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College of Science

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FIGHTING CANCER

Cancer Research at the University of Notre Dame

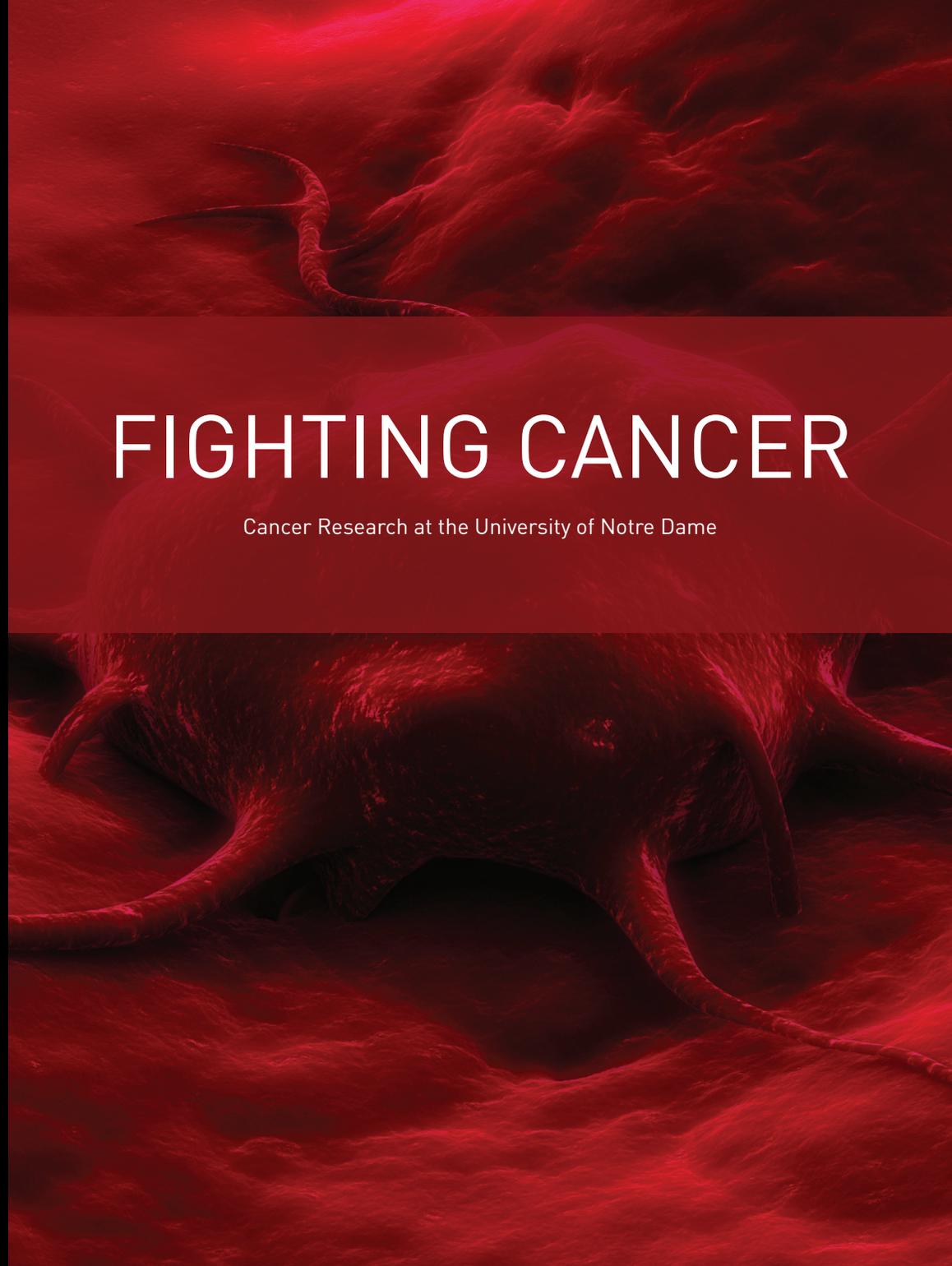


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Fighting Cancer

Here at the University of Notre Dame, our widely known and highly regarded athletic teams are known as the “Fighting Irish” for their fierce determination. There is another team on campus that is engaged in its own fight, the outcome of which affects us all. That fight is against cancer. That team—fiercely determined to win—is the faculty at the College of Science.

