INDIANA UNIVERSITY MELVIN AND BREN SIMON CANCER CENTER

2012 SCIENTIFIC REPORT

EXECUTIVE COMMITTEE

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Harikrishna Nakshatri, BVSc, PhD
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Associate Director of Administration

A LOOK INSIDE

FROM THE DIRECTOR

Marked by growth in our developing research program, 2012 also was notable for the recruitment of key faculty leaders and an extraordinary research investment.

Our developing Tumor Microenvironment and Metastasis (TMM) research program now boasts 42 members who collectively held $11.3 million in external peer reviewed funding at the end of the year. Led by internationally known cancer experts **Theresa Guise, MD,** and **Murray Korc, MD,** the TMM members are working to advance the basic understanding of the role of cancer cell stromal interactions in cancer initiation, progression and metastasis in order to evaluate the functions of the metastatic niche and to translate this knowledge into discovery of new cancer targets and therapies, focusing on the bone and pancreas.

Overall, investigators from the developing TMM program, along with their colleagues from our four other programs—Breast Cancer, Cancer Prevention and Control, Experimental and Developmental Therapeutics, and Hematopoiesis, Malignant Hematology, Immunology—all work toward our mission to ***dramatically decrease mortality and suffering from cancer by conducting outstanding translational research, by providing excellence in education and by delivering high-quality, patient-centered care.***

I invite you to learn more about each program by reading the research highlights and accomplishments from 2012 in our scientific report.

In the past year, IU Simon Cancer Center and the IU School of Medicine recruited several key faculty leaders, including:

- **Dr. Gary Dunnington,** a surgical oncologist focused on breast and endocrine diseases, was named chief of the Department of Surgery. He is founding medical director of the breast multidisciplinary programs at University of Southern California and Southern Illinois and a nationally recognized leader in medical education.
- **Dr. Helmut Hanenberg,** associate professor in the Department of Pediatrics, studies Fanconi anemia genes. He has identified five novel FA genes, three of which are recognized as cancer susceptibility genes.
- **Dr. Tao Lu,** assistant professor of pharmacology and toxicology, focuses on NFKB regulation and tumorigenesis.
- **Dr. Rebecca Silbermann,** assistant professor of medicine, is a translational researcher who focuses on multiple myeloma in the clinic and laboratory.
- **Dr. Mingjiang Xu,** associate professor of pediatrics and of medical and molecular genetics, explores the role of TETZ gene alternation in the pathogenesis of myeloid malignancies.
- **Dr. Leslie Fecher,** assistant professor in hematology/oncology, specializes in the research and treatment of malignant melanoma.
- **Dr. Fredrick Chite Asirwa** completed his hematology/oncology fellowship at the IU Simon Cancer Center and is now medical co-director of the AMPATH Oncology Program in Eldoret, Kenya. His research focus is on hematology disorders, breast cancer and multiple myeloma.
- **Dr. Linda Han,** professor of surgery, is the new surgical co-director of the IU Simon Cancer Center Breast Cancer Program.
- **Dr. Jodi Skiles** finished her hematology/oncology fellowship in the Department of Pediatrics and is now the medical co-director of pediatric oncology for the AMPATH Oncology Program in Eldoret, Kenya.

These recruitments strengthen the depth of the cancer center and the IU School of Medicine, allowing us to continue to affect the course of the disease so that patients everywhere will benefit from our research.

In early 2012, the IU School of Medicine and Indiana University Health announced an extraordinary research collaboration. Over the next five years, each will invest $75 million in the Strategic Research Initiative (SRI) to enhance the institutions' capabilities in fundamental scientific investigation, translational research and clinical trials. Development of innovative treatments for three of the most important health care areas—cardiovascular, neuroscience and cancer—is at the heart of this investment. Before the end of 2012, the SRI led to the recruitment of a dedicated leukemia researcher. **Dr. Sophie Paczesny** studies biomarkers of complications following bone marrow transplantation to personalize treatment among leukemia patients.

We accomplished much in 2012, but we have much more to do. Research is at the heart of making progress against cancer, enabling us to find better ways to prevent, detect and treat the disease. Within the core of each member of the IU Simon Cancer is the drive to make a meaningful impact in the field of cancer such that the burden of this disease is not carried by future generations. On behalf of more than 200 cancer researchers, I assure you that this is not just a job for us, but rather this is our promise.

Patrick J. Loehrer, Sr., M.D.
H.H. Gregg Professor of Oncology
Director, IU Simon Cancer Center
Associate Dean for Cancer Research
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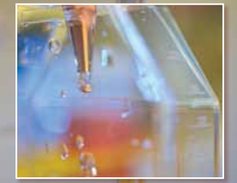
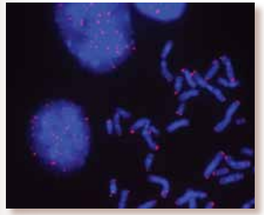


AFTER 70 YEARS OF STUDY, TELOMERES STILL FASCINATE RESEARCHERS SEEKING CANCER CURES



Up close: telomeres.

Telomeres were just a footnote in 1946 to Indiana University zoologist Hermann Müller's Nobel Prize-winning research for the discovery that mutations can be induced by X-rays. By magnifying chromosomes, Müller observed caps on their tips and appropriately named them "end parts" or telomeres. Subsequent decades of research worldwide is revealing telomeres are more than just the protective "tips" of chromosomes that activate cell death as cells mature and telomeres shorten. Now, decades later, research is revealing their potential impact on a broad spectrum of human health and diseases, including cancer.

Brittney-Shea Herbert, PhD, walked into her lab one day and saw with excitement that her breast cancer cells were dead. She was testing an "immortalization" inhibitor, imetelstat, that had been developed by her mentors at UT-Southwestern Medical Center at Dallas. The inhibitor was targeting the telomerase enzyme that denies metastatic cells senescence, the capacity to grow old and die. It had already been published that normal cells would become "immortal" when the enzyme was added, and that cancer cells almost uniformly express the active enzyme. Dr. Herbert's experiment tested what would happen if she could block this enzyme's effect on telomeres in cancer cells. She had her proof.

This method of targeting telomerase in cancer cells led to the development of a potent inhibitor of this enzyme by the Geron Corp., and which is being used in Drs. Herbert's and **Dr. Kathy Miller's** research at the IU Simon Cancer Center as part of a productive, long-term collaboration. Notably, the first breast cancer patient in the world to receive it participated in a Phase I clinical trial developed by Dr. Miller in 2006. After initial treatments, the results were very encouraging—encouraging enough to launch a nationwide Phase II trial comparing chemotherapy alone to chemotherapy and the inhibitor. However, that study exposed the inhibitor's Achilles heel. Imetelstat's impact on the enzyme was not limited to its presence in tumors. It also targets and attacks telomerase in hematopoietic stem cells. When combined with chemotherapy, and in particular paclitaxel, the effect on bone marrow function did not allow for blood-cell recovery after long-term treatment.

"We want the drug in the tumor, but not in the bone marrow," Dr. Miller said. While this remains her ultimate goal, for now she is using imetelstat with trastuzumab in highly refractory HER2+ tumors. Early studies suggest that it re-sensitizes cancer cells to trastuzumab (Herceptin). And, because chemotherapy is not part of the regimen, there is no double whammy effect on hematopoietic stem cells.

Dr. Herbert notes that imetelstat can enter almost any cancer cell type, including drug-resistant cells and in particular HER2+ cells that are resistant to Herceptin. There are several theories about drug resistance, including a faulty pumping mechanism that empties the cells of the drug, a faulty receptor on the cell surface or up-regulation of other growth factor receptors on the cell surface overwhelming the HER2 receptor. Her theory is that the sticky oligonucleotides that comprise the drug bind to these receptors allowing imetelstat to effectively enter via the HER2 receptor.

The challenge remains for Drs. Herbert and Miller to overcome the use of the inhibitor combined with chemotherapy, but they're not daunted. In fact, earlier disappointment resulting from bone marrow toxicity is now allowing them to explore new research strategies. While they continue their work with mature metastatic cancer cells, including cancer cells that are aggressive with BRCA1 mutations, Herbert is also focusing on the elusive breast cancer stem cell.

Much like their hematopoietic cousins, breast cancer progenitor cells are also rich in the telomerase enzymes. Herbert rationalizes that the enzyme's presence during hematopoiesis is essential to lifelong blood cell differentiation and proliferation. Yet this evolutionary tactic that is good for the blood cell system remains the bane of the cancer cell treatment. Breast cancer stem cells that elude initial chemotherapy are able to differentiate and give rise to metastatic cells resistant to chemotherapy.

Dr. Herbert is now capturing these developing tumor cells when they are rapidly dividing and differentiating, and she is demonstrating that imetelstat is disrupting the growth and function of these cells causing them to die before they can multiply and potentially re-populate the tumor. She and Dr. Miller are developing strategies to direct the inhibitor to cancer cells only, thereby protecting bone marrow vitality.

And so the story continues: Initial excitement is tempered by measured progress. The cascade of telomere research that now spans seven decades continues at Indiana University. Drs. Herbert and Miler represent the new generation of investigators committed to understanding and appreciating the nuances of Müller's "end tips." Armed with this knowledge, they are positioning themselves to advance care for women with metastatic breast cancer.

—By Mary Maxwell

IF YOU'RE A RESEARCHER INTERESTED IN OBTAINING SAMPLES, VISIT KOMENTISSUEBANK.IU.EDU OR CALL 866.763.0047.

