enhances the prognostic classification of glioblastoma patients over and above the traditional clinical variables, and that it will improve clinical decision-making," says Chakravarti, who also holds the Max Morehouse Chair in Cancer Research at Ohio State. "Furthermore, inclusion of the MGMT protein provides insight into the potential for resistance to radiation and temozolomide."

Published in the journal JAMA Oncology

Voices for Vaccination

Ohio State joins national call for HPV vaccination of children to prevent cancer

Recognizing a need to improve national vaccination rates for the human papillomavirus (HPV), the OSUCCC – James has again united with the 69 National Cancer Institute (NCI)-designated cancer centers to issue a joint statement supporting recently revised recommendations from the Centers for Disease Control and Prevention (CDC).

According to the CDC, incidence rates of HPV-associated cancers continue to rise; approximately 39,000 HPV-associated cancers are diagnosed each year in the United States. Although HPV vaccines provide close to 100 percent protection against cervical cancer and genital warts, and may help prevent oropharyngeal and genital cancers, vaccination rates remain low across the country.

The new CDC guidelines recommend that children under age 15 should receive two doses of the 9-valent HPV vaccine at least six months apart, and that adolescents and young adults older than 14 should continue to complete the three-dose series.

Key barriers to improved vaccination rates include a lack of strong recommendations from physicians, and parents not understanding that this vaccine protects against several types of cancer.

"Parents rely heavily on the recommendations of their child's healthcare provider for appropriate vaccination, and the medical community simply isn't consistently recommending the HPV vaccine like they do other public health prevention vaccines," says Electra Paskett, PhD, MSPH, associate director for population sciences at the OSUCCC – James, where she also leads the Cancer Control Program.

"This is the No. 1 barrier to HPV vaccination, and it must change to reduce the burden of HPV-associated cancers in our community," she adds.

To overcome these barriers, NCI-designated cancer centers have organized a continuing series of national summits to share new research, discuss best practices and identify collective action toward improving vaccination rates.

The original joint statement, published in January 2016, was the major recommendation from a summit hosted at The University of Texas MD Anderson Cancer Center in November 2015.

Published in the journal
Cancer Research

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ELECTRA PASKETT, PHD, MSPH,
associate director for population sciences at the OSUCCC – James

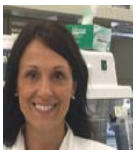
"Parents rely heavily on the recommendations of their child's healthcare provider for appropriate vaccination, and the medical community simply isn't consistently recommending the HPV vaccine like they do other public health prevention vaccines."

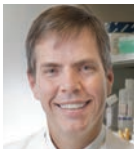
OF NOTE

Recent Recognition of OSUCCC – James Physicians and Researchers

GRANTS

RICHARD FISHEL, PhD, professor of Cancer Biology and Genetics, has received a five-year, $1.8 million renewal grant (CA067007) from the National Cancer Institute (NCI) to understand in detail the mechanism of DNA mismatch repair.





ROSA LAPALOMBELLA, PhD, assistant professor of Internal Medicine; ROBERT BAIOCCHI, MD, PhD (center), **associate professor in the Division of Hematology; and JOHN C. BYRD, MD, professor in the Division of Hematology,** have received a five-year, $2.3 million NCI grant (CA214046) titled "Targeted Therapies for Richters Transformation."

LEAH PYTER, PhD, associate professor of Psychiatry, has received a five-year, $1.78 million NCI grant (CA216290) to investigate whether chemotherapy alters the makeup of the gut community in ways that cause chemotherapy-related cognitive problems.

QI-EN WANG, PhD, assistant professor of Radiology, has received a five-year, $2.3 million grant (CA211175) from the National Cancer Institute titled "Averting Recurrent and Resistant Ovarian Tumors."

AWARDS AND HONORS

JOHN C. GRECULA, MD, FACR, professor of Radiation Oncology, has been inducted as a Fellow of the American College of Radiology (FACR). The ACR considers recognition as a fellow to be one of the highest honors it can bestow on a radiologist, radiation oncologist or medical physicist.

MICHAEL KNOPP, MD, PhD, professor of Radiology, has received a 2017 Ohio State University Distinguished Scholar Award, which recognizes exceptional scholarly accomplishments by senior professors and younger faculty who have demonstrated great scholarly potential.

THE JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE earned a 2017 Press Ganey Guardian of Excellence Award for Patient Experience in inpatient care. Press Ganey, a recognized leader in measuring patient experience, presents this award to organizations that have achieved a 95th percentile or higher overall rating on their patient-experience surveys in a given year.

THE SURGICAL INTENSIVE CARE UNIT AT THE OSUCCC – JAMES has received a three-year, silver level Beacon Award for Excellence from the American Association of Critical-Care Nurses (AACN) for exceptional patient care and professional nursing practice. The AACN includes more than 500,000 acute and critical care nurses and more than 235 chapters worldwide.

THE OSUCCC – JAMES presented the 22nd Herbert and Maxine Block Memorial Lectureship Award for Distinguished Achievement in Cancer to Mary-Claire King, PhD, the American Cancer Society Professor of Medicine and Genome Sciences at the University of Washington. The OSUCCC – James extends the annual $25,000 award to an internationally prominent scientist who presents a lecture about his or her research. The award is supported by the annual Herbert J. Block Memorial Tournament, a golf outing sponsored by the Block family of Columbus.

FACULTY AND PROGRAMS

JEFFREY PATRICK, PHARMD, is the new **director of the OSUCCC – James Drug Development Institute,** which helps accelerate promising anticancer agents discovered by Ohio State researchers through pharmaceutical development. Patrick formerly was chief scientific officer at New Haven Pharmaceuticals in Connecticut.

DENIS GUTTRIDGE, PhD, professor of Cancer Biology and Genetics, has been named associate director for basic research at the OSUCCC – James. In this role, Guttridge coordinates basic science across the five OSUCCC – James research programs and facilitates existing and new collaborative efforts.

JOANNA GRODEN, PhD, professor of Cancer Biology and Genetics, has been named director of the Pelotonia Fellowship Program, which enables Ohio State students in any discipline and at all levels to conduct cancer research with guidance by faculty mentors.

