Indiana University Melvin and Bren Simon
Cancer Center Scientific Report 2011

Quest (noun)
an act or instance
of Seeking
a : PURSUIT, SEARCH—Merriam-Webster

We're on a quest to make a difference.

It's our people—scientists, physicians, healthcare professionals and staff—who individually make contributions but collectively make a difference in the course of a disease and in the personal lives of patients with cancer.

It's people such as **George Sledge, MD, (BC),** who wrapped up his presidency of the American Society of Clinical Oncology (ASCO) in 2011. In his farewell presidential address in June, he said we are on the brink of a new era in cancer therapy—an era of genome-based treatment. This new "genomic era" holds great promise for patients, but it poses a number of challenges for oncologists who face cancers with scores of mutations that require a new generation of oncologists poised to deal with what Dr. Sledge called "smart" cancers.

This new generation includes our very own Drs. Jamie Renbarger and Bryan Schneider among others. **Jamie Renbarger, MD, (EDT),** in pioneering research, is on a quest with a national team of researchers to find out why some children suffer debilitating side effects from vincristine (Oncovin), which is often a cure for many children. She and her colleagues are working on a new diagnostic tool that may help doctors predict who might be adversely affected by the drug. Because of this work, Dr. Renbarger was honored in September at a White House ceremony as a recipient of a Presidential Early Career Award for Scientists and Engineers. *(See page 14.)*

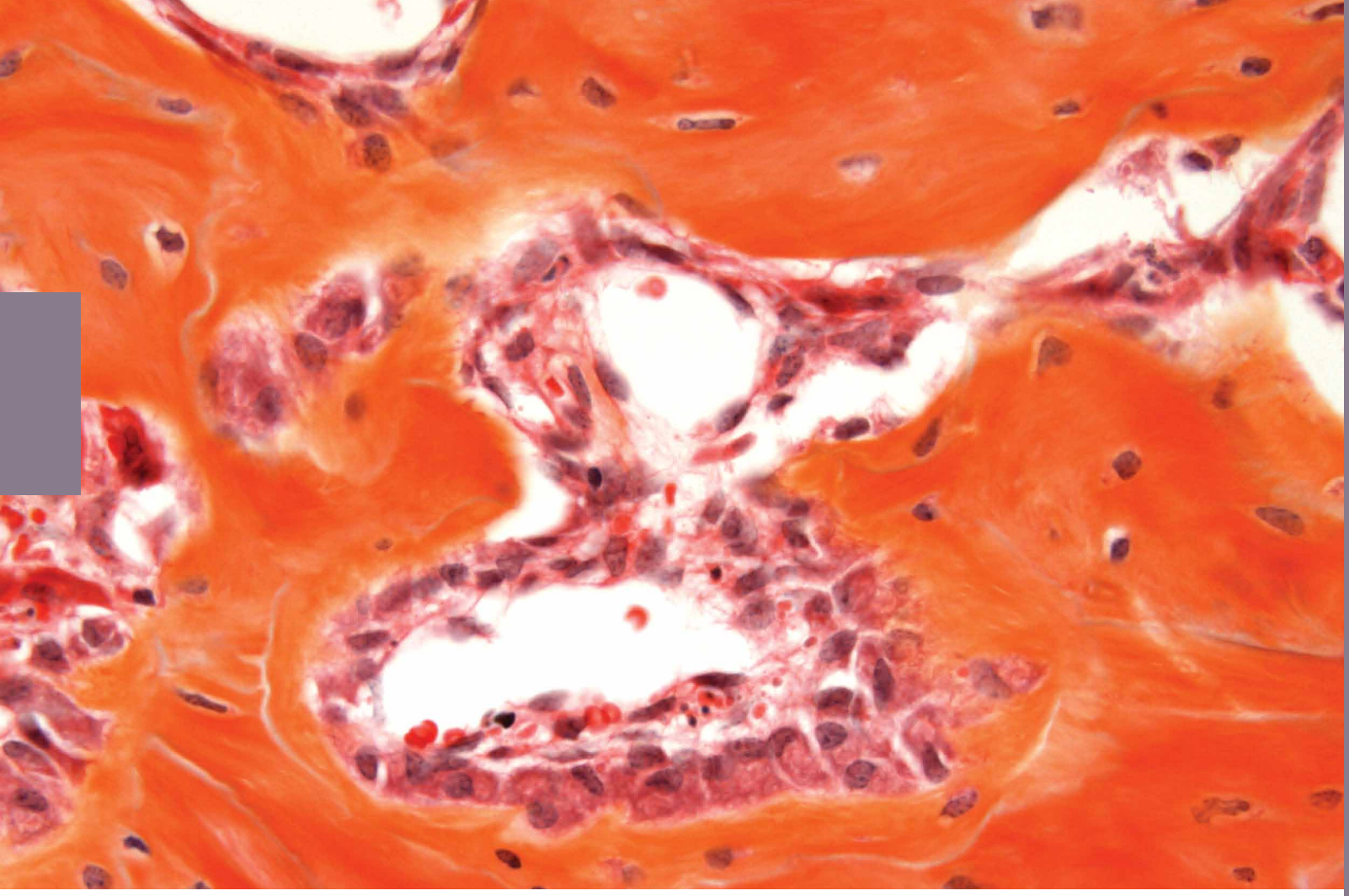
Another national research team is led by IU Simon Cancer Center investigator **Bryan Schneider, MD, (BC)**. Dr. Schneider and colleagues have identified a genetic biomarker that causes neuropathy among some breast cancer patients using a class of chemotherapy drugs called taxanes. It is one of the first genetic biomarkers to have been reported for neuropathy caused by taxanes, which includes paclitaxel (Taxol). The finding may eventually lead to a blood test to determine if a patient is at risk of developing neuropathy. That research was one of the top advances of 2011, according to ASCO. *(See page 6.)*

Those are but a few stories which I am proud to share from our research labs this past year. We are fortunate to be surrounded by an outstanding group of dedicated researchers, including three new senior recruits who joined us in 2011.

IU Simon Cancer Center executive committee

Patrick J. Loehrer, Sr., MD, director (seated). Left to right: Douglas Schwartzentruber, MD, associate director of clinical affairs; Mike Darling, associate director of administration; Harikrishna Nakshatri, PhD, associate director of education; Mark Kelley, PhD, associate director of basic science research; Victoria Champion, PhD, associate director of population science; Sherif Farag, associate director of clinical research.

Photo by David Jaynes & Tim Yates, Office of Visual Media/IU School of Medicine



In June, Douglas Schwartzentruber, MD, whose research on the role of vaccines in the treatment of malignant melanoma has gained both national and international attention, became associate director for clinical affairs and medical director of Indiana University Health's (formerly Clarian Health) statewide cancer services. He was also named to the 2010 *Time* magazine list of the 100 Most Influential People in the World. Dr. Schwartzentruber also is a member of the cancer center's executive committee.

Murray Korc, MD, (TMM) who is an internationally recognized pancreatic cancer researcher, became Indiana University's first Myles Brand Professor of Cancer Research in October. The Brand Professorship was created to help physicians and scientists at the IU Simon Cancer Center to continue investigating devastating malignancies, such as pancreatic cancer, which claimed the life of Brand, the 16th president of IU. Dr. Korc will become the co-leader of our Tumor Microenvironment and Metastasis developing research program with **Theresa Guise, MD, (TMM)** and will lead our Pancreatic Cancer Research Program. *(See page 22.)*

G. David Roodman, MD, PhD, (HMI) was named director of the IU School of Medicine's Division of Hematology Oncology in November. An internationally recognized leader in bone and myeloma research, Dr. Roodman has been at the forefront of research into understanding the role of the bone marrow microenvironment in promoting hematologic malignancies. He will become co-leader of the Hematopoiesis, Hematological Malignancies and Immunology research program with **Hal Broxmeyer, PhD, (HMI)**. *(See page 18.)*

Both Drs. Korc and Roodman come to IU as recipients of incentive funding made possible through Lilly Endowment's generous $60 million grant to the medical school to create the Physician Scientist Initiative. One of the initiative's goals is to recruit 20 top physician scientists to the IU School of Medicine by 2015. Funds from the Physician Scientist Initiative also created the Indiana Institute for Personalized Medicine, with additional funding from the IU Simon Cancer Center, IU School of Medicine, the school's Department of Medicine and Indiana University-Purdue University Indianapolis. Four capable members of the cancer

(continued on next page)

We're on a quest to make a difference *(continued)*

center were tapped as the institute's leaders: **David Flockhart, MD, PhD, (BC)** was named director, while **Lang Li, PhD, (BC), Bryan Schneider, MD,** and **Jamie Renbarger, MD,** were named associate directors. Dr. Flockhart perfectly summed up the new institute: "Much of the future of health care is in personalized medicine, meaning more precise targeting of the right medication to the right patient at the right time."

The institute will have a substantial impact on optimizing health care delivery and rationally curbing costs as we identify more precisely which drugs are likely to be more effective—or less effective and more toxic. In no discipline is this more keenly needed than in cancer care where drugs can be extremely costly and toxic.

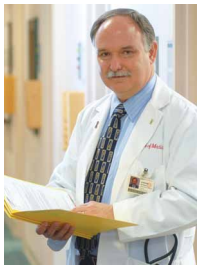
Indiana University Health and Walther Cancer Foundation also share our quest to make a difference. IU Health is committed to a statewide, comprehensive oncology network that provides preeminent cancer care and access to cancer research throughout its system. Through an accountability matrix of IU Health, IU Health Physicians and IU School of Medicine, IU Health cancer services will positively transform the strategies, quality, organization and delivery of patient-centric, outcomes-driven cancer care in Indiana. This network will serve as a model for academic/community physician partnerships, linking facilities to each other and to the IU Simon Cancer Center and reflecting IU Health cancer centers as the clear provider of choice for oncology care in the state. Our path to successful community-based patient care lies, in part, with the Hoosier Oncology Group and the Indiana Clinical Translational Science Institute, which has facilitated research among other academic institutions around the state, including Purdue University and the University of Notre Dame.

At the beginning of the year, Walther presented us with a $3.4 million grant to promote research and education of palliative care. The grant, which creates the Walther Program in Palliative Care Research and Education, will help clinicians, researchers and educators at IU Simon Cancer Center learn how to best integrate palliative care into conventional cancer care and to provide the highest quality of life for patients and their families undergoing cancer treatment.

More recently, Walther committed $1.2 million to the IU Simon Cancer Center, under the direction of Thomas Inui, MD, of the Division of General Internal Medicine and Geriatrics at IU School of Medicine and myself, to develop a sustainable and comprehensive academic clinical care program that will serve the citizens of western Kenya. The funds will allow us to add a research and education component to the IU AMPATH (Academic Model Providing Access to Healthcare) project, which has grown under the direction of **R. Matthew Strother, MD, (EDT).**

Our researchers with the Susan G. Komen for the Cure® Tissue Bank at IU Simon Cancer, the world's only repository of healthy breast tissue, have been studying the differences between healthy and cancerous breast tissue for several years now. And thanks to the 2012 Indianapolis Super Bowl Host Committee, our researchers' work will take to the world stage the weekend before the Super Bowl. On Jan. 28 and 29, 700 women are expected to selflessly donate breast tissue during Indy's Super Cure. It's an inspiring story, and you can read more on page 4.

