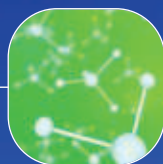
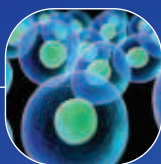
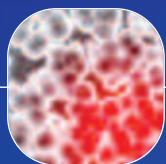


Indiana University Melvin and Bren Simon Cancer Center
SCIENTIFIC REPORT 2009-2010



INDIANA UNIVERSITY
MELVIN AND BREN SIMON CANCER CENTER

Our Senior Leaders



Patrick J. Loehrer Sr., MD
Director



Sherif Farag, MBBS, PhD
Associate Director for
Clinical Research



Mark Kelley, PhD
Associate Director of
Basic Science Research



Harikrishna Nakshatri,
BVSc, PhD
Associate Director
for Education



G. Marie Swanson, PhD
Associate Director for
Cancer Prevention and
Control Research



Michael Darling, MHA
Associate Director
of Administration



Fuad Hammoudeh
Administrator, Cancer
Programs, Clarian Health

The Indiana University Melvin and Bren Simon Cancer Center is an Indiana University School of Medicine and Clarian 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 Clarian 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 Biology and Microenvironment, is under development.



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



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.

On the cover: Joseph E. Walther Hall, Indiana University's largest and newest research building, houses many of the IU Simon Cancer Center's researchers.
On the back cover: The IU Simon Cancer Center's 405,000-square-foot clinical building sits on the IU School of Medicine campus in downtown Indianapolis.



About Us



- **IU Simon Cancer Center is Indiana's only NCI-designated cancer center that provides patient care.** Nearly 40,000 outpatients and 4,000 inpatients turn to the IU Simon Cancer Center for care each year.
- **IU Simon Cancer has an international recognition** for novel and relevant clinical cancer research which have altered or defined treatment standards.

This includes the following:

- Breast cancer
- Gastrointestinal cancer, including pancreatic and colon cancers
- Genitourinary cancer, such as germ cell tumors, bladder, and prostate cancer
- Hematologic disorders, including multiple myeloma and leukemia
- Bone marrow and stem cell transplantation programs at Riley Hospital for Children and IU Hospital
- Thoracic cancer
- Thymoma and thymic carcinoma

- **IU has become an incubator for national and international leadership.** **George Sledge, MD**, is president of the American Society of Clinical Oncology; **Peter Johnstone, MD**, is president of the American Radium Society; **Hal Broxmeyer, PhD**, is president of the American Society of Hematology; **Victoria Champion, PhD, RN, FAAN**, serves on the National Cancer Advisory Board.
- **In August 2008, a \$150,000 million, 405,000-square-foot clinical building opened**, bringing cancer care under one roof for patients.
- **The National Cancer Institute awarded the IU Simon Cancer Center its third grant renewal**, its most recent, in 2008. The IU Simon Cancer Center has been an NCI-designated cancer center since 1999.
- **In October 2009, Joseph E. Walther Hall opened.** At 254,000 square feet, it is IU's largest research building. It is home to scientists in a broad range of disciplines, but the focus of much of the research is on cancer.
- **The Hoosier Oncology Group (HOG)**, one of the most successful networks of community and academic partners that work together to conduct clinical cancer research at the local level, celebrated its 25th anniversary in 2010. Founded by faculty members at the IU Simon Cancer Center and others, it has grown to a network of more than 400 physicians and has enrolled more than 3,000 people in more than 150 clinical trials.

Letter from our **DIRECTOR** I

A little over a decade ago, the IU Simon Cancer Center was given the distinction of becoming an NCI-designated cancer center. Much of the heavy lifting for the designation fell upon the broad shoulders of the late **Steve Williams**, the first IU Simon Cancer Center director. As director, I feel a profound honor and deep responsibility to be Steve's successor.



The success of the IUSCC can be measured in the number of grants, the volume of publications, and the impact of our translational research. Yet, in truth, the success is not dependent upon a solitary pair of shoulders, but in the combined efforts of a community of scientists and physician-scientists who embrace the notion of teamwork and collaborative research. For the IUSCC to be one of the premiere cancer programs in the United States, we must be self-critical, driven to excellence, and dedicated to the premise that we must make a difference in the lives of those affected or at risk of being affected by cancer.

