





From the director

Four decades ago, when I came to Indianapolis from Chicago for an elective during my fourth year of medical school, I witnessed a miracle of medical science. A then-young assistant professor named Larry Einhorn had conceived a combination of drugs that melted away metastatic testicular cancer, which was the biggest cause of cancer deaths for young men. Larry worked with Drs. John Donohue and Ken Kesler to change the paradigm of oncology by making what seemed impossible possible.

Stephen Williams, a fellow at that time, would later do the same for ovarian germ cell tumors. He would become the founding director of the center and lead it to earning in 1999 a National Cancer Institute designation—a designation that recognized the center's outstanding research.

Twenty years later, in August 2019, we paused to celebrate another milestone: the center earned the NCI's prestigious Comprehensive Cancer Center designation for our excellence in basic, clinical, and population research, outstanding educational activities and effective community outreach across the state (see pages 2 – 3).

science in all they do.

play our part.



Patrick J. Loehrer Sr., MD Distinguished Professor Indiana University School of Medicine



Patrick J. Loehrer Sr., MD Director

Mission

To create an expanding community of researchers and health professionals who conduct outstanding translational research, provide excellence in education and deliver high quality patientcentered care.





David Boothman, PhD Associate Director of Translational Research



Mark Kelley, PhD Associate Director of Basic Science Research



Kathy Miller, MD Associate Director of Clinical Research



Michael Darling, MH

Harikrishna Nakshatri

Associate Director of Education

BVSC, PhD

Associate Direct of Data Science



Associate Director o Clinical Affairs







Richard Zellars, MD









The comprehensive designation places us in the company of only 51 other cancer centers nationwide, including the University of Texas MD Anderson Cancer Center, Dana-Farber/ Harvard Cancer Center and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. No other cancer center in the Midwest has earned this top designation for more than a decade, which is a testament to the women and men of the center who exemplify team

Perhaps no greater exemplar is Dr. David Boothman (at left), the center's first associate director of translational research, who passed away in November 2019. Dave was a tireless researcher, and he played an instrumental role in the center achieving the NCI's comprehensive status. He made a difference in his work, in the lives of many students and post-docs he taught and in the field of cancer therapeutics. He is deeply missed.

Our nation and world have long faced this enemy known as cancer. Today, we're facing many unknowns about a new virus, called SARS-CoV-2, and its disease in humans, COVID-19. The translational and clinical trials infrastructures of cancer centers are uniquely positioned to facilitate work in this area. The NCI sought ideas related to the intersection of COVID-19 and cancer. With a few days' notice to submit brief proposals, our faculty responded with more than a dozen thoughtful ideas, ranging from palliative care to biomarker discovery to therapeutic trials. The medical, sociological and financial effects of the pandemic on our medical system and society will be felt for years to come. We need to

As you flip through the following pages, you will read stories that illustrate the impact of our research and community outreach that led our center to achieve comprehensive status. More importantly, I hope that you will feel the energy of our center members in their complete dedication to eliminate the burden of cancer in Indiana and beyond.

Associate Dean for Cancer Research Director, Indiana University Melvin and Bren Simon Comprehensive Cancer Center H.H. Gregg Professor of Oncology Professor of Medicine



Cancer center earns NCI's prestigious **Comprehensive Cancer Center designation**

By Michael Schug



designation.

This moves the cancer center into an elite class of only 51 centers across the nation to hold this comprehensive designation from the NCI, the country's top cancer agency. It is the only NCI-designated Comprehensive Cancer Center in Indiana. Douglas Lowy, MD, (inset at left) then-acting director of the NCI, made the announcement during an on-campus celebratory event in August 2019.

"Designated cancer centers are recognized for their state-of-the-art research programs and strong commitment to delivering cutting-edge cancer treatment for patients. They are at the core of the nation's cancer research effort," Lowy said.

For Indiana residents, the designation affirms that they have access to the most advanced, research-guided therapies, as well as hundreds of clinical studies that test the most promising new approaches to preventing, diagnosing and treating cancer.