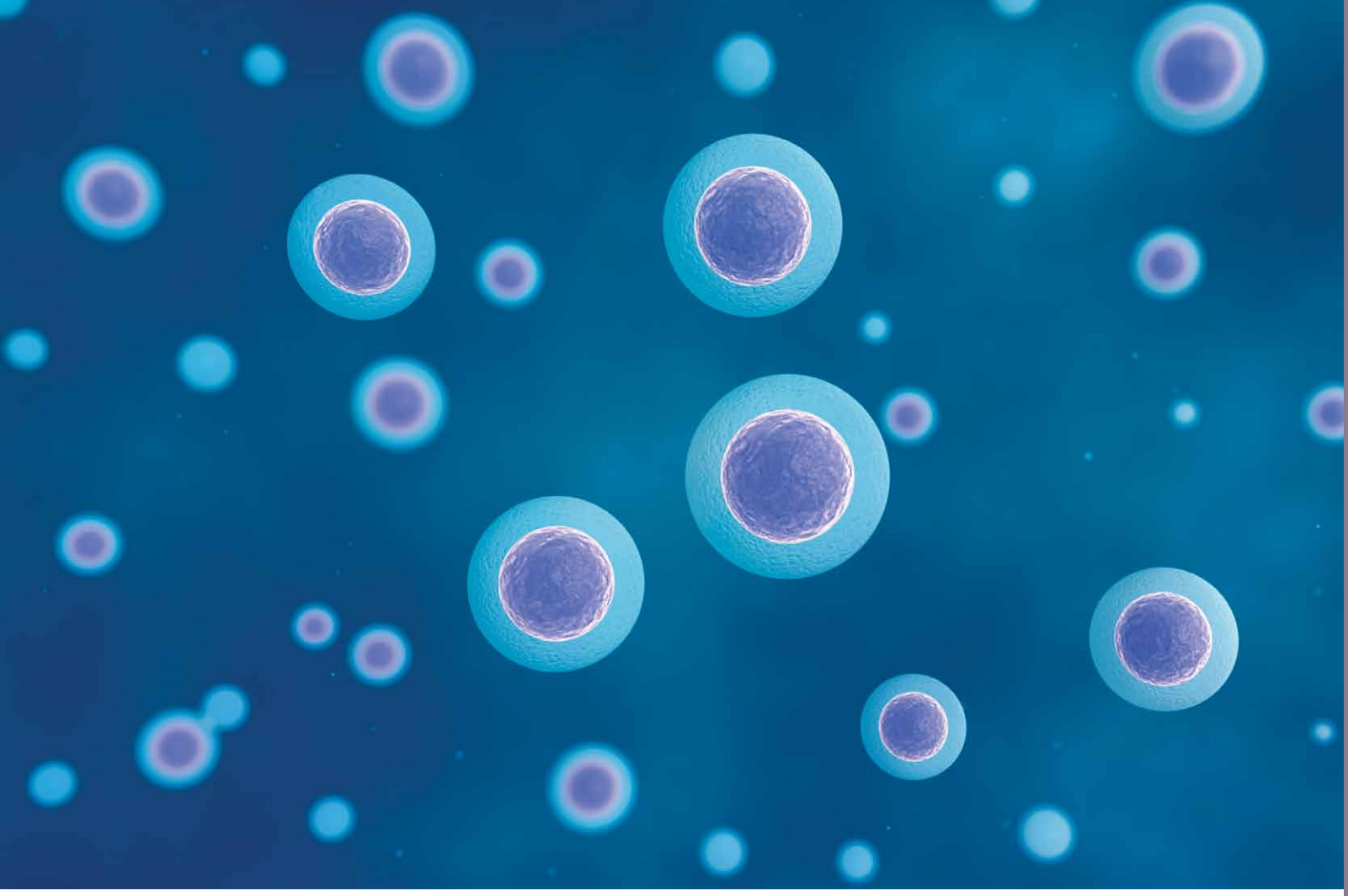
Our talented and dedicated investigators are ably moving forward on our quest to make a difference—differences discovered in the labs that will touch patients at their bedsides in Indiana, the United States and beyond.



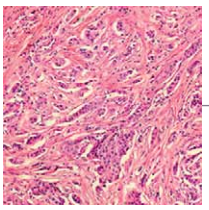
Patrick J. Loehrer, Sr., MD
HH Gregg Professor of Oncology
Director, IU Simon Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine

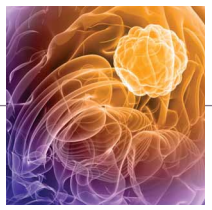
Bold denotes cancer center member

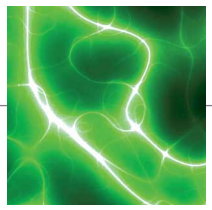
Abbreviations of research programs:
BC breast cancer
CPC Cancer Prevention and Control
EDT Experimental and Developmental Therapeutics
HMI Hematopoiesis, Microenvironment and Immunology
TMM Tumor Microenvironment and Metastases

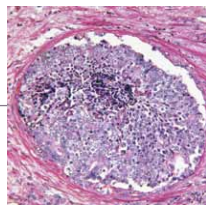


a look inside





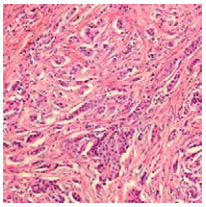




IU Simon Cancer Center mission

The mission of the IU Simon Cancer Center is to advance the understanding, prevention and treatment of cancer throughout Indiana and the world with patient-centered care, acceleration of promising science and collaborative educational programs.

Women selflessly donate breast tissue to unique bank



Would healthy women selflessly donate breast tissue, giving researchers valuable and precious clues into breast cancer?

It's a question no one had asked until 2005.

Anna Maria Storniolo, MD, a compassionate medical oncologist, was new to Indiana University when she was first approached by Connie Rufenbarger, a two-time breast cancer survivor from northern Indiana. Rufenbarger told the doctor that she wanted to create a breast cancer prevention program at IU. Dr. Storniolo needed some time to think about it, and she told Rufenbarger about all of the roadblocks to expect. "All kidding aside, Connie truly is a force of nature," Dr. Storniolo said. "I have never met anyone like her. She is truly the most selfless person I have met." Dr. Storniolo said yes.

Years earlier, Rufenbarger—a former school teacher—had taken part in the NCI's Breast Cancer Progress Review Group (BC-PRG), which in 1998, reported that progress in breast cancer research was hindered by not "understanding the biology and developmental genetics of the normal mammary gland." Six years later at a 2004 annual meeting of Indiana breast cancer scientists and clinicians, the lack of "normal" specimens once again became the topic of discussion. Rufenbarger, a woman who had been crusading since her own breast cancer diagnosis 22 years earlier, stood up at the meeting and said, "I can't do the science, but if you need women to give you tissue, done deal."

The following year, **Bryan Schneider, MD,** then a fellow in the Division of Hematology Oncology, had designed a study in which he needed DNA from women without breast cancer. Rufenbarger learned of the young Schneider's need and suggested a blood collection at the 2005 Komen Indianapolis Race for the Cure. The result? They collected an amazing 1,200+ whole blood samples. Equally impressive, the event—dubbed Friends for Life—proved that women would willingly give of themselves in the fight against breast cancer. In order to provide a permanent and secure repository for those samples, Mary Ellen's Tissue Bank, named in honor of Mary Ellen Allerding, was established.

Rufenbarger approached **Susan Clare, MD, PhD,** and inquired if she would be willing to share an Oracle-based database she had created. The talented surgeon quickly shared it. "Sue's database was absolutely a gold mine for us," Rufenbarger said. All of the right ingredients had been falling into place at the right time for the world's first healthy breast tissue bank to become a reality.

The Susan G. Komen for the Cure Tissue Bank at IU Simon Cancer Center is the only normal breast tissue bio-repository of its kind in the world. As such, it is uniquely positioned to characterize the molecular and genetic basis of normal breast development and compare it to the different types of breast cancer. The bank was established expressly for the acquisition of normal tissues—breast tissue, epithelial and stromal cell lines, serum, plasma and DNA—from volunteer donors with no clinical evidence of breast disease and/or malignancy, providing a resource to investigators around the globe.

Other collection events soon were scheduled in which saliva and serum were also obtained in addition to breast tissue and blood. The acquisition, processing, storage, retrieval and dissemination of the specimens were performed according to best practices established by the National Cancer Institute.

In the spring of 2007, Drs. Storniolo and Clare were attending the Translational Breast Cancer Research Consortium in Texas. Delayed by a snowstorm in Milwaukee, Dr. Clare arrived late at the meeting and took the last remaining seat. She happened to be seated next to a patient advocate, Cindy Geoghegan, who was also a contractor for Komen. Geoghegan wondered why the doctors had never contacted Komen before. Dr. Clare explained they had been unable to get a meeting with Komen. Geoghegan next asked Dr. Clare if she and Dr. Storniolo could remain in Texas for an extra day. So, Dr. Clare jotted down a note and passed it over to Dr. Storniolo, who responded that she could not. Dr. Clare re-sent the note, this time referencing the fact that it was for a meeting with Komen. Dr. Storniolo said yes, she'd be there. And Rufenbarger joined them.

Randy Johnson Photography©

Drs. Anna Maria Storniolo (far left) and Susan Clare (far right) co-direct the world's first and only healthy breast tissue bank. Connie Rufenbarger, (middle) a two-time breast cancer survivor, played a significant role in getting the tissue bank established.

The trio met with Hala Moddelmog, then president and CEO of Komen. When asked where the tissue bank's funding comes from, Dr. Storniolo told Moddelmog, "Well, it's month-to-month." What would it take not to be month-to-month, Moddelmog asked. "I think a million dollars a year would do it," Rufenbarger said. And so it happened. Komen gave $1 million to start the Susan G. Komen for the Cure Tissue Bank at IU Simon Cancer Center, the world's first and only healthy breast tissue bank. The threesome remained calm, cool and collected … until they got inside of an elevator at the Komen headquarters. That's when they cheered and celebrated their accomplishment, which was likely heard beyond the elevator which is located inside an open atrium.

The three had much to celebrate as they now had significant funding to continue their important work. By collecting samples from women without breast cancer, researchers may be able to determine the differences between healthy and cancerous tissues, which will lead to a better understanding of the disease. In all, more than 1,850 women had donated a precious piece of themselves by the end of 2011.

"They donate because their friend, neighbor, or aunt had breast cancer. They feel so helpless. They're frustrated because they can't do enough. When the opportunity comes up to donate, they jump at the chance," Dr. Clare said.

Another 700 women—more than one-third of the number of women who have already donated in the past—are expected to donate during Indy's Super Cure, a bold initiative developed by the 2012 Indianapolis Super Bowl Host Committee. On Jan. 28 and 29, the weekend prior to the Super Bowl, Indy's Super Cure will roll into full effect at the IU Simon Cancer Center. It will take 600 volunteers, more than seven times the number needed during a typical collection, to run Indy's Super Cure. Because Indianapolis takes to the world stage when it hosts Super Bowl XLVI, the host committee has been leveraging ongoing attention to help raise both awareness and funds for the tissue bank.

"From the very start, this has been a great idea from an advocate—Connie Rufenbarger—and a lot of hard work from a whole lot of people," Dr. Storniolo said. "If we can understand what's going wrong, we can understand how to fix it.

—Michael Schug

On Jan. 28 and 29, the weekend prior to the Super Bowl, Indy's Super Cure will roll into full effect at the IU Simon Cancer Center.

To read the full story, visit cancer.iu.edu/ktb

Program leaders

George Sledge Jr., MD
gsledge@iupui.edu
Ballve-Lantero Professor of Oncology
Professor of Medicine and Pathology
IU School of Medicine

Harikrishna Nakshatri, BVSc, PhD
hnakshat@iupui.edu
Marian J. Morrison Professor in Breast Cancer Research
Professor of Surgery
Professor of Biochemistry and Molecular Biology
IU School of Medicine

The Breast Cancer Program includes both basic investigators and clinicians, which enables laboratory findings to be quickly transferred to the clinic. It seeks to understand the biology underlying breast cancer; to apply understanding of breast cancer biology to improve prevention, diagnosis and treatment; and to foster research that is interdisciplinary and translational in nature.