This year, we have several examples of how IUSCC researchers have made tangible contributions to the field. These include, but are not limited to:

- Led by **Drs. Susan Clare** and **Anna Maria Storniolo**, the Susan G. Komen for the Cure® Tissue Bank at the IU Simon Cancer Center, the only normal breast tissue bio-repository of its kind in the world, received a \$1 million Oracle Commitment Grant. Researchers armed only with Internet access are able to conduct experiments faster and cheaper by examining digital data derived from healthy tissue collected at the tissue bank.
- **Kathy Miller, MD**, is conducting a first of its kind clinical trial. Recent laboratory and early clinical studies have identified a unique sensitivity to PARP inhibition, both as monotherapy and in combination with DNA damaging chemotherapy. Dr. Miller designed and led a randomized phase II trial of PARP-inhibition versus PARP-inhibition + DNA-damaging chemotherapy (cisplatin) in patients with triple negative disease that have substantial residual invasive disease after standard anthracycline and/or taxane containing neoadjuvant chemotherapy. The primary objective of the study is two-year disease-free survival.
- **Daniela Matei, MD**, wrote and directed a Phase I-II study of decitabine in combination with carboplatin in patients with recurrent platinum-resistant ovarian cancer in collaboration with **Kenneth Nephew, PhD**. The combination of decitabine and carboplatin appears to improve the outcome of women who have late-stage ovarian cancer.
- **Wade Clapp, MD**, and colleagues demonstrated that genetically altered mice transplanted with bone marrow containing reduced c-kit signaling did not develop neurofibromas, which informed the identification of the c-kit molecular target.
- **Hal Broxmeyer, PhD**, and **Edward Srour, PhD**, received funding to create the Center of Excellence in Molecular Hematology, which has four cores: Flow Cytometry, Animal, Imaging, and Angiogenesis/Endothelial/Proangiogenic. The cores will facilitate development of new discoveries into human trials. The program also includes a pilot and feasibility project to enhance the training of young investigators.

Further, our own cancer community has been growing with new and stellar additions to our faculty, including **Elliot Androphy, MD**, the new chair of the Indiana University School of Medicine Department of Dermatology. He explores the pathogenesis of papillomavirus infections, which serve as a model to understand how normal human cells are induced toward cancer. **Theresa Guise, MD**, a nationally acclaimed endocrinologist, is leading a new team of scientists who hope to improve treatments for bone metastases and stop them altogether. She co-leads our developing Tumor Biology and Microenvironment research program with **Wade Clapp, MD**. Also, **Giuseppe Del Priore, MD, MPH**, the new director of gynecology-oncology, is a top clinician with a research interest in fertility preservation for cancer patients. He explores less toxic treatments and develops new surgical procedures.

By drawing upon the experiences of these notable recruits and stimulating the existing faculty, the IUSCC is indeed making a difference.

These are tough economic times for our country and for research investments. The IUSCC, though, has an edge—it is our dedicated faculty and staff, our patients, and our other supporters. Steve would be proud.

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

Program leaders



GEORGE SLEDGE JR., MD
Research co-leader
*Ballve-Lantero Professor of Oncology
Professor of Medicine and Pathology
IU School of Medicine*



LINDA MALKAS, PhD
Research co-leader
*Vera Bradley Chair in Oncology
Professor of Medicine
IU School of Medicine*

The Breast Cancer Program, an interactive program with members 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 four themes:

- Theme 1: CELL SIGNALING PATHWAY ALTERATIONS
- Theme 2: ANGIOGENESIS AND THERAPEUTIC ANTI-ANGIOGENESIS APPROACHES
- Theme 3: GENOMIC DAMAGE AND REPAIR MECHANISMS
- Theme 4: THERAPEUTIC INDIVIDUALIZATIONS

MEMBERS

Sunil Badve, MD
Robert Bigsby, PhD
Susan Clare, MD, PhD
David Clemmer, PhD
Anthony Firulli, PhD
David Flockhart, MD, PhD
David Gilley, PhD
Brenda Grimes, PhD
Eyas Hattab, MD
Chunyan He, PhD
Brittney-Shea Herbert, PhD
Robert Hickey, PhD
Barbara Hocevar, PhD
Gary Hutchins, PhD
Mircea Ivan, MD, PhD
Philip Johnson, PhD
Raymond Konger, MD
Lang Li, PhD
Samy Meroueh, PhD
Kathy Miller, MD
Harikrishna Nakshatri, PhD
Kenneth Nephew, PhD
Milos Novotny, PhD
Andrew Saykin, PsyD
Bryan Schneider, MD
Todd Skaar, PhD
Roger Slee, PhD
Anna Maria Stornuolo, MD
Tracy Vargo-Gogola, PhD
Claire Walczak, PhD
Clark David Wells, PhD
Jian-Ting Zhang, PhD
Qi-Huang Zheng, PhD

