



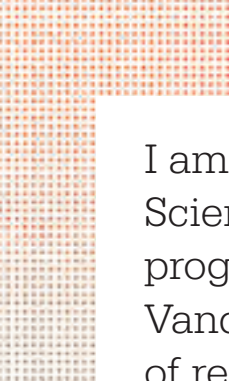
VANDERBILT-INGRAM CANCER CENTER  
Scientific Report

2010



VANDERBILT  UNIVERSITY  
MEDICAL CENTER

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I am pleased to share with you this Scientific Report, highlighting the programs and accomplishments of the Vanderbilt-Ingram Cancer Center's team of researchers.

Created in 1993 under the superb leadership of Dr. Hal Moses, the Vanderbilt-Ingram Cancer Center recently completed the 4th competing renewal of its Cancer Center Support Grant from the National Cancer Institute. The grant submission and subsequent site visit gave us an opportunity to examine our progress and strategize about our aspirations for the future.

In addition to offering an overview of our seven high-impact research programs, this report also highlights five areas of special focus for us:

[Personalized Cancer Medicine](#)

[Cancer Drug Discovery](#)

[Cancer Survivorship](#)

[Cancer Bioinformatics](#)

[Diversity and Outreach to Underserved Communities](#)

At Vanderbilt-Ingram Cancer Center, we are fortunate to have access to a broad range of technologies and expertise in informatics, proteomics, genomics, high-throughput screening, chemical synthesis and epidemiology, among others. We also have a culture that promotes a level of teamwork and collaboration unusual among academic institutions. We believe that this combination creates for us a significant opportunity to make a meaningful difference in cancer research, treatment, prevention and survivorship.

We also have a powerful motivator. Vanderbilt-Ingram Cancer Center is located in Nashville—the buckle of the cancer death belt. Tennessee is one of several connecting states in the Southeast with the highest death rates from cancer. This statistic motivates us every day to stay focused on the true competition: cancer. We know that the cancer problem is too big to be solved by one laboratory or even one institution. We are honored to work with our partners and collaborators, here in our community and across the nation and around the world.

I am pleased to serve as director of this Cancer Center and couldn't be more proud of the team of researchers here and their work. I hope you enjoy this report. Please do not hesitate to contact me if you have questions or would like to know more about our work.

**Jennifer A. Pietenpol, Ph.D.**

Director of Vanderbilt-Ingram Cancer Center



**Jennifer A. Pietenpol, Ph.D.**, is director of the Vanderbilt-Ingram Cancer Center and B.F. Byrd Jr., Professor of Molecular Oncology. She led the Center's basic and translational research programs as associate director from 2002-2007 and is past program leader for Signal Transduction and Cell Proliferation, one of seven research programs in the Center. She has served as the principal investigator of the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation Center for Cancer Genetics and Genomics since 2002.

Dr. Pietenpol's research focuses on the p53 signaling network—the most frequently targeted area for mutation in human tumors. The goals of her research are to define molecular changes that are frequent in tumor cells and to use bench-based discoveries to advance patient care. Currently, her research is funded by the National Cancer Institute and the Komen Foundation.

Dr. Pietenpol is a member of the National Cancer Advisory Board and the American Association for Cancer Research board of directors. She received her B.A. in Biology from Carleton College in 1986 and earned her Ph.D. in Cell Biology from Vanderbilt University School of Medicine in 1990, followed by a postdoctoral fellowship in Oncology at Johns Hopkins University. She has been a member of the Vanderbilt faculty since 1994.



# Vanderbilt-Ingram Cancer Center Leadership

## DIRECTOR

**Jennifer A. Pietenpol, Ph.D.**  
B.F. Byrd Professor of Molecular Oncology  
Professor of Biochemistry, Cancer Biology  
and Otolaryngology

## ASSOCIATE DIRECTOR FOR BASIC RESEARCH

**Scott Hiebert, Ph.D.**  
Professor of Biochemistry  
Ingram Professor of Cancer Research

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John Clinton Foshee Distinguished  
Professor of Surgery  
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**William Blot, M.D.**  
Professor of Medicine

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**Mark Magnuson, Ph.D.**  
Director, Vanderbilt Center for Stem Cell Biology  
Professor, Molecular Physiology and Biophysics;  
Medicine; and Cell and Developmental Biology

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**Elizabeth Williams, Ph.D.**

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**Anne Washburn, M.P.H.**

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Professor, Interim Chair of Hematology/Oncology  
Director, Specialized Program in  
Research Excellence (Breast Cancer)

### CANCER EPIDEMIOLOGY, PREVENTION AND CONTROL

**Wei Zheng, M.D., Ph.D.**  
Ingram Professor of Cancer Research  
Professor of Medicine

**Debra L. Friedman, M.D.**  
E. Bronson Ingram Chair in Pediatric Oncology  
Associate Professor of Pediatrics

### GASTROINTESTINAL CANCER

**Robert Coffey, M.D.**  
Ingram Professor of Cancer Research  
John B. Wallace Professor of Medicine  
Professor of Medicine and Cell  
and Developmental Biology  
Director, Specialized Program  
of Research Excellence (GI)

**Jordan Berlin, M.D.**  
Ingram Professor of Cancer Research  
Associate Professor of Medicine  
Medical Director, Clinical Trials Shared  
Resource and Affiliate Network

### GENOME MAINTENANCE

**William P. Tansey, Ph.D.**  
Ingram Professor of Cancer Research  
Professor and Interim Chair, Cell  
and Development Biology

**David Cortez, Ph.D.**  
Ingram Professor of Cancer Biology  
Professor of Cancer Biology

### HOST-TUMOR INTERACTION

**Mary Zutter, M.D.**  
Ingram Professor of Cancer Research  
Professor of Pathology and Cancer Biology

### SIGNAL TRANSDUCTION AND CELL PROLIFERATION

**Albert Reynolds, Ph.D.**  
Ingram Professor of Cancer Research  
Professor of Cancer Biology

**Jeffrey Sosman, M.D.**  
Ingram Professor of Cancer Research  
Professor of Medicine

### THORACIC/HEAD & NECK

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Harold L. Moses Chair in Cancer Research  
Professor of Medicine  
Director, Specialized Program  
in Research Excellence (Lung)

**Wendell Yarbrough, M.D.**  
Ingram Professor of Cancer Research  
Associate Professor of Otolaryngology  
and Cancer Biology

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CANCER PATIENT CARE CENTER**  
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**DIRECTOR,  
PEDIATRIC HEMATOLOGY/ONCOLOGY**  
**Debra Friedman, M.D.**

**CHAIR, OBSTETRICS/GYNECOLOGY  
DIRECTOR, GYNECOLOGIC ONCOLOGY**  
**Howard Jones, M.D.**

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H. Lee Moffitt Cancer Center  
and Research Institute

**Valerie Rusch, M.D.**  
Memorial Sloan-Kettering Cancer Center

**Charles L. Sawyers, M.D.**  
Memorial Sloan-Kettering Cancer Center

**Thomas A. Sellers, Ph.D.**  
H. Lee Moffitt Cancer Center  
and Research Institute

**Marcy B. Waldinger**  
University of Michigan Cancer Center



## OVERVIEW

First established in 1993 to bring together the cancer research, clinical care, community outreach and educational activities of Vanderbilt University, the Vanderbilt-Ingram Cancer Center has one competitor—cancer—and one ultimate goal: to reduce the burden of this disease in Tennessee, across the nation and around the world.

The Center recently underwent competitive renewal of its Cancer Center Support Grant from the National Cancer Institute, and this report outlines many of the research activities and accomplishments reported at the time of that renewal.

A major emphasis has been expansion of the Center's research programs through continued recruitment of talented investigators with constant focus on innovative basic research, translation to clinical investigation, and expansion of cancer epidemiology and population-based research initiatives.

The Center places great value on discovery and innovation, impact and translation, collaboration and relationships, as well as service and compassion. Its research programs emphasize innovative basic, clinical, and population-based research; interdisciplinary collaboration; and bi-directional translation.

Vanderbilt-Ingram investigators are internationally recognized for research and clinical advances in breast, colon, and lung cancers, among other organ sites; basic research in growth factors, DNA damage signaling, transcription and cell-cell/cell-matrix communication; discoveries from large cohorts in the Southeastern United States and around the world; and development and use of imaging, proteomics, genomics, and informatics and chemical biology platforms for cancer investigation.

Vanderbilt University Medical Center has a long history of excellence in basic cancer research and clinical care and investigation. The Nobel Prize in Physiology or Medicine has been awarded to two Vanderbilt faculty: Dr. Earl Sutherland in 1971, for work on cyclic AMP and signal transduction, and Dr. Stanley Cohen in 1986, for his discovery of and work with epidermal growth factor (EGF) and its receptor.

The Center's initial National Cancer Institute (NCI) Cancer Center Support Grant (CCSG) was funded in 1995, and the Center was recognized as an NCI Comprehensive Cancer Center in 2001.

### Trends in funding

Strong objective evidence of an increase in cancer focus is the overall rise in cancer-relevant extramural funding since the Center's previous competitive renewal in 2004. Vanderbilt-Ingram research funding is very cancer-focused, with 63% of total NIH funding (\$117.3 million) coming from the NCI (\$74.1 million) in 2009.

### Since the previous CCSG funding renewal, the Center experienced:

- A 46% increase in overall peer-reviewed funding, from \$85.3 million (2003) to \$124.8 million (current). Last year, VUMC was among the top 10 medical centers in total NIH grant funding (\$295.0 million) with VICC-member, cancer-relevant NIH funding making up 37% of this total.
- A 62% increase in NCI funding, from \$45.7 million (2003) to \$74.1 million (2009). VICC ranked seventh in total NCI funding among the NCI-Designated Cancer Centers in 2008.

### Internal and External Collaboration

Collegiality and collaboration are a hallmark of VUMC and VICC. Strategically, this includes working together with University and Medical Center leadership, with basic and clinical departments at Vanderbilt, and with other institutions and organizations locally and nationally, to maintain high-impact cancer-based research and clinical care through key recruitments to existing and new programs.

Other key collaborators include Meharry Medical College; Tennessee State University; members of the Tennessee Comprehensive Cancer Control Coalition; colleagues at NCI-designated and National Comprehensive Cancer Network member centers; and community organizations including, but not limited to, the American Cancer Society, Komen for a Cure, Gilda's Club Nashville, Sisters Network, and the NAACP.

## Accomplishments of Note

- Renewal of Specialized Programs of Research Excellence (SPOREs) in lung, breast and gastrointestinal cancers.
- Increase in high-impact publications in clinical and scientific journals.
- Recruitment of 66 new cancer investigators, leading to 288 VICC members.

### Award of new NCI and cancer-relevant multi-investigator grants

- Multi-scale Mathematical Modeling of Cancer Invasion (2004)
- Lipid Peroxidation and Antioxidant Mechanisms (2004)
- Minority-Based Community Clinical Oncology Program at Meharry Medical College (2004)
- Molecular Signatures of Lung Cancer (2005)
- Meharry Medical College Community Health Centers Network (2005)
- Paracrine TGF-Beta Signaling in Tumor Initiation and Progression (2006)
- Clinical Proteomic Technology Assessment for Cancer (2006)
- South-Eastern Center for Imaging Animal Models of Cancer (2007)
- Vanderbilt In Vivo Cellular and Molecular Imaging Center (2008)
- H.pylori-Induced Inflammation and Gastric Cancer (2009)
- Vanderbilt Molecular Target Discovery & Development (2009)—Grand Opportunity (GO) for multi-disciplinary drug discovery effort for triple negative breast cancer
- New Vanderbilt Clinical and Translational Science Award (CTSA; 2007)—with positive impact on VICC

### Launch of new research initiatives with recruitment of leadership and expertise in the areas of:

- Launch of new initiatives in Growth of Cancer Informatics under the leadership of Dr. Dan Masys with recent recruitment of Dr. Mia Levy (2009) as Chief of Cancer Medical Informatics and Dr. Zhongming Zhao (2009) as Chief of Cancer Bioinformatics
- Creation of a new Division of Epidemiology, under the leadership of Dr. Wei Zheng
- Cancer Control and Survivorship - Debra Friedman, M.D. (from Fred Hutchinson Cancer Research Center)
- Cancer Drug Discovery - Stephen Fesik, Ph.D. (from Abbott Laboratories)
- Genome Maintenance - William Tansey, Ph.D. (from Cold Spring Harbor Laboratory)
- Personalized Cancer Medicine - William Pao, M.D., Ph.D. (from Memorial Sloan Kettering Cancer Center)

## Strategic Plan & Vision for the Future

After the appointment of Jennifer Pietenpol, Ph.D., as director, the Center undertook a strategic planning process in 2008 to identify and articulate priorities to guide its work. Through this process, a mission and vision statement, core values, and a set of strategic priorities emerged.

### MISSION

To alleviate cancer death and suffering through pioneering research; innovative patient care; and evidence-based prevention, education, and community activities.

### VISION

To be a preeminent cancer center in the Southeast and a recognized leader, nationally and globally, in the effort to prevent and treat cancers.

### Values that guide our activities, behavior, and decision-making:

- Discovery and Innovation
- Impact and Translation
- Relationships and Collaboration
- Service and Compassion

The following overarching strategic objectives are reviewed/reaffirmed each year by Center leadership and are used to guide development of specific and measurable strategies and tactics:

- \* Ease the burden of cancer, particularly in the Southeast, through research, partnership, collaboration, and community service.
- \* Expand the research enterprise on which our reputation is built with key investments in people, programs, and technology, and by aligning aggressive clinical growth with our research strengths.
- \* Leverage our unique capabilities to expand our impact in cancer prevention, early detection, and targeted, personalized therapy.
- \* Serve more patients and families by increasing capacity to provide the highest quality cancer treatment and clinical trials.
- \* Build and nurture our reputation and image as a community resource and as a leading center for research, treatment, prevention, and survivorship.



## Cancer Survivorship



*Ron Obenauf and  
his wife, Ardeth.*

### **You've survived cancer. Now what?**

When **Ron Obenauf** turned 50, he visited his doctor for a physical and a colonoscopy. But the physician said he didn't recommend a colonoscopy until age 55. "I told the doctor that my older brother had a colonoscopy and they found three precancerous polyps," Obenauf recalled. His doctor told he'd "split the difference" and perform the procedure at 52½.

Just before turning 52, Obenauf noticed blood in his stool and immediately scheduled a colonoscopy. The surgeon's diagnosis: advanced colon cancer.

On that day in 2003, Ron Obenauf began his journey as one of nearly 12 million cancer survivors in the United States. According to the American Cancer Society, the number of cancer survivors has tripled in the past 30 years and America's aging population will lead to even more cases of cancer. A National Cancer Institute (NCI) study indicates that the number of cancer survivors in the U.S. will increase by 55 percent from 2005 to 2020.

Support for those survivors has been slower to develop. Patients ending cancer treatment often don't receive the information they will need for the rest of their lives.



To help cancer patients and their families navigate life as a survivor, the Vanderbilt-Ingram Cancer Center, the Department of Pediatrics and the Monroe Carell Jr. Children's Hospital at Vanderbilt have launched the REACH for Survivorship Program.

"Being a cancer survivor is challenging," said **Julie Means-Powell, M.D.**, an assistant professor of Medicine and breast cancer specialist at Vanderbilt-Ingram. "Even if their tumor was tiny, my patients tell me they are always waiting for the other shoe to drop."

Obenauf's journey, like that of other cancer survivors, has been full of physical and emotional shocks, setbacks and breakthroughs. "I was devastated and went through an emotional roller coaster ride for about 60 days," he said. He had a recurrence with a lesion on his liver in January 2005, but that was the last time cancer appeared.

Today he gets regular checkups, and Ron and his wife, Ardeth, have added healthy food and exercise to their daily regimen. "There are a few lingering things that I'm probably going to deal with the rest of my life, like fatigue, but my life is good," Ron said. Still, when it's time for his checkups, Ardeth has episodes of anxiety—one of the hallmarks of life after cancer for survivors and their families.

## Finding their way

Amazing advances in childhood cancer treatments have created a new generation of adults who are cancer survivors. The NCI estimates that 14 percent of survivors were diagnosed 20 or more years ago.

Some treatment regimens are keeping patients alive years longer than before, creating a patient population for whom cancer is managed like a chronic disease. Whether they have been cured or are keeping their cancer in check, patients have a range of unique life challenges.



**Debra L. Friedman, M.D.**

"The goal of our survivorship program is to provide dedicated care focused on the survivor and not simply their cancer diagnosis," said **Debra L. Friedman, M.D.**, E. Bronson Ingram Chair in Pediatric Oncology. "We look at their medical needs with respect to both cancer and the effect of cancer treatment on other organ systems, as well as their

psychosocial, functional and social needs."

A multi-disciplinary team of health professionals reviews the patient's history and concerns. Then, patients meet with a social worker, followed by a physician or nurse practitioner. Patients will be counseled about ways to keep themselves healthy.

"Cancer survivors are at uniquely high risk for medical problems related to their initial cancer or the cancer treatment," said Friedman. "They need to be educated about those risks and what they and their doctors should look for and what special screening tests they may need throughout their lives."

## Hearts and minds


Making the transition from cancer patient to long-term survivor especially can be stressful for pediatric patients and their families. Many children are at risk for neurocognitive effects that are a direct result of treatment they receive to fight the cancer. Psychologists on the survivorship staff work with schools to help students succeed after cancer treatment.

Adult cancer survivors experience their own neurocognitive challenges. "Chemo brain," the term survivors often use to describe sluggish brain function after treatment, can be frustrating for adults trying to work during and after treatment. The REACH clinic provides referrals for support services.

In addition, the very treatments that are supposed to save patients from cancer also can put them at risk for other life-threatening diseases. "We treat some forms of breast cancer with anthracyclines, which puts those patients at risk for heart failure," said Means-Powell. Vanderbilt-Ingram oncologists are collaborating with physicians at the Vanderbilt Heart and Vascular Institute to monitor and manage patients at higher risks.

## Moving forward

The Obenaufs became research advocates through the Patient Advocacy Program at Vanderbilt-Ingram. Ron also serves as a patient research advocate for the Vanderbilt Tumor Microenvironment Network, and the couple participates in the Tennessee Colorectal Polyp Study, investigating nutrition, exercise, tobacco cessation and other healthy lifestyle initiatives. Ron and Ardeth support Vanderbilt-Ingram cancer research with financial gifts, too.

"Vanderbilt is helping us and others like us get our lives back on track," Ardeth said. 

*By Dagny Stuart, first published in Momentum, Fall 2009*



## Personalized Cancer Medicine

Can cancer treatments be tailored like clothing? Can the medicine be matched to “fit” each patient? Increasingly, evidence is saying yes—cancer treatments can be tailored when tumors have specific genetic changes driving their growth, and when drugs exist that counteract those signals. Personalized oncology means “matching the right drug to the right patient at the right time,” says **William Pao, M.D., Ph.D.**, who is leading the new Personalized Cancer Medicine Initiative at Vanderbilt-Ingram Cancer Center.

By fall of this year, Vanderbilt-Ingram aims to make personalized cancer medicine a routine part of clinical care. Starting with lung cancer and melanoma, Pao and his colleagues will wrap their genetic measuring tapes around every tumor—and select therapies that fit the specific genetic changes they find.



**William Pao,  
M.D., Ph.D.**

### Off-the-rack treatments

Cancer care has always been personalized to some extent. Oncologists consider the patient’s characteristics and the cancer’s characteristics (tissue type, stage) to plan therapy. But chemotherapy treatments are often a one-size-fits-all approach—sometimes they work, sometimes they don’t. Meanwhile, the patient may suffer unpleasant side effects, without benefit.