INDY'S SUPER CURE WRAP-UP REPORT

John R. Gentry photo

Before two NFL football teams descended on Indianapolis for Super Bowl LXVI, two other teams assembled in the Circle City to help defeat breast cancer.

One team was composed of nearly 700 women—46 percent of whom represented minority populations—who selflessly donated healthy breast tissue to the Susan G. Komen for the Cure® Tissue Bank at the IU Simon Cancer Center. The other team included the 600 volunteers needed to seamlessly pull off the collections.

The two came together the weekend before the Super Bowl for Indy's Super Cure. The bold initiative was developed by the 2012 Indianapolis Super Bowl Host Committee to raise awareness about the tissue bank, the first and only healthy breast tissue bank in the world.

Indy's Super Cure also successfully increased minority participation among donors. African Americans represented 36 percent of the donors, Latinas 7 percent and other minorities 3 percent. From past collection events, African American women represented only 3.5 percent, while Latinas represented less than 1 percent.

"I'm overwhelmed by the tremendous response," **Anna Maria Storniolo, MD,** director of the tissue bank and professor of clinical medicine at IU School of Medicine, said. "In a typical year, about 500 women take time to donate a precious piece of themselves. In one weekend, a year's worth of donors showed up. It's still amazing to me, but it demonstrates the determination of women to contribute to finding a cure for breast cancer."

By collecting samples from women without breast cancer, researchers may be able to determine the differences between healthy and cancerous tissue, which will lead to a better understanding of the disease.

In addition to IU researchers, investigators from the National Cancer Institute, Mayo Clinic, George Washington University, Dana-Farber Cancer Institute, the University of Queensland-Australia, and others have used samples from the tissue bank in their research.

In July 2013, tissue bank staff will travel to Kenya to collect samples that will enhance research into why breast cancer behaves differently in people of different ethnic backgrounds.

—Michael Schug

BREAST CANCER RESEARCH PROGRAM

PROGRAM LEADERS

George Sledge Jr., MD
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Professor of Medicine and Pathology
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In late 2012, Dr. Sledge left Indiana University. Dr. Miller succeeded him as co-leader.

MEMBERS

Sunil Badve, MBBS, MD
Monet Bowling, MD
Susan Clare, MD, PhD
Jill Fehrenbacher, PhD
Anthony Firulli, PhD
David Flockhart, MD, PhD
David Gilley, PhD
Brenda Grimes, PhD
Linda Han, MD
Chunyan He, ScD
Brittney-Shea Herbert, PhD
Gary Hutchins, PhD
Mircea Ivan, MD, PhD
Philip Johnson, PhD,
Lang Li, PhD
Laurie Littlepage, PhD
Samy Meroueh, PhD
Lida Mina, MD
Kenneth Nephew, PhD
Milos Novotny, PhD
Jenifer Prosperi, PhD
Milan Radovich, PhD
Andrew Saykin, PsyD
Bryan Schneider, MD
Todd Skaar, PhD
Roger Slee, PhD
Keith Stantz, PhD
Anna Maria Storniolo, MD
Hiromi Tanaka, PhD
Tracy Vargo-Gogola, PhD
Claire Walczak, PhD
Clark Wells, PhD
William Wooden, MD
Qi-Huang Zheng, PhD
Kim Ziner, RN, PhD

Bold denotes members accepted in 2012

THE PROGRAM

The Breast Cancer Program, a collaboration of the IU School of Medicine and Indiana University-Bloomington, 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 three themes:

- Cell signaling pathway alterations
- Genomic/epigenetic alterations
- Therapeutic individualization

SELECTED RESEARCH HIGHLIGHTS

Dr. Harikrishna Nakshatri's laboratory is focused on understanding the biology of breast cancer through translational research. The group is engaged in five research projects: 1.) Serum biomarkers of breast cancer with a focus on microRNAs. In this project, the group reported that serum from cancer patients contain elevated levels of small RNA U6 compared to serum from healthy individuals. 2.) Anthrax toxin receptor one (ANTXR1) as a biomarker and target of cancer stem cells. The group observed higher ANTXR1 expression in normal breast stem and progenitor cells compared to differentiated cells. 3.) Therapeutic targeting of breast cancer stem cells in which the researchers used connectivity map and various bioinformatics tools to identify FDA-approved drugs that target breast cancer stem cells. 4.) The group identified a new brain and adrenal metastasis signature of breast cancer by comparing gene expression pattern in human cancer cells isolated from metastasis to lungs, bone, adrenal gland and brain in a xenograft model. 5.) The role of AKT1 isoform in estrogen addiction phenotype of breast cancer. The researchers discovered that AKT1 but not AKT2 isoform is essential for optimum estrogen-regulated gene expression. AKT1-dependent estrogen responsive genes constitute a good prognostic signature. They also found that specific AKT isoforms determine the sensitivity of breast cancer cells to a PI3K/mTOR inhibitor.

Dr. Tracy Vargo-Gogola and colleagues investigated the role of p190B RhoGAP, which is a major inhibitor of RhoA and Rac GTPases, in mammary epithelial morphogenesis and cancer. They discovered that p190B has pro-tumorigenic functions during ErbB2-induced mammary tumor formation and metastasis. Further, they have shown that in the absence of an initiating oncogene, targeted overexpression of p190B to the mammary epithelium *in vivo* disrupts mammary gland (MG) architecture, increases mammary epithelial cells (MEC) proliferation, and induces aberrant stromal activation. Investigation of the mechanisms underlying these phenotypes revealed that p190B overexpression increases MEC contractility that is dependent on Rac activity. The increase in MEC contractility is concomitant with the induction of stromal desmoplasia characterized by increased deposition of collagen and laminin and elevated expression of the collagen remodeling enzyme lysyl oxidase. FAK and ERK activities and proliferation are elevated in the p190B overexpressing MECs. These data have led Vargo-Gogola to propose a model where p190B overexpression in primary MECs *in vivo* leads to increased Rac-dependent contractility that perturbs the mechanical force balance between the epithelial and stromal compartments. This leads to stromal activation, including increased extracellular matrix (ECM) deposition and remodeling, resulting in a more rigid ECM. The increased ECM rigidity feeds back on the epithelium to promote aberrant proliferation and altered tissue architecture.

Dr. Vargo's lab also is interested in elucidating the role of the Rho GTPase Cdc42 in MEC morphogenesis and breast cancer. Using MECs isolated from Cdc42 conditional knockout mice in combination with a 3D culture morphogenesis assay, Dr. Vargo's group has shown that Cdc42 is required for primary MEC proliferation, survival, and apical polarity during mammary acinus formation. To investigate the contribution of Cdc42 overexpression to the stochastic process of mammary tumor formation and metastasis *in vivo*, Dr. Vargo's lab has generated conditional Cdc42 overexpressing mice. Cdc42 overexpression induces aberrant MG branching and ductal dilation suggesting that Cdc42 overexpression increases MEC proliferation and disrupts polarity *in vivo*. Reported *in vitro* studies have implicated Cdc42 in ER-positive and ErbB2-positive tumorigenesis. Thus, future studies will be aimed at investigating the contribution of Cdc42 overexpression to ER-positive ductal carcinoma in situ formation and progression and ErbB2-induced adenocarcinoma formation and metastasis using conditional mouse models.

Dr. Samy Meroueh's lab worked to optimize the potency and efficacy of small molecules that inhibit the interaction between the urokinase receptor and its serine protease ligand. The parent compounds were found to inhibit MDA-MB-231 invasion in a concentration-dependent manner. Structure-based designs followed by chemical synthesis of derivatives have shown that a carboxylate moiety on the parent compound is critical for inhibition. In addition, the position of the carboxylate appears to influence the level of cytotoxicity that the compound exhibits against breast cancer cells. The researchers also initiated an effort to assess the efficacy of this compound *in vivo* to assess the *in vivo* pharmacokinetic properties of the compound and to perform a preliminary dosage study. In a parallel effort, the researchers collaborated with **Drs. George Sledge** and **Susan Clare** to develop potent and selective inhibitors of a series of ser/thr kinases that emerged from a next-generation screening effort.

Dr. Todd Skaar and colleagues focused on determining the functional consequences of germline genetic variants in genes important to the pharmacokinetics and pharmacodynamics of endocrine therapies. His group identified a genetic variant in the 3'UTR of the HNF4A gene, which is involved in regulating many of the genes that determine the pharmacokinetics of several drugs used in the treatment of breast cancer. The researchers showed that this variant alters the ability of a miRNA to target the HNF4A mRNA. Using dextromethorphan as a CYP2D6 probe drug, they also showed that this variant has clinical consequences. Skaar's lab also published studies showing that a genetic variant in the TATA box of the estrogen receptor beta promoter reduced the promoter function. Using a variety of mechanistic *in vitro* studies, they also created a Bayes model for identifying estrogen receptor alpha regulatory networks in breast cancer cells.