Research highlights

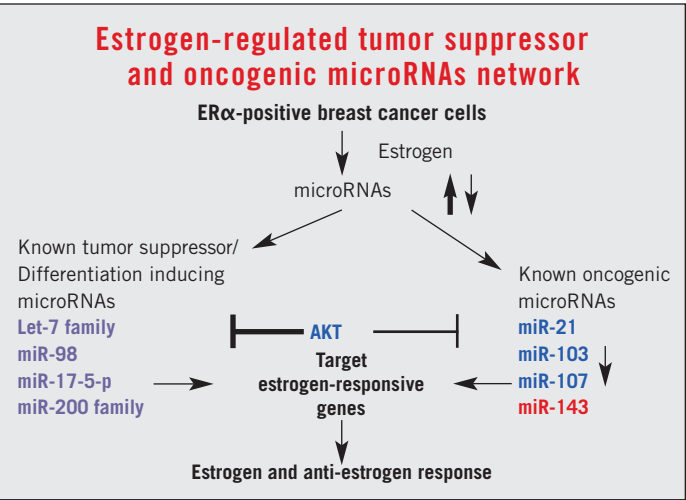
(Abbreviation used: TBM, Tumor Biology and Microenvironment)

CELL SIGNALING PATHWAY ALTERATIONS THEME

Dr. Theresa Guise (TBM) and colleagues showed for the first time that the combined treatment with a TGFb inhibitor and a bisphosphonate inhibitor of bone resorption reduced progression of established breast cancer bone metastases greater than either treatment alone.

Drs. Hari Nakshatri and **Sunil Badve** found that metastatic cells display a distinct pattern of microRNA expression compared to primary tumor cells; miR-22 is one of the microRNAs down-regulated in metastatic cancer cells. (See graphic at right.)

Dr. Kenneth Nephew reported that in normal cells, estrogen signaling induced transient formation of multiple DNA loops in specific chromosomal regions. Consequently, DNA looping brought distant loci to focal ER-docking sites for coordinate repression of a gene cluster. However, in MCF7 breast cancer cells, the plasticity of this free DNA movement was greatly reduced. Together with the acquisition of DNA methylation and repressive chromatin modifications at specific loci, he hypothesizes that an inflexible DNA scaffold may be a novel determinant used by breast cancer cells to reinforce estrogen-mediated repression.



Nakshatri and Badve

GENOMIC DAMAGE AND REPAIR MECHANISMS THEME

Drs. Linda Malkas, Robert Hickey, and **George Sledge** have identified a unique small caPCNA protein related peptide (caPeptide) as well as first-in-class small molecule compounds targeting caPCNA that promote breast cancer cell cytotoxicity with great specificity. These agents have the potential ability to block the binding of several cellular proteins that participate in DNA replication, repair, cell cycle control, transcription and chromosomal recombination in cancer cells. The trio are testing the caPCNA targeted agents for their therapeutic potential.

Dr. Kathy Miller is conducting the first clinical trial in the world of GRN163L, the first specific telomerase inhibitor to enter clinical trials, in breast cancer patients. This trial was initiated as a direct result **Dr. Brittney-Shea Herbert's** research. Drs. Miller and Herbert plan to combine their unique expertise to study the impact of telomerase inhibition in combination with trastuzumab in patients with trastuzumab-refractory HER2+ disease.

Drs. David Gilley and **Badve** are focused on an innovative method they have developed for detecting and analyzing telomere dysfunction, via the measurement of chromosome fusion junctions, in order to elucidate mechanisms responsible for the origin of genomic instability leading to breast cancer. Their work could result in a simple, accessible clinical blood test for very early breast cancer detection.

THERAPEUTIC INDIVIDUALIZATION THEME

Triple-negative breast cancer (TNBC) disproportionately affects pre-menopausal women and women of African-American descent and has been plagued by the absence of effective targeted therapies leading to poor survival. Using the ABI Whole Transcriptome Pipeline, **Drs. Bryan Schneider** and **Susan Clare** sequenced TNBC tumors and normal samples. They have bioinformatically identified for the first time several interchromosomal fusions that were present in a majority of the tumors but were absent in normal samples.

Program leaders



VICTORIA CHAMPION, PhD, RN, FAAN
*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
*Professor of Pediatrics
IU School of Medicine*

The Cancer Prevention and Control Program includes members from eight schools and nine departments within medicine. 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: PREVENTION**
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 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.

MEMBERS

Elliot Androphy, MD
Asok Antony, MD
Silvia Bigatti, PhD
Darron Brown, MD
Debra Burns, PhD
Janet Carpenter, PhD
Melissa Carpentier, PhD
M. Kathryn Coe, PhD
Betsy Louise Fife, PhD
J. Dennis Fortenberry, MD, MS
Joan Haase, PhD
David Haggstrom, MD
Chunyan He, PhD
Paul Helft, MD
Lisa Hess, PhD
Karen Hudmon, PharmD
Thomas Imperiale, MD
Peter Johnstone, MD, MA
Kurt Kroenke, MD
Patrick Loehrer Sr., MD
Anna McDaniel, PhD
Patrick Monahan, PhD
Catherine Mosher, PhD
Julie Otte, PhD
Erika Rager, MD, MPH
Susan Rawl, PhD
Douglas Rex, MD,
Sheri Robb, PhD
Andrew Saykin, PsyD
Marcia Shew, MD, MPH
Rafat Siddiqui, PhD
Daniel Sliva, 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
Alan Zillich, PharmD