JEFFREY VANDEUSEN, MD, PhD, a medical oncologist with a focus on breast malignancies, has been named **associate director for community network relations at the OSUCCC – James**. VanDeusen is an assistant professor in the Division of Medical Oncology at Ohio State.

CLAIRE F. VERSCHRAEGEN, MD, has been appointed **director of the Division of Medical Oncology at Ohio State and associate director for translational research at the OSUCCC – James.** She holds the Diane Nye and Michael Rayden Chair in Innovative Cancer Research and serves as a professor of Internal Medicine. Verschraegen came to Ohio State from the University of Vermont Cancer Center.

JAVIER GONZALEZ, MD, has joined the cancer program as an **assistant professor of Neurological Surgery.** He specializes in neuro-oncology and has a clinical and research interest in neuro-immunology. He came to Ohio State from West Virginia University.

ALLAN ESPINOSA, MD, has joined the cancer program as an **assistant professor in the Division of Medical Oncology.** His clinical and research interests include neuroendocrine and thyroid cancers. Espinosa came to Ohio State from Cary Medical Center, Northern Maine Medical Center and Millinocket Regional Hospital.

THE OHIO STATE UNIVERSITY has an agreement with Nanobio Delivery Pharmaceutical Co. Ltd. for $1.4 million to establish a Center for RNA Nanotechnology and Nanomedicine for cancer research. The director of the center is **Peixuan Guo, PhD**, **professor in the College of Pharmacy at Ohio State.**

LEADERSHIP ACTIVITIES AND APPOINTMENTS

ARNAB CHAKRAVARTI, MD, chair and professor of Radiation Oncology and director of the Brain Tumor Program, has been appointed to the NCI's Board of Scientific Counselors. He will help guide NCI program planning in radiation oncology and neuro-oncology.

Members of the gynecologic oncology team at the OSUCCC – James have been appointed to NCI steering committee or task force roles:

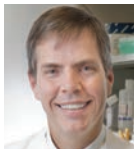
DAVID COHN, MD, professor and director of the Division of Gynecologic Oncology, was appointed to the Uterine Task Force representing NRG Oncology, a clinical cooperative group. He is also chair of NRG Oncology's Cancer Care Delivery Research (CCDR) committee and represents the organization on NCI's CCDR Steering Committee.

DAVID O'MALLEY, MD, associate professor in the Division of Gynecologic Oncology, was appointed to the Ovarian Task Force representing NRG Oncology.

FLOOR BACKES, MD, assistant professor in the Division of Gynecologic Oncology, was appointed to the Uterine Task Force representing the Southwest Oncology Group (SWOG).

JOHN HAYS, MD, PhD, **assistant professor in the Division of Medical Oncology,** was appointed to the Ovarian Task Force representing SWOG.

AWARDS AND HONORS



JOHN C. BYRD, MD, a Distinguished University Professor at Ohio State, where he co-leads the Leukemia Research Program at the OSUCCC – James, is the most recent recipient of the Leukemia & Lymphoma Society's (LLS) prestigious Return of the Child Award. The LLS established this national award in 1986 to honor individuals who have devoted their careers to blood cancer research and whose national and international leadership within the oncology and biomedical communities has helped develop treatments for blood cancers, thereby improving survival rates. Byrd was selected for his work on developing the drug ibrutinib and his leadership in the LLS's Beat AML (acute myeloid leukemia) initiative.

ERICA BELL, PhD, assistant professor-clinical in the Department of Radiation Oncology at Ohio State, is the recipient of the 2017 American Society for Therapeutic Radiology and Oncology (ASTRO) Senior Investigator Basic/Translational Research Award. Bell identified MGMT promoter methylation as a key mediator of outcome and treatment resistance in anaplastic astrocytomas based on prospective National Cancer Institute cooperative group studies.

TRAINEE RECOGNITION

JUAN BARAJAS, a doctoral student in the laboratory of OSUCCC – James researcher KALPANA GHOSHAL, PhD, has been awarded a Howard Hughes Medical Institute (HHMI) Gilliam Fellowship for Advanced Study. HHMI Gilliam Fellowships recognize exceptional doctoral students who have the potential to be leaders in their fields and the desire to advance diversity and inclusion in the sciences.

Pathology From the Cockpit

Digital pathology promises to help pathologists focus more on diagnoses and consultations and less on chasing down glass slides

Above is a microscope slide with a thin slice of tumor tissue that has been stained to bring out cellular details. The tissue will be scanned under a high-throughput slide scanner to produce a digital image of the tissue and its cellular structures. The bar code on the left links the tissue to the patient's molecule test results and medical record, which the pathologist can review while examining the tissue section in a digital cockpit, shown on page 16.

BY KENDALL POWELL

Until recently, when a pathologist wanted to review the prior slides from a complex case with an expert pathologist or colleague, he or she had to request the glass slides from the archives and wait hours to days for the slides to arrive so that they could be shared. But that is changing at Ohio State.

In May 2017, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James) initiated a comprehensive Digital Pathology Program that will fully digitize anatomical pathology services over the next 10 years.

The new system will enable OSUCCC – James pathologists to sit at a large viewer and, with a few clicks, call up a patient's digitized and annotated biopsy specimens, along with his or her medical record, complete with molecular biomarker tests and genomic data.

The program uses whole-slide imaging (WSI) technology, which scans entire glass pathology slides and converts them into digital images. "With that technology, a computer becomes a microscope," says Anil Parwani, MD, PhD, MBA, who heads the program as director of Digital Pathology at the OSUCCC – James.

The system provides fully automated end-to-end pathology workflow and a bank of ultra-fast scanners that are used to digitize both current and past glass

pathology slides.

OSUCCC – James pathologists will soon sit at desktop "digital-pathology cockpits" to view digitized histology slides and other diagnostic images, share pathology images for second opinions and report findings to treating physicians.

WSI technology was introduced in the early 1990s, but the images were low quality, enormous in size and slow to upload. Pathologists were skeptical; they could work more quickly and accurately by viewing their slides directly.

By the 2000s, the technology had improved, and desktop computers could accommodate large image files. Universities began using digital slides for teaching and research.