In mid-2007, **Rita Quigley** noticed a small bump under the skin on her upper arm. She had been seeing a dermatologist after a malignant melanoma (skin cancer) was removed from her back 17 years earlier. The tiny mass was removed, and melanoma was found. Imaging scans revealed tumors in her lungs. Malignant melanoma that has metastasized to distant sites in the body is notoriously difficult to treat. **Jeffrey Sosman, M.D.**, director of Vanderbilt-Ingram’s Melanoma Program, treated Quigley with chemotherapy, but the tumors didn’t shrink. She suffered mild side effects. “Melanoma has been the most frustrating of solid tumors... The great majority of patients do not respond to the chemotherapy or immunotherapy treatments that we have,” Sosman says.



In October 2007, Quigley's tumors were surgically removed. But a scan several months later showed new tumors in her pelvic area, and Sosman began treating her with interleukin-2, an immunotherapy aimed at stimulating the immune system to kill the cancer. Quigley was hospitalized five days for treatment, and the therapy was repeated after a week off. Side effects can be severe. "It was several weeks after the second treatment before I felt like myself again," Quigley says.

Six weeks after treatment, scans showed no tumor shrinkage. **It had been a year, and Quigley had been through two surgeries and two grueling treatments. At this point a door opened for her—Sosman and Vanderbilt-Ingram colleague Igor Puzanov, M.D., were studying a new drug in patients with metastatic melanoma. The drug was not "off-the-rack"—it was tailored to a particular genetic change in tumor cells, and Quigley's cancer had the genetic change.**

### Measuring cancer genes

For more than 30 years, cancer has been linked to genetic mutations that give cancer cells a growth and survival advantage. Recently, investigators and pharmaceutical companies have aimed drug development efforts at these mutant gene products. But how likely is it that blocking just one target—when tumor cells often have many mutated genes—will kill the cancer?

The drug Gleevec bounded onto the world stage in 2001 and was found effective in the overwhelming majority of chronic myelogenous leukemia (CML) patients with the "Philadelphia chromosome." This mutation produces an abnormal cellular-signaling protein, which is stuck in the "on" position and drives cells to become leukemic. Gleevec blocks the activity of the aberrant receptor, and kills cancer cells. "Gleevec is really the poster child of personalized cancer medicine," Pao says. About the same time, Pao and colleagues in the Memorial Sloan-Kettering Cancer Center laboratory of 1989 Nobel prize co-winner **Harold Varmus, M.D.**, were exploring the same question. Their model was lung cancer.

They showed in mice that turning off a mutant oncogene in the lung caused tumors to die. Pao and colleagues (and other investigators) were also testing two targeted therapies—Iressa and Tarceva—in patients with lung cancer. About 10 percent had a rapid clinical response.

This group and others, including **David Carbone, M.D., Ph.D.**, and colleagues at Vanderbilt-Ingram, focused on Iressa and Tarceva's molecular target, the epidermal growth factor receptor (EGFR). Subsequent

trials have shown that patients whose tumors have certain EGFR gene mutations have a 75 percent chance of tumors shrinking when treated with EGFR-targeted medicines—pills with relatively mild side effects. That's compared to a 20-30 percent with chemotherapy.

**Now the race is on, Pao says, to catalog the genetic defects in all kinds of cancers, discover which mutations are critical to tumor survival, and link those mutations to targeted therapies.**

### In the fitting room

In 2002, investigators reported that about 60 percent of melanomas contained a single mutation in a gene called BRAF. "Everyone who read that paper said...if we can target BRAF, we're going to see Gleevec-like responses in melanoma," Sosman recalls.




**Jeffrey Sosman, M.D.**

Along came PLX4032, a BRAF inhibitor produced by Plexxikon and Roche Pharmaceuticals targeting the mutant most commonly found in melanoma. Puzanov led Vanderbilt's participation in Phase I trials, and Sosman is the national principal investigator of the Phase II studies now under way.

After a reformulation of the drug, "all of a sudden, everybody started seeing responses," Sosman says. Of 16 initial Phase I patients with BRAF-positive melanoma, more than half had their cancer shrink at least 30 percent. A trial in colon cancer patients with the BRAF mutation is showing similar response rates. As for Rita Quigley, she started taking PLX4032 in August 2008. Her tumors have shrunk, and she continues taking the pills daily, with minimal side effects.

### Stitching the pieces together

**These findings highlight a shifting view of cancer—from a disease known primarily by its tissue of origin (breast, colon, lung), to a disease classified by the genetic mutations that drive it. This is the crux of the Vanderbilt-Ingram initiative.**

With the aid of **Cindy Vnencak-Jones, Ph.D.**, and colleagues in the Department of Pathology's Clinical Molecular Genetics program, Pao is developing a platform to test for multiple genetic mutations. "We're going to be able in the next five to 10 years to routinely assign therapies based on the genetic makeup of patients' tumors," Pao said. 

*By Leigh MacMillan, first published in Momentum, Fall 2009*

## Shared Resources

The Vanderbilt-Ingram Cancer Center offers 13 Shared Resources designed to offer cutting-edge expertise and technology that would be out of the reach of individual scientists or laboratories.

**These include:**

**Biomolecular & Proteomics**, which provides cost-effective, state-of-the-art instrumentation and analytical expertise to investigators in the Vanderbilt-Ingram Cancer Center (VICC). This resource uses the instrumentation, laboratory facilities, and personnel of the Vanderbilt Mass Spectrometry Research Center (MSRC). Three service cores – a mass spectrometry research core, a comprehensive set of bioanalytical service cores, and a bioinformatics support core—are now integrated into a single analytical service unit.

**Biostatistics**, which provides assistance with the statistical aspects of experimental design, sample size estimation, and study power analysis; data acquisition and database development; statistical analysis and interpretation of findings; collaboration on presentation of results; and development of new statistical procedures as required by specific projects.

**Cell Imaging**, which supplies Cancer Center researchers with access to cutting-edge technology and expert technical support for microscopic observation and analysis of tissue and cellular anatomy and physiology related to cancer research. This resource maintains multiple, modern and reliable state-of-the-art fluorescence microscopes, an electron microscope, and associated image processing systems.

**Clinical Trials**, which brings together critical human resources to ensure standardization of training of all research personnel including physicians, research nurses, data management and regulatory staff. This shared resource also facilitates the training of investigators in the proper and consistent preparation of protocols for regulatory review and budget development and greatly enhances the Cancer Center's system for efficient and thorough data collection and analysis.



**Functional Genomics**, which provides Cancer Center members with cutting-edge services related to a battery of contemporary genomic technologies including microarray, deep-sequencing, and RNAi screening efforts. Since 2004, the resource has been in an almost constant state of evolution to keep pace with the highly dynamic nature of genomic technologies.

**Flow Cytometry**, which offers polychromatic analytical flow cytometry, high-speed sorting with aerosol containment, and a schedule with expanded access. This is the only facility at VUMC or Meharry Medical College devoted entirely to research cell sorting and analysis.

**Animal and Human Imaging** which provides scientific and technical resources and support for quantitative, non-invasive imaging of both animal models of cancer as well as human cancers. The Animal and Human Imaging Shared Resource includes an expert group of imaging scientists dedicated to the development and application of advanced imaging techniques in biomedical research as well as a state-of-the-art, dedicated facility, comprising 41,000 net square feet of space on four levels.

**Informatics**, which provides a flexible physical and electronic infrastructure for acquiring, storing, communicating and analyzing data arising from wet bench, translational, and clinical cancer research, as well as senior staff- and faculty-level assistance in the interpretation of research datasets using state-of-the-art analysis methods where they are available, the development of novel bioinformatics methods where current analytical approaches are insufficient, and the translation of 'genomically enabled' best practices into clinical decision support for personalized cancer care.

**Antibody**, which provides a dedicated high-throughput resource for the generation of monoclonal antibodies as well as a start-to-finish polyclonal antibody service added last year to meet significant demand for affinity purified polyclonal antibodies. The resource also provides reagents, equipment, protocols, and expert assistance in all aspects of production, detection, and

characterization of antibodies. In addition, a wide variety of specialized services related to antibody production, assay, purification, and usage are offered at cost with rapid turnaround.

**Human Tissue Acquisition and Pathology**, which provides human tissue samples and histology services to support translational and preclinical aspects of cancer research. It also assists in banking tissue samples for initiatives targeted by VICC, such as collection of head and neck tissue samples. This resource plays a critical role in supplying anonymized or de-identified tissues to researchers and assuring compliance with Health Insurance Portability and Accountability Act (HIPAA).

**Transgenic Mouse/ES Cell**, which facilitates the generation, storage and regeneration of genetically altered mice to the entire Vanderbilt research community. It is anticipated that the technology base sustained by this resource will be vitally important for enhancing the growth of stem cell research that uses not only mESCs, but also human ES cells (hESCs) and induced pluripotent stem (iPS) cells.

**Survey and Biospecimen**, which provides the Center's substantial population-based research investigators with high quality laboratory and survey research services. The faculty and staff are trained intensively to work with biological samples, such as blood, urine, mouthwash, saliva, tissue, tissue slides, DNA, and RNA. This staff is conducting the annual follow-up telephone interviews of approximately 60,000 Southern Community Cohort Study participants and processed more than 16,000 biologic samples for multiple epidemiologic studies last year.

**High-Throughput Screening and Chemical Synthesis**, which provides high-throughput screening and chemical synthesis capabilities to rapidly identify active compounds (hits) from large chemical libraries and then optimize those hits for the desired biological activity and pharmacologic properties.

## Cancer Drug Discovery

With the promise of personalized cancer medicine comes an unsettling question: Even if we know the genetic profile of a patient's tumor, do we have the corresponding therapies to treat it effectively? Right now, probably not.

The online "Catalogue of Somatic Mutations in Cancer" lists more than 80,000 mutations in more than 13,000 genes that have been linked to cancer. Currently, only a few dozen targeted cancer therapies are in clinical use, many of them targeting the same biological pathway. And of the hundreds in clinical trials, only one or two new drugs are approved each year. That leaves a wide array of cancer-associated mutations without corresponding targeted therapies—and a lot of patients without tailored treatments.

"We need to understand those drivers for each and every tumor and have a wide menu of options to choose from so that each patient can benefit from this kind of precision," says **Jennifer Pietenpol, Ph.D.**, director of Vanderbilt-Ingram Cancer Center. Drug discovery and development was

once the exclusive realm of the pharmaceutical industry. Industry is still critical in expanding the selection of targeted cancer therapies, but academic institutions are becoming increasingly important in the discovery and development of drug candidates.

Academic centers should not only generate basic discoveries about cancer biology, "but then take that next step toward trying to use that information in a fashion that will benefit patients,"

says **Larry Marnett, Ph.D.**, director of the Vanderbilt Institute

of Chemical Biology, which is focused on applying chemical approaches to biological problems, such as drug discovery. Researchers at Vanderbilt-Ingram and across the Vanderbilt campus are taking that next step to fill the menu with new drugs to offer patients and physicians.



**Larry Marnett, Ph.D.**



## No “one size fits all” for cancer

Drug discovery in oncology is plagued by one obstacle that most diseases don't have—cancer is not one disease but many. “If someone says, ‘I have cancer,’ that's almost like saying ‘I'm sick,’ ” says **Stephen Fesik, Ph.D.**, professor of Biochemistry and Pharmacology. Cancers are driven by many genomic and cellular alterations. Even if two people have the same “tissue” type of cancer (for example, breast cancer), there may be different genetic factors driving their tumors. And even within an individual's tumor, one tumor cell may harbor vastly different mutations than its (also malignant) next-door neighbors. The complexities of cancer biology make it difficult to find treatments that are effective for even most patients.

Ready to take on this challenge, Fesik left Abbott Laboratories last year to lead the cancer drug discovery initiatives of the Vanderbilt-Ingram Cancer Center and the Vanderbilt Institute of Chemical Biology. As Abbott's vice president of cancer research since 2000, he was responsible for building a pipeline of drug candidates with promising anticancer activity. He knows that industry alone can't make the advances in cancer therapy that the half-million Americans who die each year of the disease need. **“Industry is looking more and more on the outside for their innovative drug molecules,” he says.**

Using a technique he pioneered—fragment-based drug design—Fesik believes he can help fill up the therapeutic menu with candidate compounds that could make enormous strides against cancer. “My interest is to develop therapies that will have a dramatic effect on cancer patients,” he says. “...I'm looking for the cures.”

Even though there are many different genetic alterations driving tumors, there are some common themes and pathways that all or most cancers rely on to survive. The goal, Fesik says, is to develop drugs that act on highly validated targets within these pathways. The main problem is that many of these targets are considered “undruggable” by traditional methods, says Fesik. “It is very difficult to find a small molecule that's going to bind to these targets and affect their function.”

### Putting together the pieces

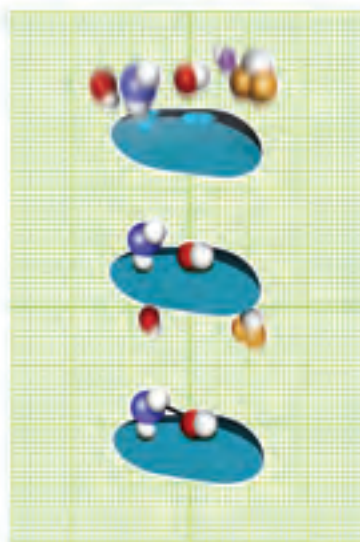
Fesik believes that building drugs one small piece at a time will overcome this problem. The traditional

approach to drug design involves the screening of a library of relatively large (at least on the chemical scale), intact compounds against the desired protein target, which has “pockets” to which drugs bind and can interfere with their activity. Then chemists make similar compounds—analogs—to try to find a molecule that will fit best into the binding pocket and affect the protein's activity.

**But a key barrier is the limited numbers of existing chemical compounds that can be tested. Instead of altering the large, intact lead molecule, Fesik's approach is to screen for fragments of that ultimate molecule and link them together, like Tinkertoys. This method, he says, “is a great way to create molecules that have never been made before.”**




**Stephen Fesik, Ph.D.**



*Drug “fragments” (top panel) are screened to find those that bind to “subpockets” on a target protein's binding surface (middle panel). The fragments are linked together into a larger molecule that better fills up the pocket (bottom panel).*

### Industrious in academia

Why would researchers at an academic institution be able to accomplish what industry hasn't achieved? Because, Fesik says, Vanderbilt has assembled the infrastructure—including strong centers in structural biology, chemical biology, imaging and proteomics—to go after these un-druggable targets.

“At Vanderbilt, I can carry these studies out and do things that might be against the ‘dogma’ about what's doable and not doable,” he adds. “What's driving me the most is the dramatic effects we may be able to have on the lives of cancer patients. The only thing that can stop this is the lack of funding.” 

*Melissa Marino, first published in Momentum, Fall 2009*

## Making Sense of Mountains of Data

On iTunes U, a lecturer predicts that we will one day be routinely giving drugs to computers. When you get sick, someone will load your medical history and your genome sequence (and perhaps other selected data about your biochemical composition) into a simulator. As various drugs are entered, you'll learn of their predicted effects in your body. While such scenarios may lie in our (perhaps still distant) future, it will take time—and some major computing power—to get there.

Biology has quite recently entered a golden age. Majestic, beckoning mountains of biological data—composed primarily of information about our genomes and the subtle differences among them—are filling up the planet's servers at explosive rates. Computer-assisted analysis of such huge data sets is the realm of “bioinformatics”—a discipline that applies information/computer science approaches to help researchers make sense of this biological information.

But that is only part of the equation; to achieve this futuristic scenario will also require the contribution of “biomedical informatics,” a field focused on applying the power of computers to health care, through, for example, electronic medical records and decision-support systems.

Though they had divergent beginnings, the fields of bioinformatics and biomedical informatics are now beginning to merge. “We've had bioinformatics, which essentially grew out of molecular biology and had the vocabulary and the cultural values of wet-bench biologists. It was just trying to figure out how life works, what's the machinery like,” says **Dan Masys, M.D.**, professor and chair of Biomedical Informatics at Vanderbilt, one of the nation's largest biomedical informatics departments. “And then we had clinical informatics, which grew historically out of people building electronic medical record systems for hospitals.

“These two types of people, if you put them in a room, would not have much to talk about, but what we're seeing is the emergence of this relentless convergence of these tools in an area we call clinical bioinformatics. And that's about understanding molecular patterns that have direct relevance to human health and disease and health care decision-making.”



**Dan Masys, M.D.**



## Life Encoded...and Corrupted

It starts with DNA, using pairs of four nucleotides to encode basic instructions for life. As cells divide and the genetic code is bequeathed to daughter cells, nucleotides are vulnerable to sporadic scrambling. Radiation, chemical exposures and viruses can also cause scrambling. We're riddled with random mutations, but fortunately, most cause no harm. Sometimes, though, cancer arises when somatic mutations randomly mount up into some unlucky combination. Odds worsen as we age and carry more mutations.

An algorithm is a set of rules for solving a puzzle. With so many ways for nucleotides to fall out of sequence, the role of computer algorithms is vital in understanding genetics and cancer. Masys says bioinformatics is about "understanding the semantics of the data...At a molecular level, it's figuring out how the hip bone is connected to the thigh bone."

Where sickness is concerned, the focus narrows to a disease phenotype, with analysis of sample after sample in search for molecular patterns—disease and normal samples, samples from patients sensitive to a particular drug and patients found not sensitive, samples from patients with a recurrence and patients remaining disease-free. The hunt is for biomarkers—traceable substances that reliably indicate biological states.

## Pattern Finders

A data pattern and a cause-and-effect are quite different things. You still have to validate the potential biomarker, says **Zhongming Zhao, Ph.D., M.S.**, who



**Zhongming Zhao,  
Ph.D., M.S.**

came to Vanderbilt-Ingram last year as chief bioinformatics officer.

Where complex diseases like cancer are concerned, molecular biomarkers — for a given diagnosis, prognosis, drug response — come with probabilities. More sophisticated integration of data is destined to yield increasingly probative, multi-dimensional

biomarkers, Zhao says. This is where proteomics comes in — proteins are seen as even more desirable fodder for computational biology.

Chemo is toxic and hit-and-miss. The emergence of molecular biomarkers is leading to finer sub-typing of cancer and a rush to discover targeted drugs designed to interfere with abnormal molecules while remaining nontoxic to normal cells.

**William Pao, M.D., Ph.D.**, director of Vanderbilt's



**William Pao,  
M.D., Ph.D.**

Personalized Cancer Medicine Initiative, has led planning at Vanderbilt for routine genotyping of tumor tissues. This capability is available at very few places, including Massachusetts General and Memorial Sloan-Kettering, but Vanderbilt will be the first in the southeast to offer it—and Vanderbilt's capability will have

an important twist. Building on its unique strengths in clinical informatics, Vanderbilt is developing a system for personalized medicine. As more tumor genotyping is digitally collated with other medical records information, a new understanding of cancer and a new level of clinical decision support are expected to emerge.

**Mia Levy, M.D.**, arriving in 2009 as Vanderbilt-Ingram's clinical informatics officer, and Masys envision a system that, practically on its own, will generate knowledge about the best ways to treat cancer. Beginning in July 2011, Levy plans to start rolling out a cancer decision-support ordering system, covering chemo, targeted drugs, labs, and imaging. "If we can harvest molecular patterns and how their stories play out clinically, in a short time we can improve the treatment rules, instead of waiting years for clinical trial results," Masys says.



**Mia Levy, M.D.**

It initially cost billions of dollars to sequence the human genome. The complete sequence of a cell now costs \$20,000-\$50,000. "Within three to five years you could get your entire genome in your electronic medical record for less than the price of a CT scan, for about \$1,000," Masys says.

We may be giving drugs to computers sooner than we thought. **V**

*By Paul Govern, first published in Momentum, Spring 2010.*

To view the full stories, visit [vicc.org/momentum](http://vicc.org/momentum)

## Diversity and Outreach to Underserved Communities



### Embracing the Obligation to Engage a Community

Like many Cancer Centers, Vanderbilt-Ingram has been challenged with too few faculty members of under-represented racial and ethnic populations and by the need and desire to engage more patients of under-represented groups in its clinical research.