CANCER PREVENTION AND CONTROL Program I

Research highlights

(Abbreviation used: BC, Breast Cancer)

Theme 1: PREVENTION

Dr. Anna McDaniel is collaborating with Gabriel Interactive of Indianapolis to develop, for commercial distribution, an interactive game targeted to female adolescents to change attitudes toward smoking and to decrease the number of smokers. (*See graphic below.*) Additionally, she is leading a team that collaborates with Free & Clear, a national leader in telephone-based nicotine dependence treatment, to test the feasibility of using interactive voice response technology to enhance existing Quitline counseling. **Dr. Karen Suchanek Hudman** has extended research into community pharmacies with “Ask, Advise and Refer,” a trial to train community pharmacists to deliver smoking cessation counseling. **Drs. Gregory Zimet** and **J. Dennis Fortenberry** continue to test the use of interactive technology 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

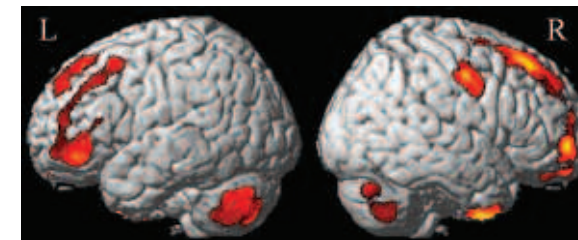
Dr. Victoria Champion has a long program of research to increase mammography screening, with the last 10 years focused on using technology to translate interventions. Her most recent funding will target breast and colorectal cancers simultaneously in women ages 50 to 75. Colorectal cancer has been the focus of several investigators: **Dr. Tom Imperiale** is developing a risk index for advanced colorectal neoplasia to guide clinicians in discussing the best risk-based screening strategies; **Dr. Susan Rawl** has been supported for more than 10 years to develop interactive interventions to increase colorectal screening in at-risk populations, such as African American men and women, as well as first-degree relatives of colorectal cancer patients; and **Dr. Patrick Loehrer** and investigators from Purdue University are collecting serum, blood, and tissue samples to identify prognostic and predictive molecular signatures for patients at risk of developing colorectal cancer.

Theme 3: SURVIVORSHIP

Dr. Janet Carpenter has developed an inter-programmatic research focus that addresses a major symptom in breast cancer patients—hot flashes—and developed a nationally used ambulatory skin conductance monitor for the purpose of measuring hot flashes objectively. A major initiative focuses on cognitive dysfunction, so-called “chemobrain,” associated with cancer both chemotherapy and radiation. Multiple investigators began an interdisciplinary working group, led by **Dr. Andrew Saykin (BC)**, that seeks to define, understand the biologic mechanisms, and ultimately prevent chemobrain. (*See graphic below.*) **Dr. Joan Haase** leads an interdisciplinary group of behavioral scientists and clinical investigators who are engaged in developing research to address problems at end of life.



McDaniel



Saykin

Program leaders



DANIELA MATEI, MD
Associate Professor of Medicine
IU School of Medicine



ZHONG-YIN ZHANG, PhD
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 seven 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**

MEMBERS

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

EXPERIMENTAL AND DEVELOPMENTAL THERAPEUTICS Program I

Research highlights

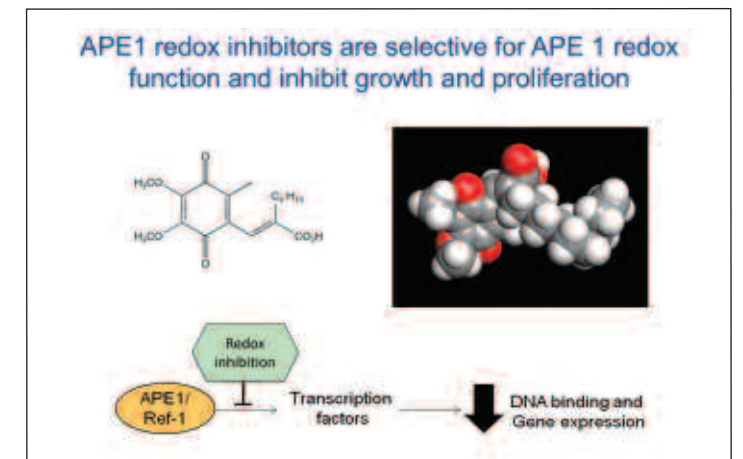
(Abbreviations used: HMI, Hematopoiesis, Hematological Malignancies, and Immunology Program; BC, Breast Cancer; TBM, Tumor Biology and Microenvironment)

Theme 1: TARGET IDENTIFICATION AND VALIDATION

Dr. Zhong-Yin Zhang's research, done in collaboration with **Rebecca Chan (HMI)**, focuses primarily on protein tyrosine phosphatases (PTPs), which constitute a large family of signaling enzymes involved in the regulation of virtually all aspects of eukaryotic biology. Over the past year, Dr. Zhang's laboratory developed a breakthrough salicylic acid-based combinatorial chemistry platform aimed to create PTP inhibitors that bind both the active site and unique nearby sub-pockets for enhanced affinity and selectivity. Screening led to the identification of a SHP2 inhibitor II-BO8 with highly efficacious cellular activity, providing supporting evidence that chemical inhibition of SHP2 may be therapeutically useful for anti-cancer and anti-leukemia treatment.