At the University of Notre Dame, we are fighting cancer in all of its forms and on all fronts, including prevention, detection, and treatment. We are investigating ways to stop the generation of new blood vessels that supply invading cancerous tumors during the process of metastasis. We are researching tissue vaccines for cancer treatments. We are improving immunological therapies for cancers based on cellular immunity. We are understanding the role of antioxidants on tumors. We are even improving doctor-patient relationships and communication. And while the fight is far from won, we are passionate about winning this fight.

The researchers profiled here have dedicated their lives to helping people they will never meet to live happier, healthier, and longer lives. And while we are not going to win the fight against cancer tomorrow, when we do, it will be because of the work the team at the College of Science is doing today.

We are the fighting Irish.

Gregory P. Crawford, Ph.D.

William K. Warren II Foundation Dean of the College of Science
Professor of Physics



Isotopes for cancer therapy and immuno-diagnosis

Ani Aprahamian

Frank M. Freimann Professor
of Physics

Ani Aprahamian is co-chair of a standing committee of the Nuclear Science Advisory Committee to study the present and potential research use of radioactive isotopes and to develop a strategy for production of the isotopes, which among other things are used to treat cancer. The committee's recommendation will coordinate implementation of the National Isotope Production and Applications Program over the next decade. Don Geesaman of Argonne National Laboratory is co-chair of the study.

Small amounts of radioactive isotopes have become an important element of diagnosing and treating many types of cancer, heart disease, and other abnormalities in the body, but the failure of a European reactor and the shutdown of a Canadian reactor in late 2007 and early

2008 led to a global shortage, revealing the need for a U.S. strategic plan for production and development.

The U.S. Department of Energy's Nuclear Energy Program has produced limited quantities of isotopes, and the Isotope Production Program is scheduled to move from the Office of Nuclear Energy to the Office of Science's Nuclear Physics.



Development of improved immunological therapies for cancer based on cellular immunity

Brian Baker

Associate Professor of
Chemistry and Biochemistry

Brian Baker in the Department of Chemistry and Biochemistry is collaborating with researchers at the National Cancer Institute and the University of Massachusetts to enhance ways that the body's own immune system can fight cancer. The "cancer immunosurveillance" process is inferred from increased cancer rates in people with weakened immune systems and from the success of drugs that boost the immune response as cancer therapeutics.

With the National Cancer Institute, Baker's team is studying a panel of T-cell receptors that recognize a melanoma-associated antigen with a variety of efficiencies. The goal is to study the structural and biophysical properties of the various receptors and identify those that are most closely correlated

with increased efficacy. With researchers at the University of Massachusetts, the team is using structure-based computational design to engineer superior T-cell receptor variants for use in generating genetically engineered, highly tumor-specific T-cells.

The strategy targets "tumor associated antigens" that cancerous cells present to the immune system, overcoming the mechanisms by which tumor's naturally escape immune destruction. Unlike earlier approaches, it does not attempt to use the antigens as therapeutic cancer vaccines.



Inflammation in cancer

Suzanne Bohlson

Assistant Professor,
Microbiology and Immunology,
Indiana University School of
Medicine–South Bend

Adjunct Assistant Professor of
Biological Sciences, University
of Notre Dame

Chronic inflammation is closely associated with the development of some of the deadliest cancers, such as lung cancer and colon cancer. Suzanne Bohlson's laboratory is investigating pathways that regulate inflammation, with the ultimate goal of developing novel therapeutics to control aberrant inflammation associated with cancer.

Macrophages are inflammatory cells that are found within and surrounding tumors. Researchers are investigating mechanisms of macrophage activation, and specifically the signals that regulate the switch between an inflammatory macrophage phenotype and an anti-inflammatory macrophage phenotype. A family of proteins called the defense collagens are involved in this switch and researchers are mapping out

the pathway defense collagens use to regulate macrophage activation.

The group is using animal models and systems in cellular and molecular biology to determine how specific components of the innate immune system regulate macrophage activation and inflammation.



Prognosis in breast cancer through gene expression

Steven Buechler

Chair, Department of
Applied and Computational
Mathematics and Statistics

Steven Buechler is developing an affordable test to predict the chance of relapse for breast cancer patients, based on the biological principle that cancer develops through a series of discrete changes in cellular state. The critical differences between aggressive and non-aggressive cancers lie in the activation or deactivation of entire pathways, rather than an increase along a continuum. The test identifies a large set of estrogen receptor positive patients who can safely go without chemotherapy, whose tumors show low expression values of four genes.

The research is important because it identifies patients who do not need chemotherapy, which has its own toxic effects. Research shows that a significant number of patients receive chemotherapy unnecessarily. In recent years, methods

of stratifying breast cancer patients according to relapse risk have been developed using multi-gene measures of mRNA concentrations, but those tests involve more than 20 genes and are expensive to implement.