Good thing there's nothing like a challenge to inspire Vanderbilt-Ingram Cancer Center's leadership. "This is a marathon, not a sprint, and Vanderbilt-Ingram Cancer Center, with significant support from the Medical Center, is committed to addressing this over the long run," said Center director **Jennifer Pietenpol, Ph.D.**

The Cancer Center and Medical Center share a goal of hardwiring "cultural competency" to increase diversity among their faculty and the patients they serve.



## But why is this so important?

“Cancer is a diverse set of diseases that disproportionately affect populations of color or racial and ethnic minorities, particularly African Americans, in our local area,” says **Elizabeth A. Williams, Ph.D.**, Associate Director for Diversity and Minority Affairs at Vanderbilt-Ingram. “Access to care is an issue, along with access to screening services. Genetics also plays a role. Important as well is the influence of social determinants of health on cancer outcomes experienced by racial and ethnic minorities.”

The proportion of minority patients enrolled on clinical trials at Vanderbilt-Ingram has steadily increased since 2003.

However, increasing diversity of the patient population remains a priority. While some efforts have been undertaken for quick results, community groups and experts that Vanderbilt-Ingram consulted recommended that the only approach likely to develop sustainable increases in minority participation in clinical research would be a comprehensive one that increases community knowledge, overcomes barriers to accessing the healthcare system and builds community trust.

## Actively engaging the community

Dr. Williams, an applied medical anthropologist and behavioral scientist with expertise in socio-cultural dimensions of cancer and health disparities



**Elizabeth A. Williams, Ph.D.**  
and **Tonya Micah**

elimination, was recruited in December to lead the Office of Minority Affairs (OMA) and to develop a strategic approach to eliminate cancer disparities. OMA Manager **Tonya Micah** is actively collaborating with more than 10 local, regional, and state groups focused on cancer prevention.

“Often underserved communities don’t feel particularly connected to academic cancer centers,” Dr. Williams says. “History—the political, social and racial divides that have occurred over time have definitely contributed to this.”

“We [OMA] seek to change this by translating across communities what’s happening around the issue of cancer, hopefully building bridges where they otherwise might not exist.”

In her role, Dr. Williams works with leadership at

Vanderbilt-Ingram as well as in the community to understand and address the barriers that may limit the population’s access to Vanderbilt for care as well as interest and enrollment in clinical trials.

“Changing perceptions requires getting to know the community better, particularly communities of color in our local area,” she says. “That means engaging communities where they are and on their terms.”

One “fruit” of this effort is the Nashville-Davidson County Witness Project—a collaborative initiative of Vanderbilt-Ingram, the Tennessee and Metro-Nashville health departments, the Cervical Cancer Coalition of Tennessee and concerned community members.


“The Witness Project uses African-American

“Cancer is a diverse set of diseases, but we see that they disproportionately affect populations of color and particularly racial and ethnic populations...”

breast and cervical cancer survivors, called witnesses, as role models, individuals who tell their story and encourage other women to have mammograms, clinical breast exams and pap smears,” Dr. Williams says. “Not only does it provide survivors an opportunity to be health advocates for their communities, it also links lay educators, concerned community residents who have an interest in these issues with training so they too can spread the message.”

Started in fall 2006, the program also gives uninsured and underinsured women access to mammograms and pap smears.

The OMA has also increased the Cancer Center’s visibility in the local minority and ethnic media, including producing two radio health talk shows, one targeted toward an African-American audience and the other to the Latino/Hispanic community. In 2006, OMA was asked to design and co-host a health talk show on WFSK 88.1 FM, a community-centered urban jazz radio station at historically black Fisk University. The weekly program, also featuring hosts from Meharry and Fisk, reaches a local audience of 40,000-50,000 (approximately 50% is African-American). Vanderbilt-Ingram extended the program’s reach world-wide in 2008 by supporting the station’s Web-streaming capability in 2008 ([www.wfsk.org](http://www.wfsk.org)).



“We can look at GIS maps to determine where people are tuning into the program. You’d be amazed to find out how diverse the listening audience is for WFSK,” Dr. Williams says. “These radio programs let people know the Cancer Center is interested in the well-being of all populations when it comes to cancer.”

The Cancer Center partnered with the Progresso Community Center and Nashville Latino Health Coalition in 2007 to conduct a needs assessment of the Latino/Hispanic population’s cancer-related needs. One outgrowth of the survey was to start a radio program aimed at the Latino/Hispanic audience. The assessment influenced the design of a promotional ad focused on the Latino and Hispanic community, Dr. Williams says.

Other community outreach efforts include performance of a live interactive program, “Unmasking the Myths, Cancer Research and Clinical Trials”; the Nashville Tobacco Prevention Initiative; Fashioned in Faith Calendar featuring African American breast cancer survivors; the Body and Soul Pastors Breakfast on NCI cancer prevention curriculum; contributions to the Nashville Bilingual Health

Guide; a local list-serve of cancer events; and Cancer Disparities series of workshops.

### Partnership with Meharry, TSU

The Cancer Center’s comprehensive diversity plan to increase accruals in ongoing trials also takes a long-term approach through key hires and several initiatives.

Notably, through the Southern Community Cohort Study and partnership with Meharry Medical Center (MMC) and Tennessee State University (TSU) in the U54 Cancer Partnership Grant, Vanderbilt-Ingram has collaborated with Southeastern community health centers to:

- [learn more about the etiology of cancer in a region with the highest cancer death rates](#)
- [understand relevant health barriers](#)
- [provide additional programs that serve diverse communities in our patient catchment area as well as throughout the Southeast](#)

The partnership with Meharry, a minority-serving institution, was initiated in 1999 and has been funded by the NCI since 2000. When the grant was renewed in 2006 for another five years, Tennessee State University was added

### Other accomplishments of the VICC-MMC partnership include:

- \* 1,125 patients screened for clinical trial participation at Metro Nashville General Hospital since 2001 with 68% of those eligible for a study agreeing to participate. Of those, 30% (343) had a study available and 21% (233) enrolled. (Some willing to enroll were unable to due to co-morbidities).
- \* A Cancer Center-funded clinical research program at MMC’s affiliated hospital (Metropolitan Nashville General), growing from zero clinical oncologists to two and including initiation of an active cancer clinical trials program.
- \* Recruitment of 17 new faculty focused on basic, clinical and population-based cancer research.
- \* Establishment of mutually beneficial collaborations between MMC, TSU, and VICC investigators with increases in cancer-related peer-reviewed publications and peer-reviewed grant submissions.
- \* Development of the Southern Community Cohort Study at VICC and MMC in 2002, resulting in NCI funding in excess of \$42 million, and successful renewal of this landmark multi-investigator R01-funded investigation into determinants of disparities in cancer incidence rates and mortality among African-Americans and low-income adults in the Southeastern U.S. More than 86,000 participants, two-thirds African-American, across 12 states have been enrolled in the SCCS, most (85%) from community health centers primarily serving America’s uninsured.
- \* Collaboration with the REACH for Survivorship program to conduct research that will identify disparities in minority patient survival and long-term outcomes.



as a partner to help engage in a community outreach program for cancer prevention.

Through this partnership, focused attention on barriers to clinical trials for racial and ethnic minorities has occurred. “We’ve conducted several town hall meetings, which are basically large focus groups with local community participants to determine what they see as issues related to clinical trials participation,” Dr. Williams says.

“Individuals were introduced to a ‘medical hero,’ a person who has actually participated in a clinical trial to speak first-hand about what occurred with them, as well as, to answer people’s questions about clinical trials.” Almost half of the participants agreed to further participation with researchers to support community education about clinical trials, serve on Institutional Review Boards, and/or serve on a clinical trials community advisory board.

### Increasing Diversity in Clinical Trials

There also have been concerted efforts to expand the clinical oncology capacity of Meharry and Nashville General Hospital, leading to an increase in innovative investigative therapies offered there. Vanderbilt and Meharry leaders have jointly recruited key faculty and staff. The Meharry Clinical Trials Shared Resource (CTSR) is staffed largely by former members of Vanderbilt-Ingram and is led by Debra Wujcik, R.N., M.S.N., Ph.D., former director of Vanderbilt-Ingram’s clinical trials office who volunteered to relocate to Meharry to oversee that initiative.

“Obviously having the capacity that some of our local sister institutions have, particularly Meharry Medical College, has helped to support increased participation of racial and ethnic minorities in clinical trials,” Dr. Williams says. “Dr. Wujcik and colleagues have not only engaged local community providers by making them aware of all clinical trials that are available, they also are present in those local offices to actually recruit individuals into clinical trials.”

### Increasing Diversity within Vanderbilt-Ingram

The Cancer Center is also committed to increase the recruitment and retention of minority, oncology-associated faculty, house staff, postdoctoral fellows, and graduate students.

According to the American Medical Association, in 2006 only 3.5% of physicians were African-American and 5% were Hispanic. The Association of Academic Medical Centers reports that in 2007, 3% of academic faculty members were African-

An assessment of cancer clinical trial accrual, reported at the 2009 American Association for Cancer Research annual meeting, found that:

**From 2001-2004,  
58% of patients offered a study  
agreed to participate.**


**From 2005-2007,  
77% of eligible patients agreed  
to participate.**

**Of those patients  
enrolled on study during this period,  
61% were African-American.**

American and 4.2% were Hispanic. To enhance minority participation in clinical trials, it is likely necessary to increase minority physician participation in clinical research. Vanderbilt-Ingram has partnered with MMC to create a joint fellowship position targeted to the recruitment of highly select minority physicians who wish to develop an academic career in Hematology and Oncology.

Some of the Vanderbilt fellows not formally part of the joint fellowship program conduct their continuity clinics at Nashville General Hospital, which offers education and research within an underserved and minority patient population. Furthermore, senior VICC faculty are committed to mentoring minority junior faculty, including those recently recruited to the nascent Meharry Medical School cancer program.

Vanderbilt-Ingram has undertaken faculty and staff educational programs to enhance physician and staff cultural sensitivity as well. **George Hill, Ph.D.**, and **Andre Churchwell, M.D.**, lead institutional efforts through the Office for Diversity.

“When it comes to the issue of health, no matter whether you are a basic scientist, clinical, applied or community-focused researcher, all of our efforts must center on improving the health of all populations,” Williams says. 

*By Carol Stuart*

## Journal Watch

Vanderbilt-Ingram Cancer Center is committed to conducting innovative, high-impact basic, translational, population-based and clinical research with the greatest potential for making a difference for cancer patients, today and in the future.

Here's a sampling of work published in peer-reviewed journals by center investigators:

### Protein suppressor of colon tumors

In the March 1, 2010 Journal of Clinical Investigation, **James Goldenring, M.D., Ph.D.**, and colleagues report that expression of Rab25—a protein known to regulate protein trafficking within the cell—may play a role in early colon tumor development. The investigators found substantially decreased Rab25 expression in human colorectal tumors compared with normal colon and that lower Rab25 expression levels predicted poorer survival. To clarify Rab25's role in colorectal tumor formation, the investigators generated mice lacking Rab25 and found that Rab25-deficient mice developed more intestinal polyps and colon tumors than parental mice. The findings suggest that Rab25 may act as a tumor suppressor in the colon lining and that reduction of Rab25 expression may be an early event in colon cancer formation.

### Gene signature for colon cancer prognosis

**R. Daniel Beauchamp, M.D.**, and colleagues have identified a gene signature that may help identify patients at risk of colon cancer recurrence—and identify patients most likely to benefit from chemotherapy. From a 300-gene expression signature initially identified in mouse colon cancer cells, the investigators developed a 34-gene signature most closely associated with metastasis and death (in a set of Vanderbilt patient samples). In a larger patient population, they found that patients with the “poor prognosis”

signature—the expression pattern seen in highly invasive mouse cells—were five times more likely to have a cancer recurrence than those with a “good” prognosis signature. Also, stage III patients with the “poor prognosis” signature appeared to benefit from chemotherapy whereas those with the “good prognosis” signature showed little benefit. The findings, published in the March 2010 issue of Gastroenterology, could help personalize treatments for colon cancer.

### Protein protector against DNA stress

Genome maintenance systems prevent and repair DNA damage to maintain the genome's stability and protect against mutations that cause cancer and other diseases. In their search for novel genome maintenance factors, **David Cortez, Ph.D.**, and colleagues have identified SMARCAL1 as a genome maintenance protein. Mutations in SMARCAL1 are known to cause the rare genetic disorder Schimke immunosseous dysplasia (SIOD), but the function of SMARCAL1 and its mechanistic role in the disease have remained unclear. In the Oct. 15, 2009 Genes & Development, the researchers report that SMARCAL1 protein acts to limit DNA damage at stalled replication “forks” (sections of unwound DNA undergoing replication). The findings suggest that mutations in SMARCAL1 that result in defective cellular responses to replication stress may at least partially explain the variety of symptoms associated with SIOD.

### Drugs join forces to overcome lung cancer resistance

**William Pao, M.D., Ph.D.**, and colleagues have found that combining two targeted cancer therapies may overcome resistance of lung cancers to Iressa and Tarceva—drugs that initially work well against lung cancers with mutations in the epidermal growth factor (EGF) receptor but lose their effectiveness over time. About



half of drug-resistant lung tumors harbor a new mutation (called T790M) in the EGF receptor. The researchers found that mouse tumors with the T790M mutation did not respond to Iressa, Tarceva, an experimental EGF receptor inhibitor (BIBW-2992), or Erbitux—an antibody that blocks the interaction of EGF receptor binding proteins with the EGF receptor. However, the combination of Erbitux and BIBW-2992 effectively “melted away” T790M-containing tumors. The results, in the Oct. 1, 2009 Journal of Clinical Investigation, suggest a way to overcome T790M-mediated resistance and support moving forward with clinical trials in patients with lung cancer.

### **New target for severing cancer’s access to supplies**

**Charles Lin, Ph.D.**, and colleagues have identified a protein—deltacatenin—involved in blood vessel development (angiogenesis) during disease conditions, but not during normal physiological processes. They found that endothelial cells from mice missing delta-catenin had reduced motility and vascular structure formation, compared to cells from normal mice. And in models of tumor growth and wound healing, mice missing delta-catenin showed reduced tumor growth and blood vessel density and impaired angiogenesis and wound closure. In contrast, these mice had normal physiological hormone-induced angiogenesis in the uterus. The findings, reported in the January 2010 Journal of Experimental Medicine suggest that delta-catenin may be a promising therapeutic target for blocking blood vessel growth in disease conditions like cancer.

### **Food, exercise and cancer**

Two studies on breast cancer survivors in Shanghai, China, have revealed dietary and lifestyle factors that influence cancer risk and quality of life. In a study published in the Dec. 9, 2009 Journal of the American Medical Association, **Xiao Ou Shu, M.D., Ph.D.**, and colleagues found

that women who reported the highest soy food intake had the lowest breast cancer mortality and recurrence rates compared with women in the lowest soy food intake group. And in the January Journal of Clinical Oncology, they reported that breast cancer patients who exercise and drink tea on a regular basis may be less likely to suffer from depression than other patients.

### **Cancer biomarker boost**

**Daniel Liebler, Ph.D., Lisa Zimmerman, Ph.D.**, and colleagues in the National Cancer Institute’s Clinical Proteomic Technology Assessment for Cancer (CPTAC) program have developed a new method for detecting and quantifying cancer-associated proteins in body fluids. The new method combines two existing mass spectrometry-based technologies: multiple reaction monitoring (MRM) coupled with stable isotope dilution mass spectrometry (SID-MS). In the July 2009 issue of Nature Biotechnology, they report that this combination of proteomics methods increases accuracy and reproducibility of candidate biomarker verification, ensuring that the best biomarker candidates are carried through to clinical validation. The findings may offer a major boost to the development of biomarkers to aid in early cancer detection and personalized cancer therapy—including the development of blood tests for cancer detection.

### **Gene signature predicts breast cancer prognosis**

Vanderbilt-Ingram researchers have uncovered a gene signature that may help predict clinical outcomes in certain types of breast cancer. In the June 2009 issue of the Journal of Clinical Investigation, **Harold (Hal) Moses, M.D.**, and colleagues report that this gene signature—which is associated with the transforming growth factor-beta (TGF- $\beta$ ) signaling pathway—correlates with reduced relapse-free survival in patients with breast cancer, especially in those with estrogen

receptor-positive tumors. The results suggest that assessing TGF- $\beta$  signaling may be a useful aid in determining breast cancer prognosis and in guiding treatment. The work also sheds light on how TGF- $\beta$  affects tumor growth and progression.

### Breast cancer 'hot spot'

**Wei Zheng, M.D., Ph.D.**, and colleagues have identified a new genetic hot spot for breast cancer on chromosome 6. Reported in the March 2009 issue of *Nature Genetics*, this genetic variation—a single nucleotide polymorphism (SNP)—may explain about 18 percent of breast cancer cases in the general population. Women with one copy of this SNP have about 40 percent increased risk of breast cancer; having two copies of the SNP increases risk about 60 percent. Although the function of the SNP is not clear, it is strongly associated with estrogen receptor (ER)-negative cases of breast cancer, which carry a worse prognosis than ER-positive cases. Zheng hopes to use this SNP and others to build a risk prediction model that could help identify high-risk women for chemoprevention or regular cancer screening to reduce their breast cancer mortality.

### Sweet approach to cancer prevention

The main sweet-tasting chemical component of licorice (glycyrrhizic acid) may offer a new approach to preventing colorectal cancer without the adverse side effects of other preventive therapies. In a study published in the April 2009 *Journal of Clinical Investigation*, **Raymond Harris, M.D., Ming-Zhi Zhang, M.D.**, and colleagues show that inhibiting the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ HSD2)—either by treatment with glycyrrhizic acid or by silencing the 11 $\beta$ HSD2 gene—prevents colorectal cancer progression in mice predisposed to the disease. While this natural chemical is an appealing drug lead in itself, the researchers are working to develop more specific and potent inhibitors of 11 $\beta$ HSD2.

### Life and death in the stomach lining

Infection with the gut bacterium *Helicobacter pylori* increases the risk of gastric cancer, in part by disrupting the delicate balance between cell proliferation and death in the stomach lining. Using gastric cell cultures and mouse models of *H. pylori* infection, **Brent Polk, M.D.**, and colleagues found that the bacterially induced activation of the epidermal growth factor receptor (EGFR)—a molecule that regulates cell survival—protects gastric epithelial cells from programmed cell death (apoptosis) and that blocking this activation increased *H. pylori*-induced apoptosis. The findings reported in the April 2009 issue of *Gastroenterology* offer insights into how *H. pylori* infection might contribute to the development of gastric cancer and support the strategy of targeting EGFR for cancer prevention or treatment.

### Lithium shields brain from radiation damage

Cranial irradiation is part of standard therapy for both primary and metastatic brain tumors. However, as with all treatment modalities, radiation often causes long-term side effects. In particular, neurological impairments—including lowered IQ, learning difficulties and memory loss—have been reported, especially in children treated for brain cancers. In the May 2009 issue of the *Journal of Clinical Investigation*, **Fen Xia, M.D., Ph.D.**, and colleagues show that lithium—a drug widely used to treat bipolar mood disorder—promotes DNA repair in healthy cells but not in brain tumor cells. The findings suggest that lithium treatment could offer a way to protect healthy brain tissue from damage that may occur during cranial radiation treatments.

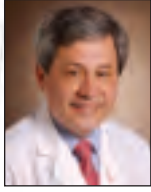


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**RESEARCH PROGRAM: BREAST CANCER**  
**PROGRAM LEADER: CARLOS ARTEAGA, M.D.**

**Carlos L. Arteaga, M.D.** is the Donna S. Hall Chair in Breast Cancer Research and interim director of the division of Hematology/Oncology. His research focuses on the role of signaling by growth factor receptors and oncogenes in the progression of breast tumor cells as well as the clinical development of molecular therapeutics in breast cancer. His laboratory is funded by the NCI, the American Cancer Society (ACS), the DOD Breast Cancer Research Program, the Susan G. Komen and Breast Cancer Research foundations, and partners in biotechnology and industry.