Theme 2: DISCOVERY AND DEVELOPMENT OF NOVEL ANTI-CANCER AGENTS

Dr. Mark Kelley's lab focuses on the preclinical drug development of E3330 (or APX3330) in both pancreatic and brain cancer models. The hypothesis is that the inhibition of base excision repair protein APE1 will result in diminished tumor cell growth. This protein has two major functions: DNA repair and redox function regulating cellular signals. *In vitro* data suggests that inhibition of either function blocks human cancer. Testing of novel APE1 inhibitors, such as E3330, is currently underway as single therapeutics or in combination with chemotherapy. (See graphic at right.)



Kelley

Theme 3: MECHANISMS OF DRUG ACTION AND CLINICAL TRIALS

In the past year, Phase I and II studies of decitabine in combination with carboplatin in patients with recurrent platinum resistant ovarian cancer were activated. **Dr. Daniela Matei** and collaborator **Dr. Kenneth Nephew (BC, TBM)** tested the hypothesis that hypomethylation induced by low-dose decitabine sensitizes patients with platinum-resistant ovarian cancer to carboplatin. In preclinical studies at IU Simon Cancer Center, DNA hypomethylating agents were shown to reverse platinum resistance by de-repressing tumor suppressor genes. The Phase I study defined the tolerated dose of decitabine in combination with carboplatin and established that this dose is biologically active, enabling activation of a Phase II protocol with this combination. Preliminary results from the Phase II study show promising clinical activity in this difficult-to-treat cancer.

Dr. Jamie Renbarger is studying biomarkers of vincristine (vcr) toxicity, pharmacokinetics, and response in children with leukemia. In an ongoing multicenter clinical trial led by Dr. Renbarger, her research group evaluates the pharmacogenetics of vincristine neurotoxicity, pharmacokinetics (PK), and response in pediatric precursor B acute lymphoblastic leukemia (preB ALL) patients treated at four major U.S. pediatric centers. In addition to identifying biomarkers of vcr-induced peripheral neuropathy (VIPN), one of the goals of this research is to assess the validity and reliability of neuropathy assessment tools in pediatric patients. The ultimate goal of this project is to develop a model to allow prediction of an individual patient's risk of VIPN. The next step of this research will be to utilize this model as a tool to optimize vcr dosing to maximize efficacy while minimizing VIPN.

Program leader



HAL BROXMEYER, PhD
Distinguished Professor
Mary Margaret Walther Professor Emeritus
Professor of Microbiology/Immunology
Department of Microbiology and 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 each other toward the goal of understanding normal cell regulation and abnormalities associated with leukemia/lymphoma and closely related preleukemic-type disorders.

Scientific goals

To continue to define cell regulation of blood and immune cells, the abnormalities of these in leukemia and related disorders, and the means to mechanistically treat disease initiation and progression through a better understanding of cell and molecular processes. The goals fall under three themes

- Theme 1: **HEMATOPOIESIS**
- Theme 2: **HEMATOLOGICAL MALIGNANCIES**
- Theme 3: **IMMUNOLOGY**

MEMBERS

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

HEMATOPOIESIS, HEMATOLOGICAL MALIGNANCIES, AND IMMUNOLOGY Program I

Research highlights

(Abbreviations used: BC, Breast Cancer; EDT, Experimental and Developmental Therapeutics; TBM, Tumor Biology and Microenvironment)

Theme 1: **HEMATOPOIESIS**

Drs. David Ingram (TBM) and **Wade Clapp** noted that p21-activated kinase regulates the degranulation of mast cells through effects on mobilization of calcium and dynamics of the cytoskeleton, which also influence cell movement.

Drs. Sunanda Basu and **Hal Broxmeyer** found that certain CCR5 ligands modulate chemotaxis, adhesion, and phosphorylation of AKT that is induced on human CD34+ cord blood cells by another member of the chemokine family, SDF-1/CXCL12.

Drs. Scott Goebel, Nadia Carlesso, Melissa Kacena (TBM), and **Edward Srour** better defined the impact of cellular components of the bone marrow hematopoietic stem cells (HSCs) and hematopoietic progenitor cells (HPC) function.

Dr. Louis Pelus increased understanding of how prostaglandin E2 enhances the homing, survival, and proliferation of HSCs, while **Dr. Kacena** elaborated on megakaryocyte-bone cell interactions.