"Indiana University has an outstanding history of advancing health care in the state of Indiana and around the world," IU President Michael A. McRobbie said. "This prestigious designation by the National Cancer Institute demonstrates that IU remains at the very leading edge of innovations in cancer care. As we celebrate the university's bicentennial and look to the future, we reaffirm our commitment to bring the most promising and innovative therapies to Indiana and to eliminate suffering caused by cancer."

Overall, the cancer center received an "outstanding" rating by NCI reviewers and was awarded a five-year, \$13.8 million grant that supports the center's four research programs and shared facilities (see pages 14 – 15 for a listing of shared facilities). That grant is an increase of 43 percent from the previous five-year funding period.

> The center's researchers—which number nearly 250 and represent the IU schools of medicine, nursing, public health and others—conduct all phases of cancer research, from laboratory studies to clinical trials to population-based studies that address environmental and behavioral factors that contribute to cancer.

In addition to recognizing the center's impressive research, reviewers cited the "very well-designed community outreach efforts to serve the needs" of the state of Indiana. This includes initiatives to increase HPV vaccination rates, as well as developing, testing and disseminating interventions to increase screenings for breast, cervical and colorectal cancer in racially diverse and rural populations in Indiana.

The center, part of IU School of Medicine, serves as a central hub of cancer education and research across Indiana University. The center's physicians train the next generation of cancer experts. As educators, they teach nearly 2,000 students, residents and medical fellows each year. The center's educational opportunities range from those geared toward teenagers exploring career choices to supporting the ongoing work of tenured faculty.

Best known for developing the cure for testicular cancer, the center's researchers also have led treatment advances for breast cancer, gastrointestinal cancer, genitourinary cancer, hematologic disorders, thoracic cancer, and thymoma and thymic carcinoma.

I Excellence in basic, clinical and population research, an effective community outreach program across the state and outstanding educational activities earned the cancer center the National Cancer Institute's prestigious Comprehensive Cancer Center

"We take our goal to eliminate cancer's burden in Indiana and beyond seriously," Patrick J. Loehrer, MD, director of the IU Simon Comprehensive Cancer Center, said. "Our research focuses upon decreasing the number of Hoosiers who develop and die from the cancers that strike our citizens. This grant bolsters support for us to uncover the biologic mysteries of cancer and define new therapies for patients here and around the globe."



Reducing Indiana's cancer burden through community outreach and engagement

By Candace Gwaltney



that list.

With high obesity and smoking rates and low physical activity, Indiana falls into the 10 least-healthy states, according to America's Health Rankings. These behaviors put Hoosiers at significant risk for both developing and dying from cancer.

Enter the cancer center's Office of Community Outreach and Engagement.

The COE's marching orders are clear: reduce preventable cancers by addressing risk factors and increasing preventative measures such as screenings and vaccinations.

Although the cancer center has engaged in such activities for many years-and its past successes played a role in the cancer center earning comprehensive status from the National Cancer Institute (see pages 2 – 3)—its efforts are growing. In fact, the NCI has charged all comprehensive cancer centers to address cancer health disparities, conduct research relevant to its local community and engage that population in its research findings.

"The ultimate purpose is to eliminate cancer mortality and morbidity," Victoria Champion, PhD, RN, associate director of community outreach and engagement and population science for the cancer center, said.

> Helping to guide the COE's initiatives is the Health Disparities Advisory Committee, chaired by Virginia Caine, MD, director of the Marion County Public Health Department. The committee brings together partner organizations, cancer survivors, patient advocates and community members to provide feedback on COE efforts.

Tobacco cessation efforts The COE is prioritizing tobacco cessation efforts to move the needle in incidences of lung cancer, the No. 1 cause of cancer-related deaths among both men and women in Indiana. Leaders are completing a statewide assessment of current tobacco cessation efforts to help develop a coalition that will set a strategy for addressing tobacco use.

In 2019, Indiana became the 12th state to allow pharmacists to prescribe tobacco cessation products, giving individuals easier access to assistance. Research by Karen Hudmon, DrPH, was vital to the statewide policy. The COE now plans to provide education and support for implementing these pharmacist-led interventions.