> "IN COLLABORATING WITH CLINICIANS AND BASIC SCIENCE INVESTIGATORS IN THE BREAST CANCER RESEARCH PROGRAM, BIOINFORMATICIANS INVESTIGATE THE GENOME, TRANSCRIPTOME AND PROTEOME. USING THESE DATA, MOLECULAR SIGNATURES ARE CONSTRUCTED TO PREDICT BREAST CANCER RISK AND CANCER DRUG RESPONSE AND CANCER MOLECULAR MECHANISMS ARE IDENTIFIED FOR FUTURE INVESTIGATION."
>
> Lang Li, PhD

INVESTIGATORS FOCUS ON IMPROVING QUALITY OF LIFE, COMMUNICATIONS AMONG PATIENTS WITH ADVANCED CANCER

Dr. Joan Haase

Patients with advanced cancer face many challenges, ranging from dealing with symptoms such as pain and fatigue to challenges with communications about their disease with both providers and family members. For some patients with advanced cancer, they face additional challenges as they undergo stem cell transplants, a life-threatening procedure that often represents the best, and sometimes the only option, for cure of the disease. Dealing with advanced cancer is almost always accompanied by physical, psychological and social problems that interfere with either short- or long-term quality of life. Researchers with the Cancer Prevention and Control program are involved in finding ways to help patients and their families with the devastating issues that accompany cancer at advanced stages.

Dr. Joan Haase is internationally known for her work in helping children, adolescents, young adults and families positively adjust to the experience of cancer and other chronic illnesses using a resilience model. **Drs.** Haase, **Sheri Robb, Debra Burns, Paul Haut** and **Patrick Monahan** evaluated the efficacy of a therapeutic music video intervention to increase resilience-related outcomes for adolescents and young adults during stem cell transplant. The R01 randomized clinical trial was the first behavioral study to be conducted through the Children's Oncology Group. Based on efficacious findings from the study, the music therapy intervention is now the standard of care for adolescents and young adults in both arms of a competing continuation R01 awarded in 2012 to Drs. Robb and Haase. The new randomized clinical trial is evaluating the efficacy of a parent communication intervention delivered by music therapists to further improve resilience related-outcomes for adolescents and young adults and to also address parent distress and improve family adaptability, cohesion and communication.

Dr. Susan Hickman, who is nationally recognized for her work with the POLST (Physician Orders for Life-Sustaining Treatment) paradigm, and Dr. Haase are involved with the interdisciplinary Palliative Care/End-of-Life Communication initiative among cancer center behavioral scientists and clinical investigators. This initiative evolved into the Research in Palliative and End-of-Life Communication and Training (RESPECT) Center, which Indiana University-Purdue University Indianapolis designated as an exploratory signature center. IUPUI signature centers represent an area of research strength and focus in an area that is not commonly studied. As such, the RESPECT Center's goals are to:

- Accelerate the development of innovative descriptive and intervention research trials relevant to communication and decision making in children, adolescents, adults and elders with serious and/or life-threatening illness
- Develop new community partnerships for translational science to enhance palliative and end-of-life care research and practice
- Create mentorship opportunities for developing scholars who will become the next generation of productive, passionate palliative and end-of-life care researchers

Other CPC investigators are designing and testing communication strategies for physicians to discuss end-of-life preferences with patients with advanced cancer and their families. That includes making sure patients fully understand their prognosis. Decades of observational data demonstrate that oncologists don't have these conversations often or in a timely fashion. **Dr. Kevin Rand,** partnering with **Dr. Larry Cripe (HMI),** explores the relationships between patient and provider communications about end-of-life health care decisions in patients with advanced cancer and quality of life outcomes.

"We've found that even when cure is no longer a goal of treatment, some patients continue to consider it the single most important life goal, and that these patients experience more psychological distress than their peers," Dr. Rand said. "We are trying to devise communication strategies that will foster not only better patient understanding of prognosis and goals of treatment, but greater acceptance as well. The ultimate aim is to help patients make more fully-informed decisions and receive care near the end of life that is consistent with their values."

Debra S. Burns, PhD, MT-BC, studies music-based interventions and coordinates the music therapy program at the cancer center. Dr. Burns partnered with a national hospice that provided data on approximately 30,000 patients who received care between 2006 and 2010. About half of those patients—many of them cancer patients—received some form of music therapy. The initial goal is to analyze the data and to characterize how music therapy has been integrated into hospice care, how it is delivered, who refers patients and family members and who actually utilizes the services. "This is just the preliminary work to see how music therapy is delivered because it's one of the fastest growing discretionary services within hospice," Dr. Burns said.

Dr. Catherine Mosher, a psychologist who is studying patients and families with advanced lung cancer, is one of a few investigators to include families and caregivers into interventions that help survivors deal with many symptoms that accompany advanced lung cancer. Dr. Mosher collaborates with **Dr. Nasser Hanna (EDT)** to test telephone interventions addressing pain, depression and fatigue in patients coupled with helping caregivers deal with the stress of providing care to their family members.

—MIchael Schug

HPV WORKING GROUP DEVELOPS INTO A RESEARCH CENTER

The human papillomavirus (HPV) working group received funding from the IUPUI Signature Center Initiative, the IU School of Medicine Department of Pediatrics and the IU Simon Cancer Center to create the Indiana University-Purdue University Indianapolis Center for HPV Research. Adolescent health specialists **Gregory Zimet, PhD,** and **Dennis Fortenberry, MD,** serve as co-directors of the center. The center's research will span the scientific continuum, ranging from improving understanding of HPV at the basic science level to conducting social and behavioral research aimed at maximizing HPV vaccination rates. The group will work to stimulate additional collaborative research projects with the goal of developing program project applications and/or multidisciplinary R01 submissions.

To translate its research into practice, the Center for HPV Research will partner with Cervical Cancer Free Indiana (CCFIN), which is jointly led by Dr. Zimet and Rivienne Shedd-Steele, director of the IU Simon Cancer Center's Office of Health Disparities and Outreach. Shedd-Steele will work to take the center's evidence-based findings and apply them to programs administrated by community partners.

The working group is composed of faculty members and postdoctoral fellows, representing five IU schools and 10 departments spanning the IUPUI and IU Bloomington campuses as well as the University of Notre Dame. Prior to joining the working group, many of these scientists were already actively engaged in collaborative, interdisciplinary, externally-funded research focused on topics such as the natural history of HPV infections in young women and men and determinants of HPV vaccination.

—Amber Kleopfer Senseny

CANCER PREVENTION AND CONTROL RESEARCH PROGRAM

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Debra Burns, PhD
Janet Carpenter, PhD
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Betsy Fife, PhD
J. Dennis Fortenberry, MD
Joan Haase, PhD
David Haggstrom, MD
Chunyan He, ScD
Susan Hickman, PhD
Karen Hudmon, DrPH
Thomas Imperiale, MD
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Chiung-ju Liu, PhD
Anna McDaniel, PhD
Brenna McDonald, PsyD
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Catherine Mosher, PhD
Julie Otte, PhD
Kamnesh Pradhan, MD
Kevin Rand, PhD
Susan Rawl, PhD
Douglas Rex, MD
Sheri Robb, PhD
Andrew Saykin, PsyD
Peter Schwartz, MD, PhD
Marcia Shew, MD, MPH
Nathan Stupiansky, PhD
G. Marie Swanson, PhD
Frederick Unverzagt, PhD
Michael Vasko, PhD
Diane Von Ah, PhD
Bree Weaver, MD
Jianjun Zhang, MD, PhD

THE PROGRAM

The Cancer Prevention and Control Program (CPC) includes members from seven schools and 13 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, including prevention, early detection and survivorship.

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: PREVENTION

- To prevent the development of cancers by studying human behavior and causative agents linked to development of cancer (e.g. smoking, HPV virus, unsafe sexual practices).

THEME 2: EARLY DETECTION

- To test interventions that increase adherence to cervical, breast and colorectal cancer screening and translate successful interventions to clinical practice.

THEME 3: SURVIVORSHIP

- To develop and test interventions to decrease symptoms experienced by cancer patients and their families/ caregivers throughout survivorship and to identify biological mechanisms that are related to neurotoxicity of cancer treatment.

SELECTED RESEARCH HIGHLIGHTS

Dr. Darron Brown and colleagues focused on the prevention of cancer through studying the transmission of HPV and development of the HPV vaccine. Building on basic science, clinical investigators study the effectiveness of HPV vaccination, while behavioral investigators identify factors related to vaccine acceptance in the community. Dr. Brown, internationally known for his research in the natural history of oncogenic HPV infections in young women, was one of the lead scientists instrumental in developing the HPV vaccine. Once fully implemented worldwide, the vaccine may save more than a million lives each year by substantially reducing the incidence of cervical, anal, vulvar, vaginal and other cancers. Dr. Brown and colleagues, including **Dr. Elliot Androphy (TMM),** who possesses significant expertise in the mechanism of HPV-induced malignancies, continue to investigate factors related to persistence of HPV infection and progression of infection to cancer.

The prevention or detection of cancer at an early stage can frequently translate to complete cure. Research has demonstrated that early detection of cervical, breast and colorectal cancer through routine screening can reduce both morbidity and mortality for these diseases. Breast and colon cancer screening are particularly relevant in Indiana where mortality from both diseases is higher than the U.S. average and screening rates are lower. Of particular concern in Indiana are screenings in underserved populations. **Dr. Victoria Champion,** in collaboration with **Dr. Susan Rawl,** has received five-year R01 funding that supports research to increase breast and colon cancer screenings.

Dr. Thomas Imperiale studies patient-centered outcomes of digestive diseases, with a special focus on colorectal cancer screening. He is studying risk factors for advanced colorectal neoplasia in order to produce risk-based CRC screening guidelines that are patient-tailored and can be implemented in the clinic. Dr. Imperiale is site co-investigator of a second R01 from the NCI in which he seeks to understand how patients consider the tradeoffs among the various screening tests and strategies related to colorectal cancer. He is collaborating with Dr. Rawl in the study of an intervention to increase screening among African-Americans. Dr. Imperiale is also involved in comparing a new fecal-based test for colorectal neoplasia against a fecal immunochemical test.