Scientific goals

The goals of the Breast Cancer Program fall under four themes:

- Cell signaling pathway alterations
- Angiogenesis and therapeutic anti-angiogenesis approaches
- Genomic damage and repair mechanisms
- Therapeutic individualization

Dr. Schneider's research: Top clinical cancer advances of 2011

Research by **Bryan Schneider, MD**, that identified a genetic biomarker that causes neuropathy among some breast cancer patients using a class of chemotherapy drugs called taxanes was named one of the top clinical cancer research advances of 2011 by the American Society of Clinical Oncology (ASCO).

Dr. Schneider's research is featured in *2011 Clinical Cancer Advances: ASCO's Annual Report on Progress Against Cancer*. The report is an annual, independent review of advances in cancer research that have had the greatest impact on patient care.

Dr. Schneider's finding is one of the first genetic biomarkers to have been reported for neuropathy caused by taxanes, which includes paclitaxel or Taxol. The finding may eventually lead to a blood test to determine if a patient is at risk of developing neuropathy. Dr. Schneider and colleagues found the gene by conducting a comprehensive genetic look of more than one million genetic variations in each of the 2,204 breast cancer patients studied. The patients were enrolled in the Eastern Cooperative Oncology Group clinical trial E5103.

The Indiana University investigators looked for variations in DNA called single nucleotide polymorphisms or SNPs. They identified genetic subgroups that were likely to develop neuropathy. Those who carried two normal nucleotides in the RWDD3 gene had a 27 percent chance of experiencing neuropathy. But those who carried one normal nucleotide and one SNP had a 40 percent chance and those who carried two SNPs had a 60 percent chance.

research highlights

The aromatase inhibitor (AI)-associated musculoskeletal syndrome (AIMSS) occurs in approximately 50 percent of AI-treated patients. Inflammatory mediators are associated with estrogen signaling and may change with estrogen depletion. **Drs. David Flockhart**, **Anna Maria Storniolo**, **Lang Li** and colleagues reported that AIMSS is probably not associated with a systemic inflammatory response. Pre-treatment cytokine levels may predict for development of AIMSS.

Dr. Chunyan He examined whether common genetic variations in candidate genes of nine groups of biologically plausible pathways and related phenotypes are associated with age at menarche and age at natural menopause, two well-established risk factors for breast cancer. The steroid-hormone metabolism and biosynthesis pathway was found significantly associated with both traits. In addition, the group of genes involved in premature ovarian failure was found significantly associated with age at natural menopause.

Dr. Susan Clare and colleagues compared the breast cancer outcomes of underinsured African American and non-Hispanic white patients who were treated at a single institution. They found in this underinsured population that African American patients had poorer breast cancer-specific survival than non-Hispanic white patients. However, after adjustment for clinical and sociodemographic factors, the effect of race on survival was no longer statistically significant.

Dr. Kenneth Nephew and colleagues, in a first in-depth investigation into the role of miR-221/222 in acquired fulvestrant resistance, found they act as "oncomirs" by activating oncogenic signaling pathways to support ERα-independent proliferation and promote breast tumor progression. Targeting these two oncomirs may be a potential therapeutic strategy for preventing the development of fulvestrant resistance or re-sensitizing breast tumors to this potent selective estrogen receptor down-regulator (SERD) and effective estrogen antagonist.

Drs. Sunil Badve and **Harikrishna Nakshatri** found that tumor microenvironment may play a significant role in determining the prognostic impact of stem/progenitor cell marker expression in human breast tumors.

Drs. Badve and **George Sledge** investigated the effect of the Oncotype Dx® (ODX) on chemotherapy (CTX) utilization in two cancer centers. They found ODX resulted in a change in management for 38 percent of women. Of 188 total patients who did not receive CTX, 71 had a recommendation favoring CTX by an oncologist blinded to the ODX score.

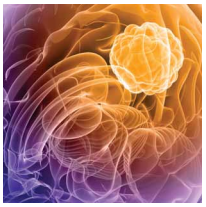
Drs. Nakshatri, Badve, Lida Mina and **Sledge** reported identification of a new small RNA biomarker U6 in the serum of breast cancer patients. Their findings suggest a "chronic inflammatory" status in patients with cancer, which may have contributed to elevated serum U6 levels.

members

Sunil Badve, MBBS, MD, FRCPath
Monet Bowling, MD
Susan Clare, MD, PhD
David Clemmer, PhD
Anthony Firulli, PhD
David Flockhart, MD, PhD
David Gilley, PhD
Brenda Grimes, PhD
Linda Han, MD
Eyas Hattab, MD
Chunyan He, ScD
Brittney-Shea Herbert, PhD
Gary Hutchins, PhD
Mircea Ivan, MD, PhD
Philip Johnson, PhD, MSc, BSc
Aparna Jotwani, MD
Raymond Konger, MD
Lang Li, PhD
Samy Meroueh, PhD
Kathy Miller, MD
Lida Mina, MD
Kenneth Nephew, PhD
Milos Novotny, PhD
Bruce Robb, MD
Andrew Saykin, PsyD
Bryan Schneider, MD
Todd Skaar, PhD
Roger Slee, PhD
Keith Stantz, PhD
Anna Storniolo, MD
Hiromi Tanaka, PhD
Tracy Vargo-Gogola, PhD
Claire Walczak, PhD
Clark Wells, PhD
Jian-Ting Zhang, PhD
Qi-Huang Zheng, PhD

Bold denotes members accepted in 2011

IU researchers: Chemotherapy Alters brain tissue in breast cancer patients



Researchers at Indiana University Melvin and Bren Simon Cancer Center have published the first report using imaging to show that changes in brain tissue can occur in breast cancer patients undergoing chemotherapy.

The cognitive effects of chemotherapy, often referred to as "chemobrain," have been known for years. However, the IU research is the first to use brain imaging to study women with breast cancer before and after treatment, showing that chemotherapy can affect gray matter.

"This is the first prospective study," **Andrew Saykin, PsyD,** director of the Indiana University Center for Neuroimaging, said. "These analyses, led by Brenna McDonald, suggest an anatomic basis for the cognitive complaints and performance changes seen in patients. Memory and executive functions like multi-tasking and processing speed are the most typically affected functions and these are handled by the brain regions where we detected gray matter changes."

Dr. Saykin, **Brenna McDonald, PsyD, MBA,** and colleagues studied structural MRI scans of the brain obtained on breast cancer patients and healthy controls. The scans were taken after surgery, but before radiation or chemotherapy, to give the researchers a baseline. Scans were then repeated one month and one year after chemotherapy was completed.

The researchers found gray matter changes were most prominent in the areas of the brain that are consistent with cognitive dysfunction during and shortly after chemotherapy. Gray matter density in most women improved a year after chemotherapy ended.

For many patients, Dr. Saykin said, the effects are subtle. However, they can be more pronounced for others. Although relatively rare, some patients—often middle-aged women—are so affected that they are never able to return to work. More commonly, women will still be able to work and multi-task, but it may be more difficult to do so.

The study focused on 17 breast cancer patients treated with chemotherapy after surgery, 12 women with breast cancer who did not undergo chemotherapy after surgery and 18 women without breast cancer.

Dr. McDaniel tests video game to teach dangers of tobacco

When she was a critical care nurse, **Anna McDaniel, RN, PhD,** took care of countless patients who had been devastated by their tobacco use. "I took care of many of them at the most critical stages of their illnesses. Many did not survive," she reflected.

Now associate dean of the IU School of Nursing Center for Research and Scholarship, her research interests over the past 15 years have focused primarily on smoking cessation and tobacco control. Most recently, she has taken a unique approach to reach young girls, ages 8 to 12, to help them make sound and informed decisions about tobacco use.

Dr. McDaniel has teamed up with a computer gaming company to develop an anti-smoking video game. The game presents recommended tobacco prevention information in a playful, interactive manner. As players solve puzzles and gather clues, they learn about topics identified by the Centers for Disease Control and Prevention and the National Institutes of Health as the most effective at preventing tobacco use. Dr. McDaniel's preliminary data indicate that girls' negative attitudes toward smoking and their knowledge of the dangers of smoking increases by playing the game.

Research shows that nearly 80 percent of current adult smokers began using cigarettes while they were adolescents. As such, early intervention, according to Dr. McDaniel, is especially crucial to prevent girls from starting smoking and developing a nicotine addiction.

David Jaynes, Office of Visual Media/IU School of Medicine

Drs. Andrew Saykin and Brenna McDonald will head to Paris in 2012 to present their "chemobrain" research at an international conference. They have published the first report using imaging to show changes in brain tissue in breast cancer patients undergoing chemotherapy.

"We hope there will be more prospective studies to follow so that the cause of these changes in cancer patients can be better understood," Dr. Saykin said.

Drs. Saykin and McDonald will present their chemobrain research at the International Cognition and Cancer Task Force Conference in Paris in March 2012.

In October 2011, they both presented at the Chemo Brain: Mechanisms & Assessments International Conference at the University of Kentucky. Dr. Saykin presented "Genetic Risk Factors for Cognitive Impairment and Imaging Genetics: Lessons for Cancer Research from Studies of Alzheimer's disease and Mild Cognitive Impairment." Dr. McDonald presented "Brain Imaging to Study Mechanisms of Chemotherapy-Induced Cognitive Changes."

Dr. Saykin started this research while he was at Dartmouth Medical School before finishing the data analyses at IU. A new, independent sample is now being studied at the IU Simon Cancer Center to replicate and further investigate this problem affecting many cancer patients.

The study was supported by a grant from the Office of Cancer Survivorship of the National Cancer Institute, National Institutes of Health and the Indiana Economic Development Corp.

—Michael Schug

Program leaders

Victoria Champion, PhD, RN, FAAN
vchampio@iupui.edu
Associate Dean for Research
Scientific Director, Mary Margaret Walther Program
Distinguished Professor
Mary Margaret Walther Professor of Nursing
Edward W. and Sarah Stam Cullipher Chair
IU School of Nursing

Gregory Zimet, PhD
gzimet@iupui.edu
Professor of Pediatrics
IU School of Medicine

The Cancer Prevention and Control Program includes members from eight schools and nine departments. Membership includes a large variety of disciplines, including medicine, nursing, public health, psychology, psychiatry, pharmacology, dentistry, radiology, surgery, pediatrics and informatics. The program's three major themes span the cancer continuum from cancer prevention to survivorship and quality of life.

Scientific goals

The Cancer Prevention and Control Program's goals of reducing the morbidity and mortality of cancer are reflected in three themes:

Theme 1: Risk Reduction

- Prevention of cancer and altering behaviors that are related to development of cancers (e.g., smoking, unsafe sexual practices).

Theme 2: Early Detection

- Improve screening compliance for breast and colorectal cancer and translate successful interventions to clinical practice.

Theme 3: Survivorship

- Identify and test interventions to decrease symptoms experienced by cancer patients and their families.

Dr. Zimet, Shedd-Steele lead Indiana Cervical Cancer Free Initiative

Shedd-Steele

Gregory Zimet, PhD, and Rivienne Shedd-Steele, director of the IU Simon Cancer Center's Office of Health Disparities and Outreach, lead Cervical Cancer Free Indiana (CCFIN), one of only six such programs in the nation.

GlaxoSmithKline most recently awarded $200,000 to CCFIN following a $150,000 grant in 2010, which was awarded to launch the Indiana program.