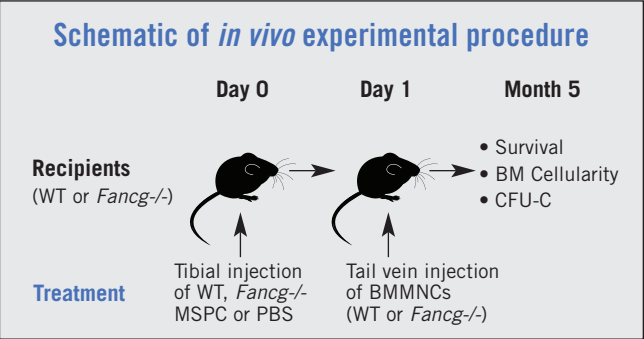
Drs. Reuben Kapur, Simon Conway (TBM), and **Ingram (TBM)** presented genetic and cellular evidence of vascular inflammation in neurofibromin deficient mice and humans.

Drs. Karen Pollok, Scott Goebel, and **Feng-Chun Yang** found that mesenchymal stem/stromal cells (MSCs) promote reconstitution of exogenous HSCs in mice with a knockout of the Fanconi anemia, Fancg, gene. (See graphic below.)

Drs. Kapur and **Laura Haneline** noted different roles of stress-activated protein kinases in Fancg-deficient Hematopoiesis.

Drs. Broxmeyer and **Yoder** collaborated with colleagues beyond Indiana University to demonstrate targeted disruption of a CCCH tandem zinc finger RNA-binding protein, Zfp3612, results in defective embryonic, fetal, and adult hematopoiesis.

Drs. Pollok and **Yoder** demonstrated enhanced engraftment of mouse HSCs after inhibiting CD26/ Dipeptidylpeptidase IV.



Pollok, Goebel, Yang

Theme 2: **HEMATOLOGICAL MALIGNANCIES**

Drs. Pollok and **Lindsey Mayo (EDT)** found that TGF(β)1-induced expression of human Mdm2 correlates with late-stage metastatic breast cancer.

Drs. Curt Balch (TBM), Kenneth Nephew (TBM, BC), David Skalnik, Lang Li (BC), and **Daniela Matei (EDT)** reviewed epigenetic changes in ovarian cancer.

Drs. Srour and **Hari Nakshatri (BC)** worked together to demonstrate that estradiol-regulated microRNAs control estradiol response in breast cancer cells.

Drs. Pollok and **Ahmad Safa (EDT)** reported that c-FLIP gene silencing eliminates tumor cells in breast cancer xenografts without effecting stromal cells.

Drs. H. Scott Boswell, Xin-Yuan Fu, and **Louis Pelus** found that survivin mediates aberrant HPC proliferation and acute leukemia induced by internal tandem duplication of Flt3, a tyrosine kinase receptor.

Theme 3: **IMMUNOLOGY**

Drs. Hua-Chen Chang, Michael Robertson, and **Mark Kaplan** noted impaired development of human Th1 cells in patients with deficient expression of STAT4.

Dr. Alexander Dent demonstrated that BCL6, a transcription factor implicated in lymphoma, cooperates with CD40 stimulation and loss of p53 function to rapidly transform B cells.

TUMOR BIOLOGY AND MICROENVIRONMENT Program I

Research highlights

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

Dr. Kent Robertson (HMI) has completed the first clinical trial using imatinib mesylate for the treatment of plexiform neurofibromas. A second trial to test the potential of new imaging modalities and biomarkers to predict drug responsiveness is underway. **Drs. Wade Clapp, David Ingram, Feng-Chun Yang (HMI), and Gary Hutchins'** U01 experimental therapeutics program has identified three drugs to advance to final milestone of preclinical testing for the treatment of plexiform neurofibromas.

Drs. Simon Conway, Clapp, David Ingram, and Feng-Chun Yang (HMI) defined the aberrant signaling networks in neurofibromatosis type 1 deficient endothelial cells and vascular smooth muscle cells. These investigators developed an *in vivo* murine knockout-out/bone marrow transplantation model of neurofibromatosis 1 vaso-occlusive disease that recapitulates the human phenotype.

Drs. Theresa Guise and Khalid Mohammad have shown that blockade of TGF β signaling is effective to block the establishment and progression of bone metastases due to melanoma.

Dr. John Chirgwin has identified that breast cancers make the receptor that recognizes fibroblast growth factor-23, which is abundant in bone, and acts on tumor cells to encourage metastasis and growth. FGF23 makes tumors resistant to growth inhibition by vitamin D.

Dr. Karen Pollok (HMI) studies dual targeting of DNA repair and p53 pathways for the treatment of brain cancer using human primary glioblastoma models. Further, activation of p53-mediated pathways in combination with standard-of-care therapy is under investigation to modulate DNA repair and the brain tumor microenvironment. **Drs. Pollok and Jamie Case** have shown that human circulating progenitor cells of hematopoietic origin promote melanoma tumor growth.