Screening for colorectal cancers Increasing colorectal cancer screening is a focus area as well since only 65 percent of ageeligible Hoosiers undergo this life-saving screening. That number is even lower in rural Indiana counties. In partnership with the Indiana Rural Health Association (IRHA), the cancer center is implementing evidence-based colorectal cancer interventions in rural clinics.

Increasing HPV vaccination rates Gregory Zimet, PhD, is examining HPV vaccination rates in Indiana to identify barriers to HPV vaccination in low administration areas and understand successes in counties where rates are higher. Researchers have interviewed nearly 100 vaccine coordinators and clinicians in 64 Indiana counties.

From basic science to evidence-based outreach, the cancer center's researchers are working to better the health of Hoosiers.

There are countless sources for Indiana pride—famed Hoosier hospitality and storied sports traditions—to name a few. The state's overall health unfortunately never lands on





Researchers predict which triple-negative breast cancer patients will likely stay cancer free and who will relapse

By IU School of Medicine



Bryan Schneider, MD, and Milan Radovich, PhD, (at left) discovered that women whose plasma contained genetic material from a tumor-referred to as circulating tumor DNAhad only a 56 percent chance of being cancer-free two years following chemotherapy and surgery. Patients who did not have circulating tumor DNA (ctDNA) in their plasma had an 81 percent chance that the cancer would not return after the same amount of time.

Triple-negative breast cancer is one of the most aggressive and deadliest types of breast cancer because it lacks common traits used to diagnose and treat most other breast cancers. Developing cures for the disease is a priority of the IU Precision Health Initiative (PHI) Grand Challenge. Schneider and Radovich, researchers at the cancer center and the Vera Bradley Foundation Center for Breast Cancer Research, lead the PHI's triple-negative breast cancer team.

The study also examined the impact of circulating tumor cells (CTCs), which are live tumor cells that are released from tumors in the body and float in the blood.

The women were participants in BRE12-158, a clinical study that tested genomically directed therapy versus treatment of the physician's choice in patients with Stage I, II or III triple-negative breast cancer.

Detection of circulating tumor DNA was also associated with poor overall survival. Specifically, the study showed that patients with circulating tumor DNA were four times more likely to die from the disease when compared to those who tested negative for it.

The authors say the next step is a new clinical study expected to begin in summer 2020, which utilizes this discovery to enroll patients who are at high risk for recurrence and evaluates new treatment options for them.

"Just telling a patient they are at high risk for reoccurrence isn't overly helpful unless you can act on it," said Schneider, who is a senior author of this study and Vera Bradley Professor of Oncology at IU School of Medicine. "What's more important is the ability to act on that in a way to improve outcomes."

IU cancer researchers have discovered how to predict whether triple-negative breast cancer will recur and which women are likely to remain disease-free.

They presented their findings in December 2019 at the San Antonio Breast Cancer Symposium, the most influential gathering of breast cancer researchers and physicians in the world. The symposium's organizers selected the research for presentation from more than 2,000

"What we found is that if patients were negative for both ctDNA and CTC, 90 percent of the women with triple-negative breast cancer remained cancer-free after two years,"

The researchers, along with colleagues from the Hoosier Cancer Research Network, analyzed plasma samples taken from the blood of 142 women with triple-negative breast cancer who had undergone chemotherapy prior to surgery. Utilizing the FoundationOne Liquid test, circulating tumor DNA was identified in 90 of the women; 52 were negative.

This study was funded by the Vera Bradley Foundation for Breast Cancer and the Walther Cancer Foundation. It is part of the Indiana University Precision Health Initiative Grand Challenge. The study was managed by the Hoosier Cancer Research Network and enrolled at 22 clinical sites across the United States.



IU cancer researcher, collaborators earn \$4.1 million grant from Cancer Moonshot

By Eric Schoch

A team of researchers from Indiana University and Memorial Sloan Kettering Cancer Center are working together to develop immunotherapy treatments for cancers in children and adolescents, especially those with leukemia, after earning a \$4.1 million National Cancer Institute "Cancer Moonshot" grant. The research promises to achieve more effective, better targeted and less toxic therapies for pediatric cancers.