Dr. Zimet and Shedd-Steele work together to develop and implement strategies to enhance awareness about cervical cancer and increase screening rates. Priority activities focus on educating the community about the human papillomavirus (HPV), which is the primary cause of cervical cancer, through outreach to disadvantaged, racial minority and ethnic communities that tend to have higher rates of HPV infection and cervical cancer. Shedd-Steele currently is working with various community partners, such as Little Red Door Cancer Agency and Wishard Health Services' Community Health Centers, to reach targeted populations. She is also training student nurses and healthcare professionals how to effectively communicate with people—primarily young people and their parents—about HPV screening and vaccination.

research highlights

Abbreviations used: BC, Breast Cancer; HMI, Hematopoiesis, Hematological Malignancies and Immunology

Theme 1: Risk Reduction

Dr. Greg Zimet formed an HPV Working Group with members who represent multiple disciplines across nine different departments. Many members are already engaged in collaborative, interdisciplinary, externally-funded research focusing on the natural history of HPV infection in young women and young men, and determinants of HPV vaccination.

Drs. Zimet and **Dennis Fortenberry** continue to test the use of interactive technology, including cell phone diaries, to gather data and deliver interventions related to the prevention of STDs in adolescents and adults with the goal of decreasing the occurrence of cervical and other cancers.

Theme 2: Early Detection

Drs. Victoria Champion and **Susan Rawl** are developing and testing an interactive Web-based program to increase both breast and colon cancer screening in women. This is the first trial that has combined breast and colon cancer screening into one intervention.

Theme 3: Survivorship

Drs. Janet Carpenter, **Debra Burns** and **Bryan Schneider (BC)** were awarded an R01 grant to evaluate two different breathing programs (one CD, one DVD) against standard care to see which one best relieves hot flashes and other menopausal symptoms such as disrupted mood and sleep. Findings will provide empirical evidence to guide clinicians' recommendations and consumers' treatment selections either in favor of or against the use of breathing programs.

Dr. Joan Haase led an interdisciplinary palliative care/end-of-life communication initiative among behavioral scientists and clinical investigators that evolved into the Research in Palliative and End-of-Life Communication and Training (RESPECT) Center. The center's mission is to build a collaborative, interdisciplinary scientific community of researchers and clinicians to advance the science of palliative communication and end-of-life care. Co-directors are **Drs. Haase**, **Susan Hickman** and **Greg Sachs**. Others affiliated with RESPECT include **Drs. Burns**, **Larry Cripe (HMI)**, **Paul Helft**, **Kevin Rand** and **Sheri Robb**.

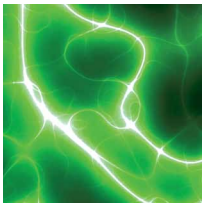
Dr. Anna McDaniel leads a Web-based information source for IUSCC patients and families to serve as a platform for translation of evidence-based cancer control behavioral interventions and information dissemination. The portal provides two levels of user interaction: the public level is fully integrated into the cancer center Web site (cancer.iu.edu) and allows any user to obtain quality-filtered, evidence-based cancer information. A second, secure level requires authorized access to applications that involve user input of personal information for delivery of tailored interventions. A trial study suggested that the secure site is feasible and acceptable to patients and providers. Also, fewer symptoms were reported at follow-up than at baseline, with significantly lower symptom severity.

members

Elliot Androphy, MD
Asok Antony, MD
Silvia Bigatti, PhD
Darron Brown, MD
Debra Burns, PhD
Janet Carpenter, PhD
Won Cho, MD
M. Kathryn Coe, PhD
Betsy Fife, PhD
J. Dennis Fortenberry, MD, MS
Joan Haase, PhD
David Haggstrom, MD
Chunyan He, ScD
Paul Helft, MD
Lisa Hess, PhD
Susan Hickman, PhD
Karen Hudmon, PharmD
Thomas Imperiale, MD
Peter Johnstone, MD, MA
Kurt Kroenke, MD
Chiung-ju Liu, PhD
Patrick Loehrer, MD
Anna McDaniel, PhD
Brenna McDonald, PsyD, MBA
Patrick Monahan, PhD
Catherine Mosher, PhD
Julie Otte, PhD
Kevin Rand, PhD
Susan Rawl, PhD
Douglas Rex, MD
Sheri Robb, PhD
Andrew Saykin, PsyD
Marcia Shew, MD MPH
Rafat Siddiqui, PhD
Daniel Sliva, PhD
Nathan Stupiansky, PhD
G. Marie Swanson, PhD, MPH
Frederick Unverzagt, PhD
Michael Vasko, PhD
Terry Vik, MD
Diane Von Ah, PhD
Bree Weaver, MD
Jianjun Zhang, MD, PhD
Matthew Ziegler, MD
Alan Zillich, PharmD

Bold denotes members accepted in 2011

Late-stage Ovarian cancer therapy shows promise



An experimental two-drug combination for treating late-stage ovarian cancer continues to produce strong results, leading its Indiana University researchers to actively pursue the next step, conducting a larger clinical trial to test the therapy and to see how it compares with existing treatments for ovarian cancer.

Not only did a surprising 70 percent of patients in the phase II trial show a positive effect from the new therapy, the researchers say they may have discovered biomarkers that could help identify women who would respond best to the therapy.

"The potential that this regimen is efficacious, combining decitabine with the carboplatin therapy, is very exciting," **Kenneth Nephew, PhD, (BC, TMM)** said. "It's well tolerated and didn't have any dose-limiting toxicities. We could enroll patients with confidence because of these results."

Ovarian cancer is aggressive and incurable and is the fifth leading cause of cancer death in women. Carboplatin is considered the most efficient drug therapy, yet women with recurring ovarian cancer often become resistant to the drug after one or two rounds of treatment. Once this occurs, they often survive less than a year because no effective second-line treatment exists.

The 17 women who enrolled in the IU Simon Cancer Center clinical trial all had become resistant to carboplatin, with their cancer progressing. The 12 women who benefited from the experimental therapy saw their tumor growth slow down or completely stop. In one woman, doctors could no longer find the tumor. Dr. Nephew said the progression of the cancer in these women resumed, on average, after 336 days.

Lead investigator **Daniela Matei, MD,** has been treating women with ovarian cancer for 10 years and has conducted numerous clinical studies. The women in this phase II study had already undergone other experimental therapies once their cancer had become resistant to carboplatin, so the high rate of women experiencing a positive effect from their carboplatin-decitabine combo was surprising, as was the number of women who remained in remission after six months, Dr. Matei said.

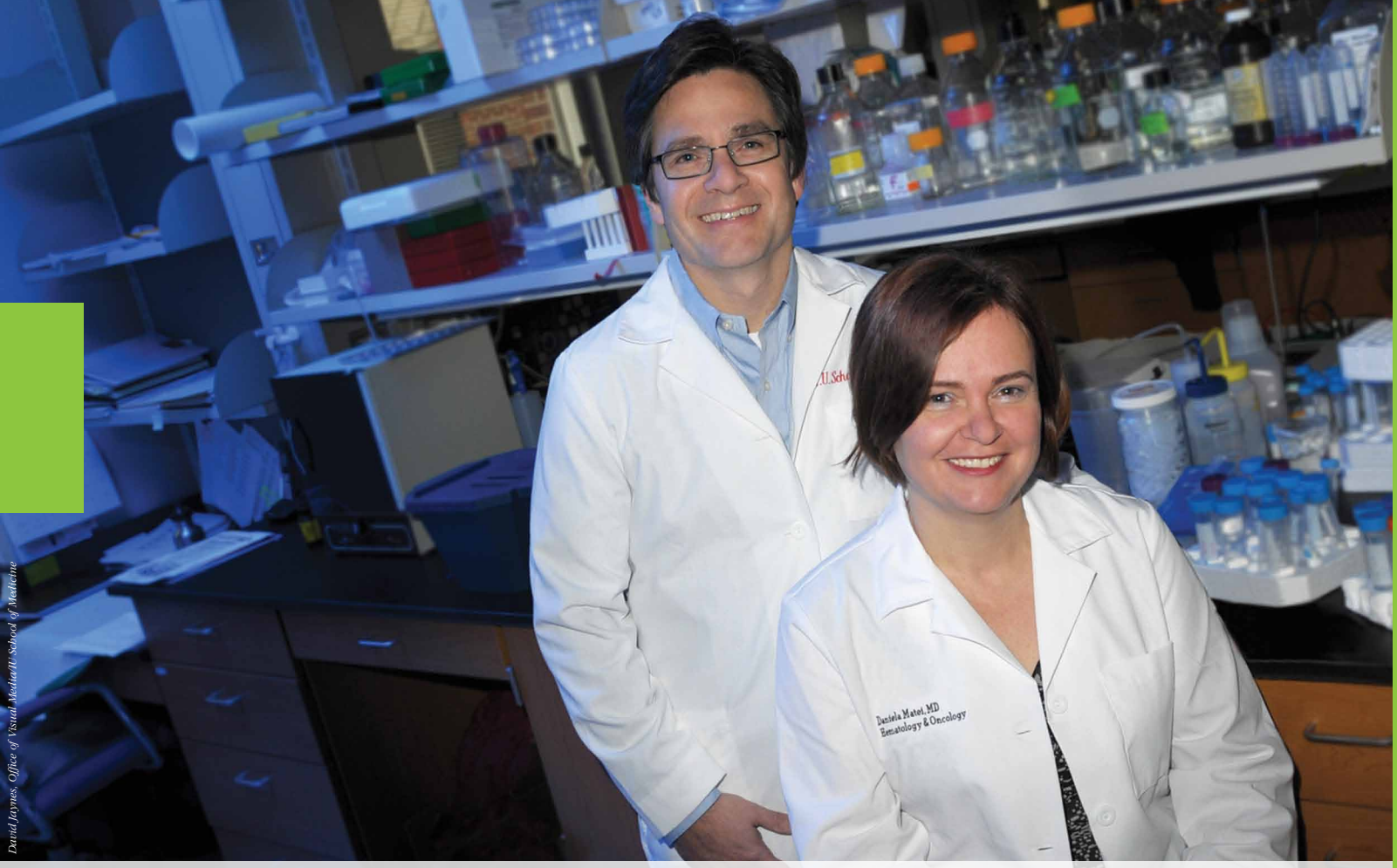
"Typically in this group of patients you'd anticipate response rates of less than 5 percent and no patients would be expected to be in remission at six months," Dr. Matei said. "In our trial, more than half (nine women) of the patients were without progression at six months."

Dr. Matei discussed the findings of the phase II trial in June 2011 during a presentation at the American Society of Clinical Oncology national meeting.

Ovarian cancer is the deadliest of all gynecologic cancers. Worldwide, about 200,000 women are diagnosed with ovarian cancer and 125,000 women die from this disease annually. In the United States alone, there will be approximately 22,000 new cases of ovarian cancer each year and about 15,500 women will die of the disease. Currently there is no effective means of early detection.

Their research, which Dr. Nephew describes as "truly translational" because of its dependence on both lab and clinical work, has been supported by the National Institutes of Health, National Cancer Institute, Walther Cancer Foundation in Indianapolis and the Ovarian Cancer Research Foundation. It began with a competitive pilot project from the IU Simon Cancer Center. The researchers are seeking grant funding for the larger trial during which they will test the current combination and compare it with other approved therapies for ovarian cancer.

In the phase I and phase II trials, decitabine was administered daily to patients intravenously for five days followed on the eighth day with carboplatin. After a month, the regimen begins again.