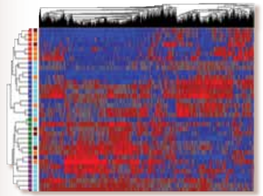
Dr. Diane Von Ah worked collaboratively with **Drs. Janet Carpenter, Frederick Unverzagt, George Sledge (BC), Patrick Monahan,** and Champion to identify the incidence of cognitive dysfunction among breast cancer survivors (BCS). They found that BCS reported significantly higher levels of subjective memory loss and scored significantly worse than controls on learning and delayed memory recall. This research suggested that a sizeable percentage of BCS have clinically significant cognitive impairment. In addition, Dr. Von Ah worked with Drs. Carpenter and **Storniolo (BC)** to understand the impact of cognitive dysfunction on quality of life in BCS. In a biracial sample of 134 BCS (46% African American, 54% Caucasian women), they found that deficits in attention were related to poorer quality of life, including more depressive symptoms, lower well-being, poorer physical functioning and greater fatigue. In attempting to understand the underlying mechanisms of cognitive dysfunction, Dr. Von Ah worked collaboratively with Drs. Carpenter, **Todd Skaar (BC), Bryan Schneider (BC),** and Unverzagt to explore the role of serotonin on cognitive functioning in female BCS. They found that serotonin may play a key role in deficits related to long-term memory recall and psychomotor functioning by using the acute tryptophan depletion paradigm. Other collaborators included **Drs. Andrew Saykin (BC),** Unverzagt and Monahan.

Drs. Patrick Monahan and **Kurt Kroenke** are recipients of a R01 grant to validate the NIH Patient Reported Outcomes Measurement Information System (PROMIS) pain and depression profile and short-form measures with respect to: sensitivity to change, establishment of minimum important differences including a Delphi expert panel and diagnostic accuracy of depression measures compared to structured clinical interview. Measurement of pain and depression are key to identifying and treating these problems in cancer populations.

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

> "RESEARCHERS AT THE IU SIMON CANCER CENTER ARE LEADING THE NATION IN TREATMENTS TO MINIMIZE THE SIDE EFFECTS OF CHEMOTHERAPY. WE ARE RESEARCHING WHETHER AND HOW MUCH MEDICATION, ACUPUNCTURE, LIFESTYLE CHANGES, MEMORY TRAINING AND OTHER TREATMENTS CAN HELP PATIENTS COPE WITH SIDE EFFECTS TO IMPROVE THEIR QUALITY OF LIFE."
>
> Janet Carpenter, PhD, RN

IU RESEARCH LEADS TO RISK FACTOR TEST FOR RARE CHEST CANCERS



Up close: A heat map showing unsupervised hierarchical clustering of 34 fresh-frozen thymomas.

Predicting the risk of recurrence, as well as the best course of post-operative treatment, is a challenge faced by oncologists working on all types of cancer. But research by Indiana University physician scientists **Sunil Badve, MBBS, MD, Patrick Loehrer Sr., MD,** and Yesim Gökmen-Polar, PhD, could result in a genetic test to predict the risk of recurrence for thymoma, a rare tumor of the upper chest.

Castle Biosciences, a cancer-based molecular diagnostics company whose mission is to serve individuals afflicted with rare or orphan cancers, announced in June 2012 worldwide exclusive license for the intellectual property and technology rights related to a gene expression profiling test for use in thymoma. The test is based upon research presented by Drs. Badve, Loehrer and Gökmen-Polar at the American Society of Clinical Oncology's annual meetings in 2011 and 2012. The agreement was made possible by Indiana University Research and Technology Corp. (IURTC) and the Indiana Clinical and Translational Sciences Institute (CTSI), which provided pilot funds to the project.

"Obtaining objective molecular data to support traditional histological assessment will lead to improved diagnostic accuracy for thymomas and thymic cancers," Dr. Badve said. The test under development, called DecisionDx-Thymoma, could provide an objective, accurate assessment of an individual's risk of metastasis. This knowledge could assist physicians in developing individualized treatment plans that reduce the amount of painful side effects caused by adjuvant treatments such as radiation and chemotherapy, he said.

Thymomas and thymic cancers are rare, but they are one of the most common types of cancers found in the upper chest. Tumors are often discovered on a chest X-ray when a patient suffers from chest pain, cough or difficulty swallowing—or a previously associated autoimmune disorder—and can spread throughout the chest and body. Treatment consists of surgical removal followed in some cases by radiation or chemotherapy. However, Dr. Badve said that experts are not yet able to accurately assess patients' risk of metastasis or recurrence. While clinical analysis of tumor size, excision and patient symptoms can help determine a tumor's severity, they cannot predict an individual patient's risk.

A more accurate assessment of recurrence risk provided by DecisionDx-Thymoma could reduce or eliminate the need for these painful additional treatments following the tumor removal in patients who test at low risk for re-developing thymic tumors.

"The ability to accurately assess metastatic risk based upon the thymoma's molecular signature will enable personalizing therapeutic options," Dr. Loehrer, director of the Indiana University Melvin and Bren Simon Cancer Center and an international expert on thymomas and thymic carcinomas, said. "This will assist in deciding which patients should receive post-operative therapy."

Dr. Badve said IU is uniquely positioned to collect and analyze thymomas and thymic tumors because of researchers such as Dr. Loehrer, who has been sought by patients for expert care for the past 15 years. Dr. Badve himself has developed one of the largest bio-epositories with more than 600 thymic tumors, including tumors from patients at referring institutions.

Drs. Badve and Loehrer and their colleagues recently published their work on molecular analysis of thymoma from 34 thymoma patients, which contributed to the selection of the target genes using Prediction Analysis of Microarrays (PAM) for the development of the genetic test.

The partnership between Castle Biosciences and the IU investigators was brokered by the IURTC in the fall of 2011 after the group worked with the IU investigators to file disclosure on the genes used in their research prior to their poster presentation at ASCO 2011. The partnership with Castle Biosciences provides access to state-of-the-art facilities capable of technical validation of the thymoma test in CAP-accredited, CLIA-certified laboratories. The third investigator on the research that led to the partnership with Castle Biosciences, Dr. Gökmen-Polar, is an assistant research professor in the Department of Pathology & Laboratory Medicine at the IU School of Medicine.

With the molecular diagnostic company's assistance, Dr. Badve said the validation process was significantly expedited and a clinical test made available to the public much sooner than if the work had been performed in a university laboratory. The thymoma test was available for clinical use in July 2012—less than one year after the license with IURTC was signed.

"This whole effort has been the perfect combination of a research scientist, clinician and pathologist working together," Dr. Badve said. "Everyone played complementary research roles to bring about a real change in cancer treatment for patients with thymoma."

—Kevin Fryling

Cancer center members' names appear in bold.

IU RESEARCHERS IDENTIFY PROTEIN TARGET THAT COULD LEAD TO THERAPIES FOR HARD-TO-TREAT CANCERS

Drs. Chan (left) and Kapur

IU Simon Cancer Center researchers identified a compound that targets a cancer-related protein, suggesting it could offer a future therapy for difficult-to-treat cancers. The protein, called SHP2, emerged as a potential new "druggable target" in research published in *Blood*, the journal of the American Society of Hematology.

Rebecca Chan, MD, PhD, and **Reuben Kapur, PhD,** and colleagues determined that SHP2 was hyperactive in cells with a mutation in the KIT receptor in several types of leukemia, including acute myeloid leukemia and mast cell leukemia. Patients with the mutation were considered to have a poor prognosis.

The researchers noted that patients with the mutation who were diagnosed with gastrointestinal stromal tumors responded well to treatment with the drug Gleevec. However, in patients with other diseases such as acute myeloid leukemia who had the same mutation, Gleevec was much less effective. That, the authors noted, made it vital to identify other drug targets for diseases with the particular mutation.

Chan and Kapur collaborated with **Zhong-Yin Zhang, PhD,** a biochemist who had identified a small molecule that inhibits that activity of SHP2, to assess the effectiveness of the small molecule inhibitor in shutting down the protein. In the laboratory tests, the compound IIB-08 was moderately effective in blocking the activity of SHP2 in samples of patient cancer cells and in mouse models of leukemia. Growth of the laboratory cell lines was reduced and the survival time of the animals was prolonged. However, when combined with other small molecule inhibitors, the impact of the drug was much greater.

"The combination significantly enhanced the survival of the animals bearing the mutation," Dr. Kapur said. "It's more than a synergistic effect. It's pretty profound." The results indicate that SHP2, working with other proteins in the body, induces growth of cancerous cells and that the IIB-08 compound is a promising candidate for blocking that SHP2 activity, Dr. Kapur said.

The research was supported, in part, by grants from National Institutes of Health: R01 HL077177, R01 HL08111 and CA152194.