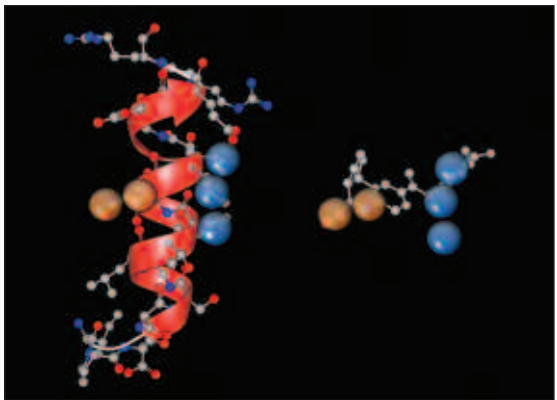
Drs. Daniela Matei (EDT), Robert Bigsby (BC), and Harikrishna Nakshatri (BC) demonstrated that tissue transglutaminase (TG2) facilitates the intra-peritoneal dissemination of ovarian tumors by stabilizing the interaction of integrins with the extracellular matrix by regulating MMP expression and function and by inducing EMT.

Dr. Simon Conway has shown that the tumor microenvironment marker, periostin, mediates vascular smooth muscle cell migration through the integrins and focal adhesion kinase pathway, can suppress Notch1 signaling in aortic valve disease, is required for sclerostin inhibition in bone, and is upregulated in response to wound healing.

Dr. Jingwu Xie is investigating activation of the hedgehog signaling pathways in a variety of tumor types and the clinical implications.

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.

Dr. Elliot Androphy has identified and characterized small molecule inhibitors of the HPV E6 protein, which is necessary for viral replication and for oncogenic progression. Androphy and colleagues are also studying the functions of E6 protein in HPV type 16, the most common type associated with malignant progression and interaction with the tumor suppressor p53. (See graphic at right.)



Androphy

Program leaders



WADE CLAPP, MD

*Richard L. Schreiner Professor and Chairman,
Department of Pediatrics
Professor of Biochemistry and Molecular Biology
IU School of Medicine*



THERESA GUISE, MD

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

The tumor biology and microenvironment group, 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

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.

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
Judd Cummings, MD
A. Keith Dunker, PhD
John Foley, PhD
Brenda Grimes, PhD
Michael House, MD
David Ingram Jr., MD
Travis Jerde, PhD
Melissa Kacena, PhD
Lisa Kamendulis, PhD
James Klaunig, PhD
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
Christian Max Schmidt, MD, PhD
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

Angiogenesis, Endothelial & Pro-Angiogenic Cell Core

Jamie Case, PhD
Director
317.278.7928

www.cancer.iu.edu/angiogenesis

The Angiogenesis, Endothelial and Pro-Angiogenic Cell Core Facility was established through the IU Simon Cancer Center to conduct validated and highly reproducible *in vitro* and *in vivo* angiogenesis assays. These assays will function as experimental platforms for understanding the basic mechanisms of 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, 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

Kenneth Dunn, PhD
Director
317.278.0436

www.cancer.iu.edu/biomics

The Indiana Center for Biological Microscopy is one of a handful in the world providing researchers with access to low-light level microscopy, confocal microscopy, multiphoton microscopy, intravital microscopy, and the latest methods of digital image analysis and visualization. Funding from Indiana University, the National Institutes of Health (NIH), and the Lilly Endowment have given IU a world-class center for biomedical imaging. In addition to providing efficient, state-of-the-art biomedical imaging support, the center is also actively involved in developing advanced methods of microscopy, in particular intravital microscopy and three-dimensional image analysis.

Biostatistics & Data Management

Susan Perkins, PhD
Director
317.274.2626

www.cancer.iu.edu/biostats

The Biostatistics and Data Management Core (BDMC) of the IU Simon Cancer Center has statistical and data management responsibilities as well as related administrative functions, including education, training, and facilitation of the collaborative research effort of cancer center investigators. Consisting of a group of biostatisticians, data managers, and information technology professionals, 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 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.



Chemical Synthesis & Organic Drug Lead Development

Eric Long, PhD
Director
317.274.6888

Tax Georgiadis, PhD
Director of Synthesis
317.274.6804

www.cancer.iu.edu/chemsyn

The goals of the Chemical Synthesis Core are to provide IU Simon Cancer Center investigators, as well as other biomedical academic entities at Indiana University-Purdue University Indianapolis and throughout the state, with convenient access to chemical expertise and resources necessary to support custom organic synthesis requests and medicinal chemistry/translational drug development needs. Services provided by the core are also available to the broader life sciences industrial community of central Indiana and nationally. The Chemical Synthesis Core is supported, in part, by the Purdue School of Science, Department of Chemistry & Chemical Biology.