David Jaynes, Office of Visual Media/IU School of Medicine

Dr. Daniela Matei, co-leader of the EDT program, and Dr. Kenneth Nephew of the Breast Cancer program and the developing Tumor Microenvironment and Metastases program, collaborate on ovarian cancer research with a two-drug combination of carboplatin and decitabine.

The researchers have been investigating the addition of decitabine, which is marketed as Dacogen in the United States, because they suspect it reactivates tumor suppression genes that are turned off in ovarian cancer cells and improves cells' susceptibility to anti-cancer drugs like carboplatin.

One of the hallmarks of ovarian cancer is the aberrant methylation of cytosine, one of the components of DNA. DNA methylation prevents affected genes from being properly expressed. Some of the silenced genes may not be important, but others, like tumor suppressor genes, are. By silencing tumor suppressor genes, the cancer becomes more aggressive or resistant to conventional treatment. Decitabine is a known DNA methylation inhibitor that can help return tumor suppressor genes to an active state, and by doing so, can improve cells' susceptibility to anti-cancer drugs, like carboplatin.

"Our hypothesis is that decitabine isn't just targeting active ovarian cancer cells, but also cancer stem cells that seem to survive the first treatments," Dr. Nephew said. "By keeping tumor suppressor genes from being methylated, carboplatin and other platinum-based treatments for ovarian cancer have a better chance of killing tumor cells."

The two-drug treatment protocol is not approved for general use. The IU Simon Cancer Center was the only site for this clinical study.

Dr. Matei said they were very fortunate because the NCI funding for the phase II trial let them perform exploratory work involving tumor biopsies from the women. This allowed them to identify significant changes in gene make-up before and after treatment. She said they are narrowing this down to focus on specific genes so the information can be used in subsequent trials.

"The science associated with the trial is novel and exciting and could have an impact in the future," she said.

–Tracy James & Mary Hardin

Abbreviations used: BC, Breast Cancer; TMM, Tumor Microenvironment and Metastases

Program leaders

Daniela Matei, MD
dmatei@iupui.edu
Associate Professor
IU School of Medicine

Zhong-Yin Zhang, PhD
zyzhang@iupui.edu
Chair and Robert A. Harris Professor,
Department of Biochemistry and Molecular Biology,
IU School of Medicine

The Experimental and Developmental Therapeutics (EDT) Program consists of members from six departments of the IU School of Medicine. The EDT program includes both clinical and basic science investigators committed to translating findings from the bench to the bedside. The mission of the program is to discover and develop novel cancer therapeutics.

Scientific goals

The goals of the Experimental and Developmental Therapeutics Program fall under three themes:

Theme 1: Target identification and validation

Theme 2: Discovery and development of novel anti-cancer agents

Theme 3: Mechanisms of drug action and clinical trials

Dr. Renbarger wins prestigious National Presidential Award

Jamie Renbarger, MD, was named a recipient of a Presidential Early Career Award for Scientists and Engineers by President Obama in September.

Dr. Renbarger was selected to receive the award for pharmacogenomic studies aimed at optimizing the use of vincristine in the treatment of children with cancer. A primary research focus for Dr. Renbarger has been to use genomic tools to reduce the impact of side effects that frequently affect children with cancer who are being treated with the drug vincristine. The drug, widely used and effective, can cause nervous system side effects—neuropathies—that can range from jaw pain to foot drop to severe constipation. She and colleagues at several institutions across the country are working to better detect, predict and prevent the onset of those side effects.

"I am honored to have been selected for this prestigious award. It is a privilege to enjoy a career as a physician-scientist, participating in research that I love. It is exciting to make discoveries from research based on practical clinical questions that allow us to improve the treatment of children with cancer. It is especially gratifying to be recognized for my efforts in that research," Dr. Renbarger said.

The Presidential awards are the highest honor bestowed by the U.S. government on science and engineering professionals in the early stages of their independent research careers and reflect the administration's priority "on producing outstanding scientists and engineers to advance the nation's goals, tackle grand challenges and contribute to the American economy," the White House said in its announcement. There were 94 recipients this year.

research highlights

Abbreviation used: HMI, Hematopoiesis, Hematological Malignancies and Immunology

Dr. Lindsey Mayo investigating how the oncogene human murine double minute (Hdm2) is elevated in late-stage metastatic breast cancer discovered a novel pathway to induce its expression. Hdm2 regulates p53 stability via ubiquitination and Hdm2 has also been implicated in promoting the growth function of TGF-ß1. TGF-ß1 is a cytokine that has been implicated in stimulating tumor progression. Whether TGF-ß1 signaling induces Hdm2 expression leading to Hdm2-mediated destabilization of p53 has not been investigated. **Drs. Mayo, Karen Pollok (HMI)** and colleagues reported that TGF-ß1–activated Smad3/Smad4 (Smad3/4) transcription factors specifically bound to the second promoter region of *Hd2*, leading to increased Hdm2 protein expression and destabilization of p53 in human cancer cell lines. Additionally, TGF-ß1 expression led to Smad3 activation and murine double minute 2 (Mdm2) expression in murine mammary epithelial cells during epithelial-to-mesenchymal transition (EMT). Further, histological analyses of human breast cancer samples demonstrated that approximately 65 percent of late-stage carcinomas were positive for activated Smad3 and Hdm2, indicating a strong correlation between TGF-ß1–mediated induction of Hdm2 and late-stage tumor progression. Identification of Hdm2 as a downstream target of TGF-ß1 represents a critical pro-survival mechanism in cancer progression and provides another point for therapeutic intervention in late-stage cancer.

Targeting uncontrolled cell proliferation and resistance to DNA-damaging chemotherapeutics with a single agent has significant potential in cancer treatment. Replication protein A (RPA), the eukaryotic ssDNA-binding protein, is essential for genomic maintenance and stability via roles in both DNA replication and repair. **Dr. John Turchi** identified a novel small molecule that inhibits the *in vitro* and cellular ssDNA-binding activity of RPA, prevents cell cycle progression, induces cytotoxicity and increases the efficacy of chemotherapeutic DNA-damaging agents. These results provide new insight into the mechanism of RPA-ssDNA interactions in chromosome maintenance and stability. This represents the first molecularly targeted eukaryotic DNA-binding inhibitor and reveals the utility of targeting a protein-DNA interaction as a therapeutic strategy for cancer treatment.

Although approximately 50 percent of all types of human cancers harbor wild type TP53, this p53 tumor suppressor is often deactivated through a concerted action by its abnormally elevated suppressors: Mdm2, Mdmx, or SIRT1. Thus, targeting this p53-negating pathway is an attractive approach to identify small molecules that could kill cancerous cells. **Dr. Hua Lu's** laboratory, in collaboration with **Drs. Samy Meroueh** and **Qizhuang Ye**, has identified a small molecule called Inauhzin that can suppress tumor cell growth by activating p53 in both cell-based and animal model systems. Inauhzin can effectively stabilize and reactivate p53 by inhibiting SIRT1 activity as well as promote p53-dependent apoptosis of human cancer cells without causing apparently genotoxic stress. Remarkably, Inauhzin inhibits cell proliferation, induces tumor-specific apoptosis and represses the growth of xenograft tumors derived from p53-harboring H460 and HCT116 cells without causing apparent toxicity to the tumor-bearing SCID mice. It is a novel anti-cancer therapeutic candidate that will be potentially useful for human lung and colon cancers as well as other cancers that harbor wild type, but inactive, p53.

members

Navin Bansal, PhD
Elena Chiorean, MD
Romnee Clark-Seaberg, MD
Timothy Corson, PhD
Giuseppe Del Priore, MD, MPH
Joseph Dynlacht, PhD
Lawrence Einhorn, MD
Leslie Fecher, MD
Melissa Fishel, PhD
Thomas Gardner, MD
Millie Georgiadis, PhD
Noah Hahn, MD
Nasser Hanna, MD
Thomas Hurley, PhD
Shadia Jalal, MD
Hiremagalur Jayaram, PhD
Matthew Johnson, MD
Chinghai Kao, PhD
Mark Kelley, PhD
Mark Langer, MD
Suk-Hee Lee, PhD
Hyun-Suk Lim, PhD
Patrick Loehrer, MD
Theodore Logan, MD
Hua Lu, MD, PhD
Lindsey Mayo, PhD
Marc Mendonca, PhD
Samy Meroueh, PhD
Amber Mosley, PhD
Jamie Renbarger, MD
Ahmad Safa, PhD
Sonal Sanghani, PhD
Chie-Schin Shih, MD
R. Matthew Strother, MD
John Turchi, PhD
Jingwu Xie, PhD
Qizhuang Ye, PhD
Xiao-Ming Yin, MD, PhD
Jian-Ting Zhang, PhD
Adam Zlotnick, PhD

Bold denotes members accepted in 2011

NIDDK awards grant to Center of Excellence in Molecular Hematology

The National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) awarded a $480,000 grant to the Center of Excellence in Molecular Hematology (CEMH), which is co-directed by **Hal Broxmeyer, PhD,** who also leads the Hematopoiesis, Hematological Malignancies and Immunology research program.

Indiana University's CEMH was one of only five such centers to receive funding. The others were Fred Hutchinson Cancer Research Center (Seattle), Children's Hospital of Philadelphia, Children's Hospital Medical Center (Cincinnati) and Children's Hospital Boston.

The CEMH, which will receive more than $3.6 million over five years from NIDDK, brings together investigators from relevant disciplines to enhance and extend the effectiveness of research related to hematologic diseases and their complications, according to the NIDDK.

"This is a center of excellence in molecular hematology," **Edward F. Srour, PhD,** the center's other co-director, explained. "Our focus is on mechanisms that will facilitate or improve stem cell clinical utilization."

The center's membership draws from a group of well-funded investigators with a diverse but complementary experience in hematopoiesis and stem cell biology, viral mediated gene transfer, molecular genetics, virology, hematopoietic stem cell transplantation (cord blood, bone marrow and mobilized peripheral blood), neonatology and vascular and developmental biology.

Overall, the center is composed of four cores: administration; Angiogenesis, Endothelial and Pro-Angiogenic Cells; Experimental Mouse Resources; and Optical Microscopy.

Dr. Abonour physically pushes himself for his patients

Most men in their early 50s don't typically start running at midnight. **Rafat Abonour, MD,** is not most men. He's on a mission. He's passionate about finding a cure for multiple myeloma, an incurable but treatable blood cancer.

Dr. Abonour, professor of medicine at the IU School of Medicine and a multiple myeloma researcher/physician, treats people with the disease, but he does more than that. He listens to them. He empathizes with them. "They are my friends," he said. "We become family. We cry together. We laugh together."