**Dr. Arteaga** received the 2007-2012 ACS Clinical Research Professorship Award, the 2009 Gianni Bonadonna Award from the American Society of Clinical Oncology (ASCO), and the 2003 AACR Richard & Hinda Rosenthal Foundation Award. He co-chaired the Developmental Therapeutics Committee of ECOG and chaired the Special Conferences Committee of the AACR (2002-2008). **Dr. Arteaga** also chaired the AACR Special Conferences Advances in Breast Cancer Research in 2003, 2005, 2007, and 2009. He serves or has served as a member of the NCI Parent Committee for Review of Cancer Centers (Subcommittee A; 2004-2008), the Board of Scientific Counselors (BSC) of NCI (1999-2004), the Breast Cancer Core Committee of the Eastern Cooperative Oncology Group (ECOG), and the Board of Directors of the American Association for Cancer Research (AACR; 2004-2007). He is Deputy Editor of Clinical Cancer Research and Associate Editor or member of the Editorial Board of Cancer Cell, Journal of Mammary Gland Biology & Neoplasia, Breast Cancer Research, Molecular Cancer Therapeutics, Journal of Clinical Oncology, and Cancer Biology & Therapy.

**Dr. Arteaga** joined the Vanderbilt faculty in 1989 and is Professor of Medicine and Cancer Biology and a member of the Division of Hematology-Oncology in the Department of Medicine.

**PROGRAM MEMBERS**

Vandana Gupta Abramson, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Carlos L. Arteaga, M.D.	Professor, Medicine (Hematology/Oncology)
Anuradha (Bapsi) Chakravarthy, M.D.	Associate Professor, Radiation Oncology
Gautam Chaudhuri, Ph.D.	Professor, Microbiology & Immunology (Meharry)
Rebecca S. Cook, Ph.D.	Research Assistant Professor, Cancer Biology
William D. Dupont, Ph.D.	Professor, Biostatistics
John G. Huff, M.D.	Associate Professor, Radiology & Radiologic Sciences
Mark C. Kelley, M.D.	Associate Professor, Surgery (Surgical Oncology)
Alecia Malin, Ph.D.	Assistant Professor, Surgery (Meharry)
Lynn M. Matrisian, Ph.D.	Professor & Chair, Cancer Biology
Ingrid Mayer, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Ingrid M. Meszoely, M.D.	Assistant Professor, Surgery
Harold L. Moses, M.D.	Professor, Cancer Biology
David L. Page, M.D.	Professor, Pathology
Fritz F. Parl, M.D., Ph.D.	Professor, Pathology
Jennifer A. Pietenpol, Ph.D.	Professor, Biochemistry
Sheila Ridner, Ph.D.	Research Associate Professor, Nursing
Marylyn DeRiggi, Ritchie, Ph.D.	Associate Professor, Molecular Physiology & Biophysics
Melinda E. Sanders, M.D.	Assistant Professor, Pathology
Douglas Sawyer, M.D., Ph.D.	Professor, Medicine (Cardiology)
Claus Schneider, Ph.D.	Assistant Professor, Pharmacology
Jeffrey Smith, M.D., Ph.D.	Assistant Professor, Medicine (Genetic Medicine)
Fen Xia, M.D., Ph.D.	Assistant Professor, Radiation Oncology
Baogang Jonathan Xu, Ph.D.	Assistant Professor, Neurological Surgery
Thomas E. Yankeelov, Ph.D.	Assistant Professor, Radiology & Radiological Sciences
Wei Zheng, M.D., Ph.D.	Professor, Medicine (Epidemiology)



## PROGRAM OVERVIEW

The Breast Cancer Program (BC) includes 26 members from 15 academic departments from Vanderbilt University School of Medicine (VUSM), Vanderbilt School of Nursing, and Meharry Medical College. Program members have expertise in cellular signaling and molecular biology, breast pathology, medical, surgical, and radiation oncology, clinical trial design, epidemiology and quality of life studies, mass spectrometry, biostatistics, and biomedical informatics.

The Breast Cancer Program (BC) has increased the number of therapeutic and non-therapeutic investigator-initiated clinical trials (IITs) over the previous CCSG funding period. In 2007, the program renewed its Breast Cancer Specialized Program of Researh Excellence (SPORE) grant, in which three of the four translational projects led to six IITs. This achievement illustrates the capacity and productivity of this multidisciplinary program and the impact of its translational studies as recognized through peer review. Because of the impact of this program's translational studies, members were co-investigators in two of the eight Stand Up To Cancer (SU2C) grant finalists in January 2009. The program is an active member of the funded SU2C Multi-institutional Team "Targeting PI3 Kinase in Women's Cancers" (Dr. Cantley, PI Harvard).

The program's ability to conduct clinical trials was expanded in 2009 with the opening of a new Vanderbilt Breast Center, a multi-specialty breast disease clinic with an emphasis on breast cancer management. Since its opening, total outpatient visits have increased 15 percent and new breast cancer diagnoses have increased 30 percent. The center is one of few in the country that offers mammograms without an appointment.

## SCIENTIFIC GOALS

**The program has a strong emphasis on breast epithelial cell and molecular biology, basic science driven translational and clinical research, and molecular epidemiology. Main scientific goals include:**

- 1) To stimulate collaborative, extramurally fundable basic science-based translational and clinical research in breast cancer.
- 2) To enhance communication between program members and dissemination of new data and cutting edge methodologies.
- 3) To stimulate novel, investigator-initiated pre-surgical and neoadjuvant clinical trials of new therapies and therapeutic combinations with an emphasis on biomarker discovery.
- 4) To mentor and train investigators in translational research in breast cancer.
- 5) To establish research partnerships with biotechnology and industry that will enhance the program's translational and clinical research.

**BC focuses on several themes that cover the spectrum from mechanistic science to clinical investigation.**

**Areas of interest include the following:**

- 1) Role of oncogene signaling (ErbB2, ErbB3, PI3K, TGFb) and tumor suppressors (TGFb) in mammary development, transformation, and tumor progression.
- 2) Role of the p53 family of transcription factors on the pathogenesis of triple negative (basal-like) breast cancer and its response to therapy.
- 3) Discovery of pharmacodynamic and non-invasive imaging biomarkers predictive of response to established and novel anti-cancer agents.
- 4) Association of gene variants and gene-environment interactions with progression of premalignant breast disease and risk of breast cancer.
- 5) Cellular and molecular mechanisms of bone metastasis and markers of bone quality in patients with breast cancer disseminated to bone.
- 6) Discovery of mechanisms of de novo and acquired resistance to anti-HER2 and endocrine therapy.
- 7) Advocacy, education, and outreach activities to inform patients and community about breast cancer research and enhance accrual into clinical trials.

## AREAS OF PROGRAM EXPERTISE

Breast Cancer Research Program members have expertise over a wide range of disciplines from molecular and cell biology to translational and clinical research in breast cancer.

**Vandana Abramson, M.D.**, a recent recruit from the University of Pennsylvania, is a breast cancer clinical investigator with expertise in Phase I development of new agents and the use of pharmacodynamic endpoints to assess drug action. She recently obtained a Bonadonna Fellowship Award from ASCO (2009). Her main role is to generate, implement, and lead IITs based in BC.

**Dr. Arteaga** focuses on the role of TGFb and ErbB receptor signaling in mammary gland development and transformation. There is also emphasis on discovery of biomarkers of drug action and mechanisms of resistance to anti-oncogene (HER2, PI3K, IGF-IR) and endocrine therapies in breast cancer.

**Anuradha (Bapsi) Chakravarthy, M.D.**, co-Director of the Tissue Core of the Breast Cancer SPORE, is co-investigator in several IITs focused on discovery of pharmacodynamic and non-invasive imaging predictors of response to neoadjuvant chemotherapy.

**Gautam Chaudhuri, Ph.D.**, Professor of Microbiology & Immunology at Meharry Medical College, has research interests in understanding the genetic and epigenetic regulation of the BRCA2 gene.

**Rebecca S. Cook, Ph.D.**, has expertise in using the applications of cell biology and developmental biology to interrogate stages of cancer formation and malignant progression in mouse models.

**William D. Dupont, Ph.D.**, has collaborated for the past 32 years with **David Page, M.D.** and more recently with Jeffrey Smith, M.D., Ph.D., both BC members, in the discovery of histopathologic, genetic and molecular risk factors for breast cancer in women with benign breast disease.

**John G. Huff, M.D.**, who joined the Vanderbilt faculty in 2007 as Director of Breast Imaging and Imaging Director of the Breast Center, has a special interest in the multidisciplinary approach to breast cancer management as well as advanced breast imaging including MRI.

**Mark C. Kelley, M.D.**, Director of the Division of Surgical Oncology, is collaborating with colleagues in the Department of Biomedical Engineering on the development of optical spectroscopic methods for the intra-operative demarcation of breast tumors.

**Alecia Malin, Ph.D.**, focuses her research on lifestyle epidemiology and health services research factors related to breast cancer risk. She is funded by the ACS to examine the role of serial mammography in minority and medically underserved women with breast cancer and by the NCI to study the role of vitamin D, obesity and breast density in breast cancer risk in African-American women.

**Lynn M. Matrisian, Ph.D.**, was one of the first to report that growth factors and oncogenes induce the expression of extracellular matrix-degrading matrix metalloproteases (MMPs). She is PI of the Vanderbilt Tumor Microenvironment Network U54 Grant, which focuses on studying mechanisms of paracrine TGFb signaling in mammary tumor initiation and progression.

**Ingrid A. Mayer, M.D.**, implements and conducts investigator-initiated, mechanism-based clinical and translational trials focusing on HER2, PI3K, and IGF-IR pathways as mechanisms of resistance in HER2-overexpressing, triple-negative, and hormone-sensitive breast cancers. She is a member of the ECOG Breast Committee.

**Ingrid M. Meszoely, M.D.**, is Clinical Director of Vanderbilt's Breast Center at One Hundred Oaks, the primary point of tissue/body fluids collection and entry of patient accrual to our IITs, and is PI of a SPORE-based IIT and is liaison with the NSABP.

**Harold L. Moses, M.D.**, utilizes elegant transgenic mouse models expressing active TGFb1 or dominant-negative type II TGFb receptor (TbRII) under the control of conditional tissue-specific promoters, either in epithelium or in stroma.

**David L. Page, M.D.**, is co-investigator in the Breast Cancer SPORE, where he studies molecular markers in pre-neoplastic lesions of the breast that predict for the subsequent progression to invasive breast cancer.

**Fritz F. Parl, M.D., Ph.D.**, investigates estrogen-induced carcinogenesis and breast cancer. The research focuses on the role of phase I (CYP1A1, CYP1B1) and phase II enzymes (COMT, GSTs) in estrogen metabolism.



**Jennifer A. Pietenpol, Ph.D.**, focuses on the role of the p53 family of transcription factors and biochemical pathways that control cell cycle checkpoint response in human breast cancer cells. **Dr. Pietenpol** also serves as co-director of the Breast Cancer SPORE.

**Sheila H. Ridner, Ph.D., R.N.**, assistant Professor in the School of Nursing, has research directed toward developing a better understanding of the impact of treatment-related lymphatic damage on cancer patients and survivors.

**Marylyn D. Ritchie, Ph.D.**, is a statistical and computational geneticist with a focus on detecting disease-susceptibility genes associated with common, complex human disease.

**Melinda E. Sanders, M.D.**, research pathologist for all VICC-based breast cancer clinical trials, focuses her translational research on genomic and proteomic profiling studies in breast cancer.

**Douglas B. Sawyer, M.D., Ph.D.**, Director of the Division of Cardiology, conducts basic and translational work examining mechanisms of treatment-induced heart failure in patients with breast cancer.

**Claus Schneider, Ph.D.**, focuses on the biosynthesis of lipid mediators in inflammatory and human breast cancer cells as well as the biochemistry and biology of oxidative transformation of the dietary cancer chemopreventive agent curcumin.

**Jeffrey R. Smith, M.D., Ph.D.**, employs genomics, bioinformatics, statistical genetics, and high-performance computational approaches to determine the role of genes in the onset and course of both breast and prostate cancer.

**Fen Xia, M.D., Ph.D.**, focuses research on elucidating the mechanisms that regulate the repair of chromosomal double-strand breaks (DSB) that arise during physiological DNA metabolism and after radiation therapy or chemotherapy.

**Baogang Jonathan Xu, Ph.D.**, who trained with **Richard Caprioli, Ph.D.** at the Vanderbilt Mass Spectrometry Research Center, is interested in the application of proteomics-based approaches for studying of the breast tumor microenvironment.

**Thomas E. Yankeelov, Ph.D.**, focuses on development and application of multi-modal, non-invasive, in vivo imaging methods for monitoring treatment response in breast cancer patients.

**Wei Zheng, Ph.D., M.P.H.**, an internationally recognized epidemiologist with a major research interest in host and environmental factors in breast cancer, is the PI of multiple NCI-funded studies, including a genome-wide association study of breast cancer. [V](#)

**RESEARCH PROGRAM: CANCER EPIDEMIOLOGY, PREVENTION AND CONTROL  
PROGRAM LEADERS: WEI ZHENG, PH.D., AND DEBRA FRIEDMAN, M.D.**

**Wei Zheng, M.D., Ph.D.**, is Ingram Professor of Cancer Research in the Department of Medicine at Vanderbilt University, Chief of the Division of Epidemiology and Director of the Vanderbilt Epidemiology Center. **Dr. Zheng** is a National Cancer Institute MERIT Award holder with major research interests in nutritional and molecular epidemiologic studies of breast and colorectal cancer.



**Dr. Zheng** has directed multiple research projects to better understand the causes of cancer and other illnesses, as described in over 350 peer-reviewed scientific publications. Currently, he is principal investigator of six NCI-funded grants for large epidemiologic studies of cancer, including both case-control and prospective cohort studies. **Dr. Zheng** obtained his medical degree from the Shanghai Medical College in 1983, completed a post-doctoral position at the National Cancer Institute and then obtained his Ph.D. from Johns Hopkins School of Medicine.

**Debra L. Friedman, M.D., M.S.**, is an Associate Professor of Pediatrics and the E. Bronson Ingram Chair in Pediatric Oncology, director for the division of Pediatric Hematology/Oncology and the Director of the REACH for Survivorship Program. She was recruited in 2008 from the Fred Hutchinson Cancer Research Center, where she served as the first director of survivorship and the principal investigator of the Lance Armstrong Foundation (LAF)-funded Survivorship Center of Excellence.



**Dr. Friedman's** research interests lie in the long-term outcomes for cancer survivors, as well as in the design of novel therapeutic protocols for childhood cancer, designed to decrease adverse long-term effects of therapy. **Dr. Friedman** has leadership roles in survivorship as well as pediatric, adolescent and young adult oncology in the Children's Oncology Group (COG) and the LAF. She is currently the principal or co-investigator of six NCI-funded grants examining outcomes for cancer survivors. She also serves on the External Scientific Advisory Committee of the Meharry Medical College (MMC)/VICC Partnership.

**PROGRAM MEMBERS**

Daniel A. Barocas, M.D., M.P.H.	Assistant Professor, Urologic Surgery
William J. Blot, Ph.D.	Professor, Medicine (Epidemiology)
John D. Boice, Jr., Sc.D.	Professor, Medicine (Epidemiology)
Stewart Michael, Bond, Ph.D.	Assistant Professor, Nursing
Scott C. Borinstein, M.D., Ph.D.	Assistant Professor, Pediatrics
Stephen P. Bruehl, Ph.D.	Associate Professor, Anesthesiology
Maciej S. Buchowski, Ph.D.	Research Associate Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Raymond F. Burk, M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Qiuyin Cai, M.D., Ph.D.	Assistant Professor, Medicine (Epidemiology)
Liana D. Castel, Ph.D.	Assistant Professor, Medicine (Epidemiology)
Dai H. Chung, M.D.	Professor, Pediatric Surgery
Bruce Compas, Ph.D.	Professor, Psychology & Human Development
Qi Dai, M.D., Ph.D.	Assistant Professor, Medicine (Epidemiology)
Sandra L. Deming, M.D., Ph.D.	Assistant Professor, Medicine (Epidemiology)
Robert S. Dittus, M.D.	Professor, Medicine (Internal Medicine & Public Health)
Meira Epplein, Ph.D.	Assistant Professor, Medicine (Epidemiology)
Ann Marie Flores, Ph.D.	Assistant Professor, Orthopaedics & Rehabilitation
Jay H. Fowke Ph.D.	Assistant Professor, Medicine (Epidemiology)
Haydar A. Frangoul, M.D.	Associate Professor, Pediatrics (Hematology/Oncology)
Debra L. Friedman, M.D.	Associate Professor & Director, Pediatrics (Hematology/Oncology)
Mary Jo Gilmer, Ph.D.	Professor, Nursing
Marie R. Griffin, M.D.	Professor, Preventive Medicine
Kirsten L. Haman, Ph.D.	Research Assistant Professor, Psychiatry



Margaret Hargreaves, Ph.D.	Professor, Internal Medicine (Meharry)
Katherine E. Hartmann, M.D., Ph.D.	Associate Professor, Obstetrics & Gynecology)
Asha Kallianpur, M.D.	Assistant Professor, Medicine (Epidemiology)
Jirong Long, Ph.D.	Assistant Professor, Medicine (Epidemiology)
Beth Malow, M.D.	Professor, Neurology
Joseph McLaughlin, Ph.D.	Professor, Medicine (Epidemiology)
Barbara Murphy, M.D.	Associate Professor, Medicine (Hematology/Oncology)
Reid M. Ness, M.D.	Assistant Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
John A. Oates, M.D.	Professor, Medicine (Clinical Pharmacology)
Neeraja Peterson, M.D.	Assistant Professor, Medicine (Internal Medicine & Public Health)
Wayne A. Ray, Ph.D.	Professor, Preventive Medicine
Sheila Ridner, Ph.D.	Research Associate Professor, Nursing
Lyman Jackson, Roberts, M.D.	Professor, Pharmacology
Vikrant V. Sahasrabudhe, M.B.B.S., DrPH	Assistant Professor, Pediatrics (Institute for Global Health)
Maureen Sanderson, Ph.D.	Professor, Obstetrics & Gynecology (Meharry)
David G. Schlundt, Ph.D.	Associate Professor, Psychology
Martha J. Shrubsole, Ph.D.	Assistant Professor, Medicine (Epidemiology)
Xiao-Ou Shu, M.D., Ph.D.	Professor, Medicine (Epidemiology)
Lisa B. Signorello, Sc.D.	Assistant Professor, Medicine (Epidemiology)
Flora A. M. Ukoli, M.B.B.S.	Associate Professor, Surgery (Meharry)
Nancy Wells, DNsc	Research Professor, Nursing
Wanqing Wen, M.D.	Research Assistant Professor, Medicine (Epidemiology)
Steven N. Wolff, M.D.	Professor, Internal Medicine (Meharry)
Gong Yang, M.D.	Research Assistant Professor, Medicine (Epidemiology)
Yajun (Andrew), Yi, M.D., Ph.D.	Research Assistant Professor, Medicine (Genetic Medicine)
Wei Zheng, M.D., Ph.D.	Professor, Medicine (Epidemiology)

## OVERVIEW

The Cancer Epidemiology, Prevention & Control Research Program focuses on understanding cancer etiology, control, long-term outcomes, and identifying mechanisms for prevention. A variety of approaches are employed to achieve these goals, with significant interaction with other Cancer Center programs, the clinical enterprise and community outreach.