The digital images were easily stored and transferred—no more hunting down archived glass slides only to find that a slide was lost, broken or faded. What's more, multiple people could simultaneously analyze digital slides from anywhere, vastly speeding up consultations. Their use became more widespread.

But could digital slides be used for the primary diagnosis of cancer and other diseases? In 2009, the U.S. Food and Drug Administration categorized WSI scanners as Class III *in vitro* diagnostic devices, indicating a high risk that a misdiagnosis could be associated with high morbidity or mortality. A leading question was whether information was lost when a glass slide was converted to a digital image.

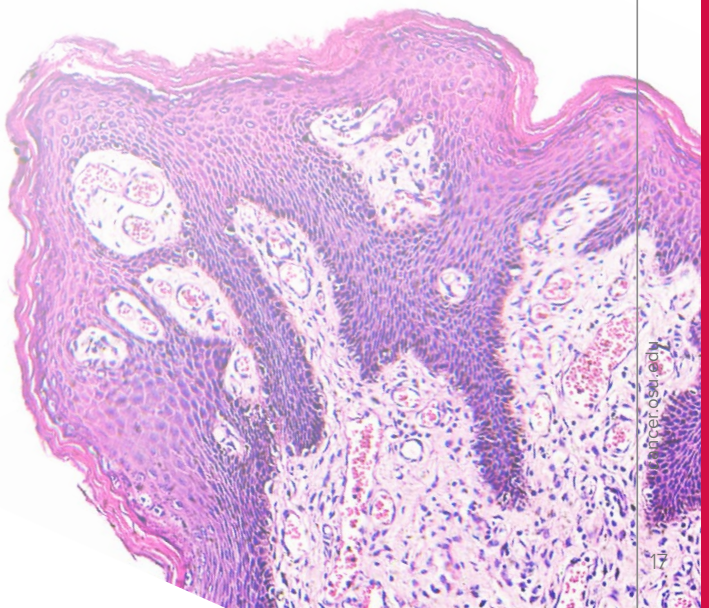
That concern is being addressed by improvements in the technology and by studies that show high concordance between glass and digital slide diagnoses, Parwani says. In addition, OSUCCC – James researchers will run large validation studies to show how digital slide diagnoses compare with those made from glass slides.

Other hurdles remain, also. "Digital pathology in the clinical arena is still in its infancy," Parwani says.

For example, different WSI scanners use different image formats, making transfers between systems difficult. Parwani says the field should choose a standard format like the DICOM standard used for digital radiology images. And, he says, his generation of pathologists remains reluctant to adopt a technology that was not

ANIL PARWANI, MD, PHD, MBA,
director of Digital Pathology at the OSUCCC – James

"In reality, the technology is very good now, the images move seamlessly and viewing them is much like viewing an image on your iPhone."



Digital Pathology Director Anil Parwani, MD, PhD, MBA, examines a digitized tissue section in a digital cockpit at The James. The screen at left displays the gross tumor; the center screen displays the digitized tumor section; the screen at right displays the patient's medical record.

mature when they first tested it nearly 20 years ago. They are wary of the time and cost required to convert to digital pathology and scan thousands of old slides.

"In reality, the technology is very good now, the images move seamlessly and viewing them is much like viewing an image on your iPhone," he says. Parwani recalls a senior pathologist at another center who thought that digital pathology would slow her down, but he persuaded her to give the technology another try. "She fell in love with it. She was consulting on difficult cases from China, and she got really excited. It extended her spectrum of things that she might not have otherwise seen."

Since his recruitment from the University of Pittsburgh in 2016, Parwani has created that same excitement at the OSUCCC – James. "We brought in Anil as someone already experienced who could lead the OSUCCC – James into this vital space," says Wendy Frankel, MD, professor and chair of Pathology at The Ohio State University Wexner Medical Center.

Parwani highlights three major advantages in adopting digital pathology. First is efficient information management. He estimates that pathologists spend 10-15 percent of their time manually managing cases, matching paperwork to patient slides or finding prior samples from a patient and ordering those slides from storage.

"Once a slide is digitized, the image has a barcode that stores all of the patient's information, and it will be integrated into our information systems," he says. "This puts all the material associated with a particular patient at my fingertips."

This idea has been referred to as the "digital pathology cockpit," with a patient's electronic medical record, including molecular data on biomarkers and gene sequencing, attached to the digitized slides. Ease of image sharing is another advantage to digital pathology. Pathologists have long sent photomicrographs to colleagues, but they provide only a limited view of a sample. Entire digital slides, on the other hand, can be easily emailed to colleagues anywhere.

Freeing the image from a physical slide also means that multiple

"At Ohio State, we're creating a Digital Pathology Center that at its core will create an end-to-end digital pathology solution for primary diagnosis, research, education, consultations and all aspects of pathology."

—Anil Parwani, MD, PhD, MBA

people can simultaneously review an image for quality assurance checks, training students, quick consultations, tumor-board presentations and collaborating on research. "You are more likely to get a second opinion on something if it's easy to do," notes Parwani, who says it takes about a week to ship glass slides to colleagues in other states.

"As a comprehensive cancer center and an academic medical center, we can use digital pathology to bring our expertise to others in an efficient way," says Kris Kipp, MSN, RN, executive director, patient services and chief nursing officer at the OSUCCC – James.

He explains that it may one day allow smaller or more rural hospitals to submit images for second opinions or even primary diagnoses. It will also facilitate referrals from other parts of the region or the country. "We can't see patients here until we have their previous radiology images and pathology slides," says Kipp. "By digitizing slides, we'll receive that information more quickly and see patients sooner."

Finally, digitized slides allow remarkable analytical possibilities. Computer-assisted analysis could perform tedious cell counts and tumor measurements that are currently done by the pathologist.

Or, such analysis could quantitate an immunostained cancer marker such as HER2 for breast cancer more objectively than a pathologist.

"The computer can more quickly and efficiently quantitate rare events such as mitoses or positive nuclei that are larger than a particular size, or identify areas that are chaotic and disordered," says Parwani. "Digital pathology enables me to spend more time as a physician making diagnoses and frees me from counting cells, chasing paperwork and other tedious tasks."