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/or metabolites
- protein binding of drugs
- pharmacokinetic analysis of data

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 (CRO) is a shared resource available to all clinical investigators of the IU Simon Cancer Center whose services enable the efficient conduct of adult and pediatric trials. The administrative and information technology staff of the CRO supports the coordination of the IU Simon Cancer Center Protocol Review and Monitoring System, the submission to and review of protocols by the IU Simon Cancer Center Scientific Review Committee, the training and supervision of research staff, and the maintenance of computerized databases to track protocols and patient data.

Flow Cytometry Resource Facility

Edward Srour, PhD
Director
317.274.3589

www.cancer.iu.edu/flow

The Flow Cytometry Resource Facility provides essential and varied flow cytometric analysis and cell sorting services to IU Simon Cancer Center investigators. The facility provides consultation on both experimental design and data interpretation, technical advice, and collaboration, thus, promoting the application of cutting-edge flow cytometric technology for a wide range of scientific investigations conducted at the cancer center. Because it is used by a large number of IU Simon Cancer members, it serves as a central common area for the investigators to interact, collaborate, and exchange scientific information.



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. 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

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

Karen Pollok, PhD
Director
317.274.8891
www.cancer.iu.edu/therapeutic

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. The TVC 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

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

To successfully investigate the biological basis of cancers, translate basic research to the clinical setting and better understand the relevance of observed clinical or population-based phenomena through laboratory-based research, the IU Simon Cancer Center Solid Tissue Bank began providing solid tumors in 1996. In 2008, the Hematologic Malignancies Tissue Bank was established to provide hematological malignancies. Since that time, the bank has continued to provide samples for the discovery of new drug targets and biomarkers, the development of cancer cell lines, and for DNA and RNA research. It serves as a resource for the centralized banking of tissue, blood, bone marrow, leukapheresis, and buccal swab specimens procured from patients with malignancies and normal controls.

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 transgenic mice and knockout mice for use in basic science research at Indiana University. The facility also provides advice concerning construction of transgenic and gene targeting constructs, animal breeding, and maintenance of the resulting mouse colonies.

Translational Genomics

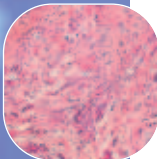
Sunil Badve, MD
Director
317.491.6484
www.cancer.iu.edu/transgen

The Translational Genomics Core Laboratory 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).

Outreach and education are key aspects of the IU Simon Cancer Center’s mission as we are dedicated to enhancing community awareness of cancer-related issues.

2009 HIGHLIGHTS:

- During Cancer Research Day, 93 abstracts were presented. Cancer Research Day is an annual event that aims to increase understanding and awareness of IU Simon Cancer Center research endeavors and encourage collaboration with other cancer research institutions in Indiana.
- Sixteen students spent their summer vacations exploring possible careers as cancer researchers during the IU Simon Cancer Center’s annual Summer Research Program. Working alongside physicians and researchers, the students gained real-life, hands-on experiences. The program seeks to increase the number of cancer researchers among underrepresented groups.
- The IU Simon Cancer Center participated in Outrun the Sun Race Against Melanoma by forming Team Williams. Team Williams, named in honor of the late Stephen Williams, MD—the founding director of the IU Simon Cancer Center—was the largest team with 75 members.
- As title sponsors of the Unite 2 Fight Race Against Prostate Cancer, the IU Simon Cancer Center and its affiliate Midwest Proton Radiotherapy Institute (MPRI) helped to raise awareness of and educate people about prostate cancer during the downtown Indianapolis walk/run event.
- At the Indiana State Fair, volunteers helped to teach kids—and adults—the importance of protecting their skin from the sun while still having fun. Volunteers helped fairgoers make UV bracelets as a way to learn how sunscreens help to protect them. Also, with the retractable roof open under sunny skies at Lucas Oil Stadium, volunteers distributed 1,200 UV bracelets at an Indianapolis Colts game.
- While at the Indiana Black Expo’s INShape Indiana Black & Minority Health Fair, the IU Simon Cancer Center reached out to people, providing information about the importance of clinical trials and how to lower cancer risks. Also, the cancer center partnered with IU-CABS (Indiana University Cancer Biomarker Study), a study designed to help identify genetic and environmental risk factors that lead to the development of cancer. More than 220 people participated in the study.
- Approximately 5,000 breast self-exam cards were handed out to women attending an Indianapolis Colts home game during National Breast Cancer Awareness Month, coinciding with the NFL’s focus on breast health.
- Throughout the year, an impressive 1,829 women donated a blood and / or breast tissue sample to the Susan G. Komen for the Cure® Tissue Bank at the IU Simon Cancer Center. The tissue bank—the nation’s first and only healthy breast tissue bank—collects blood and tissue from women with and without breast cancer, helping researchers to determine the differences between these populations. Those differences could lead to a better understanding of the disease.



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