—Eric Schoch

EXPERIMENTAL AND DEVELOPMENTAL THERAPEUTICS RESEARCH PROGRAM

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Ahmad Safa, PhD
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Jian-Ting Zhang, PhD
Adam Zlotnick, PhD

Bold denotes members accepted in 2012

THE PROGRAM

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 and back. 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

SELECTED RESEARCH HIGHLIGHTS

The molecular mechanisms of NER and NHEJ repairs of therapy-induced DNA damage in lung cancers are the focus of the research in **Dr. John Turchi's** laboratory. Previous studies have demonstrated the essential role of two proteins, replication protein A (RPA) and xeroderma pimentosum group A protein (XPA), in the recognition of cisplatin-damaged DNA. Dr. Turchi's lab developed a high throughput screening assay to identify small molecule inhibitors of these proteins and, in collaboration with **Dr. Zhong-Yin Zhang**, they identified and confirmed a series of hits on RPA. In collaboration with **Dr. Jian-Ting Zhang** for in-silico screening of XPA inhibitors, Dr. Turchi found a number of compounds that sensitized cells to cisplatin DNA damage as expected for XPA inhibitors. The hypothesis is that by reducing repair of cisplatin-damaged DNA the damage is longer-lived and induces greater cell killing. Tumor types that typically do not respond to or resist cisplatin because repair has been activated can be sensitized to this agent. Likewise, cancers that have developed resistance as a result of increased DNA repair can be sensitized to this agent. Human cancer xenograft studies are being developed to determine *in vivo* activity of these agents.

Dr. Jian-Ting Zhang's laboratory elucidated the role of eIF3a in regulating cisplatin sensitivity and in translational control of nucleotide excision repair (NER) of nasopharyngeal carcinoma. Translational control is a major and important regulatory mechanism of gene expression. eIF3a has been shown to play an important role in regulating translation of a subset of mRNAs and found to correlate with cancer prognosis. Using nasopharyngeal carcinoma (NPC) cells as a model system, the researchers tested the hypothesis that eIF3a negatively regulates synthesis of NER proteins, consequently, NER activities and cellular response to cisplatin treatment. They found that eIF3a expression is increased in a cisplatin-sensitive subclone S16 isolated from a NPC cell line CNE2 via limited dilution. Knocking down its expression in S16 cells increased cisplatin resistance, NER activity and synthesis of NER proteins such as XPA and XPC. Altering eIF3a expression also changed cellular response to cisplatin and UV treatment in other NPC cell lines. Dr. Zhang and colleagues concluded that eIF3a plays an important role in cisplatin response and NER activity of NPC by suppressing synthesis of NER proteins.

Dr. Mark Kelley and colleagues, including **Dr. Michael Vasko (CPC)**, showed that targeting APE1's DNA repair function may be beneficial for peripheral neuropathy resulting from certain cancer therapies. There is clear evidence that peripheral neuropathy and cognitive dysfunction occur following treatment with ionizing radiation (IR) as well as with a host of chemotherapeutic agents, including alkylating and cross-linking agents. To date, the cellular mechanisms for cognitive dysfunction or peripheral neuropathy have not been identified. Furthermore, there are no standard and effective treatments available to prevent or reverse therapy-induced neurotoxicity. One promising area that requires further exploration is the ability of DNA repair mechanisms to reverse the neurotoxic effects of a number of anti-cancer drugs. Studies in animal models show that enhancing the base excision repair pathway attenuates neuronal damage by chemotherapeutic agents, suggesting that manipulating DNA repair mechanisms may be a novel approach to diminish neurotoxicity during or after cancer therapy. The overall hypothesis of these studies is that small molecules that enhance APE1's DNA repair function, acting to protect neurons after cancer therapy and to help maintain normal neuronal function. The DNA base excision repair (BER) pathway, including APE1 (apurinic/apyrimidinic endonuclease/redox factor) has been shown to be the major DNA repair pathway for alkylating agent DNA damage as well as DNA damage caused by reactive oxygen species (ROS) such as generated by a number of chemotherapeutic agents. It is likely that DNA repair would be critical to the maintenance of the genome to express correct proteins and that DNA damage could result in abnormal protein production in response to alkylation and oxidative stress that can occur following cancer treatments. This damage could alter the function of neurons and have pathological consequences on the peripheral (and central) nervous systems. DNA repair enzymes, including APE1, could play a critical role in maintaining homeostasis in neuronal tissue after chemotherapy or IR treatments. Understanding the importance of APE1 in regulating neuronal function during cancer therapy is critical to understanding the etiology of neuronal damage and repair.

Dr. Samy Meroueh's laboratory studies new drugs targeting the urokinase receptor (uPAR). His central hypothesis is that the inhibition of the interaction between the urokinase receptor (uPAR) and its ligand urokinase (uPA) will shut down proteolysis in the cellular milieu as well as signaling through other cell surface receptors such as integrin. This is expected to result in significant impairment of tumor invasion and metastasis. Dr. Meroueh's group identified a series of molecules that inhibit the uPAR/uPA interaction. One compound in particular revealed suitable pharmacokinetic (PK) properties *in vitro*, which was reflected by the favorable PK properties *in vivo*. The compound was not only bioavailable, reaching nearly 40 uM concentration in plasma, but it had a stable half-life of two hours. Dr. Merouch and colleagues are assessing the compound for its ability to block metastasis of MDA-MB-231 cells from breast to lung in mouse models.

Abbreviation used: CPC, Cancer Prevention and Control

> "ONLY INCREMENTAL ADVANCES IN THE CLINIC CAN BE EXPECTED FROM INCREMENTAL ADVANCES IN SCIENCE. DRAMATIC INCREASES IN CANCER TREATMENT HAVE AND WILL COME FROM PURSUING NOVEL, RISKY IDEAS. EDT RESEARCHERS PUSH THAT BOUNDARY BY DEVELOPING NOVEL AGENTS THAT TARGET NEW MOLECULAR INTERACTIONS AND PATHWAYS NEVER BEFORE TARGETED, HOLDING THE POTENTIAL FOR DRAMATIC INCREASES IN TREATMENT EFFICACY AND PATIENT SURVIVAL."
>
> John Turchi, PhD

IU CORD BLOOD RESEARCH MAY SPEED UP ENGRAFTMENT FOR HIGH-RISK LEUKEMIA PATIENTS

Rick Reifenberg sports a "Terrible Two" shirt, celebrating the second anniversary of his successful umbilical cord blood transplant to treat high-risk acute myelogenous leukemia (AML), with his wife, Sara, and daughter, Kate, on Thanksgiving Day 2012.

(Photo courtesy Rick Reifenberg.)

On Nov. 22, which happened to be Thanksgiving Day in 2012, Rick Reifenberg exercised, showered and shaved. All routine activities for most people; but not that long ago, they would have been overwhelming for Reifenberg. For him, the day marked the second anniversary of his umbilical cord blood transplant to treat high-risk acute myelogenous leukemia (AML). His ability to get up and exercise served as a reminder of his progress because it used to exhaust him to simply move from the couch to the bathroom. Shaving also was a sign of progress. He purposely sported a beard for two years as a symbolic reminder of the months when his platelet count was too low and a simple nick with a razor could have resulted in a visit to the emergency room.

He was truly thankful for this day. Reifenberg, 47, who was a primary care physician before his diagnosis and is now a health care administrator, was familiar with AML because he had seen and referred patients with the disease in the past. "I had never seen anyone with AML survive," he said. "Needless to say, when I went into this, my assumption was that I probably would not survive."

In the summer of 2010, Reifenberg developed flu-like symptoms: low grade fever, chills and body aches. Instead of getting better, the symptoms worsened, and he soon saw his doctor. A blood test revealed he had leukemia. He began chemotherapy right away, but he had a severe reaction to it. He was hospitalized for 42 days, including two in the intensive care unit. He eventually improved and achieved a complete remission, although it would only be temporary without a bone marrow transplant because of his high-risk disease.

However, Reifenberg's four siblings were not a match for a bone marrow transplant. He was then added to a national bone marrow registry. Six hundred matches were found. Unfortunately, he was looking at a minimum of four to six weeks before anything would get started with an allogeneic bone marrow transplant. Time was not on his side.

Sherif Farag, MBBS, PhD, presented Reifenberg with another option—an option that could happen much more quickly. Dr. Farag, a physician researcher at the IU Simon Cancer Center, told Reifenberg about umbilical cord blood transplantation. Since the cord blood is already collected and stored, the wait is much shorter. And Dr. Farag was leading a clinical trial in which patients were orally taking sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor approved for treating Type 2 diabetes. The trial was testing to see if sitagliptin would enhance the engraftment process after a single cord blood transplant. Dr. Farag is the principal investigator of the multi-center, National Institutes of Health-supported study.

Now Reifenberg, a husband and father, had to make a decision. He understood the risks with both the bone marrow and cord blood procedures. He understood that engraftment—a process when the donated cells home to the bone marrow and start to grow and make new blood cells—may not happen with an umbilical cord blood transplant, especially since the numbers of stem cells in a single collection of cord blood is more limited than that which can be obtained after multiple aspirations of bone marrow.

"I wanted to try everything that I could," Reifenberg said. He enrolled in the clinical trial. Surrounded by his wife, parents and sister—all in gowns and masks in an isolation unit—Reifenberg and his family watched as the stem cells made their way into his body via the intravenous line placed in his right upper chest. He would then take sitagliptin for four days. On day 18, engraftment occurred for Reifenberg. The average time for engraftment for the 17 patients with high-risk disease—including Reifenberg—enrolled in Dr. Farag's pilot study was 21 days.

"You would typically expect engraftment at 28 days for such patients given the number of cord blood cells and disease risk and stage. We've cut that by a week," Dr. Farag said. "Obviously, it needs to be proven with additional studies."

The early results are encouraging because minimizing the time until engraftment reduces the risk of infection and the number of platelet and blood transfusions a patient may receive. It also increases a patient's chance of long-term survival.

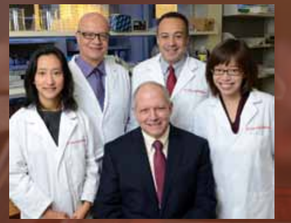
Dr. Farag's study is based on earlier work done by **Hal Broxmeyer, PhD,** a pioneer in the field of umbilical cord blood stem cell transplantation. As one of the first scientists to recognize the value of harvesting stem cells from cord blood, Dr. Broxmeyer was a member of the international team that performed the first transplant of this kind in France in 1988.