Since the recruitment of Friedman, the Cancer Center and the Monroe Carell Jr. Children's Hospital at Vanderbilt and the Department of Pediatrics have launched the REACH (Research, Education, Advocacy, Clinical Care, Health Promotion) for Survivorship initiative for cancer patients and their families. In addition, a division of Epidemiology was created within the Department of Medicine. A new methods-oriented doctoral program in Epidemiology admitted its first class last fall.

## SCIENTIFIC GOALS

- 1) To establish and further develop population-based resources, including large-scale cohort studies with extensive data and biospecimen repositories, for research into the etiology, prevention, control and long-term outcomes of cancer.
- 2) To identify environmental and genetic factors that may influence the risk and outcomes of cancer.
- 3) To evaluate biomarkers that could be informative for cancer risk assessment, early detection and prediction of adverse long-term outcomes.
- 4) To identify the incidence, prevalence, spectrum, and severity of adverse long-term health-related outcomes following cancer diagnosis and treatment and develop interventions to prevent or ameliorate such outcomes.
- 5) To assess the magnitude and determinants of disparities in cancer risk and survivorship associated with race, gender, geography and other group characteristics.

## AREAS OF RESEARCH EXPERTISE

- 1) Establishment and development of resources in large cohorts
- 2) Genetic and molecular epidemiology
- 3) Epidemiology of nutrition, lifestyle and environmental factors
- 4) Cancer survivorship
- 5) International studies and cancer disparities

Each relies at least in part on large cohort studies with extensive biospecimen repositories. These ongoing studies position Vanderbilt-Ingram Cancer Center at the leading edge of molecular and genetic cancer epidemiology and survivorship now and in the future. Key among these are:

**The Southern Community Cohort Study (SCCS), one of the nation's major investigations into determinants of the higher rates of many forms of cancer among African Americans and among persons of low income**

**The Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS), unique cohorts of Chinese men and women with high quality data and biological samples**

**The Genetic Consequences of Cancer Treatment cohort of survivors of childhood and young adult cancers.**

When the specimen repositories from the SCCS, SWHS and SMHS are combined, survey data from nearly 223,000 adults are available, and biological samples from most study participants are stored at Vanderbilt and available for molecular epidemiologic research into the causes of cancer.

### GENETIC AND MOLECULAR EPIDEMIOLOGY

Program members and colleagues from the Breast Cancer Program study breast cancer etiology and survivorship using biological samples collected primarily from more than 9,000 breast cancer cases and approximately an equal number of controls recruited in four NCI-funded studies conducted in Shanghai and Tennessee. With maturation of the SCCS, additional breast cancer cases diagnosed in African and European Americans will be included.

**Dr. Zheng** recently launched the first breast cancer genome-wide association (GWA) study in non-European women, collaborating with scientists from multiple other studies. **Dr. Shu** is organizing a similar GWA consortium to identify genetic risk variants for breast cancer survival.

Program investigators are conducting large studies to investigate genetic risk variants for other tumors: corpus uteri (**Dr. Shu**), lung (**Dr. Cai**), prostate (**Dr. Fowke**) and colorectal polyps (**Dr. Zheng**). The population-based case-control study of endometrial cancer is one of the largest epidemiologic studies of this malignancy to date.

In collaboration with members in the GI program (**Coffey, Murff**), Program members launched a large epidemiologic study—the Tennessee Colorectal Polyp Study (TCPS)—in 2002 to investigate biomarkers and lifestyle factors for colorectal polyps.

**Qiuyin Cai, M.D., Ph.D.** directs a large molecular epidemiologic study of lung cancer using data and biologic samples collected in the SCCS and SWHS.

**Dr. Fowke** is conducting a large prostate cancer study investigating the association between obesity, prostatic intraepithelial neoplasia (PIN) and prostate cancer. Recruitment of **David Penson, M.D., M.P.H.**, will enable enhanced research on the determinants and outcomes in prostate cancer and its precursor lesions.

**Meira Epplein, Ph.D.**, is working closely with **Dr. Correa's** (GI) strong research program on gastrointestinal cancer and Helicobacter pylori infection. **Dr. Blot** is also working with **Dr. Correa** and colleagues in China exploring possibilities for a large-scale intervention trial in high-risk Chinese communities to test whether H. pylori eradication might reduce stomach cancer incidence.

Vanderbilt-Ingram has a long tradition of studying the role of the COX pathway in carcinogenesis as well as some of the landmark work for lipid peroxidation. We are evaluating urinary PGE-M using samples from the various large cohorts in cancers of the colon, pancreas, ovary, lung and corpus uteri, and evaluating the association of urinary isoprostane levels with breast cancer.



## EPIDEMIOLOGY OF NUTRITION, LIFESTYLE AND ENVIRONMENTAL FACTORS

A major focus of nutritional epidemiology research is to identify dietary protective factors (such as soyfood, tea, and cruciferous vegetables) for cancer as well as dietary factors that may influence survivorship and quality of life among women diagnosed with breast cancer.

In a spin-off of the SCCS supported by the Komen for the Cure Foundation, investigators are evaluating nearly 20 biomarkers related to energy balance and a 1,500-SNP panel spanning multiple areas of the genome. This will lead to an assessment of obesity and physical activity in breast cancer risk and survivorship.

Dr. Correa continues assessment of potential protective effects of vitamin C and beta carotene in gastric cancer.

**John Boice, Sc.D.** and **Joseph McLaughlin, Ph.D.** have carried out research showing that risk of neither brain cancer nor acoustic neuroma was elevated among users of cellular telephones.

Using a pharmacy database in the Tennessee Medicaid system, **Wayne Ray, Ph.D.**, and colleagues have conducted a series of follow-up studies estimating risk of cancer, cardiovascular disease and other health outcomes among persons prescribed a number of different medications.

Program investigators (**McLaughlin, Blot**) used linked pharmacy and cancer registries in Denmark to show lower risks of colorectal cancer among long-term users of low-dose aspirin. The potential link between NSAID use and lung cancer has been investigated in collaboration with the Thoracic/ Head and Neck Program.

## CANCER SURVIVORSHIP RESEARCH

With Dr. Friedman's recruitment, Vanderbilt-Ingram is growing an integrated, interactive and scientifically focused program of survivorship research. A major strength is use of large cohort studies for cancer control and survivorship research.

Prevalent breast cancer survivors in the SCCS are being targeted for a study of functional outcomes and psychosocial well being in a recently funded R21 proposal (**Flores, PI; Friedman, Blot, Signorello, Co-Is**). A pilot study is planned, led by **Drs. Friedman, Signorello and Blot** to obtain medical records, updated outcomes data and tissue specimens from a subcohort of SCCS cancer survivors.

**Dr. Compas** studies the processes of coping and self-regulation in response to stress. His studies have compared psychological interventions for newly diagnosed breast cancer patients; analyzed interactions between mothers and daughters coping with the risk of breast cancer; study of pathways through which psychological stress can affect tumor progression; communication between parents and children with cancer, and neurocognitive outcomes of childhood cancer survivors. **Dr. Friedman** is studying an innovative telephone counseling intervention for parents of children who have just completed cancer treatment and family function among parents and siblings of childhood cancer patients.

**Robert Dittus, M.D., M.P.H.** studies the cost-effectiveness of alternative strategies for colorectal cancer screening and surveillance. **Neeraja Peterson, M.D.** is creating and evaluating an innovative electronic data collection system to enhance understanding of the delivery and utilization of colorectal cancer screening. **Drs. Murff, Fowke and Cui** have used the SCCS and other cohorts to examine disparities in colorectal, breast and prostate screening. **Dr. Murff** is conducting research to better delineate the complex genetic and environmental factors associated with familial colon cancer and to develop an intervention to decrease colorectal cancer health disparities along the cancer control continuum. With the recruitment of **Dr. Penson** in 2009, similar efforts will be undertaken for genitourinary cancers.

**Katherine Hartmann, M.D., Ph.D.**, has expertise in customizing and implementing smoking cessation interventions for prenatal and postpartum women, surgical patients, and those receiving care for cervical dysplasia.

## OTHER CANCER SURVIVORSHIP RESEARCH STUDIES

Multiple Program members are conducting observational and intervention studies to examine a number of potential adverse effects of cancer and its therapy, including second neoplasms among stem cell transplant and childhood cancer survivors; adverse long-term outcomes in Hodgkin lymphoma survivors; exercise and energy consumption in childhood cancer survivors; symptom clusters, measurement techniques, educational interventions, co-morbidities and self-care practices; psychosocial well-being, health related quality of life, communication and caregiver coping in head and neck patients; and the arthralgia syndrome associated with aromatase inhibitors in breast cancer survivors.

### **CLINICAL CORRELATIVE AND COMMUNITY PROGRAMS IN CANCER SURVIVORSHIP**


A major new initiative is the REACH (Research, Education, Advocacy, Clinical Care, Health Promotion) for Survivorship Program, led by **Dr. Friedman**. At VICC, more than 4,500 new adult and 135 pediatric patients are seen annually. With an approximate 70% survival rate, 2,800 new cancer survivors could benefit from the program and contribute to the research each year. All cancer survivors are eligible regardless of age, place or type of treatment. To our knowledge, this is a unique program, serving a racially, ethnically and socioeconomically diverse patient population of adults and children.

### **CANCER DISPARITIES RESEARCH**

Within the United States, particular emphasis has been devoted to research to identify the determinants of, and eventually remedy, the disproportionate share of the cancer burden borne by African Americans. Vanderbilt-Ingram has intensified its commitment to the U54-funded partnership with minority-serving Meharry Medical College (MMC). Indeed, several faculty members from MMC are members of this Program and are active in our initiatives.

This Program uses the strength of the Partnership to further decrease the burden of cancer for patients and families with such research and clinical projects as the SCCS (**Dr. Blot**), the study of stress and tumor progression (**Dr. Compas**), a breast cancer study in African Americans (**Drs. Cui/Zheng**), a study of vitamin D and mammographic density (**Drs. Malin-Fair/Dupont**). In addition, a survivorship component has been added to the Partnership to compare adverse long-term outcomes of African American versus Caucasian cancer survivors and to establish a patient navigation program to facilitate transition from acute oncology care to survivorship.

Adolescents and young adults are also considered an underserved group when it comes to cancer survivorship.

**Dr. Friedman** is leading efforts to understand the determinants of these survival disparities for this young age group. Vanderbilt-Ingram is one of only six centers in a biorepository network for AYA cancers, and one of three centers participating in a pilot AYA cohort study, both funded by LAF (**Friedman, PI**). Vanderbilt is a member of the LIVESTRONG Young Adult Alliance; Dr. Friedman serves on the steering committee. 



**RESEARCH PROGRAM: GASTROINTESTINAL CANCER****PROGRAM LEADERS: ROBERT J. COFFEY JR., M.D., AND JORDAN D. BERLIN, M.D.**

**Robert J. Coffey Jr., M.D.**, who has led GI since its inception in 1993, holds two endowed chairs and is Principal Investigator of the NCI-funded GI SPORE and MMHCC. He also directs the newly formed VUMC Epithelial Biology



Center (EBC). He remains clinically active but devotes 90% of his effort toward basic research. His major research interests are in epithelial growth and differentiation, trafficking of EGFR ligands in polarized epithelial cells, GI malignancy, and Ménétrier's disease.

**Dr. Coffey** is Professor of Medicine (Gastroenterology and Medical Oncology) and Cell and Developmental Biology. He is a member of the American Society of Clinical Investigation and American Association of Physicians. **Dr. Coffey** attended Princeton University and Georgetown Medical School. He trained in internal medicine at Emory University and then received fellowship training in medical oncology at Georgetown and gastroenterology at the Mayo Clinic. He was a staff member at the Mayo Clinic before coming to Vanderbilt as an Assistant Professor in 1986.

**Jordan D. Berlin, M.D.**, is Director of the Phase I team and is Ingram Associate Professor of Medicine in the Division of Medical Oncology. **Dr. Berlin** serves as Medical Director of the Clinical Trials Shared Resource, and is a member of the IRB, the Resource Allocation Committee, and the Vanderbilt-Ingram Cancer Center Data Safety and Monitoring Committee. He has served on design studios for two projects as part of the Vanderbilt Clinical and Translational Science Award.



**Dr. Berlin** serves on the core GI committees at the Eastern Cooperative Oncology Group (ECOG) and American College of Surgeons Oncology Group (ACOSOG) and was selected for the ECOG Young Investigators' Award in 2004. He represents ECOG as chairman of the Intergroup Task Force on Pancreas Cancer. **Dr. Berlin** has served on the program committees of several national and international cancer meetings. He was a 2008 member of the NCI Think Tank on the coding, decoding, transfer, and translation of information in cancer. **Dr. Berlin** has represented Vanderbilt on the Guidelines Steering Committee for the National Comprehensive Cancer Network (NCCN) and serves on the Neuroendocrine Guidelines Panel.

**PROGRAM MEMBERS**

Claudia D. Andl, Ph.D.	Assistant Professor, Surgery
Dana C. Backlund, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
R. Daniel Beauchamp, M.D.	Professor & Chair, Surgery
Jordan D. Berlin, M.D.	Associate Professor, Medicine (Hematology/Oncology)
Emily Chan, M.D., Ph.D.	Assistant Professor, Medicine (Hematology/Oncology)
Robert J. Coffey, Jr., M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Pelayo Correa, M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Timothy L. Cover, M.D.	Professor, Medicine (Infectious Diseases)
Natasha G. Deane, Ph.D.	Research Assistant Professor, Surgery
Wael El-Rifai, M.D., Ph.D.	Professor, Surgery
Jeffrey L. Franklin, Ph.D.	Research Assistant Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Laura Williams, Goff, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
James R. Goldenring, M.D., Ph.D.	Professor, Surgery
David Lee Gorden, M.D.	Assistant Professor, Surgery
Steven K. Hanks, Ph.D.	Professor, Cell & Developmental Biology
Raymond C. Harris, M.D.	Professor, Medicine (Nephrology)
Ethan Lee, M.D., Ph.D.	Assistant Professor, Cell & Developmental Biology
Daniel C. Liebler, Ph.D.	Professor, Biochemistry
Anna L. Means, Ph.D.	Assistant Professor, Surgery
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Albert B. Reynolds, Ph.D.	Professor, Cancer Biology
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John L. Tarpley, M.D.	Professor, Surgery
Michael Vaezi, M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Mary Kay Washington, M.D., Ph.D.	Professor, Pathology
Christopher S. Williams, M.D., Ph.D.	Assistant Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Keith T. Wilson, M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Christopher V. Wright, D.Phil.	Professor, Cell & Developmental Biology
Alexander Zaika, Ph.D.	Assistant Professor, Surgery

## OVERVIEW

This Program is highly interactive and rooted in basic, translational, and clinical studies of gastrointestinal epithelial cell biology. In 2009, the Program garnered \$13.6 million in total peer-reviewed funding, \$8.8 million from the NCI, representing a 96% increase in NCI funding since the previous competing renewal. The program stimulated its members to use emerging technologies within Vanderbilt-Ingram—Vanderbilt's GI SPORE was the first SPORE in the country to propose high-throughput screening (HTS) within projects and used the proposed HTS Shared Resource within its SPORE to support this effort.

In 2004, the program played an integral role in establishing the Jim Ayers Institute for Precancer Detection and Diagnosis (Ayers Institute), whose major goal is to identify a serum biomarker for the early detection of colon cancer. Since 2004, 12 therapeutic investigator-initiated trials (IITs) have been completed, with six more open and 11 in development.

Vanderbilt University Medical Center and Vanderbilt-Ingram have also made a large commitment to the newly launched EBC in terms of space and recruitment. The focus will be on establishment and maintenance of epithelial cell polarity, vesicle trafficking, and issues related to stem cell biology with a particular focus on the GI tract and GI neoplasia.

## SCIENTIFIC GOALS

- 1) To support the basic, translational, and clinical research in gastrointestinal (GI) cancer and Vanderbilt-Ingram Cancer Center
- 2) To develop investigator-initiated clinical trials in GI cancer with an emphasis on agents that target critical signaling pathways studied by GI members and other VICC investigators, and to diversify the clinical trials menu conducted in terms of disease type, source, and integration with other cancer centers
- 3) To foster internal and external scientific interactions to develop innovative diagnostic and/or predictive markers of and therapeutic approaches to GI neoplasia
- 4) To continue colorectal and gastroesophageal research and to launch a pancreatic cancer initiative
- 5) To continue training students and postdoctoral fellows, and mentoring junior faculty to be the next generation of leaders in the field of GI cancer

The Program has leveraged existing and newly developed institutional strengths to advance its basic and translational goals. These include the Ayers Institute, the Digestive Diseases Research Center (DDRC), Vanderbilt Institute of Chemical Biology (VICB), and the EBC. The Program focuses on several themes that range from basic mechanisms to clinical trials.

### Areas of interest include:

- \* Optimizing EGFR blockade with emphasis on inhibiting complementary pathways, including COX-2, Src, and Notch
- \* Utilizing chemical high-throughput screens (HTS) to identify antagonists of canonical Wnt signaling and to restore cell surface E-cadherin as a surrogate marker for reversal of epithelial-to-mesenchymal transition (EMT)



- \* Continuing to develop pharmacodynamic and non-invasive imaging biomarkers predictive of response to established and novel anti-cancer agents
- \* Identifying predictors of colorectal adenoma recurrence
- \* Evaluating the importance of epithelial polarity and vesicle trafficking in the maintenance of epithelial homeostasis and their dysregulation in GI neoplasia
- \* Elucidating the relationship between inflammation and cancer with a particular focus on the role of H. pylori in gastric cancer
- \* Developing prognostic and predictive biomarkers of colorectal cancer (CRC)
- \* Interrogating the relationship between normal colonic stem cells and colon cancer stem cells
- \* Continuing patient advocacy, education, and outreach activities to inform patients and community about GI cancer research and enhance accrual into clinical trials
- \* Refining medical treatment of Ménétrier's disease

## AREAS OF RESEARCH EXPERTISE

### COLORECTAL CANCER

Our most highly developed focus area is colorectal cancer (CRC). Vanderbilt's GI Specialized Program of Research Excellence (SPORE), renewed in 2007, focuses exclusively on CRC. We take a three-pronged approach to CRC, with a dynamic, bi-directional, iterative interplay between in vitro and in vivo systems to advance innovative diagnostic and therapeutic approaches.

First, we use a battery of polarizing human CRC cell lines developed from well-differentiated CRCs to examine the spatial compartmentalization of the EGFR receptor (EGFR) and its cognate ligands. Second, we focus on the study of various aspects of colon cancer in the mouse, work recognized by funding of a Mouse Models of Human Cancer Consortium (MMHCC) grant in partnership with Dr. Kevin Haigis from Harvard University. A major focus of the MMHCC renewal is to determine the cell-of-origin of colon cancer using tamoxifen-inducible Cre drivers that target three discrete compartments in the colon (stem cell, transient amplifying, and differentiated compartment) to create compartment-specific loss-of-function Apc or non-degradable b-catenin. And third is our study of human CRC. A unique component of our GI SPORE application, renewed in 2007, was judged to be our high-throughput screening (HTS) core. A successful screen has already been conducted for the restoration of cell surface E-cadherin as a surrogate marker for reversal of EMT, and an epidemiological study within the GI SPORE is designed to identify factors that predict recurrence of colorectal adenomas. Additional projects are elucidating fundamental roles for p120 in the pathogenesis of CRC and developing non-invasive imaging modalities to monitor response to targeted therapies in mouse models of intestinal cancer.

Vanderbilt-Ingram and the Program have also been instrumental in the establishment of the Meharry-Vanderbilt Alliance Colorectal Screening Project. This effort is led by **Dr. Harvey Murff**, who will coordinate efforts to enhance CRC screening in an underserved, predominantly African American inner-city population.