Experimental evidence suggests that the new test yields an accurate prognosis for a larger set of patients than competing tests. Applications to other forms of cancer are under development.



Hemostasis and cancer

Frank Castellino

The Kleiderer-Pezold Chair in
Biochemistry

Professor of Chemistry and
Biochemistry

Director, W. M. Keck Center for
Transgene Research

Victoria Ploplis

Research Professor of
Chemistry and Biochemistry

Associate Director, W. M. Keck
Center for Transgene Research

Frank Castellino and Victoria Ploplis of the W.M. Keck Center for Transgene Research are using mice to study the mechanisms by which components of the hemostasis system regulate the initiation and progression of cancer. Earlier studies have identified a relationship between the regulation of the hemostasis system and tumor growth and metastasis. While it has been shown that elevated levels of proteins of this system are associated with carcinomas of breast, colon, skin, prostate, lung, kidney, and brain, the specific mechanisms by which they contribute to this disease process are still unclear.

By using a colon cancer model in which genetic mutations and deficiencies of hemostasis genes have been introduced in the mouse genome, Keck Center researchers are determining the

effects these alterations have on tumor initiation, growth, angiogenesis, and metastasis. Initial studies at the Keck Center have identified urokinase as a major participant in the initial stages of tumor development. Recent studies of the anticoagulant Protein C pathway, have demonstrated that this system may serve as a new therapeutic target for arresting not only ulcerative colitis but also the incidence of colorectal cancer.



Active sunscreen, UV-damaged skin repair

Gregory Crawford

William K. Warren Foundation
Dean of the College of Science
Professor of Physics

Sun exposure is one of the most prominent risk factors for cancer in the world today, ranked alongside smoking and HPV. A large portion of the permanent damage caused by the sunlight leading to sunburns is caused by ultraviolet radiation from the sun. The rays can enter cells and damage DNA in a way that causes significant problems during replication and leads to errors that are propagated down the generations of affected cells, possibly leading to cancer if sufficient errors accumulate.

Studies have found that certain forms of blue light may reverse this type of DNA damage through photochemistry mechanisms. Crawford's lab adds fluorescent nanoparticles in sunscreens to convert UV light into blue light—both shielding cells from damaging UV radiation through absorption

and repairing sun-damaged DNA through emission of blue light. The work has shown that cells protected by the fluorescent nanotechnology sunscreen have a 98 percent chance of resembling cells that have not been exposed to damage, while unprotected cells have a 5 percent chance, and cells protected by ordinary sunscreen have only a 25 percent chance.



Chemical cytometry for more accurate cancer prognosis

Norman Dovichi

Grace-Rupley Professor in
Chemistry and Biochemistry

Norman Dovichi's laboratory provides a molecular basis for prognosis in cancer and precancerous conditions. The hypothesis of the project is that heterogeneity of cell-to-cell expression increases in later stages of progression. The lab's tool is chemical cytometry, a term the lab has coined for the analysis of single cells using modern analytical tools. For this project, chemical cytometry uses two-dimensional capillary electrophoresis and ultrasensitive laser-induced fluorescence detection to characterize protein expression.

As a model system, the lab uses Barrett's esophagus, a premalignant condition that is a complication of acid reflux and the only known precursor of esophageal adenocarcinoma, a disease that has increased fourfold in 30 years. About

8,000 new cases are reported in the United States each year, and about 8,000 die from the disease. Dovichi's lab has worked for nearly 10 years with collaborators at the Fred Hutchinson Cancer Research Center to employ chemical cytometry to improve the accuracy of prognosis of progression from neoplasia in Barrett's esophagus to esophageal adenocarcinoma. This system serves as a model for the general problem of accurate cancer prognosis.



New insights into tumor progression: biology and clinical promise

Crislyn D'Souza-Schorey

University of Notre Dame Chair
in Cancer Research

Associate Professor of
Biological Sciences

Crislyn D'Souza-Schorey joined the Notre Dame faculty as the Walther Cancer Institute Junior Chair. Over the past decade, her laboratory in biological sciences has investigated cellular changes that lead to metastasis, the major life-threatening clinical manifestation of cancer. The acquisition of the invasive phenotype—when cells acquire the ability to break away from the primary tumor and invade through the surrounding tissue—is a critical step in metastasis, and has been the focal point of the laboratory's research. This development drastically reduces the patient's chance of survival.