Eventually, says Kipp, auto-diagnosing algorithms might be developed using sets of digitized slides of, say, hundreds of samples of a type of breast cancer. These algorithms could then be used to do a first-pass screening of patient slides to generate preliminary diagnoses, which would be confirmed by a pathologist.

The success of digital pathology ultimately depends on how well WSI scanners, image storage, image analysis tools and information systems are integrated. And, of course, on how well pathologists adopt these technologies. At Ohio State, their training begins with the Digital Pathology Innovation Center, which houses a training cockpit.

"We're creating a Digital Pathology Center that at its core will create an end-to-end digital pathology solution for primary diagnosis, research, education, consultations and all aspects of pathology," says Parwani. It's year one of a 10-year project, and OSUCCC – James pathologists are already sending slides with frozen sections and fine-needle aspirate samples to the Digital Pathology scanning center.

"Digital pathology is a very innovative way to go," Frankel says. "It has the potential to change how pathology is practiced in clinical care, teaching and research, and it can help us as an academic medical center with all three of those missions."

She points out that digitized slides are more easily annotated for diagnostic and research purposes, and more easily archived and accessed than glass slides. The images also can be merged with other patient and outcome data to guide prognosis and treatment.

"Digital pathology cannot replace pathologists," Frankel stresses, "but it can help us do our jobs better."

That includes improving the quality of patient care by providing more timely diagnoses, and it ultimately may improve how physicians assess a patient's prognosis and treatment, she says. "Digital pathology can promote precision cancer medicine by helping us make the right diagnosis for the right patient at the right time."

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

Breaking the *RAS* Ceiling

After more than 30 years of research, there is still no effective RAS *inhibitor, but OSUCCC – James researchers may help change that*

BY DARRELL E. WARD

In 2014, Ohio State cancer researchers were deep into a study investigating a question related to microRNAs in melanoma when they made an astonishing discovery. Analysis of their data revealed that an infamous oncogene called *NRAS* encodes five proteins, not just one as was thought.

ALBERT DE LA CHAPELLE, MD, PHD, *professor of Medicine and the Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research*

WILLIAM CARSON III, MD, *professor of Medicine*

"*RAS* oncogenes are of immense importance in many cancers," says principal investigator Albert de la Chapelle, MD, PhD, Distinguished University Professor in the Molecular Biology and Cancer Genetics Program at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). "Virtually thousands of labs are working on various aspects of *RAS*, so our findings could have important implications."

The three-member family of *RAS* genes—*KRAS, HRAS* and *NRAS*—has been notoriously difficult to understand and to target. After more than 30 years of research, there is still no effective *RAS* inhibitor, earning these proteins a reputation as "undruggable." Agents that are approved for *RAS*-mutant tumors target downstream molecules, but these inhibitors have been largely ineffective, especially as single agents.

"*RAS* mutations drive some of the most deadly types of cancer, and they do so by activating many signaling pathways that facilitate cancer-cell growth and progression," says William Carson III, MD, professor of Surgery and associate director for clinical research at the OSUCCC – James. "Targeting one downstream molecule isn't enough to block the action of this cancer-causing gene because cancer cells often develop alternate pathways and escape the block. Inhibiting *RAS* directly would be much more effective in halting cancers driven by these mutations."

In fact, nearly one-third of cancers contain a *RAS* mutation, but the gene that is mutated varies with cancer type. For example, *RAS* mutations are present in:

95 percent
of pancreatic cancers *(KRAS)*

45 percent
of colorectal cancers *(KRAS)*

35 percent
of lung cancers *(KRAS)*

15 percent
of AML *(NRAS)*

15 percent
of melanoma *(NRAS)*

10 percent
of bladder cancers *(HRAS)*

In some cases, *RAS* mutations make cells resistant to therapy, and their presence in tumor cells can influence treatment decisions. OSUCCC – James researchers are studying *NRAS* and *KRAS* in particular to better understand and treat these cancers.

In healthy cells, RAS proteins help regulate the transduction of signals triggered by hormones, cytokines and growth factors. All three proteins have GTPase activity and are involved in transmitting signals involved in cell growth, proliferation and migration. Normally, RAS proteins receive signals that cause them to switch between an active state (bound to guanine triphosphate, or GTP) and an inactive state (bound to guanine diphosphate, or GDP).

In cancer cells, mutated *RAS* is locked into its active state

and continuously promotes proliferation, survival and invasion.

"All three RAS proteins are widely expressed throughout the body, so it is unclear why certain *RAS* genes are preferentially mutated in each cancer type," says OSUCCC – James researcher Christin E. Burd, PhD, assistant professor of Molecular Genetics and of Cancer Biology and Genetics at Ohio State. "Certain lung-cancer-associated *KRAS* mutations have been attributed to the carcinogens in cigarette smoke, but the origins of other mutations are completely unknown."

RAS was one of the earliest oncogenes to be discovered, and its family closet bulges with oddities and surprises. For example:

- The three genes are located on three different chromosomes;
- All three RAS proteins share over 80 percent of their amino acid sequence;
- Mutations in all three genes occur predominantly in only three positions in the protein: codons 12, 13 and 61.

ANOTHER *RAS* SURPRISE

The research that led to the discovery of the four new *NRAS* isomers began with a study led by de la Chapelle, Carson, Ann-Kathrin Eisfeld, MD, who is part of Ohio State's Medical Scientist Training Program, and OSUCCC – James researcher Clara D. Bloomfield, MD, a Distinguished University Professor at Ohio State who also serves as cancer scholar and senior adviser to the OSUCCC – James.

"We discovered the four *NRAS* isoforms 'by accident' when looking at the impact of *NRAS* mutations and differential *NRAS* expression in AML patients," Eisfeld says. "We were surprised that the existence of four isoforms of *NRAS* had gone unnoticed by researchers for 30 years, even though the *RAS* genes are so central to oncogenic signaling and so intensely studied worldwide."

They reported the 2014 findings in the journal *Proceedings of the National Academy of Sciences*. The researchers found that the *NRAS* gene can produce five naturally occurring NRAS proteins, not just the one known protein, now called isoform 1. Isoforms 2 to 5 are produced through alternative splicing of the *NRAS* messenger RNA (see box, Alternative Splicing, pg. 28).