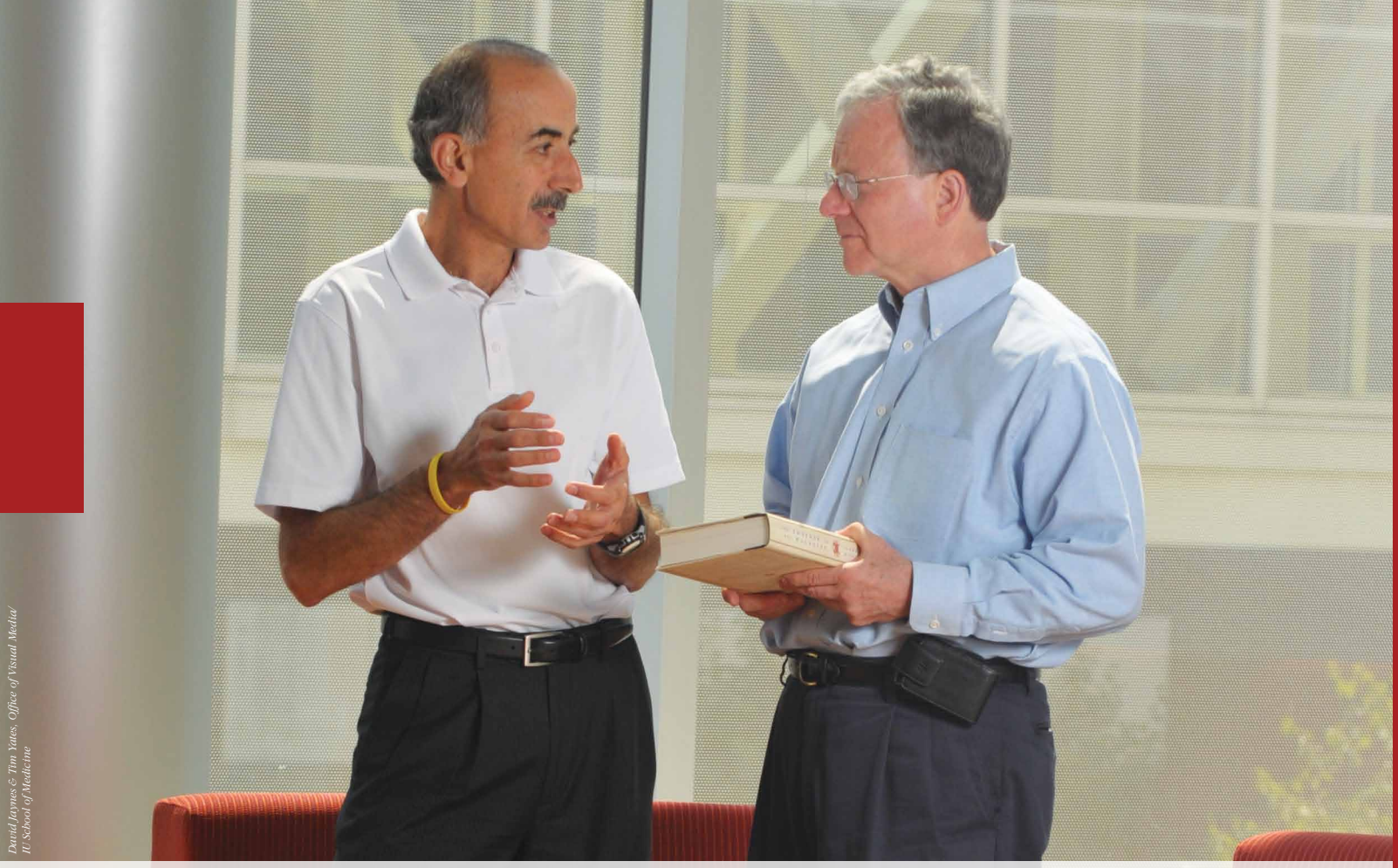
For the past seven years, Abonour—an avid amateur marathon runner—has put his body to the test to raise money for his research devoted to finding a cure. In all, he has either run—including a 50-mile trek that began at midnight—or biked more than 1,000 miles throughout Indiana for his annual Miles for Myeloma event. In doing so, he has raised $1.7 million for myeloma research. All of the funds are used by IU Simon Cancer Center investigators for pilot research projects as well as recruitment.

Why does he push himself physically? While a fellow at the University of Wisconsin, he followed some myeloma patients and was struck by how they dealt with an incurable disease. "They were able to live with the fact that it's incurable. They were so faithful to the medical field and the caregiver and giving back more than I was giving them," Dr. Abonour said.

Although Dr. Abonour has made a great impact upon his patients and the disease, he almost chose another path in life. "The last thing I wanted to do was to go to medical school," he said. "I wanted to become a mathematician." His mother's influence led him to medicine, but "I hated it the first couple of years," he said. "I couldn't relate to the anatomy, physiology and memorizing all of those compounds."

All of that changed, though, when he started seeing patients. "It was rewarding to see the trust they (patients) placed in me," he said.

Still, his focus lies on making further inroads against the disease. "We're still losing patients," he said. "It's disheartening that we can't cure these people. I think the mission is to find out why we can't cure them and correct that."



David Jaymes & Tim Yates, Office of Visual Media/ IU School of Medicine

Drs. Edward Srour (left) and Hal Broxmeyer co-direct the Center of Excellence in Molecular Hematology, one of only five such centers to receive funding.

Drs. Srour and Broxmeyer form the center's administration core.

The Angiogenesis, Endothelial and Pro-Angiogenic Cell Core, led by **Jamie Case, PhD,** and **Mervin Yoder, MD,** conducts validated and highly reproducible *in vitro* and *in vivo* angiogenesis assays. These assays function as experimental platforms for understanding the basic mechanisms of angiogenesis and discovering compounds that inhibit new blood vessel formation in tumor microenvironments.

Led by **Karen Pollok, PhD,** and **Simon Conway, PhD,** the Experimental Mouse Resources Core is designed to fulfill the extensive demand for immunodeficient and genetically modified mice for *in vivo* lineage mapping, transplantation and tumor xenograft studies to functionally examine the therapeutic potential for hematopoietic cells.

The Optical Microscopy Core provides access, training and services in high resolution optical microscopy. **Ken Dunn, PhD,** and **Nadia Carlesso, MD, PhD,** serve as co-directors.

"There are certain crucial cores that we need in order for IU investigators to do the best research that they can," **Dr. Broxmeyer** said. "Having these cores not only allows us to do the work but also allows our members to have access at a lower cost. The center is really about facilitating collaborations and interactions. It gives us cutting-edge technology, which makes us more competitive.

All of the cores support the basic and translational studies that underlie the CEMH's mission and will facilitate the development of new discoveries into human trials.

CEMH also includes a pilot and feasibility program, to be funded in part through university funds, in order to enhance the training of young investigators and to enhance their ability to successfully compete for extramural funding.

—Michael Schug

Program leader

Hal E. Broxmeyer, PhD
hbroxmey@iupui.edu
Distinguished Professor
Mary Margaret Walther Professor Emeritus
Professor of Microbiology/Immunology
IU School of Medicine

The Hematopoiesis (H), Hematological Malignancies (M) and Immunology (I) Program encompasses a group of highly interactive and collaborative investigators working in areas that complement the goal of understanding normal cell regulation and abnormalities associated with cancer and closely related preleukemic-type disorders.

Scientific goal

To continue defining cell regulation of blood and immune cells, enhancing hematopoietic stem cells (HSC) transplantation, understanding abnormalities of regulation in leukemia and related disorders and finding the means to mechanistically treat disease initiation and progression through a better understanding of cell and molecular processes.

Bone malignancy expert to become HMI co-leader

G. David Roodman, MD, PhD, the new director of the Division of Hematology Oncology at IU School of Medicine, will become co-leader of the Hematopoiesis, Hematological Malignancies and Immunology research program with long-time program leader **Hal Broxmeyer, PhD.**

A specialist in the diseases of the bone, Dr. Roodman is also the Kenneth Wiseman Professor of Medicine at IU. His research focuses on osteoclasts and osteoblasts, which are responsible for bone growth and bone resorption. He holds three National Institutes of Health grants and funding from the Multiple Myeloma Research Foundation and the U.S. Department Veterans Affairs. Over the past 10 years, Dr. Roodman has received significant financial support for his research, including more than $13.2 million in grant funding from the NIH.

Dr. Roodman said he was drawn to join IU because of the strength of the bone disease program and the university's researchers, clinicians and leadership.

"Indiana University has a world class bone (disease) group and a very strong hematologic malignancies program," Dr. Roodman said. "I hope to take advantage of that outstanding talent and organization already in place to build hematology oncology into an even stronger translational research program and recruit additional physician investigators to make the IU Simon Cancer Center a leader in the field."

Dr. Roodman has published more than 500 articles, book chapters, abstracts and editorials and serves on multiple editorial boards for professional journals, as well as being on the Scientific Advisory Board of the International Myeloma Foundation.

research highlights

Abbreviation used: EDT, Experimental and Developmental Therapeutics

Dr. Hal Broxmeyer's group found that inhibition of CD26/DPPIV on donor mouse bone marrow cells with small peptides (ILE-PPO-ILE=Diprotin A, or VAL-PYR) enhanced the engraftment of a long-term repopulating self-renewing population of HSC in lethally-irradiated congenic mice in a competitive and non-competitive transplant setting. This group, along with other colleagues, also showed that pretreating CD34+ cells from normal donors with Diprotin A enhanced their engraftment in sub-lethally-irradiated mice with a NOD/SCID genotype. Based on these and other studies, a pilot study was initiated under the direction of **Dr. Sherif Farag** in which single collections of cord blood (with either four of six or five of six HLA matched cells) were transplanted into end-stage patients with leukemia and lymphoma who were given myeloablative conditioning and treated with an orally active DPPIV inhibitor. More than 15 patients have been treated, with encouraging results. More patients will be treated to statistically analyze the results.

Dr. Louis Pelus's group found that the non-steroidal anti-inflammatory drug (NSAID), Meloxicam, enhances mobilization of HSCs and hematopoietic progenitor cells (HPCs) from mice and baboons. **Drs. Farag** and **Pelus** demonstrated that Meloxicam increases HSC/HPC mobilization in normal healthy volunteers. A pilot study to enhance mobilization of HSC/HPC by Meloxicam, alone and in combination with granulocyte-colony stimulating factor (G-CSF) is underway.

Drs. Christopher Touloukian, **Robert Nelson, Kenneth Cornetta** and **Theodore Logan (EDT)** have a pilot phase I study in preparation to treat patients with metastatic melanoma through infusion of gene-modified autologous G-CSF peripheral blood mobilized CD34+ cells. They hope to determine overall safety and toxicity.

Drs. Michael Robertson and **Mark Kaplan** continue their clinical collaboration evaluating the treatment of patients with relapsed/refractory B cell lymphoma in a phase I clinical trial of IL-18 and Rituximab.

Drs. Robertson and **Shivani Srivastava** are working on IL-18 augmentation of antibody dependent cellular toxicity (ADCC) against rituximab-sensitized human B cell lines *in vitro*.

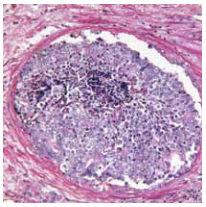
Drs. Reuben Kapur, **H. Scott Boswell** and colleagues have discovered a potential therapeutic target for treating hematological malignancies involving mutation of FLT3, KIT and BCR-ABL that may otherwise be resistant to imatinab and similar next generation tyrosine kinase inhibitors. Also, they found that using genetic approaches and a novel SHP2 inhibitor, II-BO8, identified from a focused library of indole-based salicylic acid derivatives, along with targeting a lipid kinase, may be useful for treating myeloproliferative neoplasms.

members

Rafat Abonour, MD
Jose Azar, MD
Chris Ballas, PhD
Janice Blum, PhD
H. Boswell, MD
Hal Broxmeyer, PhD
Randy Brutkiewicz, PhD
Angelo Cardoso, MD, PhD
Nadia Carlesso, MD, PhD.
Jamie Case, PhD
Rebecca Chan, MD, PhD
Hua-Chen Chang, PhD
Kristin Chun, PhD
D. Wade Clapp, MD
Kenneth Cornetta, MD
Larry Cripe, MD
James Croop, MD, PhD
Magdalena Czader, MD, PhD
David Delgado, MD
Alexander Dent, PhD
Robert Fallon, MD, PhD
Sherif Farag, MBBS, PhD
Xin-Yuan Fu, PhD
W. Goebel, MD, PhD
Shreevrat Goenka, PhD
Laura Haneline, MD
Helmut Hanenberg, MD
Paul Haut, MD
Mark Kaplan, PhD
Reuben Kapur, PhD
Yan Liu, PhD
Manjari Mazumdar, PhD
Christie Orschell, PhD
Louis Pelus, PhD
Karen Pollok, PhD
Kent Robertson, MD, PhD
Michael Robertson, MD
Hamid Sayar, MD
David Skalnik, PhD
Shivani Srivastava, MBBS
Edward Srour, PhD
Attaya Suvannasankha, MD
Christopher Touloukian, MD
Mingjiang Xi, MD, PhD
Feng-Chun Yang, MD, PhD
Mervin Yoder, MD

Bold denotes members accepted in 2011

Dr. Guise works to Improve bone metastases treatments



Cancer is a mischievous and persistent enemy that manages to invade other parts of the body, a process called metastasis. Certain tumors are prone to travel to different organs. In the case of breast, prostate and kidney cancers, bones are a favorite destination. Multiple myeloma, a cancer of the plasma cells, also manifests in the skeletal system.