IU's Sophie Paczesny, MD, PhD, (*at left*) is collaborating with Nai-Kong Cheung, MD, PhD, of Memorial Sloan Kettering on this research.

Paczesny and her colleagues want to better understand how tumors and the tissues that surround them—called the tumor microenvironment—put up defenses to protect the tumor cells. The body routinely creates immune system cells called T cells that attack foreign invaders such as bacterial infections, but the tumor microenvironment creates barriers to thwart those "killer" T cells from attacking cancer cells.

Cancer researchers currently are working on treatments to counteract the molecules called checkpoint molecules—that prevent the immune system from attacking cancer cells. Deactivating those checkpoint molecules could enable the T cells to go to work on the cancer cells.

Paczesny and her team have identified a new checkpoint molecule, a protein called ST2. They have been working on ST2 for several years because it plays an important role in how the immune system reacts to bone marrow transplants used in cancer therapy. Now they plan to study how ST2 functions in the complicated sequence of chemical signals that creates tumor defense systems.

Early studies in mice have indicated that restricting ST2 activity resulted in reduced proliferation of acute myeloid leukemia cells. Further, in collaboration with Xiongbin Lu, PhD, also an IU cancer center researcher, the scientists have shown that blocking ST2 inhibits colorectal cancer growth, the third most commonly diagnosed tumor and the second leading cause of cancer death in the United States.

"If we can block the pathways used by these checkpoint molecules, such as ST2, we can enable the body to more effectively use its 'killer' T cells to attack the tumor cells," said Paczesny, who is also a scientist at the Herman B Wells Center for Pediatric Research.

Cheung and his team at Memorial Sloan Kettering in New York are working to develop promising antibodies to target and block these pathways, initially for testing in mice and then for human clinical trials. Cheung is a pediatric oncologist who has developed antibodies to treat neuroblastoma, a rare nerve-tissue cancer that often spreads to the brain and is most common in young children. The neuroblastoma antibody currently is used to treat pediatric patients at Riley Hospital for Children at IU Health.

Paczesny and Cheung are working together because the Cancer Moonshot grant application process encourages researchers from different cancer centers to collaborate to achieve various goals, including the creation of a network of pediatric immunotherapy experts.

The Cancer Moonshot's goal to accelerate cancer research aims to make more therapies available to more patients, while also improving the ability to prevent cancer and detect it at an early stage. Congress passed the 21st Century Cures Act in December 2016, authorizing \$1.8 billion in funding for the Cancer Moonshot over seven years.





Trio tackles leukemia

By Sara Buckallew

Cancer loves to grow. In fact, that's its deadliest trait. Cancer's will to survive is so fierce that it will morph and spread in the most poisonous terrain. When chemotherapy is used to treat patients with cancer, some cells alter their behavior to promote survival. This is called an adaptive response, and blood cancer is particularly good at it.

In pediatrics, the most common blood cancer is acute lymphoblastic leukemia (ALL), which accounts for about 75 percent of blood cancers in kids. One chemotherapy, called L-asparaginase, works for many ALL patients by diminishing an amino acid called asparagine, which ALL cells need to survive. But that doesn't work for everyone. Ji Zhang, PhD, (at center) wondered why.

In a recent study, his team demonstrated that a cell's response to the chemotherapy is dictated by expression of the ASNS gene, or asparagine synthetase. Genes are not active at all times—and in this case when the ASNS gene is unmethylated, or turned on, the gene produces more amino acid to combat the depletion caused by the chemotherapy, leading to tumor resistance.

Now, Zhang's team is working to identify the mechanisms that control the on or off status of the ASNS gene and target that gene in combination with chemotherapy to improve outcomes for people who are resistant to L-asparaginase chemotherapy.

Clearly, mutations play a big role in cellular activity and can even impact disease development. If a mutation is a doorway to disease, what twists and turns lurk in the hallways between the mutation and cancer? This has been a central question for Yan Liu, PhD, (at far left) as he worked to identify the mechanisms of a common age-related condition called clonal hematopoiesis of indeterminate potential, or CHIP. CHIP occurs when mutated blood stem cells replicate rapidly, flooding the blood stream.