CLARA D. BLOOMFIELD, MD, *Distinguished University Professor, cancer scholar and senior adviser to the OSUCCC – James, and William Greenville Pace III Endowed Chair in Cancer Research*

The five NRAS proteins differ in size, in expression levels in different human malignancies and in their intracellular location and effects (see box, Characteristics of the Five *NRAS* Splice-Variant Proteins).

Notably, isoform 5 consists of just 20 amino acids and triggers highly aggressive behavior in melanoma cells. The researchers published its structure in the

Characteristics of the Five *NRAS* Splice-Variant Proteins

***NRAS* isoform**	**Protein length** (number of amino acids)	**mRNA components**	**Cellular location**
1: The previously known NRAS protein with four component exons, 2-5	**189**		Cytoplasm
2: Contains a previously unknown exon, 3b (red)	**208**		Cytoplasm
3: Exon 2 and a little of exon 4	**40**		Nucleus
4: Exons 2 and 5 only	**76**		Cytoplasm
5: Part of exon 2 and a little of exon 5	**20**		Nucleus

journal *Protein Science*. "We are hopeful that our discovery will go beyond being a surprising biological observation and have implications for overcoming the 'undruggable' attribute of *NRAS*," Eisfeld adds.

The researchers' efforts to elucidate the functions of each isoform are also yielding insights into isoform 2.

Megan Duggan, PhD, a graduate fellow in Carson's lab, examined *BRAF*-mutated melanoma cells exposed to vemurafenib, a drug approved for the treatment of *BRAF*-mutated melanoma.

"Patients using the drug have fantastic responses, but then a few weeks later the disease returns in full," Duggan says.

She found that after exposing *BRAF*-mutant melanoma cells to the drug, expression of isoform 2 shoots up, when formerly it had been undetectable. "We hypothesize that this is an escape mechanism for the cells, and it may explain why the disease recurs after a great response to the anti-*BRAF* agent.

"When we knocked down isoform 2 in a mouse model, the animals became responsive again to vemurafenib. These results in the animal model were very encouraging," she says.

KATHRIN-ANN EISFELD, MD, *of Ohio State's Medical Scientist Training Program*

MEGAN DUGGAN, PHD, *OSUCCC – James graduate fellow*

UNLOCKING *RAS* MUTATIONS

Christin Burd wants to learn why particular *RAS* mutants are common in some cancers and not others. For example, why *NRAS* is by far the most frequently mutated *RAS* gene in melanoma, and why these mutations seem to always appear in location 61. This is contrary to other cancer types like acute myeloid leukemia, where *NRAS* is also selectively mutated, but typically at codon 12 or 13.

"There appears to be evolutionary selection for particular *RAS* mutations in each cancer type," Burd says. "The question is, can we better understand why these specific mutations evolve in each tumor type such that drugs can be made to target only their cancer-inducing functions?"

To begin her work, she is focusing on melanoma, a cancer type for which more than 10 new therapeutic regimens have been FDA-approved since 2011. Unfortunately, not one of these drugs directly targets mutant *NRAS*, the second most common genetic alteration in melanoma, after *BRAF* mutations, Burd explains.

"We have drugs that directly target *BRAF*-mutant tumors, but for melanoma patients with an *NRAS*-mutant tumor, therapeutic options are limited.

"A person can do most everything right and still be diagnosed with highly metastatic disease," she says. "We know that sunlight contributes to melanoma, but we don't know the fundamental cause of the disease, which makes it very hard to prevent."

The idea that evolutionary selection might be the key to identifying the Achilles' heel of *NRAS*-melanoma began with another surprising Ohio State observation. Burd and her colleagues designed a mouse model in which they can switch on an *NRAS* gene mutation in just the melanocytes of mice. They generated one mouse model containing an inducible *NRAS* mutation at codon 12 and another with a mutation at codon 61.

"We were shocked to learn that, of the mice with an inducible codon-12 *NRAS* mutation, none developed melanoma, but when we activated the codon 61 mutation, 80 percent of the mice spontaneously developed tumors," Burd says.

This experiment, published in the journal *Cancer Discovery,* was the first to suggest that the cancer-causing potential of *NRAS* codons 12, 13 and 61 mutants were different, and it led to an "Aha!" moment for Burd, who reasoned that the findings might offer a way to discover vulnerabilities specific to each *NRAS*-mutant cancer type. She hypothesized that forcing an *NRAS* codon-61 mutant, which causes melanoma, to behave like a codon 12 mutant, which doesn't cause melanoma, could prevent cancer formation or shut down

tumor growth.

"This approach was drastically different from ongoing tactics in the field," she says. While others aimed to completely shut down mutant *NRAS* activity, Burd hypothesized that inhibiting only a small subset of *NRAS* functions would be sufficient to stop melanoma in its tracks.

"The idea of targeting mutation-specific pathways to stop cancer growth is completely new," Burd says. "Furthermore, we believe that the critical *NRAS*-driven pathways in melanoma may be different from those in AML. Thus, the drug for a patient with *NRAS*-mutant melanoma may be completely different than that needed to treat *NRAS*-mutant AML."

To identify these critical pathways, Burd proposed her novel idea to the Damon Runyon Cancer Research Foundation and was selected as the first ever Ohioan to receive the foundation's prestigious Innovator Award. Using these funds, she is developing nine mouse models containing distinct, inducible *NRAS* mutations localized to codons 12, 13 and 61. She and her team will then examine and compare the properties of these mutants, determining why each can or cannot drive melanoma.

Furthermore, because these mutations can be activated in any tissue, she plans to share these mice with colleagues around the world aiming to understand the role of *RAS* in other tumor types.

"It's incredibly exciting to have so many possibilities. These models will help us better understand *RAS* as a cancer driver not only in melanoma, but in the brain, the bone marrow, the colon and many other tissues," Burd says. "*RAS* is such a big problem that we can't expect to tackle it on our own, and I am extremely hopeful for what will come from sharing these models with the scientific community. After all, our ultimate goal is not just to end melanoma, but to provide answers for all *RAS*-mutant cancer types."