What we don't know is why. Why does cancer hide there? Why does it flourish in certain places like bone?

Led by nationally acclaimed endocrinologist **Theresa Guise, MD**, a team of newly recruited Indiana University School of Medicine scientists is tackling these very questions with the hope of improving treatments for bone metastases and stopping them all together.

While bones may seem solid and unchanging, they are constantly fixing themselves and regenerating. As part of the body's normal function, cells called osteoclasts basically chew up old bone. Then osteoblasts build new bone to replace what was lost.

But when cancer spreads to the bone, it hijacks the process. The result can be that osteoclasts are thrown into overdrive, gobbling up too much and making the bone porous and weak. Or, on the flip side, osteoblasts can become hyperactive, spurring abnormal growth.

Dr. Guise has dedicated the better part of her career to figuring out how cancer disrupts bone remodeling.

She has identified a specific growth factor, called TGF-ß, that is key to cancer's success, and she is now working to block the factor from doing its dirty work. But the solution is not simple. TGF-ß can be found elsewhere throughout the body and in some places plays a helpful role, including—ironically—in tumor suppression.

So Dr. Guise and her team are investigating ways to deliver TGF-ß inhibitors directly to the bone in a way that avoids causing damage elsewhere in the body.

The co-leaders of the Tumor Microenvironment and Metastases developing research program each hold an RO1 and an UO1.

Dr. Guise's R01 is entitled "TGF-ß in the Bone Microenvironment: Role in Tumor Metastases." Her UO1 is "Differential TGF-ß Signaling in the Bone Microenvironment: Impact on Tumor Growth."

Dr. Clapp's UO1 is "Preclinical Testing of Targeted Therapies for Neurofibromas," and his RO1 is "Neurofibromatosis Type 1 Gene Regulates Myelopoiesis." Dr. Clapp is internationally recognized for his research in neurofibromatosis type 1, a crippling tumor-creating disorder. He led a team that developed the first promising, non-surgical treatment for this disease, which is one of the most common genetic conditions in humans.

Dr. Guise was recruited here from the University of Virginia in July 2009 and brought with her seven other members of her lab, including an orthopedic surgeon and three scientists with doctoral degrees. She has since added four more members to her team.

Though she looked at some of the top institutions in the country, including Yale, Vanderbilt, Johns Hopkins, Cleveland Clinic and MD Anderson, she ultimately chose IU School of Medicine because of the opportunity it offered to spend time in both the lab and the clinic and to collaborate with physicians and researchers across a range of disciplines.

Clinically, she treats patients whose bones may have been compromised due to radiation, chemotherapy, hormones and other therapies. That ties in nicely with another aspect of her research: focusing on the long-term effects of cancer therapies on the bone—an area that's becoming increasingly important as more patients are cured.

David Jaynes, Office of Visual Media/IU School of Medicine

Theresa Guise, MD, a nationally acclaimed endocrinologist, leads a team of scientists who hope to improve treatments for bone metastases. She has identified a specific growth factor and is working to block it from doing its dirty work.

Among those patients is Jerry Throgmartin, executive chairman of the board of electronics retailer HH Gregg. Throgmartin was diagnosed with lymphoma, a cancer of the lymph glands, some 30 years ago when he was just 24 years old. The cancer was first detected because of a nagging pain in his leg. At first, he thought it was a college football injury, but doctors discovered a tumor.

Throgmartin was treated with radiation and chemotherapy, but the cancer recurred a few years later in his intestine. He had surgery and an experimental bone marrow transplant. It worked.

Though Throgmartin has been cancer-free for decades, the effects still linger. While skiing, he planted his foot and snapped his leg—the result of bones rigid from disease and treatment. He now has a rod running through the center of his bone.

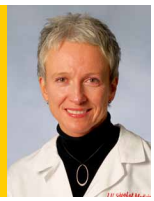
"As treatments get better and people live longer, they now have to look at the effects of treatment. I guess that's a good thing," Throgmartin said. "When I went through my treatment, they weren't thinking about the effects 30 years later. They were thinking about three years later."

Throgmartin serves as director of the IU Simon Cancer Center Development Board, and he and his wife, Peggy, made a gift to establish the Jerry W. and Peggy S. Throgmartin Chair in Oncology to support cancer research. The Throgmartins didn't specify that the money be used for bone-related research and instead gave cancer center leaders broad discretion to use the fund as they see fit. Fittingly, though, Dr. Guise has been named the first holder of the Throgmartin chair. Proceeds from the endowed fund support her work.

—Karen Spataro

Program leaders

Wade Clapp, MD
dclapp@iupui.edu
Richard L. Schreiner Professor and Chairman
Department of Pediatrics
Professor of Biochemistry and Molecular Biology
IU School of Medicine



Theresa Guise, MD
tguise@iupui.edu
Jerry and Peggy Throgmartin Professor of Oncology
Professor of Medicine
IU School of Medicine

The developing Tumor Microenvironment and Metastases research program spans the gamut from basic to clinical research in a wide range of environments to include brain, pancreas, prostate, breast, lung, liver, skin, neural plexus and ovary.

Scientific goals

To understand the role of the tumor microenvironment in cancer initiation, progression and metastases and focus on delineating the mechanisms of tumor-stromal interactions in human cancer.

Dr. Murray Korc is first Myles Brand Professor

Internationally recognized cancer researcher **Murray Korc, MD,** became the first Myles Brand Professor of Cancer Research on Oct. 1 at IU Simon Cancer Center.

"I feel humbled by the privilege of having been selected as the first physician-scientist to be the inaugural Myles Brand Professor, a position created to honor the memory and legacy of a transformative leader who championed academic excellence and integrity," Dr. Korc, most recently of Dartmouth Medical School, said. "I hope to work with my colleagues to design strategies for early pancreatic cancer detection, improved prevention and treatment modalities and meaningful prolongation of pain-free survival."

Dr. Korc, also professor of medicine and of biochemistry and molecular biology at IU School of Medicine, will become co-leader of the Tumor Microenvironment and Metastasis developing research program with **Theresa Guise, MD,** and he will be the director of the Pancreatic Cancer Research Program at the cancer center.

Dr. Korc's research has been continuously funded by the National Institutes of Health (NIH) since 1981. His focus is on aberrant growth-factor signaling in pancreatic cancer and genetic mouse models of pancreatic cancer, with the goal of designing novel therapeutic strategies. He has published more than 260 peer-reviewed manuscripts, and he is internationally recognized for his seminal contributions to the understanding of the role of the EGF receptor and transforming growth factor-beta in pancreatic cancer.

The Myles Brand Professorship was created to help physicians and scientists at the IU Simon Cancer Center to continue investigating devastating malignancies, such as pancreatic cancer, which claimed the life of Brand, the 16th president of Indiana University. Brand was president of the National Collegiate Athletic Association (NCAA) at the time of his death.

research highlights

Abbreviations used: BC, Breast Cancer; EDT, Experimental and Developmental Therapeutics; HMI, Hematopoiesis, Hematological Malignancies and Immunology

Drs. James Fletcher, **Mark Green** (unaligned member), **Gary Hutchins (BC)** and colleagues have completed two years of a four-year RO1 NIH Grant concerning whole-body 62Cu-ETS PET tumor perfusion imaging in patients with head and neck cancers. The study is designed to compare two approaches to quantitative analysis of 62Cu-ETS tumor images: the standardized uptake value (SUV) vs. more rigorous normalization of tumor uptake to an image-derived arterial input function by direct comparison to 15O-water perfusion imaging. These investigators are continuing to validate the 62Cu-ETS agent against the 15O-water reference standard in its capacity for measuring tumor perfusion and to assess how 62Cu-ETS PET perfusion data complements information available from the standard clinical whole-body 18F-FDG PET/CT studies of these patients for predicting response to therapy.

Drs. Kamnesh Pradhan and **Jamie Case** showed that polychromatic flow cytometry can identify a unique subset of cells that can serve as biomarkers of tumor-induced angiogenesis in children and young adults with malignant solid tumors. They are now testing it prospectively in children and young adults with sarcomas to study if these unique cells can serve as predictive and/or prognostic bio-markers of cancer directed therapies.

Dr. Jingwu Xie identified a new link between hedgehog signaling and tumor microenvironment. **Drs. Xie** and **E. Gabriela Chiorean (EDT)** are collaborating to identify new ways to treat pancreatic cancer through pre-clinical studies and clinical trials.

Dr. Yan Xu has received a five-year RO1 from the NIH TME (The Tumor Microenvironment) study section for "The Role of Immune Cell OGR1 in Prostate Cancer Development and the Mechanisms Involved." Dr. Xu's lab also has shown that calcium-independent phospholipase A2 (iPLA2) is a novel target for ovarian cancer.

Drs. Melissa Kacena, **Edward Srour (HMI)** and **Nadia Carlesso (HMI)** have shown that osteoblast lineage cells expressing high levels of Runx2 enhance hematopoietic progenitor cell proliferation and function. These studies reflect the importance of osteoblasts in the bone marrow microenvironment and in maintaining hematopoietic stem and progenitor cell function.

Drs. Melissa Kacena, **Lindsey Mayo**, **Theresa Guise** and **George Sandusky** have begun a collaboration examining the effects of regulating Mdm2 in osteosarcoma.

Drs. Kenneth Nephew and **Michael House** have shown that defects in the antioxidant system may contribute to tumorigenesis of a wide spectrum of human malignancies. Further, loss of glutathione peroxidase 3 (GPx3), a plasma antioxidant enzyme that maintains genomic integrity by inactivating reactive oxygen species by promoter hypermethylation, correlates with head and neck cancer (HNC) chemoresistance and may serve as a potential prognostic indicator for HNC patients treated with cisplatin-based chemotherapy.