For Reifenberg, the IU research and the compassionate care he received from Dr. Farag and his "talented" team made him especially thankful. "We spent the rest of the day visiting with family and celebrating the unbelievable miracle this has been for me," he said of the two-year anniversary. "My brother asked a priest friend of his to come to the house, and we finished the day with a special celebratory mass that was held in honor of my healing. I could not have asked for a better day."

—Michael Schug

STRONG IU MYELOMA RESEARCH PROGRAM EXPANDS

Indiana University has widely expanded its efforts to address bone-related aspects of myeloma research. Since the IU School of Medicine is home to one of the strongest bone research programs in the world, with multiple scientists who are international leaders in various aspects of bone development and metastasis, the myeloma team is capitalizing on this expertise to explore how the marrow microenvironment and myeloma patients' abnormal immune systems contribute to tumor growth, bone destruction and chemotherapy resistance.



Front, left to right: Drs. Suvannasankha, Roodman (seated) and Silbermann. Back, left to right: Drs. Abonour and Farag.

The team is currently exploring a number of critical questions specific to myeloma:

- How are non-myeloma cells in the bone marrow microenvironment changed by the presence of myeloma? How do the myeloma cells "co-opt" the normal cells to further increase tumor growth, chemotherapy resistance and the bone disease associated with myeloma?
- How do we prevent bone disease associated with myeloma? How do we reverse these changes to make the bone marrow inhospitable to myeloma?
- How do we improve quality of life for patients by repairing damage already caused to the bones?

Among those working on answering those questions is **G. David Roodman, MD, PhD,** director of the Division of Hematology/Oncology at IU School of Medicine. He is an internationally known expert in myeloma bone disease whose work focuses on increasing the understanding of osteoclasts and osteoblasts, which are the cells that build and destroy bone, respectively.

Dr. Roodman recruited **Rebecca Silbermann, MD,** a physician scientist whose research focuses on the role of angiogenesis—thought to be a major contributor to tumor growth and poor outcomes for patients—in the development of bone lesions in myeloma patients. She also conducts research related to proteins in the blood that regulate bone destruction in patients, with the long-term goal of preventing bone loss by exploiting the protein as a drug target.

As a member of many national and international boards and committees dedicated to myeloma, **Rafat Abonour, MD,** continues to build collaborations for improving myeloma treatment options and ensuring that IU patients have early access to new drugs through the most promising clinical trials. Dr. Abonour has fueled much of the growth of the IU myeloma program through his annual Miles for Myeloma event, generating more than $2 million for research in the past eight years.

Sherif Farag, MD, PhD, continues to serve as director of the IU Health Simon Cancer Center's nationally-ranked Hematological Malignancies and Bone Marrow and Blood Stem Cell Transplantation Program. In addition to drug development and novel combination therapies, Dr. Farag's research focuses on novel stem cell transplant approaches for patients with myeloma and other blood cancers, including ways to harness the immune cells of patients against their cancer.

Attaya Suvannasankha, MD, is a physician scientist whose research is aimed at better understanding why some myeloma patients respond well to certain drugs and others do not. Her team's long-term goal is to identify specific differences in each individual patient's cancer cells so that each person can receive highly tailored therapies to address his or her specific cancer.

—Amber Kleopfer Senseny

HEMATOPOIESIS, MALIGNANT HEMATOLOGY, IMMUNOLOGY RESEARCH PROGRAM

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Mervin Yoder, MD
Baohua Zhou, PhD

Bold denotes members accepted in 2012

THE PROGRAM

The Hematopoiesis, Malignant Hematology, Immunology Program encompasses a group of highly interactive and collaborative investigators working in areas that complement each other toward the goal of understanding normal cell regulation and abnormalities associated with cancer and closely related pre-leukemic-type disorders.

SCIENTIFIC GOALS

To continue defining cell regulation of blood and immune cells, enhancing hematopoietic stem cell (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.

SELECTED RESEARCH HIGHLIGHTS

Work begun in **Dr. Hal Broxmeyer's** laboratory identified the cell surface protein CD26, a dipeptidylpeptidase IV (DPPIV), as a negative effector of the action of the homing molecule, the CXC chemokine stromal derived factor (SDF)-1/CXCL12. DPPIV truncated CXCL12 such that the truncated CXCL12 was no longer chemotactic for hematopoiesis stem (HSC) and progenitor (HPC) cells and truncated CXCL12 blocked the chemotactic activity of the full-length CXCL12. The Broxmeyer lab then demonstrated that inhibition of DPPIV activity with small peptides such as Diprotin A (ILE-PRO-ILE) or Val-Pyr enhanced the engrafting capacity of limiting numbers of mouse bone marrow cells in lethally irradiated congenic mice and of human cord blood cells engrafting sub-lethally irradiated immune deficient mice. Based on this information and more recent work from the Broxmeyer lab that demonstrated that DPPIV had similar negative effects on hematopoietic growth factors, a clinical study was initiated by **Dr. Sherif Farag** in which an FDA-approved orally active DPPIV inhibitor (sitagliptin) was used to treat patients with leukemia and lymphoma in context of cord blood transplantation. The primary objectives of this trial were to evaluate safety and efficacy of *in vivo* DPPIV inhibition. The study demonstrated safety and a median time to neutrophil engraftment of 21 days, which is quite rapid based on the relatively low cell numbers and the 2 of 6 HLS disparate grafts used for many of the adult patients. Analysis of DPPIV inhibition *in vivo* by sitagliptin, as well as more information from Drs. Broxmeyer, Farag, **Louis Pelus** and **Edward Srour** indicated that the full effectiveness of DPPIV inhibition for enhancing engraftment of single cord blood units in adult patients with leukemia and lymphoma has not yet been realized. Drs. Broxmeyer and Farag received a five-year multi-PI NIH R01 grant to study mechanisms of DPPIV inhibition and to initiate a multi-center clinical trial to verify and expand their studies.

Drs. Pelus, Farag, **Magdalena Czader, Theresa Guise (TMM)** and Srour demonstrated the HSC/HPC mobilizing capacity of the non-steroidal anti-inflammatory (NSAID) drug meloxicam in mice, baboons and in healthy normal human volunteers. Meloxicam synergizes with G-CSF to further mobilize HSCs and HPCs.

Abbreviation used: TMM, Tumor Microenvironment and Metastases

Multiple Myeloma (MM) is the most frequent malignancy that involves bone and is characterized by extensive osteolytic bone destruction. The marrow microenvironment plays a critical supportive role in MM and enhances tumor growth and bone destruction through activation of signaling pathways in marrow stromal cells. Several such pathways converge on p62. **Dr. G. David Roodman** and colleagues used small molecules that target the ZZ domain of p62 in marrow stromal cells to decrease the growth of cells from patients with MM, the expression of VCAM-1, an adhesion molecule, IL-6 production, known to be involved in growth of MM cells, and osteoclast formation. Studies are ongoing to utilize this information regarding blocking protein interactions involving the p62-ZZ domain to develop a novel therapeutic approach for treating MM.

Dr. H. Scott Boswell and colleagues used a novel Flt3/raf inhibitor (sorafenib) plus a pan HDAC inhibitor (vorinostat) to treat patients with relapsed/refractory acute myelogenous leukemia (AML). Among patients with Flt3 ITD positive cells and complex karyotypes, a 71 percent overall response rate occurred with the first cycle of therapy, including a complete remission that lasted eight months. In contrast, the group that was not selected only had a 46 percent response rate. **Drs. Reuben Kapur, Boswell** and others are evaluating constitutive activation of RHO kinase (ROCK) in cells bearing oncogenic forms of KIT, Flt3, and BCR-ABL, which is dependent on PI3 kinase and Rho GTPase as a potential therapeutic target for treating hematological malignancies involving mutations of Flt3, KIT and BCR-ABL that may otherwise be resistant to imatinab and similar next-generation inhibitors. They also used 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 for possible use in treating myeloproliferative neoplasms.

Dr. Michael Robertson and colleagues, based on pre-clinical and clinical studies, are developing a Phase I study of interleukin-18 and ofatumumab after autologous stem cell transplantation for CD20+ B cell lymphoma.

"WITH A PERSONALIZED MEDICINE INSTITUTE AND ONE OF THE MOST COMPREHENSIVE BIOBANK STRUCTURES IN THE UNITED STATES, IU SIMON CANCER CENTER RESEARCHERS ARE AT THE FRONTLINE TO DISCOVER NEW BIOMARKERS AND THERAPEUTICS THAT WILL CHANGE MEDICAL PRACTICE AND CUSTOMIZE IT TO EACH PATIENT."

Sophie Paczesny, MD, PhD

YOUNG INVESTIGATORS FIND COLLABORATIVE SPIRIT AT CANCER CENTER

Drs. Travis Jerde and Melissa Kacena

Cancer center membership is at the heart of the research progress that **Melissa Kacena, PhD,** and **Travis Jerde, PhD,** have realized at Indiana University. Each anticipated access to high-quality shared facilities and pilot project opportunities. But it was the cancer center's naturally collaborative environment with an eye on translational research that has fueled their team science opportunities.

Dr. Kacena traded a top bone research environment at Yale in 2007 for an equally strong program at IU. Since her arrival, though, the recruitment of an additional seven bone investigators has resulted in what is now the largest bone group in the world with a growing expertise in cancer.