Using cell and animal model systems, the laboratory has identified key regulators of epithelial glandular disruption characteristic of early breast tumor development as well as

mechanisms that remodel the tumor microenvironment, characteristic of advanced disease. With a focus on breast and ovarian cancer, current efforts involve an interdisciplinary collaboration between cell biologists, biochemists, physicians, and bioengineers to develop a program that builds on recent findings and will aid in discovery of cancer biomarkers and new drug targets.



Collaborative research in development of new anticancer drug therapies

Paul Helquist

Professor of Chemistry and Biochemistry, University of Notre Dame

A combined chemical, biochemical, biological, and clinical team of investigators has formed to study natural products with potential anticancer activity. This team reflects the highly interdisciplinary research environment required to develop new treatments for cancer in a timely way that can translate to the clinical setting as quickly as possible.

The specific aims of the project are focused on the iejimalides and other naturally occurring compounds that present new cellular mechanisms of action that have not been exploited previously to combat cancer. This work includes synthesis of novel compounds, assay of their activity in cellular systems, determination of their targets and mechanisms, and studies in animal models of human cancer.

The establishment of the Harper Cancer Center at Notre Dame in association with the Indiana University School of Medicine–South Bend is facilitating the collaboration, which includes Paul Helquist, Mark Suckow of the Freimann Life Science Center, Rudolph Navari at the Indiana University School of Medicine–South Bend, and Cynthia Stauffacher and Vincent Jo Davisson, both of Purdue University.



Modeling tumor growth

Bei Hu

Professor of Applied and
Computational Mathematics
and Statistics

Associate Dean for
Undergraduate Studies

Bei Hu of Mathematics is studying mathematical models of tumor growth, based on density of cells and concentrations of nutrients and signaling molecules. Tumor growth is usually modeled by dynamical systems, and because of spatial effects due to cell proliferation, it is natural to model the evolution of tumors in terms of partial differential equations.

Tumors grow or die when the amount of nutrients available to them is above or below a certain threshold (equilibrium). There is also an internal pressure governed by either Darcy's law (solid tumor) or Stoke's equation (breast cancer and brain tumor). One way to study whether and how the tumor grows is to focus on the steady state solution. An asymptotically stable solution means that the tumor will not grow much,

while an unstable solution means that the tumor will likely grow and spread. The study and simulation showed that a larger tumor aggressiveness coefficient will likely cause the steady state tumor to become unstable. The numerical simulation showed how the shape of the tumor actually changes over time.



The proteomics of cancer cells

Amanda Hummon

Walther Cancer Foundation
Assistant Professor of
Chemistry and Biochemistry

The Hummon research group studies the misbehaving genes that trigger colorectal cancer. Colorectal cancer is the third most common type of cancer, with an estimated 51,000 deaths in the United States in 2010 alone. More than other types of cancer, colorectal cancer progresses with a defined pattern of genetic changes and we are advancing the effort to elucidate them. The Hummon research group develops high-throughput methods to evaluate both the transcriptome and the proteome in cancer cells. Because cancer involves genomic damage that alters the expression levels of genes, changes commonly repeated among cancer patients, a better understanding of which genes, transcripts and proteins are affected could have broad health implications.

The group is developing and adapting current mass spectrometric and sampling protocols for global molecular profiling to understand cancer systems. They examine the expression of mRNA and proteins in cancerous tissues and compare them against healthy tissues to understand signaling pathways that are altered in cancerous cells. By identifying these changes, they can not only understand colorectal cancer, but also predict drug targets that will be used to halt the progression of the disease.