Drs. Kent Robertson, **David Ingram**, **Feng-Chun Yang**, **Gary Hutchins**, **Cynthia Hingtgen** and **Wade Clapp** submitted a pilot phase 2 trial for the treatment of plexiform neurofibromas for publication. The group was awarded site selection in a national consortium of institutions focused on neurofibromatosis type 1 and 2 and Schwannomatosis. They also were selected to be members of a pre-clinical consortium for the treatment of NF1-associated associated cancers funded by the Children's Tumor Foundation.

members

Elliot Androphy, MD
Curt Balch, PhD
Jamie Case, PhD
Naga Chalasani, MD
Jonathan Cherry, PhD
John Chirgwin, PhD
Kai-ming Chou, PhD
Simon Conway, PhD
Karen Cowden Dahl, PhD
Judd Cummings, MD
Hong Du, PhD
A. Dunker, PhD
James Fletcher, MD
John Foley, PhD
Pierrick Fournier, PhD
Brenda Grimes, PhD
Peter Hollenhorst, PhD
Michael House, MD
David Ingram, MD
Travis Jerde, PhD
Melissa Kacena, PhD
Lisa Kamendulis, PhD
James Klaunig, PhD
Murray Korc, MD
Suk-Hee Lee, PhD
Hua Lu, MD, PhD
Mary Maluccio, MD, MPH
Keith March, MD, PhD
Khalid Mohammad, MD, PhD
Samisubbu Naidu, PhD
Kenneth Nephew, PhD
Beth Pflug, PhD
Kamnesh Pradhan, MD, MS
Lawrence Quilliam, PhD
Ernestina Schipani, MD, PhD
Christian Schmidt, MD, PhD, MBA
Hongmiao Sheng, MD
Dan Spandau, PhD
Lei Wei, PhD
Ronald Wek, PhD
Kenneth White, PhD
Jingwu Xie, PhD
Yan Xu, PhD
Cong Yan, PhD
Xiao-Ming Yin, MD, PhD

Bold denotes members accepted in 2011

Angiogenesis, Endothelial & Pro-Angiogenic Cell Core
Jamie Case, PhD – Director
317.278.7928
www.cancer.iu.edu/angiogenesis

The AEPCC conducts validated and highly reproducible in vitro *and* in vivo *angiogenesis, hematopoietic and polychromatic flow cytometry assays, which function as experimental platforms for understanding the basic mechanisms of hematopoiesis, angiogenesis and discovering compounds that inhibit new blood vessel formation in tumor microenvironments.*

Behavioral and Cancer Control Recruitment Core
Kim Wagler Ziner, PhD – Director
317.274.4342
www.cancer.iu.edu/behavioral

The Behavioral and Cancer Control Recruitment Core coordinates and supports recruitment of human subjects for behavioral oncology protocols. It will recruit participants directly or provide training and coordination of recruitment and it also provides consultation to investigators in the process of developing study protocols.

Biological Microscopy
Kenneth Dunn, PhD – Director
317.278.0436
www.cancer.iu.edu/biomicroscopy

The Indiana Center for Biological Microscopy is a comprehensive facility providing access to epifluorescence, confocal and multiphoton microscopy, as well digital image analysis systems. The center is also actively involved in developing methods of microscopy, in particular intravital microscopy.

Biostatistics & Data Management
Susan Perkins, PhD – Director
317.274.2626
www.cancer.iu.edu/biostats

The Biostatistics and Data Management Core of IU Simon Cancer Center has statistical, data management, administrative and educational responsibilities. The core participates in every level of research, from study planning and monitoring to data analysis and dissemination of results.

Chemical Genomics
Zhong-Yin Zhang, PhD – Director
317.274.8025
www.cancer.iu.edu/chemgen

The Chemical Genomic Core provides IU investigators with cost-effective access to high throughput screening of structurally-diverse, drug-like small molecules in biological assays provided by the investigators. This enables investigators to discover small molecule tools for basic research, therapeutic development and diagnostic applications.

Clinical Pharmacology Analytical Core
David Jones, PhD – Director
317.630.8726
www.cancer.iu.edu/cpac

The Analytical Core provides services to IU Simon Cancer Center members as well as the Indiana University School of Medicine faculty to assist in the:

- Quantification of drugs and metabolites
- Pharmacokinetic data analysis (noncompartmental, one or two compartmental analysis)
- Metabolite identification
- Protein binding of drugs

Clinical Research Office
Rafat Abonour, MD
Director, Adult CRO
317.274.3589

Kerry Bridges, MBA, RN, CCRC
Administrator, Adult CRO
317.274.2552

James Croop, MD, PhD
Director, Pediatric CRO
317.274.8784

Melissa Lee, BS, CCRA
Clinical Research Manager, Pediatric CRO
317.274.4281

www.cancer.iu.edu/cro

The Clinical Research Office is a shared resource for IU Simon Cancer Center members. Services enable the efficient conduct of adult and pediatric trials and include Protocol Review and Monitoring, training and supervision of staff and maintenance of research databases.

Flow Cytometry Resource Facility
Edward Srour, PhD – Director
317.274.3589
www.cancer.iu.edu/flow

The Flow Cytometry Resource Facility (FCRF) provides flow cytometric analysis and cell sorting services to IU Simon Cancer Center investigators. FCRF provides consultation, technical advice and collaboration, thus, promoting the application of cutting-edge flow cytometric technology to varied scientific investigations conducted at the cancer center.

***In Vivo* Biomedical Imaging**
Gary Hutchins, PhD – Director
317.274.3687
www.cancer.iu.edu/imaging

In Vivo *Biomedical Imaging provides IU Simon Cancer Center investigators with access to numerous state-of-the-art* in vivo *imaging technologies for both pre-clinical and clinical research applications. Technologies supported by the core include X-ray, CT, MRI, PET and optical imaging systems.*

***In Vivo* Therapeutics Core**
Karen Pollok, PhD – Director
317.274.8891
www.cancer.iu.edu/ivt

The mission of the In Vivo *Therapeutics (IVT) Core is to provide IUSCC investigators with cost-effective and comprehensive services to facilitate the development and testing of novel pharmacological and cellular therapies.*

Therapeutic Validation
Nagendra K. Prasad, BVSc, PhD
Director
317. 278.6608
www.cancer.iu.edu/therapeutic

The Therapeutic Validation Core (TVC) supports clinical investigators by offering basic science expertise to develop and implement correlative, pharmacodynamic and predictive biomarker assays necessary to validate mechanism(s) of action of novel anti-cancer agents/therapies and to formulate/test new hypotheses.

Tissue Procurement and Distribution
Colleen Mitchell – Operations Manager
317.274.2213

George Sandusky, DVM, PhD
Associate Director
317.274.3523

Oscar Cummings, MD – Director
317.274.3523

www.cancer.iu.edu/tissue

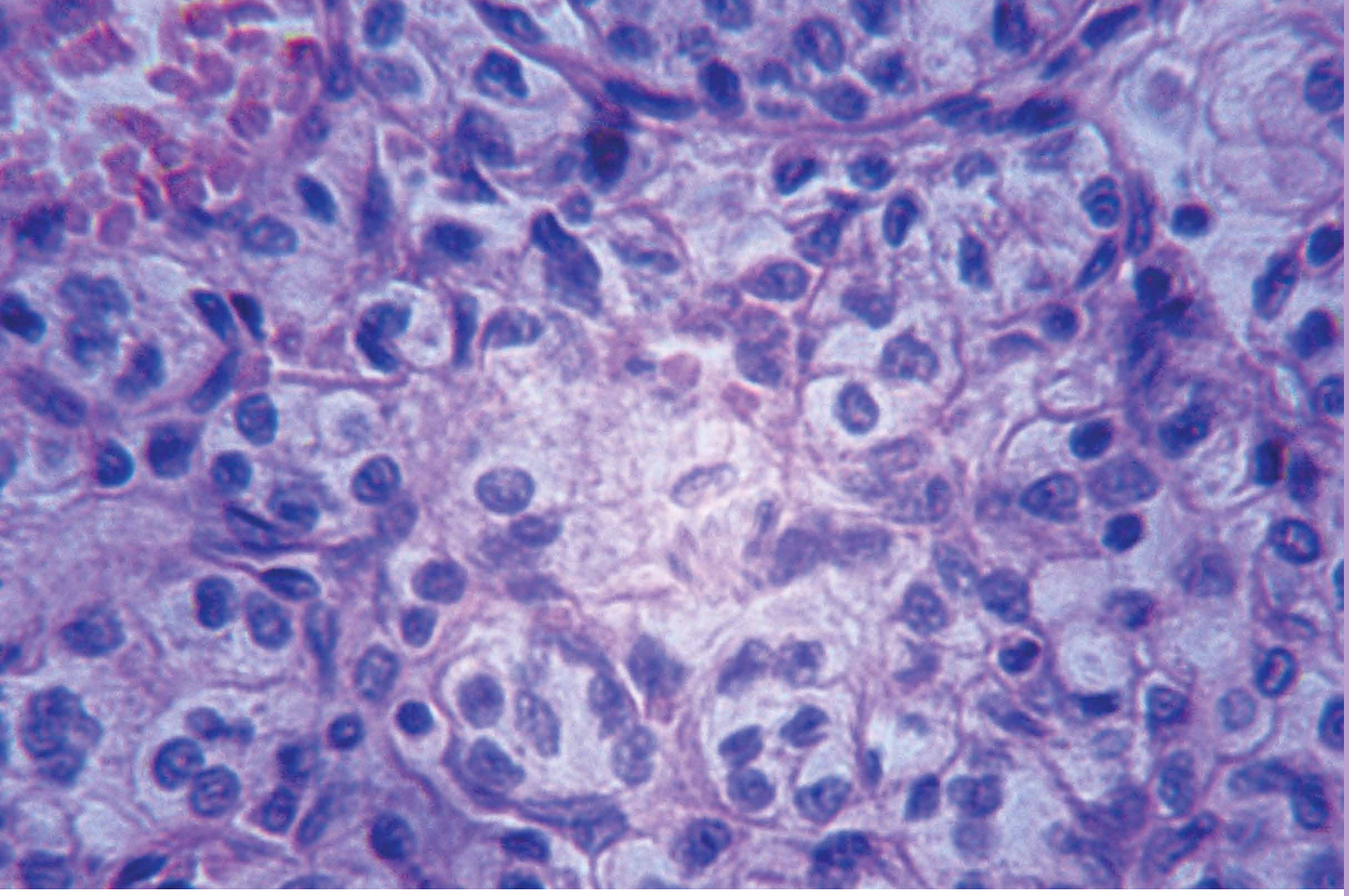
Tissue Procurement and Distribution provides samples for the discovery of new drug targets and biomarkers, the development of cancer cell lines and DNA and RNA research. It serves as a resource for the centralized banking of tissue, blood, bone marrow and buccal swab specimens procured from patients.

Transgenic and Knock-Out Mouse
Loren Field, PhD – Director
317.630.7776
www.cancer.iu.edu/mouse

The Transgenic and Knock-Out Mouse Core provides services for the production of genetically modified mice. The facility also provides advice concerning construction of transgenic and gene targeting constructs, animal breeding and maintenance of the resulting mouse colonies.

Translational Genomics
Sunil Badve, MD – Director
317.491.6484
www.cancer.iu.edu/transgen

The Translational Genomics Core Laboratory provides services for nucleic acid preparation, genotyping and gene expression profiling. Other services include microRNA profiling using TaqMan Array MicroRNA Cards and assessment of gene expression using individual TaqMan Gene Expression Assays or TaqMan Arrays.



The Indiana University Melvin and Bren Simon Cancer Center is an Indiana University School of Medicine and Indiana University Health partnership. Located in Indianapolis, IU Simon Cancer Center serves as a regional and national referral center for state-of-the-art cancer treatment and is Indiana's only National Cancer Institute-designated cancer center that provides patient care. The partnership between IU School of Medicine and IU Health is dedicated to establishing a state-wide health care delivery system that is supported by the scientific resources and clinical expertise of the medical school. The IU Simon Cancer Center research physicians and scientists include more than 200 investigators who conduct research in four programs: Breast Cancer, Cancer Control, Experimental and Development Therapeutics and Hematopoiesis, Microenvironment and Immunology. A fifth program, Tumor Microenvironment and Metastases, is under development. In addition, IU Simon Cancer Center physicians lead 300 clinical trials for pedicatric and adult cancers.

This report is also available at cancer.iu.edu/news.

MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

NCI·CC
A Cancer Center Designated by the National Cancer Institute


MELVIN AND BREN SIMON
CANCER CENTER
INDIANA UNIVERSITY