### GASTROESOPHAGEAL CANCER INITIATIVE

A major focus of the gastroesophageal initiative has been on the role of H. pylori-induced inflammation in the pathogenesis of gastric cancer. A new PPG titled H. pylori and Gastric Cancer was funded in 2009. **Dr. Richard Peek** is PI of this grant; other key investigators include **Drs. Goldenring, Cover, Correa, Wilson, and Polk (ST)**, Director of the Division of Pediatric Gastroenterology at Vanderbilt. A second PPG, Etiological Studies of Gastric Cancer (P01 CA028842), was successfully renewed in 2009 with **Dr. Correa** as PI; **Dr. Wilson** directs a project within this PPG.


**Dr. Correa's** PPG (Etiological Studies of Gastric Cancer) is in its 24th year of continuous funding. His seminal work identified and defined the precancerous stages of gastric cancer.

**Dr. Goldenring** continues to study the origin of a pre-neoplastic gastric metaplasia he has identified, spasmolytic polypeptide-expressing metaplasia (SPEM).

**Dr. El-Rifai's** group investigates the molecular basis of adenocarcinoma of the stomach and esophagus by applying integrated molecular biology and translational genomics and epigenomic approaches.


### PANCREATIC AND HEPATOBILIARY CANCER

Data from **Dr. Merchant's** laboratory show significant benefit by combining Src kinase inhibition and EGFR



inhibition with gemcitabine both in vitro and in vivo. In 2007, **Dr. Merchant** developed and now serves as Director of the Central Pancreas Consortium, bringing together surgeons from nine major academic institutions with an expertise in pancreatic surgery and pancreatic neoplasms. The group is complemented by extensive expertise in pancreatic development under the leadership of **Drs. Wright** and **Means** that provides basic and translational support for this work.

In 2009, **Dana Backlund, M.D.**, a Vanderbilt-trained and GI-mentored medical oncologist, was recruited to focus on pancreatic cancer translational research. She is currently finishing her Masters of Science in Clinical Investigation (MSCI) degree. As a fellow, she authored GI0815, a Phase II IIT of erlotinib and sorafenib in second-line treatment of pancreatic cancer, under the mentorship of **Dr. Berlin**.

Early efforts in hepatobiliary cancer has been largely clinical, with development of clinical trials in hepatocellular cancer (HCC) and, more recently, biliary tract cancers. **Dr. Berlin** successfully completed his R21-supported HCC trial, conducted in ECOG (E6202) with correlative studies performed as an inter-programmatic collaboration with **Ann Richmond, Ph.D.** The preliminary results were reported at ASCO in 2008. A multidisciplinary focus group was established two years ago and has been very successful. **Dr. Goff** has worked with the Southeast Phase II Consortium to conduct trials of a novel MEK inhibitor in hepatocellular and biliary tract cancer. She is currently working with the Phase II Consortium on a new trial for temserolimus and bevacizumab for patients with HCC. **Dr. Bill Russell** uses mouse models to study growth regulation within the liver and **Dr. Gordon** is establishing mouse models of primary and metastatic liver cancer. 



**RESEARCH PROGRAM: GENOME MAINTENANCE****PROGRAM LEADERS: DAVID CORTEZ, PH.D., AND WILLIAM TANSEY, PH.D.**

**David Cortez, Ph.D.**, was chosen as co-leader of this program at its inception in 2007 because of his research expertise and demonstrated leadership in genome maintenance at Vanderbilt. **Dr. Cortez**, who organizes the program's activities, is a Professor of Biochemistry and Ingram Professor for Cancer Research.



He has organized and led the DNA Repair, Replication and Damage Response interest group since 2005. **Dr. Cortez's** research focuses on the cellular responses to DNA damage. He is a leader in the field of DNA damage signaling by the ATM/ATR kinases, which regulate DNA repair, cell cycle transitions, DNA replication, and apoptosis. **Dr. Cortez's** laboratory uses a variety of experimental systems, including yeast genetics, human cell culture, mass spectrometry, and structural biology.

**Dr. Cortez** also serves as Director of Graduate Studies in the Department of Biochemistry, has served as an ad hoc member of several study sections, including Molecular Genetics A, and serves on the editorial board of Journal of Biological Chemistry.

**William Tansey, Ph.D.**, joined the Department of Cell and Developmental Biology (CDB) in the Vanderbilt University School of Medicine in June 2009 and is an Ingram Professor of Cancer Biology. **Dr. Tansey's** research is focused on understanding the mechanisms of regulation of Myc, an oncoprotein transcription factor that features prominently in human cancer. **Dr. Tansey** pioneered understanding of how Myc levels and activity are controlled by the ubiquitin-proteasome system, and how this process is deregulated in blood-borne cancers.



**Dr. Tansey** is currently an Associate Editor for the journal Molecular Biology of the Cell. He has also served as an ad hoc member of National Cancer Institute Program Project review panel, and was a permanent member and chair of the Molecular Genetics A Study Section.

Prior to joining the Vanderbilt faculty, **Dr. Tansey** was a professor at Cold Spring Harbor Laboratory (CSHL) in New York for 17 years, where he directed graduate studies for the Watson School of Biological Sciences. He also served as Scientific Head of the Flow Cytometry Shared Resource within the CSHL Cancer Center.

**PROGRAM MEMBERS**

Walter J. Chazin, Ph.D.	Professor, Biochemistry
David Cortez, Ph.D.	Assistant Professor, Biochemistry
Martin Egli, Ph.D.	Professor, Biochemistry
Brandt F. Eichman, Ph.D.	Assistant Professor, Biological Sciences
Christine M. Eischen, Ph.D.	Assistant Professor, Pathology
Ellen H. Fanning, Dr.rer.nat	Professor, Molecular Biology
Michael L. Freeman, Ph.D.	Professor, Radiation Oncology
Katherine L. Friedman, Ph.D.	Assistant Professor, Biological Sciences
Kathleen L. Gould, Ph.D.	Professor, Cell & Developmental Biology
F. Peter Guengerich, Ph.D.	Professor, Biochemistry
Zhaozhong, Han, Ph.D.	Assistant Professor, Radiation Oncology
Daniel L. Kaplan, Ph.D.	Assistant Professor, Biological Sciences
Dineo Khabele, M.D.	Assistant Professor, Obstetrics & Gynecology (Meharry)
Laura A. Lee, M.D., Ph.D.	Assistant Professor, Cell & Developmental Biology
Lawrence J. Marnett, Ph.D.	Professor, Biochemistry
Melanie Ohi, Ph.D.	Assistant Professor, Cell & Developmental Biology
Ryoma Ohi, Ph.D.	Assistant Professor, Cell & Developmental Biology
Neil Osheroff, Ph.D.	Professor, Biochemistry
Ned A. Porter, Ph.D.	Professor & Chair, Chemistry
Carmelo J. Rizzo, Ph.D.	Professor, Chemistry

H. Earl Ruley, Ph.D.	Professor, Microbiology & Immunology
Michael P. Stone, Ph.D.	Professor, Chemistry
William P. Tansey, Ph.D.	Professor & Interim Chair, Cell & Developmental Biology
Brian E. Wadzinski, Ph.D.	Associate Professor, Pharmacology
Sandra S. Zinkel, Ph.D.	Assistant Professor, Medicine (Hematology/Oncology)

## OVERVIEW

This program, established in January 2007, provides a well-defined intellectual framework for Cancer Center members studying DNA-based processes. Its mission is to understand the mechanisms that govern genome integrity, stability, expression, and the relationships between them.

Although the program is new and significantly smaller than its predecessor program (the Cancer Proteomics and Genomics program), it is already more efficiently and effectively stimulating interactions and collaborations. The average peer-reviewed NCI grant support per PG member in 2004 was ~\$98,000; currently, the average is ~\$169,000 per member.

## SCIENTIFIC GOALS

**Given that some of the most fundamental unresolved questions in cancer biology relate to the processes that connect different aspects of DNA homeostasis, the Program has two broad specific aims:**

- 1) To foster interactions among program members, providing them with a forum to exchange ideas and expertise, and to identify emerging areas of connectivity between different facets of DNA biology.
- 2) To serve as a common intellectual resource for the Cancer Center, providing members of other programs with access to contemporary understanding of the mechanisms and technologies that relate to DNA and DNA-dependent transactions.

The faculty of 26, representing 11 departments across the Vanderbilt campus, establish a research base that extends from control of DNA replication and mitosis through to mechanisms of DNA damage, the DNA damage response, and the regulation of gene activity. Members of the Genome Maintenance Program provide expertise in biochemistry, cell biology, genetics, molecular biology, mouse model systems, proteomics, and structural biology. Interactivity is key to developing and maintaining the success of the program.

## AREAS OF RESEARCH EXPERTISE

- 1) Carcinogen metabolism and the biochemistry of DNA adducts
- 2) Cellular responses to DNA damage, including signaling, checkpoints and apoptosis
- 3) DNA metabolism including replication, repair and recombination
- 4) Cell Cycle Control
- 5) Chromosome and chromatin structure and function

**Because the mechanisms controlling genome maintenance are highly evolutionarily conserved, program members use multiple model systems and approaches in their research, including:**

- \* E. coli and archaeobacteria genetics and biochemistry
- \* Saccharomyces cerevisiae and Schizosaccharomyces pombe
- \* D. melanogaster
- \* Xenopus laevis
- \* Structural biology, including X-ray crystallography and NMR
- \* Human and mouse cell culture
- \* Mouse models of human cancer

## CARCINOGEN METABOLISM AND THE BIOCHEMISTRY OF DNA ADDUCTS

A strength at Vanderbilt, and now a strength of this Program, is in the area of carcinogen metabolism and mutagenesis. **Fred Guengerich, Ph.D.** studies how cytochrome P450 enzymes metabolize carcinogens into active compounds that produce DNA adducts leading to mutation. **Dr. Guengerich** uses a biochemical approach

with human and bacterial enzymes. **Michael Stone, Ph.D.** and **Dr. Egli** collaborate with **Dr. Guengerich** in these research activities. In particular, **Dr. Stone** studies the chemistry of the carcinogen-DNA adduct and **Dr. Egli** uses X-ray crystallography to define the structures of polymerases bound to damaged DNA.

**Lawrence Marnett, Ph.D.** has had a long interest in cyclooxygenase (the molecular target of non-steroidal anti-inflammatory drugs) and DNA damage. **Dr. Marnett**, also the leader of the Vanderbilt Institute for Chemical Biology (VICB), is interested in the chemistry and biology of DNA damage caused by oxidative stress.

#### CELLULAR RESPONSES TO DNA DAMAGE

**Dr. Cortez** studies the signaling cascades that are controlled by the ATM/ATR/DNA-PK family of protein kinases, including multiple tumor suppressors such as p53 and BRCA1.

**Brian Wadzinski, Ph.D.** and **Dr. Zinkel** are also interested in DNA damage responses. **Dr. Wadzinski** is investigating how protein phosphatases regulate the checkpoint signaling cascades. **Dr. Zinkel** studies the cell cycle arrest or apoptosis decision point.

**Dr. Eischen** utilizes mouse models to study the influence of tumor suppressors and oncogenes on apoptosis, proliferation, chromosomal stability, and cellular transformation.

**Michael Freeman, Ph.D.** is interested in cancer drug development. In particular his laboratory is developing sensitizers to ionizing radiation and chemopreventive agents.

#### DNA METABOLISM INCLUDING REPLICATION, REPAIR AND RECOMBINATION

**Dr. Fanning** studies replication origin control and primer synthesis by DNA Pol alpha. One of her model systems is the SV40 tumor virus. **Dr. Cortez** studies the replication checkpoint and the connections between DNA damage signaling and replication proteins. **Dr. Chazin** studies the replication apparatus with a view of it as a molecular machine. His structural studies on replication protein A (RPA) impact both **Drs. Fanning** and **Cortez's** research. **Drs. Kaplan** and **Eichman** are junior investigators that study the biochemistry of replication initiation and elongation. **Daniel Kaplan, Ph.D.** is focusing on the mini-chromosome maintenance proteins 2-7 (MCM2-7) that act as the replicative helicase. **Dr. Eichman** has recently solved the structure of another mini-chromosome maintenance protein MCM10 that functions in origin initiation. **Niel Osheroff, Ph.D.** has a long-standing program in the enzymology of topoisomerase II, which is a major target of chemotherapeutic agents (i.e., etoposide).

**Dr. Chazin** is using the nucleotide excision repair system as a model to study how dynamic protein-protein and protein-DNA interactions accomplish excision and repair. **Dr. Eichman** has determined the structure of several DNA glycosylases that function in base excision repair. **Dr. Guengerich** has an active research program studying the mechanisms of DNA lesion bypass by specialized polymerases.

**Dr. Ruley** is interested in the mechanisms of DNA recombination, especially those that lead to loss of heterozygosity.


#### CELL CYCLE CONTROL

An important mechanism controlling genome stability is cell cycle control. In particular, chromosome instability and aneuploidy is caused by defects in mitotic control. **Dr. Gould** is a Howard Hughes Investigator with an interest in the mechanisms controlling chromosome segregation and cell division. **Dr. Gould's** is collaborating with **Melanie Ohi, Ph.D.**, now recruited to Vanderbilt as an Assistant Professor, on the structural studies of the anaphase promoting complex (APC).

**Laura Lee, M.D.** is also interested in chromosome segregation and uses *D. melanogaster* as a model system.

#### CHROMATIN STRUCTURE AND FUNCTION

Chromatin regulation is critical for DNA repair and DNA damage responses. **Dr. Hiebert** studies the molecular mechanisms of acute leukemia and is particularly interested in how chromatin-modifying enzymes, including histone deacetylases (HDACs), regulate transcription and DNA repair.

**Dr. Tansey's** laboratory studies the mechanisms of ubiquitin-mediated proteolysis as they relate to the control of chromatin function and gene expression. 



**RESEARCH PROGRAM: HOST-TUMOR INTERACTION**  
**PROGRAM LEADER: MARY ZUTTER, PH.D.**



**Mary M. Zutter, M.D.** is Professor of Pathology and Cancer Biology, Ingram Professor of Cancer Research, and Director of Hematopathology within the Department of Pathology. Her interests and expertise merge both basic science and clinical relevance to host-tumor interactions.

**Dr. Zutter** focuses on the role of cell adhesion molecules in host-tumor interactions. She has been funded continuously from the NIH for 17 years and is currently supported by three R01 grants from the NCI. Her laboratory focuses on the molecular basis of cell adhesion to collagen and its role in cancer biology. Much of this effort has been centered on the  $\alpha 2\beta 1$  integrin.

**Dr. Zutter** is on the Steering Committee for the Tumor Microenvironment subcommittee of the American Association of Cancer Research and is an associate editor of Cancer Research. She is a past member of both the Pathology B and Tumor Microenvironment Study Sections of the NCI/NIH. She received her medical degree from Tulane University School of Medicine and completed a residency and hematopathology fellowship training in the Departments of Pathology and Laboratory Medicine at the University of Washington. She was recruited to the faculty of the Vanderbilt University School of Medicine in 2003 from the Department of Pathology at Washington University School of Medicine.

**PROGRAM MEMBERS**

Sarki Abdulkadir, M.D., Ph.D.	Associate Professor, Pathology
Ty W. Abel, M.D., Ph.D.	Assistant Professor, Pathology
Donald J. Alcendor, Ph.D.	Assistant Professor, Microbiology & Immunology (Meharry)
Dean W. Ballard, Ph.D.	Professor, Microbiology & Immunology
Neil A. Bhowmick, Ph.D.	Assistant Professor, Urologic Surgery
Mark R. Boothby, M.D., Ph.D.	Professor, Microbiology & Immunology
Darryl J. Bornhop, Ph.D.	Professor, Chemistry
Richard M. Caprioli, Ph.D.	Professor, Biochemistry
Jin Chen, M.D., Ph.D.	Associate Professor, Medicine (Rheumatology)
Peter E. Clark, M.D.	Assistant Professor, Urologic Surgery
James E. Crowe, M.D.	Professor, Pediatrics (Infectious Diseases)
Benoit Dawant, Ph.D.	Professor, Electrical Engineering & Computer Sciences
Punita Dhawan, Ph.D.	Assistant Professor, Surgery
Moneeb Ehtesham, M.D.	Assistant Professor, Neurological Surgery
Todd Giorgio, Ph.D.	Professor & Chair, Biomedical Engineering
Stacey A. Goodman, M.D.	Associate Professor, Medicine (Hematology/Oncology)
John C. Gore, Ph.D.	Professor, Radiology & Radiological Sciences
John P. Greer, M.D.	Professor, Medicine (Hematology/Oncology)
Rizwan Hamid, M.D., Ph.D.	Assistant Professor, Pediatrics
Steven K. Hanks, Ph.D.	Professor, Cell & Developmental Biology
Simon W. Hayward, Ph.D.	Associate Professor, Urological Surgery
Richard H. Ho, M.D.	Assistant Professor, Pediatrics (Hematology/Oncology)
Ginger E. Holt, M.D.	Assistant Professor, Orthopaedics & Rehabilitation
Billy G. Hudson, Ph.D.	Professor, Medicine (Nephrology)
Madan Jagasia, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Jason R. Jessen, Ph.D.	Assistant Professor, Medicine (Genetic Medicine)
Adetola Kassim, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Irina N. Kaverina, Ph.D.	Assistant Professor, Cell & Developmental Biology
P. Charles Lin, Ph.D.	Associate Professor, Radiation Oncology
Anita Mahadevan-Jansen, Ph.D.	Assistant Professor, Biomedical Engineering
H. Charles Manning, Ph.D.	Research Assistant Professor, Radiology & Radiological Sciences

Lynn M. Matrisian, Ph.D.	Professor & Chair, Cancer Biology
Paul L. Moots, M.D.	Associate Professor, Neurology
David S. Morgan, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Harold L. Moses, M.D.	Professor, Cancer Biology
Claudio A. Mosse, M.D., Ph.D.	Assistant Professor, Pathology
Josiah Ochieng, Ph.D.	Professor, Cancer Biology (Meharry)
Richard M. Peek, M.D.	Professor, Medicine (Gastroenterology, Hepatology & Nutrition)
Wellington Pham, Ph.D.	Assistant Professor, Radiology & Radiological Sciences
Ambra Pozzi Ph.D.	Assistant Professor, Medicine (Nephrology)
Ronald R. Price, Ph.D.	Professor, Radiology & Radiological Sciences
Vito Quaranta, Ph.D.	Professor, Cancer Biology
Christopher Chad, Quarles, Ph.D.	Research Assistant Professor, Radiology & Radiological Sciences
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Ann Richmond, Ph.D.	Professor, Cancer Biology
Bipin N. Savani, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Friedrich G. Schuening, M.D.	Professor, Medicine (Hematology/Oncology)
Stephen A. Strickland, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Takamune, Takahashi, M.D., Ph.D.	Assistant Professor, Medicine (Nephrology)
Reid C. Thompson, M.D.	Professor & Chair, Neurological Surgery
Luc Van Kaer, Ph.D.	Professor, Microbiology & Immunology
Alissa M. Weaver, M.D., Ph.D.	Assistant Professor, Cancer Biology
John P. Wikswow, Ph.D.	Professor, Molecular Physiology & Biophysics
Eugenia Yazlovitskaya, Ph.D.	Research Assistant Professor, Radiation Oncology
Pampee Paul, Young, M.D., Ph.D.	Assistant Professor, Pathology
Roy Zent, M.D., Ph.D.	Assistant Professor, Medicine (Nephrology)
Andries Zijlstra, Ph.D.	Assistant Professor, Pathology
Mary M. Zutter, M.D.	Professor, Pathology

## OVERVIEW

The Host-Tumor Interaction Research Program focuses on the concept that tumor growth, invasion, and metastasis depend not only on the tumor cell alone but also on complex interactions between the tumor cells and the host. The important role that the host microenvironment plays in tumor biology provides an exceptional opportunity for novel therapeutic strategies.

During the past four years, the program has expanded its scientific focus, publication rate and impact, collaborative funding, and efforts in translation. This program has seen a two-fold increase in funding, including program member participation in NCI SPORE and U54 grants, five-fold increase in publications including high-impact publications in Nature, Nature Methods, Cancer Cell, Science, and others.