"Many people with CHIP don't have any signs of disease, but they do have an increased risk of developing hematological malignancies, such as blood cancer," Liu said. "Our goal was to study the role of a specific mutated gene in the path from CHIP to blood cancer."

> That gene is called p53, and Liu said that many older adults with blood cancer possess p53 mutations. His team defined a number of mechanisms at work from mutant p53 on the path to blood cancer. One such mechanism is another gene called EZH2, which interacts with mutant p53 to promote cell division and growth of the mutated cells.

and leukemia.

Reuben Kapur, PhD, (at right) knows the value of target discovery. His lab has found new targets for treatment of the second most common type of pediatric blood cancer, acute myeloid leukemia (AML). And they might have a drug that can help.

Many AML patients do not respond well to established therapies. Kapur found that in some of these patients, treatment resistance is due to certain genetic mutations, including those that affect a protein called SHP2. It turns out that SHP2 is key to the growth of mutated cells. Kapur's lab partnered with Novartis Pharmaceuticals to target the protein and halt growth. Now, they're trying it on human tumors by growing models made from tumors from AML patients.

With these new discoveries and varied approaches, Zhang, Liu and Kapur have a common goal: halting leukemia in its tracks.



Liu said that his team is now working on preclinical studies to collect more data on the effectiveness of blocking EZH2 for potential therapies to treat people with both CHIP



Reducing stress and improving survivorship in children is music to a researcher's ears

By Candace Gwaltney



A music therapist strums her guitar and guides a distressed preschool-aged cancer patient in singing a familiar children's song. Slowly the child starts to open up, and the giggles that once were constant are shared again among the child, parent and therapist. The child isn't just engaging in a fun respite from treatment but is experiencing much-needed independence, choice and support.

"There's nothing inherently therapeutic or magical about singing—it's the way that the therapist is using the activities in that particular moment," cancer center researcher Sheri Robb, PhD, said.

A nationally renowned music therapy researcher, Robb is exploring how music and play interventions can reduce stress, improve survivorship and boost the immune system in children ages 3 – 8 during cancer treatments.

Awarded a \$2 million grant from the National Institutes of Health, Robb is examining the effects of active music and play interventions on multiple biomarkers to provide a more holistic understanding of how music therapy reduces cancer-related stress.

"The work that we're doing looks at the use of music play, which is an intervention that's delivered by a music therapist," Robb said. "It uses music and play as a way to address the distress that young children and their parents experience as they go through cancer treatment."

control," Robb said. "Supportive environments give that back to you."

The music play intervention is grounded in three elements: creating a structured environment, offering choice and control, and building supportive relationships.

In a music play session, the therapist may offer a menu of activities so the child can guide the therapy by choosing songs and who will play which instrument. Simultaneously, the therapist uses improvisational strategies to change what she's doing with the music to match how the child is leading. The therapist is also leveling the elements of choice based on the child's stress levels.

"One of the theoretical premises of why we think this therapy works is because we have the opportunity to bring something normalizing amid a not-normal-life experience to buffer the impact of cancer treatment for parents and kids," Robb said.

Robb's project is part of the exclusive group of first research projects of the NIH's Sound Health Initiative to advance the understanding of music's mechanism of action in the brain and how it may be applied more broadly to treat symptoms of diseases like cancer and disorders such as stroke and chronic pain.

"Sound Health is bringing together clinicians and scientific scholars from diverse fields, including music therapy, music perception and neuroscience to better understand uses of music for health," Robb (at *right*) said. "Over the past five years, we have seen sustained national attention on the importance of music for health. It will be exciting to see the scientific and clinical advances that will result from these initiatives."

With this grant, Robb and colleagues will measure cortisol (a stress hormone) from saliva samples in both the child and parent as a biomarker for stress. The study will also use patient blood tests to explore if music therapy can lower biological markers of stress enough to also improve the child's immune function. Because child and parent distress is interrelated, researchers are aiming to reduce stress levels in both the patient and caregivers.