"I feel like I won the lottery," she said about the expansion of the bone program. Dr. Kacena's membership in the Tumor Microenvironment and Metastasis (TMM) research program is leading to research that addresses osteosaracoma, a rare and aggressive primary cancer of the bone that strikes children.

Dr. Kacena, together with **Theresa Guise, MD,** and **Lindsey Mayo, PhD,** has begun examining the function of proto-oncogene Mdm2 that is highly expressed in osteosarcoma. When a normal gene is altered by mutation, it becomes an oncogene that will either die a natural death or contribute to cancer. Proto oncogenes play a major role in determining this outcome. The team has found that Mdm2 appears to differentially regulate osteosarcoma metastasis and osteolysis (breakdown of bone causing significant bone pain).

It was her search for a flow cytometer on campus that led to her first collaborative opportunity and initial membership in the cancer center's Hematopoiesis, Malignant Hematology, and Immunology (HMI) research program. There she met **Edward Srour, PhD,** and **Nadia Carlesso, MD.** Their expertise in hematopoiesis combined with Dr. Kacena's focus on megakaryocytes (platelet producing cells) and their role in osteoblast proliferation (cells that form bone) allowed them to explore blood/bone interactions together. They are now studying the complex hematopoietic microenvironment, or hematopoietic niche, with special focus on osteoblast cells.

In this environment, the full lineage of stem cells stimulate and respond to cell signaling instructions as they mature and differentiate. Recently, they identified ALCAM as an important marker on cells in this niche. It is a universal marker on mouse and human hematopoietic stem cells and osteoblasts, and ALCAM expression impacts the interaction of these cells and can determine stem cell fate.

Dr. Jerde also was looking for a dynamic pharmacology program when he was recruited to IU in 2010. On a more practical level, however, he needed sophisticated microscopy and flow cytometry facilities for his prostate cancer studies. He found both. Like Dr. Kacena, his first visit to the flow cytometry facility led to collaborations with Dr. Srour. Although a member of the TMM program, Dr. Jerde finds the cancer center programs highly interactive.

"Collaboration is not an accident here. It's part of the environment. In fact, if you tried to keep me in a silo, I'd find some way to get out," Dr. Jerde said. He is collaborating with HMI members **Drs. Srour** and **Hal Broxmeyer, PhD,** and Timothy Ratliff, PhD, director of the Purdue University Center for Cancer Research. Together they have identified four markers involved in prostate cancer epithelial cell proliferation. They are learning that these cells, when present in the highly inflammatory prostate cancer environment, expand rapidly and adapt easily. Comparative analysis of epithelial stem cells and human prostate cancer cells is now beginning.

Another of his collaborations focuses on how prostate cancer cells evade chemotherapy. Dr. Jerde was studying the survival pathway that prostate cancer cells develop to evade standard chemotherapy when he learned that **Mark Kelley, PhD,** and **Melissa Fishel, PhD,** had developed a compound that re-sensitizes cancer cells to treatment. Together they are working with **Jian-Ting Zhang, PhD,** and have developed a hypothesis on the critical role that survivin, a key cellular survival protein in prostate cancer cells, plays in the development of drug resistance to prostate cancer. The group—all members of the Experimental and Developmental Therapeutics research program—is showing that APE1/Ref-1 inhibition works through survivin-mediated pathways and sensitizes previously resistant prostate cancer cells to docetaxel.

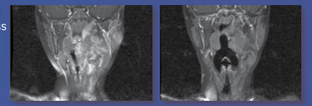
Jerde is also the founder and director of Indiana Basic Urologic Research working group, a collaboration of 22 prostate cancer researchers at the Indiana and Purdue cancer centers. Both centers are providing pilot project funding to foster dynamic interactions with an eye on leveraging extramural grant funding.

Drs. Kacena's and Jerde's passion for research is realized in the interactions they enjoy with other scientists and the potential that exists to improve lives devastated by cancer.

—Mary Maxwell

CANCER RESEARCHERS REPORT FIRST EFFECTIVE TREATMENT OF TUMORS ARISING FROM COMMON GENETIC DISEASE NF1

Physician researchers at IU School of Medicine and the IU Simon Cancer Center have reported the first effective therapy for a class of previously untreatable and potentially life-threatening tumors often found in children.



The scan on the left reveals an inoperable tumor that was progressively obstructing a toddler's airway, while the scan on the right shows an open airway three months later after treatment with imatinib.

Announcing their findings in *Lancet Oncology*, the researchers said the drug imatinib mesylate, marketed as Gleevec as a treatment for chronic myeloid leukemia, provided relief to a significant number of patients with plexiform neurofibromas, tumors caused by neurofibromatosis type 1, or NF1.

"Although this was a small study, the results were significant, particularly given that such patients have had few treatment options for what can be a very debilitating disease," said first author **Kent Robertson, MD, PhD.** "We believe these findings warrant larger trials of both imatinib mesylate as well as other similar compounds that would appear promising in laboratory tests."

Affecting about one in every 3,000 children born, NF1 is the most common neurological disorder caused by mutations in a single gene.

Symptoms can include development of café au lait spots and disfiguring tumors on or just under the skin. Internally, tumors can develop along nerve tissue and cause problems if they begin to press against vital organs or the windpipe.

The tumors have been nearly impossible to treat with radiation or chemotherapy drugs and are poor candidates for surgery. In the study, of 23 patients who received the drug for at least six months, six experienced a 20 percent or more decrease in the volume of one or more plexiform neurofibromas, and 30 percent of patients had improvements in symptoms.

Primary investigator **D. Wade Clapp, MD,** noted that even relatively small reductions in tumor size can result in significant relief of symptoms for patients, such as improved breathing and restoration of bladder control. Dr. Clapp led a team that developed the first promising, non-surgical treatment for this disease.

In earlier laboratory research, the researchers determined that Gleevec was effective in tissue culture and mouse models of NF1 tumors after discovering that a cellular signaling mechanism that Gleevec targets in chronic myeloid leukemia also played an important role in development of NF1 tumors.

—Eric Schoch

TUMOR MICROENVIRONMENT AND METASTASES RESEARCH PROGRAM

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Dan Spandau, PhD
M. Sharon Stack, PhD
David Waning, PhD
Ronald Wek, PhD
Kenneth White, PhD
Jingwu Xie, PhD
Yan Xu, PhD
Cong Yan, PhD

Bold denotes members accepted in 2012

THE PROGRAM

The Tumor Microenvironment and Metastasis Program, a developing 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

The research goals of the Tumor Microenvironment and Metastasis (TMM) Program are to advance our basic understanding of the role of cancer cell stromal interactions in cancer initiation, progression and metastasis; to evaluate the functions of the metastatic niche; and to translate this knowledge into discovery of new cancer targets and therapies. This will entail collaborations among TMM members and researchers from the cancer center's other programs. The long-term goals are to take advantage of the new genomics to devise novel preventive and targeted therapeutic strategies that improve cancer care.

SELECTED RESEARCH HIGHLIGHTS

Drs. Melissa Kacena and **Edward Srour (HMI)** have shown that ALCAM or CD166 is a common surface marker expressed on murine and human hematopoietic stem cells and on cells of the hematopoietic niche.

Drs. Kent Robertson, David Ingram, Feng-Chun Yang, Gary Hutchins (BC), Cynthia Hingtgen, Wade Clapp and **Simon Conway** submitted a pilot Phase II trial for the treatment of plexiform neurofibromas for publication. They were 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 cancers funded by the Children's Tumor Foundation.

Dr. Kenneth Nephew found cisplatin resistance in ovarian cancer is associated with aberrant methylation of tumor suppressor genes. Drs. Nephew and **Daniela Matei (EDT)** planned a clinical trial study to evaluate if decitabine can reduce methylation and sensitize ovarian cancers to cisplatin in recurrent ovarian cancer patients.

Dr. Nephew has an R01 from the NCI on DNA methylation and ovarian cancer, a R01 investigating novel bioconjugates as probes of estrogen receptors and a U54 with **Dr. Lang Li** on interrogating epigenetic changes in cancer genomes.

Drs. Melissa Kacena, Lindsey Mayo and **Theresa Guise** continue to collaborate to examine the effects of regulating Mdm2 in osteosarcoma.

Drs. James Fletcher, Mark Green and Gary Hutchins (BC) and colleagues completed the third year of a four-year RO1 NIH grant concerning whole-body 62Cu-ETS PET tumor perfusion imaging in patients with head and neck cancers. They compared 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. The group, in collaboration with **Dr. Theodore Logan (EDT),** more recently evaluated patients with renal cell cancer before and after receiving Sutent.

Drs. Hong Du and **Cong Yan** are studying how inflammation induces cancer formation and metastasis. They identified that myeloid-derived suppressor cells (MDSCs) are critical in this pathogenic process, over-activation of the mTOR pathway controls development and function of MDSCs in lysosomal acid lipase knock-out mice and they identified a number of cancer-associated secretory biomarkers that can be used for lung cancer prediction and verification.

Dr. Yan Xu conducted studies with an RO1 from the NIH TME (The Tumor Microenvironment) study section In addition, Dr. Xu and colleagues showed that the PLA2 activities in ovarian cancer microenvironment elevated and secreted phospholipase A2 activities as new potential therapeutic targets in human epithelial ovarian cancer.