RADIATION RESISTANCE

Terence M. Williams, MD, PhD, associate professor of Radiation Oncology, and his laboratory team are working to understand how mutations in *KRAS* cause resistance to radiation and other DNA-damaging agents.

About half of patients with cancer undergo radiation therapy during treatment, and about 95 percent of pancreatic cancer patients, 45 percent of colorectal cancer patients and 25 percent of lung cancer patients have an active *KRAS* mutation.

"Evidence from laboratory studies and emerging data in humans suggest that *KRAS* mutations foster radioresistance in these tumors, but the mechanism is not well understood," Williams says. "Our work suggests that it happens because *KRAS* mutations heighten the repair of DNA double-strand breaks by a mechanism called non-homologous end-joining."

The researchers presented their initial findings at the 2016 American Society for Radiation Oncology meeting. More specifically, their work implicates a well-characterized protein involved in double-strand break DNA repair in *KRAS*-mutant cells called 53BP1.

"Cells hit with radiation sustain DNA damage and then go into cell-cycle arrest," Williams explains. "During that period, DNA repair occurs, and mutated *KRAS* seems to hijack the 53BP1 pathway to accelerate that process. After proper repair, tumor cells can resume cell division and growth, enabling them to survive therapy."

CHRISTIN E. BURD, PHD,
assistant professor of Molecular Genetics

TERENCE M. WILLIAMS, MD, PHD,
associate professor of Radiation Oncology

KRAS mutations also activate the MEK kinase signaling pathway to facilitate DNA repair, Williams says. "Inhibiting MEK kinase has been shown to help make radiation work effectively, especially in *KRAS*- mutated cancer cells."

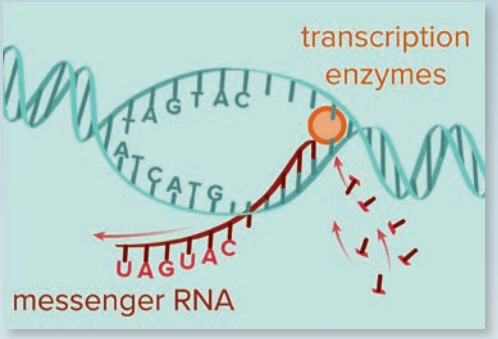
Overall, their findings suggest how *KRAS*-mutated cells rescue themselves from radiation-induced DNA damage and provide insight into potential pathways to target downstream of *KRAS*.

WHY NOT TARGET *KRAS* ITSELF?

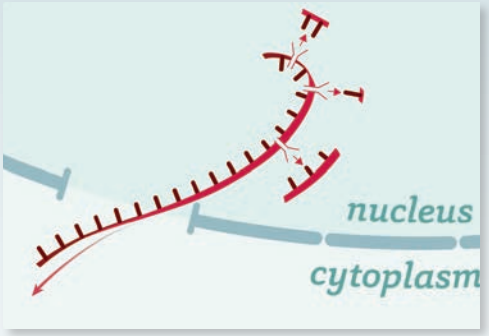
The KRAS protein is so difficult to target because of its small size and because the mutant form

ALTERNATIVE SPLICING

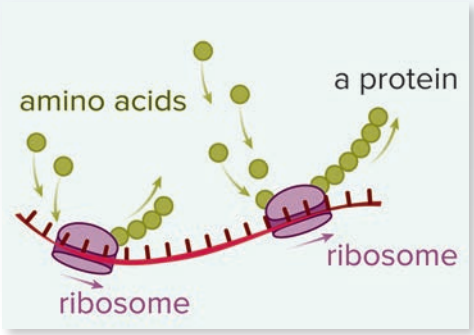
Alternative splicing enables a single gene to code for multiple proteins. It refers to a regulated process that happens in the cell nucleus during protein synthesis.



During protein synthesis, the information in a gene is transcribed to produce messenger RNA (mRNA).



Next, the mRNA is edited. Certain gene sequences are removed, and the remaining sequences are spliced together.



The mature mRNA then enters the cell cytoplasm, where it is read by ribosomes, and the information is translated into a chain of amino acids that becomes a protein molecule.

During alternative (or differential) splicing, different mRNA sequences are removed and spliced together during the editing step. The translation of that mRNA results in different proteins. For example, if a gene were to code for a protein called SMASH, alternative splicing might produce variant proteins (isomers) called MASH, ASH, AS and SASH, each of which could have different properties or cell functions.

Illustrations by Anthony Baker

binds so strongly to GTP, Williams says. "No one has succeeded yet in finding a molecule that kicks the GTP out of the binding pocket, which would likely make an effective inhibitor."

The preclinical data from Williams' lab suggesting that MEK inhibition would block the DNA pathways that sustain *KRAS*-mutant cancers after radiation helped lead to a phase I clinical trial (ClinicalTrials.gov NCT01740648) evaluating the combination of pre-operative 5-fluorouracil (5-FU), radiation and the MEK inhibitor trametinib in patients with locally advanced rectal cancer.

"That trial is nearly done, and then we will apply to continue the trial in a larger multi-institutional phase II trial," he says. "Our results so far show that the combination is safe and tolerable, and that there are initial signs of activity."

WILL *RAS* REMAIN UNDRUGGABLE?

"All these areas of *RAS* research are building upon one another," Burd says. "And that, along with new data emerging in the field, is changing how we think about targeting *RAS*. From understanding how expression of the newly discovered isoforms changes during therapy, to defining cancer-specific dependencies and testing drugs to overcome *RAS*-induced radiation resistance, investigators at the OSUCCC – James are helping to move the field forward.

"It will take creativity, hard work and collaboration," Burd adds, "but I am confident that the field will ultimately devise novel strategies that target these proteins and improve outcomes for patients with *RAS*-mutant tumors."

BENCH TO BEDSIDE

From the Laboratory to the Pharmacy

A Phase I/II Study of the PD-1 Antibody Nivolumab in Combination With Lenalidomide in Relapsed/Refractory Non-Hodgkin Lymphoma and Hodgkin Disease

HYPOTHESIS: The combination of nivolumab and lenalidomide will be safe, tolerable and effective in patients with B-cell non-Hodgkin lymphoma (NHL) or with Hodgkin disease (HD), regardless of their prognostic marker profile. Patient responses to the combination are expected to be better than responses to the agents when used alone.