Shared facilities

The IU Simon Comprehensive Cancer Center provides its members (researchers) with access to cutting-edge equipment, technology and services with 15 shared facilities. Each facility, staffed by experts, helps members make advances in cancer research.

Angio BioCore

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Biostatistics and Data Management Hao Liu, Director cancer.iu.edu/biostats

Cancer Bioinformatics Jun Wan, Director cancer.iu.edu/bioinformatics

Clinical Pharmacology Analytical Core Zeruesenay Desta, Scientific Director Andi Masters, Director cancer.iu.edu/cpac

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Susan G. Komen Tissue Bank at the IU Simon Cancer Center Anna Maria Storniolo, Executive Director Jill Henry, Chief Operating Officer komentissuebank.iu.edu

Tissue Procurement and Distribution Oscar Cummings, Director Mary Cox, Operations Manager cancer.iu.edu/tissue

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Photography: Tim Yates (p 2, 8 & 10), Office of Visual Media, IU School of Medicine Chris Bergin (p 6 & 12), IU Health Learning Solutions

On the cover: A three-dimensional digital illustration of the human genome



Research programs

The IU Simon Comprehensive Cancer Center is Indiana's only National Cancer Institute (NCI)-designated Comprehensive Cancer Center and one of only 51 in the nation. The prestigious NCI designation recognizes that its four research programs meet rigorous criteria for world-class, state-of-the-art programs in multidisciplinary cancer research that reaches all 92 counties in Indiana. The goals of those programs range from understanding the molecular changes that cause cancer to developing targeted therapies to prevent and treat cancer.



Cancer Prevention and Control (CPC) research program

The long-term goal of the Cancer Prevention and Control research program is to reduce the incidence, morbidity and mortality of cancer for the citizens of Indiana and beyond.

Susan Rawl, PhD

Professor of Adult Health, IU School of Nursing

Todd Skaar, PhD

Professor of Medicine, IU School of Medicine

Members

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Experimental and Developmental Therapeutics (EDT) research program

The mission of the Experimental and Developmental Therapeutics research program is to promote, develop and exploit mechanismbased research for improved therapy of human cancer.

David Boothman, PhD (deceased)

Sidney and Lois Eskenazi Professor of Hematology-Oncology Professor *IU School of Medicine* Associate Director of Translational Research *IU Simon Comprehensive Cancer Center*

Roberto Pili, MD

Robert Wallace Miller Professor of Oncology, Professor of Medicine, Professor of Urology, *IU School of Medicine* Co-leader, Comprehensive Indiana Genitourinary Cancers Research Consortium *IU Simon Comprehensive Cancer Center*

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Hematopoiesis and Hematologic Malignancies (HHM) research program

The goal of the Hematopoiesis and Hematologic Malignancies research program is to enhance treatment of hematologic malignancies—with a focus on leukemia, pre-leukemia and multiple myeloma—through rigorous basic mechanistic scientific laboratory efforts.

G. David Roodman, MD, PhD

Director, Division of Hematology/Oncology, Kenneth Wiseman Professor of Medicine Professor of Biochemistry & Molecular Biology *IU School of Medicine*

Hal E. Broxmeyer, PhD

IU Distinguished Professor, Mary Margaret Walther Professor Emeritus Professor of Microbiology/Immunology *IU School of Medicine*

Reuben Kapur, PhD

Frieda and Albrecht Kipp Professor of Pediatrics IU School of Medicine

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*accepted in 2019



Tumor Microenvironment and Metastasis (TMM) research program

The Tumor Microenvironment and Metastasis research program advances the basic understanding of the role of cancer cell-stroma interactions in cancer initiation, progression and metastasis and studies the mechanisms of the systemic consequences of metastatic disease, particularly on muscle and bone dysfunction as well as metabolism.

Theresa Guise, MD

Jerry and Peggy Throgmartin Professor of Oncology Professor of Medicine IU School of Medicine

Kenneth Nephew, PhD

Professor of Cellular and Integrative Physiology IU School of Medicine

Members

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