## SCIENTIFIC GOALS

**The overarching objective of this Program is to define the interactions between tumor cells and the host, then develop strategies to target these interactions in order to control tumor progression and metastasis. The scientific goals fit into defining the role and mechanisms of the stromal cells, including the fibroblasts, endothelial and lymphatic elements, the matrix and the inflammatory/immune cells and/or the hematopoietic cells as critical targets for therapeutic intervention. Thus the scientific goals of the program are to:**

- 1) Identify molecules involved in communication between the tumor and host.
- 2) Advance new reagents and techniques capable of validating a molecular therapeutic target (imaging techniques, antibodies, probes, genetically altered mice, small molecules, etc).
- 3) Cultivate in vitro and in vivo model systems for proof-of-principle experimentation and testing of therapeutics.
- 4) Foster interactions and collaborations that will accelerate these discoveries.

## AREAS OF RESEARCH EXPERTISE

### CELL: CELL AND CELL: MATRIX INTERACTIONS

The focus of the HT program subgroup is to identify the molecules involved in communication between tumor cells and their cellular and structural microenvironment. The molecules being investigated fall into several broad classes, including growth factors and their receptors, extracellular matrix (ECM) and ECM-degrading proteases, and adhesion molecules and the associated cytoskeleton. The cellular components include blood-borne inflammatory/immune cells and resident fibroblasts, in addition to the focus on endothelial cells represented in the angiogenesis/vasculogenesis subgroup.

Work in the area of cell: cell and cell: matrix interactions has resulted in the development of two NHI funded centers, the Center for Matrix Biology and the Vanderbilt Center for Bone Biology. Vanderbilt has a strong tradition in the discovery and characterization of growth factors and growth factor receptors that dates back to the discovery of EGF by **Stanley Cohen**. **Harold Moses, M.D.**, focuses on the interactions between TGF $\beta$  and TGF $\beta$  receptor signaling in the tumor stroma in modulating tumor progression of several epithelial cancers, including, pancreas, stomach and breast. **Drs. Moses, Matrisian, Lin, Carbone**, and **Richmond** demonstrated that TGF $\beta$  controls other cytokine networks including CXCR4 and SDF1, to stimulate the recruitment of Gr1+/CD11b positive, pro-tumorigenic inflammatory cells. **Neil Bhowmick, Ph.D.** and **Simon Hayward, Ph.D.** focus on the crosstalk between cytokines and chemokines, including TGF $\beta$  in prostate differentiation and cancer. **Dr. Hayward** continues his work with tissue recombinants and has demonstrated the critical role tumor-associated fibroblasts and TGF $\beta$  play in the development of prostate cancer. Many of these investigators work coordinately on understanding TGF $\beta$  as a master regulator of host: tumor interactions through the NCI-supported Vanderbilt University Tumor Microenvironment Network (VUTMEN).

**Jin Chen, M.D., Ph.D.** studies the role of another receptor tyrosine kinase, EphA2, in promoting breast cancer growth and metastasis. Her lab has recently identified the functional residues within the EphA2 receptor. **Mark Boothby, M.D., Ph.D.** focuses on the differentiation of T lymphoid cells mediated by IL-4 and downstream Stat6 signaling responses such as proliferation and lineage-specificity. **Roy Zent, M.D., Ph.D.** is interested in the interactions of TGF $\beta$  with its receptor in K-ras-mediated transformation of mammary cancer.

Vanderbilt has assembled a group of matrix biology researchers that encompasses the Center for Matrix Biology, an interdepartmental group of basic and clinical scientists, whose research involves different aspects of biology of the extracellular matrices. **Vito Quaranta, M.D.** arrived with a strong expertise in laminin and the interactions of laminin and integrins and their impact on tumor biology and cell motility. This expertise expanded to areas of mathematical modeling, and he oversees a U54 titled "Multiscale Mathematical Modeling of Cancer Invasion." **Dr. Matrisian's** interest in the role of matrix-degrading metalloproteinases (MMPs) in tumor progression has been enhanced into molecular imaging and the prospect of translational analysis of MMP activity in vivo using a proteolytic nanobeacon.

This Program also has considerable expertise in cell: cell and cell: matrix adhesion molecules. **Ambra Pozzi, Ph.D.** has defined the role of the collagen receptor integrin, the  $\alpha$ 1 $\beta$ 2 integrin in modulating tumor progression and initiation. Similarly, **Dr. Zutter** focuses on another collagen receptor integrin, the  $\alpha$ 2 $\beta$ 1 integrin and its role in tumor progression and metastasis. **Alissa Weaver, M.D., Ph.D.** brings an understanding of how tumor cell cytoskeleton responds to the microenvironment to stimulate invasion. Her work has demonstrated the critical role that cortactin plays in invadopodia formation and tumor cell invasion. **Andries Zijlstra, Ph.D.**, a new recruit to Vanderbilt, has developed a novel chicken embryo model in which human alu PCR in conjunction with the chick embryo spontaneous metastasis assay can be used to quantify metastatic behavior of human tumor cells in vivo. He used this novel methodology in conjunction with a unique metastasis-blocking monoclonal antibody (mAb 1A5) to define the role of the tetraspanin CD151 in tumor cell dissemination.

### ANGIOGENESIS/VASCULOGENESIS

Investigators from VICC have led the way in a number of exciting advances that demonstrate the importance of the hematopoietic/inflammatory system to tumor angiogenesis. Work from **Charles Lin, Ph.D.** published in *Cancer Cell*, demonstrated very early the importance of a population of myeloid immune suppressor (Gr+/CD11b+) cells in promoting tumor angiogenesis. This work was carried out in collaboration with **Drs. Matrisian** (HT), **Shyr**, and **Carbone** (T/HN). Additional work from his laboratory defined pathways downstream of angiopoietin/Tie2 signaling that lead to angiogenesis, including a role for Akt as a major angiogenic mediator. This work was a collaborative effort with **Dr. Hallahan**. Recently, **Dr. Lin** and **Pierre Massion, M.D.** (T/HN) showed that I $\kappa$ B kinase- $\alpha$  regulates endothelial cell motility and tumor angiogenesis. Both **Drs. Zutter** and **Pozzi** focus on



the integrin family of cell adhesion receptors. Data from the Zutter laboratory revealed that the  $\alpha 2\beta 1$  integrin, a collagen receptor, plays an important role in angiogenesis via regulation of VEGFR1 expression. This work was carried out in collaboration with **Dr. Pozzi**. **Dr. Pozzi** has focused on the role of another collagen receptor, the  $\alpha 1\beta 1$  integrin in endothelial cell biology. **Dr. Chen's** expertise and interests also lie in both angiogenesis and cell-matrix interactions, and she has focused her research on the EphA2 receptor and ligands. **Dr. Hallahan** focused on the development of immunotherapy targeted to radiation-inducible neoantigens within tumor vasculature. **Pampee Young, M.D., Ph.D.** has focused on the role of hematopoietic progenitor cells in tumor angiogenesis. **Takamune Takahashi, M.D., Ph.D.** is interested in the regulation and control of endothelial cell growth by tyrosine phosphatases. **Jason Jesson, Ph.D.**, is using zebrafish as a model for understanding angiogenesis.

#### INFLAMMATION/HEMATOPATHOLOGY


The incorporation of area of hematopathology into the HT has created an extremely strong program with common interests and an even greater translational focus. The work of **Ann Richmond, Ph.D.** intersects chemokines, chemokine receptors, and the downstream signaling events that involve NFkappaB. **Dr. Boothby's** research focuses on T cell regulation of the immune response as well as a novel protein, PARP-14, a member of the B aggressive lymphoma family, that transduces survival signals in B cells.

**Dr. Alcendor** focuses on Kaposi's sarcoma and **Dr. Peek** focuses on the role of Helicobacter pylori, inflammation and gastrointestinal cancer. **Dr. Peek** was recently awarded an NCI program project grant that focuses on inflammation and cancer. **Dr. Van Kaer** focuses his research efforts on tumor immunology, NK cells and NKT cells, and their role in the innate immune response. **Dr. Alcendor**, a member of the HT and the Vanderbilt-Meharry Alliance, focuses on Kaposi's sarcoma in HIV-positive patients and also is interested in the role of viral infection in the pathogenesis of cancer. **Dr. Ballard** also focuses on the interaction between viruses and the immune system, including deregulation of cellular I $\kappa$ B Kinases by HTLV1 Tax. **James Crowe, M.D.** recently published a novel method for imaging mRNA in live cells by flow cytometric analysis.

**Dr. Zutter** has specific interest in hematopathology and has worked to develop a hematologic malignancy program within VICC. A plan was initiated over a year ago to build a comprehensive, state-of-the-art hematologic malignancy research focus at Vanderbilt University School of Medicine.

The strategic plan includes coordinating the collaborative work between the basic scientists in leukemia, lymphoma and multiple myeloma and the clinical-translational physicians. There is significant expertise in these areas at VICC, both in HT and in ST. **Drs. Goodman, Greer, Jagasia, Kassim, Morgan, Mosse** and **Schuening** bring exceptional expertise in both the treatment and pathobiology of hematological malignancies. **Dr. Mundy's** bone program has a major focus on multiple myeloma. Other investigators involved in the hematological malignancy program reside in other basic science programs to facilitate cross-fertilization (e.g., **Drs. Hiebert** (ST and GM) and **Brandt** (ST)).

#### CELL AND MOLECULAR IMAGING

The area of molecular imaging includes the Vanderbilt In Vivo Cellular and Molecular Imaging Center, supported by a P50 grant. **Dr. Gore** has provided leadership for the Center in collaboration with **Drs. Hallahan, Matrisian, Quarles, Caprioli**, Coffey (GI) and Marnett (GM). The collaborations between **Drs. Gore** and **Caprioli** have seen tremendous advancements in both basic science studies and in translational aspects through the merging of molecular, proteomic-based imaging with anatomical imaging. The program has grown significantly with the addition of a number of young investigators with an interest in imaging science. 

**RESEARCH PROGRAM: SIGNAL TRANSDUCTION AND CELL PROLIFERATION**  
**PROGRAM LEADERS: AL REYNOLDS, PH.D., AND JEFFREY SOSMAN, M.D.**

**Albert Reynolds, Ph.D.**, Ingram Professor of Cancer Research and Professor of Cancer Biology, is an expert in the oncogene field with a broad base of experience in areas of signal transduction and cell proliferation. **Dr. Reynolds** joined the Vanderbilt faculty in 1996. He trained with **Dr. J.T. Parsons** at the University of Virginia, where he was



instrumental in discovery of many of the first bone fide Src substrates. He is best known for his discovery of p120-catenin (p120), and its identification as a key regulator of the tumor and metastasis suppressor E-cadherin.

**Dr. Reynolds** is currently a permanent member of the NIH/NCI study section 'Intercellular Interactions' (ICI) and serves on the Board of Directors for the Ayers Institute at Vanderbilt. He also is Executive Director of the Vanderbilt Antibody Shared Resource (VASR) and has been a Project Leader in the Vanderbilt GI SPORE since its inception in 2002. **Dr. Reynolds** has prominent roles in the Epithelial Biology Center, the Breast Cancer SPORE, and the MMHCC (Mouse Models of Human Cancers Consortium). He is also co-founder and remains on the Board of Directors of Stovall Life Sciences Inc., which designs and constructs equipment for the biotech industry.

**Jeffrey Sosman, M.D.**, Ingram Professor of Cancer Research and Professor of Medicine (Hematology/Oncology), directs Vanderbilt-Ingram's Melanoma Group and works closely with the Phase I program in drug development in melanoma and renal cell carcinoma. He is currently a permanent member of the NIH/NCI study section for Cancer Immunology and Immunotherapy (CII) from 2006-2010. He is recognized nationally for his expertise in melanoma, clinical tumor immunology, and most recently targeted therapy for melanoma. He was recently named first honoree of the five-year Mary Hendrickson-Johnson American Cancer Society Melanoma Research Professor award, for his career achievements and new research initiatives in translational research in melanoma.



**Dr. Sosman** recently was awarded a NCI K24 to support mentoring individuals in clinical investigations in melanoma. Most of his research has shifted focus from immunologic approaches in melanoma and renal cancer to clinical efforts utilizing inhibitors of tumor signaling pathways, surface growth factors, or vascular growth factors that target the cancer cell biology. He was an important catalyst behind the development of Vanderbilt-Ingram's Translational Research Laboratory and is heavily involved in its activity.

**PROGRAM MEMBERS**

Samuel E. Adunyah, Ph.D.	Professor and Chair, Cancer Biology (Meharry)
Thomas Andl, Ph.D.	Assistant Professor, Medicine (Dermatology)
Mary Ann Thompson, Arildsen, M.D., Ph.D.	Assistant Professor, Pathology
Thomas M. Aune, Ph.D.	Associate Professor, Medicine (Rheumatology)
Stephen J. Brandt, M.D.	Professor, Medicine (Hematology/Oncology)
Alan R. Brash, Ph.D.	Professor, Pharmacology
Richard M. Breyer, Ph.D.	Professor, Medicine (Nephrology)
H. Alex Brown, Ph.D.	Associate Professor, Pharmacology
Graham F. Carpenter, Ph.D.	Professor, Biochemistry
Bruce D. Carter, Ph.D.	Associate Professor, Biochemistry
Zhenbang Chen, Ph.D.	Assistant Professor, Cancer Biology (Meharry)
Chin Chiang, Ph.D.	Associate Professor, Cell & Developmental Biology
Roger J. Colbran, Ph.D.	Professor, Molecular Physiology & Biophysics
Michael K. Cooper, M.D.	Assistant Professor, Neurology
Pran K. Datta, Ph.D.	Assistant Professor, Surgery
Utpal P. Davé, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Mark P. deCaestecker, M.D., Ph.D.	Assistant Professor, Medicine (Nephrology)
Josiane Eid, Ph.D.	Assistant Professor, Cancer Biology
Michael E. Engel, M.D., Ph.D.	Assistant Professor, Pediatrics

Stephen W. Fesik, Ph.D.	Professor, Biochemistry
Stephen R. Hann, Ph.D.	Professor, Cell & Developmental Biology
Jacek J. Hawiger, M.D., Ph.D.	Professor & Chair, Microbiology & Immunology
Scott W. Hiebert, Ph.D.	Professor, Biochemistry
Stacey S. Huppert, Ph.D.	Assistant Professor, Cell & Developmental Biology
Andrzej M. Krezel, Ph.D.	Assistant Professor, Biological Sciences
Ethan Lee, M.D., Ph.D.	Assistant Professor, Cell & Developmental Biology
Taekyu Lee, Ph.D.	Assistant Research Professor, Biochemistry
Daniel C. Liebler, Ph.D.	Professor, Biochemistry
Craig W. Lindsley, Ph.D.	Associate Professor, Pharmacology
Andrew J. Link, Ph.D.	Associate Professor, Microbiology & Immunology
Harold N. (Bo), Lovvorn, M.D.	Assistant Professor, Pediatric Surgery
Mark A. Magnuson, M.D.	Professor, Molecular Physiology & Biophysics
Robert Matusik, Ph.D.	Professor, Urologic Surgery
Edward T. Olejniczak, Ph.D.	Research Professor, Biochemistry
David F. Penson, M.D.	Assistant Professor, Urologic Surgery
Jason Phan, Ph.D.	Research Assistant Professor, Biochemistry
Jennifer A. Pietenpol, Ph.D.	Professor, Biochemistry
Igor Puzanov, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Albert B. Reynolds, Ph.D.	Professor, Cancer Biology
Ann Richmond, Ph.D.	Professor, Cancer Biology
Olivia W. Rossanese, Ph.D.	Research Assistant Professor, Biochemistry
Linda J. Sealy, Ph.D.	Associate Professor, Molecular Physiology & Biophysics
Jeffrey A. Sosman, M.D.	Professor, Medicine (Hematology/Oncology)
Roland W. Stein, Ph.D.	Professor, Molecular Physiology & Biophysics
LaMonica V. Stewart, Ph.D.	Assistant Professor, Cancer Biology (Meharry)
Zu-Wen Sun, Ph.D.	Assistant Professor, Biochemistry
David L. Tabb, Ph.D.	Assistant Professor, Biomedical Informatics
John M. Thomson, Ph.D.	Assistant Professor, Cancer Biology
Alex G. Waterson, Ph.D.	Assistant Professor, Pharmacology
P. Anthony, Weil, Ph.D.	Professor, Molecular Physiology & Biophysics
Susan Wentz, Ph.D.	Professor, Cell & Developmental Biology
Elizabeth Yang, M.D., Ph.D.	Associate Professor, Pediatrics

## OVERVIEW

The Signal Transduction and Cell Proliferation Research Program is a group of investigators connected by a common interest in cell growth control related to cancer.

## SCIENTIFIC GOALS

**This Program is focused on promoting basic and translational research in the area of cell growth control.**

**Activities are aimed at two broadly defined objectives:**

- 1) To promote outstanding basic research, with an eye toward maintaining the strongest possible foundation of fundamental knowledge (including technology) in the relevant disciplines.
- 2) To encourage and cultivate translational research through targeted recruitment of new faculty, selective funding of translational pilot projects, and other avenues aimed at leveraging the capabilities of outstanding basic and clinical research contingents at Vanderbilt.

The formal aims for the program are: 1) to increase awareness of the research going on within each member's laboratory and thereby encourage collaborative interactions within the program, and 2) to aggressively cultivate



the cutting-edge basic science expertise required to foster and promote effective translational research within the Cancer Center. The program will continue to proactively build out translational capabilities by engaging specific opportunities—such as the recruitment of **Dr. Fesik**, who brings to the program world-class expertise in drug discovery, and creation of the Innovative Translational Research Laboratory, spearheaded by **Drs. Sosman** and **Hiebert**, an expressly translation-oriented resource, now shared by all programs within the VICC. Thus, the ST program now encompasses basic science that focuses on some of the best therapeutic targets (signaling pathways), cancer drug discovery and medicinal chemistry, and translational research/clinical trials to attack these pathways.

## AREAS OF RESEARCH EXPERTISE

### GROWTH FACTORS AND RECEPTORS

The Center's strength in growth factor and receptor signaling harkens back to 1986 Nobel laureate **Stanley Cohen, Ph.D.** and his seminal work on epidermal growth factor (EGF). **Graham Carpenter, Ph.D.**, uses EGF stimulation of mammalian cells as a model system for identifying mechanisms by which growth factors regulate cell proliferation. Current areas of interest include endocytic trafficking of the different EGFR family members and a novel signaling mechanism involving the cleavage and nuclear translocation of the ErbB4 cytoplasmic domain. **Dr. Carpenter** is credited with discovery of phospholipase C-g (PLCg) as a key EGFR substrate.

**Bruce Carter, Ph.D.** is studying p75 neurotrophin receptor signaling mechanisms involved in context-dependent activation of survival or apoptosis. **Chin Chiang, Ph.D.** and **Ethan Lee, M.D., Ph.D.** study signaling pathways stimulated by Wnt and Hedgehog, respectively. **Stacey Huppert, Ph.D.** is using mouse models to distinguish whether Notch is acting as a general tumor suppressor in the liver.

**Ann Richmond, Ph.D.**, investigates chemokine receptor signaling associated with chronic inflammation, wound healing, and tumorigenesis. In collaboration with **Dr. Sosman**, she has integrated basic and clinical areas of expertise to study the efficacy of NFkB inhibition in mouse models of melanoma, and in related human clinical trials. Meharry colleague **Samuel Adunyah, Ph.D.** is evaluating roles for other cytokines in immune function (e.g., IL-17), with emphasis on their roles in cancer susceptibility. The laboratory of **Richard Breyer, Ph.D.** is evaluating role(s) for the PGE2 receptor in colorectal tumorigenesis using a PGE2 receptor knockout mouse model. A very different approach in the Krezel laboratory relies on structural NMR studies to evaluate protein-protein and protein-DNA interactions involved in H. Pylori signaling. The Reynolds and Peek laboratories have joined forces to show that p120-catenin, and its transcription factor binding partner Kaiso, are also modulators of H. Pylori-induced inflammation.