STUDY DESIGN: This phase I/II, open-label, single-institution study will determine the safety, tolerability and maximum tolerated dose or the recommended phase II dose of lenalidomide combined with nivolumab in patients with relapsed/refractory NHL, with an expansion cohort in HD and a phase II study in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and relapsed/refractory follicular lymphoma (FL). Along with assessing response, it will help determine whether a particular NHL histology results in greater benefit from the combined agents.

RATIONALE: This trial will help meet the need for therapies that are effective and have minimal toxicity in subsets of patients with NHL and HD.

NHL is often curable with front-line therapy, but 30-40 percent of DLBCL patients relapse. The only curative option is high-dose therapy (HDT) followed by autologous stem cell transplant (ASCT). For patients who are not candidates for HDT/ASCT due to age or comorbidities, salvage regimens provide short responses and unacceptable toxicity.

FL is the most common indolent NHL. Some patients require no therapy for several years and achieve long remissions with treatment; others require immediate therapy, relapse quickly or are refractory to treatment and experience shortened survival. About 30 percent of FL patients transform to aggressive disease and require intensive therapy. FL is usually considered incurable, although outcomes have significantly improved with the use of rituximab and other monoclonal anti-CD20 antibodies.

HD shows five-year progression-free survival (PFS) rates of 61-89 percent after front-line therapy, but patients with poor prognostic factors relapse or have refractory disease. As in NHL, relapsed patients are treated with HDT/ASCT, and about 50 percent have prolonged PFS.

Lenalidomide is an immune modulator that shows clinical activity in both aggressive and indolent relapsed/refractory NHL and in relapsed/refractory HD. It is well tolerated with minimal toxicity, primarily myelosuppression and rash.

Nivolumab is a PD-1 inhibitor that is approved in relapsed/refractory HD and has shown early signs of efficacy in other hematologic malignancies. The most frequent adverse events include fatigue, rash, diarrhea, decreased appetite, nausea and pruritis.

Preclinical evidence suggests that nivolumab in combination with lenalidomide might improve response rates, depth of remission, and duration of responses in patients with relapsed/refractory NHL and HD.

AT A GLANCE

Trial no.: ClinicalTrial gov identifier: **OSU-16167** **NCT03015896**

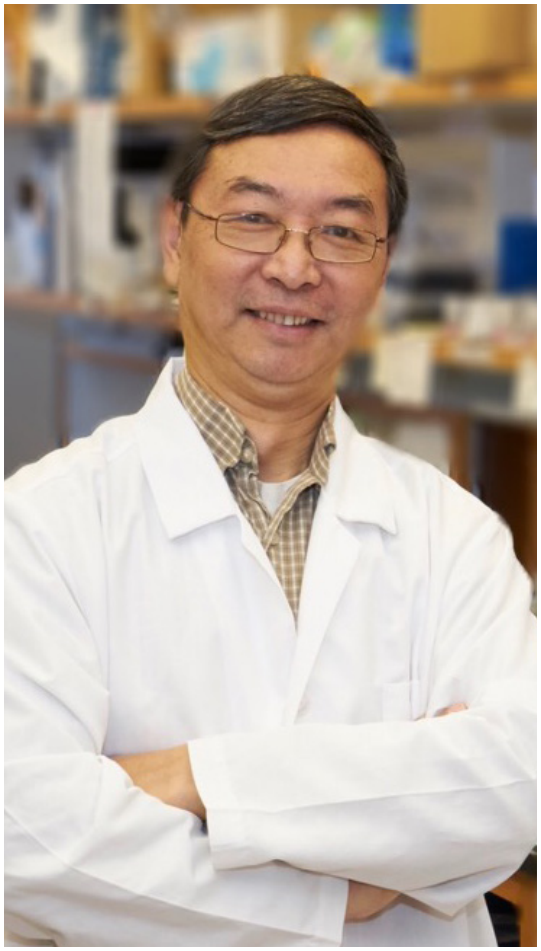
PI: KAMI MADDOCKS, MD
Phone: 614-293-3196
Email: *Kami.Maddocks@osumc.edu*

Eligibility: Histologically confirmed B-cell NHL (DLBCL, FL, MCL, MZL, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia); Burkitt lymphoma transformed to DLBCL; confirmed classical or lymphocyte predominant HD that is relapsed or refractory after at least one prior chemotherapy; has had at least one prior therapy, including prior ASCT; 18 years of age or older, and must be willing and able to provide written informed consent/assent.

Solid Tumor Translational Science Shared Resource

The Solid Tumor Translational Science Shared Resource (STTSSR) assists OSUCCC – James clinical investigators in designing and managing correlative studies for the identification or validation of biomarkers as part of phase I and II trials.

STTSSR experts provide both assay development and data analysis, and they work with the OSUCCC – James Clinical Trials Processing Laboratory Shared Resource to provide seamless coordination of assays during clinical trials.



In addition, the STTSSR:

- Serves as a central laboratory for the acquisition and processing of clinical-trial specimens, a particularly valuable service for clinician investigators who want to perform correlative studies but lack laboratory space;
- Helps develop strategic partnerships between OSUCCC – James investigators and pharmaceutical and biomedical companies that are conducting clinical trials at Ohio State that require correlative laboratory studies;
- Works closely with the OSU Pathology Core Facility to ensure that assays required for patient selection and stratification, to determine treatment, are performed under Clinical Laboratory Improvement Amendments (CLIA) standards.

A liquid-biopsy assay developed by the STTSSR for a recent OSUCCC – James clinical trial (OSU-12064) offers an example of the translational research services provided by the STTSSR. The randomized phase II trial involved patients with advanced or metastatic iodine-refractory thyroid cancer with mutated *BRAF* or *BRAF* gene fusion.

The STTSSR designed a correlative study for this trial that used a liquid-biopsy technique to evaluate whether levels of *BRAF* mutations in circulating tumor-cell DNA from patient samples collected at baseline and throughout treatment could predict response to treatment and tumor progression.