Dr. Karen Pollok, in collaboration with **Drs. Lindsey Mayo (EDT)** and **Marc Mendonca (EDT),** completed two years of a five-year NIH/NCI grant. They identified novel combination therapies that target the p53/p73-signaling network and DNA repair in human glioblastoma multiforme, using orthotopic humanized brain tumor models. Dr. Pollok established a have established a pipeline for obtaining fresh patient brain tumor tissue for the humanized orthotopic xenograft animal model, generating new lines from both primary and recurrent GBM patients as well as patients with lung, breast or melanoma cancers that have metastasized to the brain.

Dr. Pollok has also assembled a multi-disciplinary effort in collaboration with Lindsey Mayo (EDT), Samy Merouen (EDT), and others. The goal is to find new chemical entities to target dysregulated signaling pathways in glioblastoma multiforme, including small molecule inhibitors to the MDM2-signaling network that can be efficiently delivered across the Blood Brain Barrier (BBB), and using an *in vivo* BBB screening model which will facilitate campus-wide development of compounds which cross the BBB.

Dr. Elliott Androphy obtained an R01 in which he and his colleagues used a structure-based drug design high throughput binding assays and synthetic chemistry to identify small molecules that inhibit HPV E6 interaction with E6AP. This complex targets p53 and other interacting factors for ubiquitination proteasomal destruction.

Dr. Murray Korc's work is focused on the deleterious role of TGF-beta in pancreatic cancer and on designing novel therapeutic strategies using human cell lines, genetically engineered mouse models and orthotopic models.

A major theme of **Dr. Ernestina Schipani's** research is the role of hypoxia, HIFs and VHL in mesenchymal cell biology. Adaptation to hypoxia is a critical cellular event both in pathological settings, such as cancer and ischaemia, and in normal development and differentiation. Oxygen is thought to be not only an indispensable metabolic substrate for a variety of *in vivo* enzymatic reactions, including mitochondrial respiration, but also a key regulatory signal in tissue development and homeostasis by controlling a specific genetic program. Hypoxia-inducible transcription factors (HIFs) HIF 1 and HIF 2 are central mediators of the homeostatic response that enables cells to survive and differentiate in low-oxygen conditions. Dr. Schipani's laboratory used genetically altered mice to identify important roles for HIF 1 and HIF 2 in the regulation of skeletal development, bone homeostasis and haematopoiesis.

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

> "WHILE MANY RESEARCHERS, INCLUDING MYSELF, ARE MORE FOCUSED ON UNDERSTANDING AND TARGETING THE TUMOR CELLS DIRECTLY, BEING A MEMBER OF THE TMM PROGRAM REINFORCES THE CRITICAL IMPORTANCE OF EXPANDING OUR KNOWLEDGE ON ANGIOGENESIS, HYPOXIA AND TARGETING OTHER FACTORS IN THE MICROENVIRONMENT TO UNLOCK THE POTENTIAL OF THE TUMOR MICROENVIRONMENT FOR IMPROVING THE CLINICAL SUCCESS OF CANCER THERAPEUTICS."
>
> Kenneth Nephew, PhD

SHARED FACILITIES

Angiogenesis, Endothelial & Pro-Angiogenic Cell Core
cancer.iu.edu/angiogenesis

Jamie Case, PhD – Director
317.278.7928

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
cancer.iu.edu/behavioral

Kim Wagler Ziner, PhD – Director
317.274.4342

The Behavioral and Cancer Control Recruitment Core, a developing core of the IU Simon Cancer Center, has been established to optimize behavioral and cancer control research recruitment. Its purpose is to coordinate and support accrual of all approved behavioral oncology protocols by preparing recruiters for all studies. The core minimizes the number of recruiters needed for each clinic/organization. Its recruiters become part of the care team, screen for all studies and approach/consent eligible individuals. The core provides supervised recruitment throughout the IUSCC, other sites and regional social networks. In addition, it provides recruiter training, communication with clinical care groups, recruitment material preparation and ongoing recruitment strategy assessment.

Biological Microscopy
cancer.iu.edu/biomicroscopy

Kenneth Dunn, PhD – Director
317.278.0436

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
cancer.iu.edu/biostats

Susan Perkins, PhD – Director
317.274.2626

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
cancer.iu.edu/chemgen

Zhong-Yin Zhang, PhD – Director
317.274.8025

The mission of the Chemical Genomic Core is to provide 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. The core incorporates instrumentation, compound libraries, computer database and a staff experienced in assay development, high throughput screening and laboratory robotics. It is a service and collaborative research resource where facility staff works closely with each investigator through all stages of the screening process, providing an opportunity for IU students and fellows to gain experience and training in high throughput screening at the facility.

Clinical Pharmacology Analytical Core
cancer.iu.edu/cpac

Jamie Renbarger, MD – Scientific Director
317.944.8784

David Jones, PhD – Director
317.630.8726

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

- Quantification of drugs and metabolites
- Protein binding of drugs
- Pharmacokinetic analysis of data

Clinical Research Office
cancer.iu.edu/cro

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Director, Adult CRO
317.274.3589

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Linda Battiato, MSN, RN, OCN
Associate administrator, CRO
317.278.4971

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.

MISSION

The mission of the Indiana University Melvin and Bren Simon Cancer Center is to dramatically decrease mortality and suffering from cancer by conducting outstanding translational research, by providing excellence in education and by delivering high quality, patient-centered care.

VISION

To eradicate cancer as a health care burden to our global society

GOALS

- Foster excellence in transdisciplinary research
- Translate research into the clinic to provide the highest quality multidisciplinary patient care
- Provide nationally recognized interdepartmental graduate and post-graduate education and training programs
- Expand the statewide comprehensive cancer control program

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

SHARED FACILITIES

Flow Cytometry Resource Facility
cancer.iu.edu/flow

Edward Srour, PhD – Director
317.274.3589

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 needs of cancer center scientists.

***In Vivo* Biomedical Imaging**
cancer.iu.edu/imaging

Gary Hutchins, PhD – Director
317.274.3687

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. The core is an integral component of the Indiana Institute for Biomedical Imaging Sciences that was developed through funds provided by a National Cancer Institute planning grant, the Indiana 21st Century Technology Development Fund, and the Indiana Genomics Initiative (or INGEN, funded in part by the Lilly Endowment). Matching funds to develop this program were provided by the Indiana University Radiology Associates and the Indiana University School of Medicine.

***In Vivo* Therapeutics Core**
cancer.iu.edu/ivt

Karen Pollok, PhD – Director
317.274.8891

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

Therapeutic Validation
cancer.iu.edu/therapeutic

Nagendra K. Prasad, BVSc, PhD
Director
317.278.6608

The Therapeutic Validation Core (TVC) assists clinical investigators in the development and execution of correlative biological assays needed to validate mechanism(s) of action of candidate drugs/therapies and to develop and test new hypotheses. It also provides technical and intellectual support in the development, implementation, and validation of predictive and pharmacodynamic biomarkers for novel, molecularly-targeted anti-cancer agents.

Tissue Procurement and Distribution
cancer.iu.edu/tissue

Colleen Mitchell – Operations Manager
317.274.2213

Sherif Farag, MD, PhD – Director
317.278.0460

George Sandusky, DVM, PhD
Associate Director
317.274.3523

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
cancer.iu.edu/mouse

Loren Field, PhD – Director
317.630.7776

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

Translational Genomics
cancer.iu.edu/transgen

Sunil Badve, MD – Director
317.491.6484

The Translational Genomics Core is an IU Simon Cancer Center shared facility that provides services to all cancer center members as well as IU School of Medicine faculty for nucleic acid preparation, genotyping, and gene expression profiling. The core utilizes the Illumina Beadstation platform to perform gene expression and genotyping analysis. Other services include microRNA profiling using TaqMan Array MicroRNA Cards and assessment of gene expression using individual TaqMan Gene Expression Assays or TaqMan Arrays (signature and custom panels).

THIS REPORT IS ALSO AVAILABLE AT CANCER.IU.EDU/NEWS.

IU SIMON CANCER CENTER DEVELOPMENT BOARD

The philanthropic arm of the Indiana University Melvin and Bren Simon Cancer Center—the IU Simon Cancer Center Development Board—bolsters the research and education missions of the cancer center. This vigorous volunteer force positions the cancer center to realize significant national and international recognition through the funding of programs vital to advancing research to help people with cancer.

Pete Ward, COO of the Indianapolis Colts, serves as board chair. He and his wife, Lena, founder and CEO of Reaid and also a board member, reside in Zionsville, Ind.

John "Spike" and Anne Abernethy
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Fort Wayne, Ind.

Gene Bate
Indiana Knitwear Corp.
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Indianapolis

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Hochberg Family Fund
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Dan Hoyt
Dan Hoyt & Associates
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Norman Lockshin, MD
Derm Associates PC
Silver Spring, Md.

Mike Mascari
Indianapolis Fruit Co.
Indianapolis

Judy McAtee
Moesart
Indianapolis

H. Richard "Dick" McFarland
McFarland Foods Corp.
Indianapolis

V. Richard "Dick" and Jane Miller
MMM Investments
Boca Raton, Fla.

John and Carol Myers
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Covington, Ind.

Peggy Throgmartin
Vista Verde Ranch
Steamboat Springs, Colo.

Vince and Cynthia Todd
The Heroes Foundation
Indianapolis

James and Laquata Warren
Indiana Elks Association
Muncie, Ind.

Barbie Wentworth
Miller Brooks Inc.
Zionsville, Ind.

Jack Wentworth
Indiana University Kelley School of Business
Bloomington, Ind.

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CANCER CENTER
INDIANA UNIVERSITY