### SIGNALING INTERMEDIATES

**Jacek Hawiger, M.D., Ph.D.** is studying mechanisms associated with excessive and persistent cytokine production in response to bacterial lipopolysaccharides (LPS) or super antigens. The Hawiger laboratory has devised a cell-permeable peptide that antagonizes nuclear import of NFkB and other SRTFs. **Drs. Richmond, Sosman**, and **Reynolds** also study signaling pathways linked to NFkB and inflammation. **Elizabeth Yang, M.D., Ph.D.** brings expertise in Bcl-2 and other pathway members associated with regulation of apoptosis.

**Alex Brown, Ph.D.** studies the role(s) of phospholipases and their lipid derivatives in a variety of cellular functions linked to cancer using a "lipidomics" mass spectrometry approach. One area of focus is the role of phospholipase D (PLD). In a multi-laboratory collaboration, **Drs. Brown** and **Lindsey** have designed the first isoform-selective phospholipase D inhibitors and finds that a subset of these can block invasiveness in metastatic breast cancer models.

**Roger Colbran, Ph.D.**, is interested in the structure, function and subcellular targeting of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII), a ubiquitous integrator of the dynamics of calcium oscillations. **Pran Datta, Ph.D.** has identified a novel WD-40 domain containing protein, STRAP (Serine Threonine Kinase Receptor Associated Protein), that negatively regulates TGF- $\beta$  signaling via association with TGF- $\beta$  type I and type II receptors. **Alan Brash, Ph.D.** works on biosynthesis and/or metabolism of cancer-relevant lipid intermediates, including eicosanoids, lipoxigenase, arachidonic acid, prostaglandins, and cyclooxygenases.

**Susan Wente, Ph.D.**, focuses on the nuclear pore complex, including NUP98 and NUP214, both of which are linked to multiple chromosomal translocations associated with human leukemias. In addition, she reported recently on DEAD-box proteins, which are misexpressed in prostate, colon, and lung carcinomas. **Andrew Link, Ph.D.** has applied proteomics to identify a number of novel proteins involved in translation and protein synthesis.

**Mark Magnuson, M.D.**, has developed a recombinase-mediated cassette exchange (RMCE) method to generate cassette acceptor alleles for in vivo structure-function experiments. As leader of the newly established Vanderbilt Stem Cell Biology Center, **Dr. Magnuson** brings both embryonic and adult stem cell expertise to the program.


Of note, several Program members bring to the table important cutting-edge technologies. For example, **Dan Leibler, Ph.D.** (Director of the Ayers Institute) uses mass spectrometry to identify early markers for colon cancer. **David Tabb, Ph.D.** dedicates part of his effort to improvement of proteomic tools, **Dr. Link** brought shotgun proteomics to Vanderbilt, **Dr. Magnuson** has been instrumental in advancing technology in the transgenic mouse shared resource, and **Dr. Reynolds** recently took over and restructured the Vanderbilt Antibody Shared Resource to increase productivity and throughput. **John Thomson, Ph.D.**, is one of the country's foremost experts in miRNA biology. **Thomas Andl, Ph.D.** also is focused on the role of miRNAs in melanoma development.

**Ethan Lee, M.D., Ph.D.** focuses on Wnt signal transduction pathways and the development of novel therapeutics aimed at blocking the pathway downstream of the colon cancer tumor suppressor APC. Using an assay based on *Xenopus* egg extracts, he devised a novel high-throughput screen to identify compounds that suppress the Wnt signaling pathway at the level of Axin.

#### GENE EXPRESSION

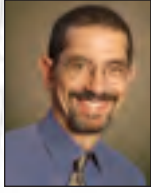
An overall focus of the **Pietenpol Laboratory** is to elucidate role(s) of the p53 gene family (p53, p63, p73) in normal cell proliferation and cancer. A recent finding identified mTOR as a regulator of p73, opening a window of opportunity for therapeutic intervention. In a high-impact report, the laboratory of **Stephen Hann, Ph.D.** has identified differential effects of the p14ARF tumor suppressor (referred to as ARF) on c-Myc function.

**Stephen Brandt, Ph.D.**, focuses on the control of blood cell production and how it is subverted in hematologic malignancy. A particular interest is the TAL1 (or SCL) oncogene, whose abnormal expression constitutes the most frequent gain of function mutation in T-cell acute lymphoblastic leukemia (T-ALL). **Josiane Eid, M.D.**, uses SYT-SSX, the translocation product responsible for synovial sarcoma, as a model to study mechanisms of gene expression in cancer. One area of interest is the role of the proto-oncogene SYT and SYT-SSX in chromatin remodeling and polycomb repression. **Mark deCaestecker, Ph.D.** and **Harold Lovvorn, M.D.** are interested in the role and regulation of the Cited family of transcriptional co-factors in Wilm's tumorigenesis. **Linda Sealy, Ph.D.**, has identified a role for the transcription factor CCAAT/Enhancer Binding Protein (C/EBP $\beta$ ) in epithelial to mesenchymal transition (EMT). **LaMonica Stewart, Ph.D.**, a Meharry colleague, is investigating the role of PPAR $\gamma$  in cellular and mouse models for prostate cancer. **Robert Matusik, Ph.D.**, is widely recognized for development of several mouse models for prostate cancer, including LADY and TRAMP, as well as key transgenic models for targeting Cre-mediated gene ablation to the prostate.

**Dr. Hiebert** studies the molecular mechanisms of acute leukemia, cell cycle control, and the action of tumor suppressors. **Zu-Wen Sun, Ph.D.**, uses budding yeast as a eukaryotic model to study histone ubiquitination and gene regulation. The Weil laboratory studies the structure-function relationships of the TFIID complex in the yeast model system. **Roland Stein, Ph.D.** has identified a novel transcription factor important in pancreatic development. **Thomas Andl, Ph.D.**, is examining the role of Dicer and miRNAs in squamous epithelial carcinogenesis and melanoma. 

## RESEARCH PROGRAM: THORACIC AND HEAD & NECK CANCER

PROGRAM LEADERS: DAVID CARBONE, M.D., PH.D., AND WENDELL YARBROUGH, M.D.



**David Carbone, M.D., Ph.D.**, is also Director and Principal Investigator of the Vanderbilt Specialized Program in Research Excellence (SPORE) in Lung Cancer and the Strategic Partnering to Evaluate Cancer Signatures (SPECS) U01 consortium. He is a Professor in the departments of Medicine, Cancer Biology, and Cell and Developmental Biology and is the Harold L. Moses Chair in Cancer Research.

His research interests have focused on lung cancer, and specifically proteomic and expression array signature development, lung cancer genetics, cancer immunotherapy, tumor-associated immunosuppression mechanisms, and gene therapy. Recent research directions include molecular profiling of lung cancers and pre-neoplasias, especially the use of mass spectrometry-based proteomics. **Dr. Carbone** has more than 200 peer-reviewed publications and review articles and has served on several NCI grant review panels. He currently chairs the Lung Biology subcommittee for the Eastern Cooperative Oncology Group and serves on the Board of Scientific Counselors for NCI.

**Dr. Carbone** received an M.D. and a Ph.D. in Molecular Biology and Genetics at Johns Hopkins University in 1985. He did an internal medicine internship and residency at Johns Hopkins Hospital through 1988, followed by a medical oncology fellowship at the NCI. **Dr. Carbone** became assistant professor at the University of Texas Southwestern Medical Center in 1991 and associate professor with tenure in 1995. Recruited to Vanderbilt in 1996, he was promoted to full professor in 1998.

**Wendell Yarbrough, M.D.**, was recruited to Vanderbilt in 2003 to initiate the translational research program in head and neck cancer. He is a tenured Associate Professor with appointments in Otolaryngology and Cancer Biology and is an Ingram Professor of Cancer Research at Vanderbilt. He directs the Barry Baker Laboratories for



Head and Neck Oncology and previously served as vice chair of the Head and Neck Organ Site Committee of the American College of Surgeons Oncology Group. He is on the Editorial Board of Head & Neck.

Research in the Yarbrough lab is centered on tumor suppressors and regulation of cell growth and survival with strong interest in molecular distinctions that segregate head and neck squamous cell carcinoma, particularly related to human papilloma virus infection (HPV). **Dr.**

**Yarbrough** has served as the PI of clinical trials and is the PI at Vanderbilt for the recently initiated Inter-SPORE lung and head and neck trial, "Comparison of Biomarker Modulation by Inhibition of EGFR and/or Src Family Kinases Using Erlotinib and Dasatinib in Head and Neck and Lung Cancers."

### PROGRAM MEMBERS

Timothy S. Blackwell, M.D.	Professor, Medicine (Allergy, Pulmonary & Critical Care)
David P. Carbone, M.D., Ph.D.	Professor, Medicine (Hematology/Oncology)
Anthony J. Cmelak, M.D.	Associate Professor, Radiation Oncology
Mikhail M. Dikov, Ph.D.	Assistant Professor, Medicine (Hematology/Oncology)
Jill Gilbert, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
David Gius, M.D., Ph.D.	Associate Professor, Pediatrics
Adriana L. Gonzalez, M.D.	Assistant Professor, Pathology
Eric L. Grogan, M.D.	Assistant Professor, Thoracic Surgery
Kenneth R. Hande, M.D.	Professor, Medicine (Hematology/Oncology)
Leora Horn, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Vicki L. Keedy, M.D.	Assistant Professor, Medicine (Hematology/Oncology)
Eric Lambright, M.D.	Assistant Professor, Thoracic Surgery
James E. Loyd, M.D.	Professor, Medicine (Allergy, Pulmonary & Critical Care)
Bo Lu, M.D., Ph.D.	Assistant Professor, Radiation Oncology
Pierre Massion, M.D.	Assistant Professor, Medicine (Allergy, Pulmonary & Critical Care)
Barbara, Murphy, M.D.	Associate Professor, Medicine (Hematology/Oncology)



Jonathan C. Nesbitt, M.D.	Associate Professor, Thoracic Surgery
James L. Netterville, M.D.	Professor, Otolaryngology
John H. Newman, M.D.	Professor, Medicine (Allergy, Pulmonary & Critical Care)
William Pao, M.D., Ph.D.	Associate Professor, Medicine (Hematology/Oncology)
Tetyana Pedchenko, Ph.D.	Research Instructor, Medicine (Allergy, Pulmonary & Critical Care)
Joe B. (Bill), Putnam, M.D.	Professor & Chair, Thoracic Surgery
Otis Rickman, D.O.	Assistant Professor, Medicine (Allergy, Pulmonary & Critical Care)
Dan M. Roden, Ph.D.	Professor, Medicine (Clinical Pharmacology)
Robbert J.C. Slebos, Ph.D.	Research Assistant Professor, Cancer Biology
Carmen C. Solorzano, M.D.	Associate Professor, Surgery
John A. Worrell, M.D.	Associate Professor, Radiology & Radiological Sciences
Wendell G. (Dell), Yarbrough, M.D.	Associate Professor, Otolaryngology

## OVERVIEW

Substantial growth and development of the thoracic and head and neck oncology research activities at Vanderbilt-Ingram Cancer Center led to the creation of this new clinical science program in 2009. This program builds upon the previous Experimental Therapeutics Program (ET), led by Carbone. Through targeted recruitment and mentoring junior investigators, Program investigators have expertise that spans basic, translational, and clinical research to lead Vanderbilt-Ingram's initiative in personalized cancer medicine, to develop lung cancer and head and neck biomarkers, and to identify mutations that can be rapidly translated to clinical use. A large number of head and neck cancers are treated each year at Vanderbilt University Medical Center, which allowed development of an annotated Head and Neck Cancer Biorepository and Clinical Database, with 1,700 tumor specimens to date and linkage to clinical data. This repository supported translational research that was published in *Cancer Cell* and *The New England Journal of Medicine*.

## SCIENTIFIC GOALS

- 1) To support patient-focused translational thoracic and head and neck cancer research.
- 2) To develop and implement strategies for personalized medicine in thoracic and head and neck cancer, including appropriate selection of patients for current therapies, and development, testing, and selection of appropriate novel therapies for individual patients.
- 3) To promote research focused on thoracic and head and neck cancer within the Cancer Center.
- 4) To support intra- and inter-programmatic and external collaborations to develop new biological insights and treatment strategies for thoracic and head and neck cancer.
- 5) To develop new investigators and leaders who focus on thoracic and head and neck cancers through mentoring and training activities as well as research support.

## AREAS OF RESEARCH EXPERTISE

### NEW DRUG DEVELOPMENT FOR METASTATIC/RECURRENT DISEASE

Our dedicated head and neck oncologists are responsible for the development and implementation of a number of investigator-initiated trials and cooperative group studies evaluating the efficacy, toxicity, and biologic mechanisms for a number of new agents. Investigators have recently reported the results of three consecutive studies evaluating irinotecan in metastatic/recurrent disease. Additional investigator-initiated studies include a Phase II trial of docetaxel and bortezomib and a CTEP-sponsored head and neck cancer study comparing cetuximab plus sorafenib vs. placebo, with laboratory and supportive care correlatives.

**Dr. Gilbert** served as co-PI on ECOG 1302, a phase III randomized trial comparing docetaxel vs. docetaxel + gefitinib in previously treated patients with recurrent or metastatic head and neck cancer.

### COMBINED MODALITY THERAPY

Vanderbilt investigators have been instrumental in the development and conduct of key trials examining the use of taxanes as primary treatment for locally advanced head and neck cancer. **Dr. Cmelak** served as the study PI and **Dr. Murphy** served as the quality-of-life PI for E2399, a larynx-perseveration trial based on the results of an IIT

conducted through our Affiliate Network. This study (E2399) was the first prospective trial to demonstrate a survival benefit for head and neck cancer patients with HPV-positive disease. **Drs. Cmelak, Murphy,** and **Gilbert** are involved in the development of the follow-up ECOG trial for patients with HPV positive disease. **Dr. Lu** has several radiation therapy-related trials under way, including a study testing the utility of lithium for central nervous system protection, and a trial combining RAD001 an inhibitor of mTOR with radiation for NSCLC brain metastases.

**Dr. Cmelak** reported the results of a pilot trial with single agent docetaxel in high-risk post-operative patients, and **Dr. Chung** has reported the result of a novel combination of Phase II trial of induction chemotherapy (oxaliplatin and pemetrexed) in patients with locally advanced head and neck cancer (ASCO).

#### **SUPPORTIVE CARE**

**Dr. Murphy** has assembled research and clinical teams that focus on several key areas related to thoracic and head and neck cancers: swallowing function, nutrition and metabolism, psychiatric issues, neurocognitive changes, coping, and lymphedema.

Investigators in this Program have participated in 22 investigator-initiated supportive care trials over the past five years. The IITs primarily focused on lung and head and neck cancer have enrolled 490 patients.

#### **THYROID CANCER**

**Dr. Gilbert** is responsible for development of a portfolio of clinical trials for advanced thyroid cancer and serves as the local PI for these investigations. Ongoing studies include a Phase II trial of the MEK inhibitor, AZD6244 (AstraZeneca), in refractory papillary thyroid cancer patients, and a Phase III trial of the multi-kinase inhibitor XL184 (Exelixis) in medullary thyroid cancer.

#### **AIRWAY EPITHELIAL CANCER BIOLOGY**

Research within the Epithelial Biology Center focuses on signaling pathways, tumor suppressors, viral initiators, and molecular characterization of tumors of the lung and head and neck. Based on basic and translational research at Vanderbilt-Ingram, we have established collaborations with Merck (MK-0752) and Eli Lilly to test the effects of their  $\gamma$ -secretase inhibitors on Notch3 function in NSCLC and pancreatic cancers, and will soon open a Phase I/II clinical trial based on this work. The trial is to be funded in part through an R21 currently under review and written by **Dr. Keedy**.

**Dr. Yarbrough** has both interest and expertise in HPV and characterization of molecular differences between HPV-associated and non-HPV-associated HNSCC. His lab continues to investigate the role of a putative tumor suppressor, LZAP, whose expression is decreased in up to 30% of HNSCC.

#### **PERSONALIZED CANCER MEDICINE**

Development of personalized therapy and molecular targeting are major goals of this Program, which is leading the effort at Vanderbilt-Ingram to routinely fingerprint cancers for informing clinical decision-making. **William Pao, M.D., Ph.D.**, recently recruited from Memorial Sloan-Kettering Cancer Center, is widely known for his pioneering work in the discovery and characterization of EGFR mutations and acquired secondary resistance mutations. Most exciting is his recent finding that the combination of an irreversible tyrosine kinase inhibitor and cetuximab is highly active in refractory EGFR-mutated NSCLC (Regales et al., 2009).

**Dr. Carbone's** group examined the prospect of using matrix-assisted laser desorption ionization (MALDI) mass spectrometry (MS) of unfractionated, pretreatment sera to identify NSCLC patients with improved survival after treatment with the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) gefitinib and erlotinib.

**Pierre Massion, M.D.**, focuses on lung tumorigenesis and the use of genomic and proteomic approaches to identify molecular markers of lung neoplasia and to test those in multidisciplinary early detection strategies. He has also become a leader in applying proteomic approaches to study lung cancer.

**Dr. Cmelak** was involved in the most definitive study to date suggesting that HNSCC associated with HPV responds better to therapy. **Dr. Yarbrough** has established CLIA-certified screening for all patients with oral cavity and oropharynx squamous cell carcinoma who have tissue diagnosis performed at Vanderbilt. An investigator-initiated trial for intensification of therapy in HPV-negative oropharyngeal patients is under development.

The head and neck team also initiated a study that identified the portion of the cetuximab molecule (galactose- $\alpha$ -1,3-galactose) likely responsible for a relatively high rate anaphylactic reaction to cetuximab (the first targeted agent approved for HNSCC).

### MODELING/PRECLINICAL TESTING


Inadequacy of animal models of cancer to mimic the human condition has slowed development of new therapeutic agents and led the Yarbrough lab to focus on creation of a human-in-mouse model of HNSCC that more faithfully represents the diversity human tumor compared to modeling of cell lines. This model has been optimized and currently can successfully model tumors in more than 70% of patients.

Expertise of the Yarbrough lab in short-term culture of HNSCC has led to inter-programmatic collaborations within the Cancer Center. **Dr. Alissa Weaver's** (HT) lab collaborated with the Yarbrough lab and showed that primary cultures of HNSCC formed invadopodia and degraded extracellular matrix, and that cortactin was localized to areas of invadopodia. **Dr. Andries Zijlstra** (HT) is currently using primary HNSCC cells to determine the effect of hypoxia on mobility and invasiveness using the chorioallantoic membrane (CAM) model.

### OUTREACH

**Dr. Yarbrough** leads annual Oral and Head and Neck Cancer Awareness Week (OHANCAW) activities at Vanderbilt each year. Meharry colleagues have also used the infrastructure and expertise at Vanderbilt to initiate head and neck cancer awareness activities and screenings on that campus. Other outreach activities include education and screenings at churches, the Meharry School of Dentistry, the NASCAR truck series racing garage, and the National Bluegrass Music Convention. International outreach is led by **James Netterville, M.D.**, who organizes and travels to Nigeria each year with a full-service surgical team.

### BIOSPECIMEN REPOSITORY

The thoracic biorepository, directed by pathologist **Adriana Gonzalez, M.D.**, has been in operation since 2000 and has collected more than 2,000 tissue and 10,000 biofluid samples to date, with complete clinical outcome annotation data. It has assembled and maintains 18 lung cancer tissue microarrays for research use. The lung biorepository has more than 27,000 samples collected to date. The head and neck repository has accrued more than 1,700 patients and 263 non-cancer volunteers who contributed more than 8,191 biospecimens. 



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