The STTSSR plans to use this liquid-biopsy capability in future translational research studies. Other laboratory services provided by the STTSSR include:

- Purifying circulating miRNA from plasma, urine and saliva;
- Purifying RNA, miRNA and protein from cells, blood or fresh frozen samples;
- Custom-designed targeted sequencing panels;
- Allele-specific PCR;
- Identifying signaling pathways using immunohistochemistry and immunoflourescence;
- Luminex multiplex protein assays.

For more information about the STTSSR, visit https://cancer.osu.edu/research-and-education/shared-resources/solid-tumor-translational-science.

XIANGLOU (TOM) LIU, PHD,
senior research associate with the Solid Tumor Translational Research Shared Resource.

Meeting Special Needs

Despite advances in early detection, treatment and prevention, cancer is the No. 1 disease killer of adolescents and young adults (AYAs), people aged 15-39. An estimated 72,000 AYAs are diagnosed with cancer annually, and about 10,000 of them die of these diseases each year.

AYA survival has not improved at the same rates as it has for other age groups. The reasons include unique tumor biology, less access to clinical care, inadequate insurance coverage, feelings of invincibility, delayed or missed clinical diagnoses and lack of awareness that cancer is a leading cause of death for the age group.

Also, cancers in AYAs may be biologically different than the same cancers in children and older adults, and a lack of research and low clinical-trial participation make it difficult to identify suitable treatments. Finally, once treatment is completed, AYA survivors can find it difficult to make friends, to date, to get careers and finances back on track and to have children.

The OSUCCC – James survivorship program works in partnership with specialists at Nationwide Children's Hospital in Columbus to meet the diverse needs of this unique patient population.

"These young patients are our future, and we are working to help them live longer and better lives after diagnosis, and we do so through dedicated treatment and research programs," says Maryam Lustberg, MD, MPH, medical director for survivorship at the OSUCCC – James.

"We strive to address the unique needs of the AYA population," Lustberg adds. "As we further expand our program, we hope to provide additional AYA-specific services to address social, psychologic, fertility, and family and return-to-work issues throughout the cancer continuum."

Optimizing reproductive potential is an important goal of the program, says oncofertility specialist Leslie Appiah, MD, associate professor clinical of Obstetrics and Gynecology at The Ohio State University Wexner Medical Center.

"We see both male and female patients at diagnosis to discuss the risk their treatment regimen poses to their fertility," says Appiah. For fertility concerns, the program follows female AYA survivors through age 45 and male survivors through age 50; otherwise, the AYA program follows survivors through age 39.

Appiah provides care for female patients; Lawrence Jenkins, MD, clinical assistant professor of Urology and a specialist in male reproductive health, cares for male patients.

Appiah and Jenkins collaborate with local reproductive endocrinology and infertility providers to offer pretreatment assisted reproductive technologies that include egg and embryo freezing and sperm banking. "When pretreatment measures are not an option," Appiah says, "we discuss fertility-preservation choices that can be implemented after treatment. Equally important, we provide reassurance for those patients who are not at risk of infertility after treatment."

Contraception is also important. "Contraception is a widely under-appreciated aspect of oncofertility," Appiah says. "We want to be sure that AYA patients use contraceptives appropriately and understand the implications of an unplanned pregnancy either during or after treatment."

The program also addresses late effects of cancer treatment that affect quality of life, such as ovarian or testicular failure and radiation injury to the reproductive organs. In women, these changes can lead to hot flashes and an inability to engage in sexual activity; in men, they can cause fatigue and sexual dysfunction, and reduce endurance. In both women and men, they can reduce bone-mineral density, leading to osteoporosis.

The goal of the program, Lustberg and Appiah add, "is to reach these young people before they begin treatment and help them maximize their quality of life as cancer survivors."

From left:

LESLIE APPIAH, MD, *associate professor clinical of Obstetrics and Gynecology*

LAWRENCE JENKINS, MD, *clinical assistant professor of Urology and a specialist in male reproductive health*

MARYAM LUSTBERG, MD, MPH, *medical director for survivorship*

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PELOTONIA FUNDING ALLOCATIONS WILL SUPPORT STUDENT & FACULTY CANCER RESEARCH

New allocations of funding from Pelotonia, an annual grassroots bicycle tour that raises money for cancer research at Ohio State, will support eight projects by teams of OSUCCC – James scientists and 42 projects by Ohio State students working in the labs of faculty mentors.

The faculty-team projects will be funded by the OSUCCC James' Intramural Research Program (IRP), which receives extensive Pelotonia support. IRP funding, which includes Idea Grants and other awards, goes to teams of scientists who competitively propose groundbreaking studies that will generate data to help them compete later for larger grants from external sources such as the National Cancer Institute.

The newest IRP projects, collectively funded at $1.14 million, range from evaluating targeted therapies for thyroid cancer and immunotherapy treatment approaches in breast cancer, acute myeloid leukemia and brain tumors, to laboratory research aimed at understanding cancer stem cell differentiation in ovarian cancer. Over the past seven years, 108 OSUCCC – James research teams have received Pelotonia-supported IRP awards totaling $11.1 million. Each award provides research support for two years.

The Pelotonia Fellowship Review Committee at the OSUCCC – James recently awarded 42 fellowships totaling $2 million to students from multiple disciplines and at various levels of scholarship, including 26 undergraduates, 14 graduates and two postdoctoral fellows.

The undergraduates will receive funding for one year; graduates and postdoctoral fellows will receive funding for two years. Since the fellowship program began, it has allocated $13 million for 436 awards to 205 undergraduates, 128 graduates, 97 postdoctoral researchers and six medical students.

INSIDE THE NEXT FRONTIERS

The OSUCCC's New Leader

Raphael Pollock, MD, PhD, a globally respected cancer surgeon, researcher and educator, is the new director of The Ohio State University Comprehensive Cancer Center (OSUCCC). Pollock was recruited to Ohio State in 2013 from MD Anderson Cancer Center, where he had worked for 31 years and held several leadership positions. A story in the next *Frontiers* will introduce Pollock and relate his vision for propelling Ohio State's cancer program forward.