Iron chelation as a breast cancer therapy

Marvin Miller

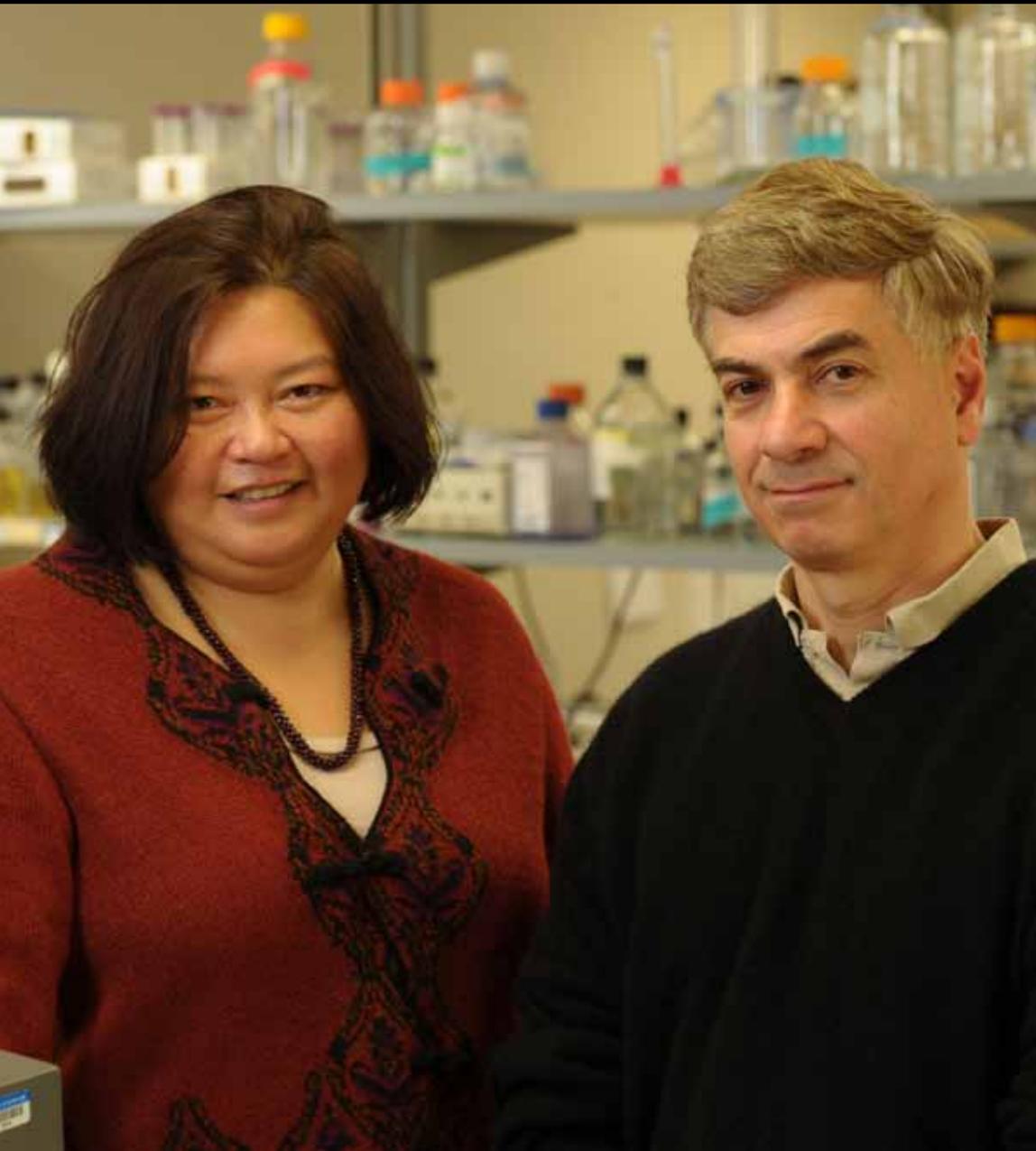
The George and Winifred Clark
Chair in Chemistry

Professor of Chemistry and
Biochemistry

The Marvin Miller laboratory is applying its extensive expertise in the design and synthesis of both natural and synthetic iron chelating siderophores to a novel approach for fighting cancer. Recent research has revealed that proliferating cells require more iron than normal cells for their growth and metabolism, possibly because of iron's role in supporting transcription of key cell-growth-associated genes as well as in hematopoietic cell differentiation. Excess iron is strongly correlated to growth in tumor cells, especially certain breast cancer lines. Iron starvation of these lines by siderophores, natural products that strongly and specifically sequester iron, leads to apoptosis of breast cancer cells but not normal breast cells.

The laboratory has shown that the amamistatin family of

siderophores isolated from the actinomycete *Nocardia* asteroids are potent *in vitro* anticancer agents. Its goal is to enhance the amamastatins' potency, pharmacological properties and specificity toward breast cancer, using synthetic analogs of these natural products. Medicinal siderophore drugs will be made in an attempt to sequester iron and starve breast cancer cells of an element needed for their survival and proliferation.



Mechanism-based gelatinase inhibitors for the treatment of metastasis

Shahriar Mobashery

Navari Family Chair in Life Sciences

Professor of Chemistry and Biochemistry

Mayland Chang

Professional Specialist

Director, Indiana Clinical Translational Sciences Institute Notre Dame Project Development Team

Shahriar Mobashery and Mayland Chang of the Department of Chemistry and Biochemistry are working on ways to inhibit cancer metastasis, the spreading of the out-of-control cells to other organs. Although metastasis is a leading reason that cancer becomes fatal—primary tumors rarely kill and often can be treated—no anti-metastatic agent has been commercialized to treat aggressive cancers. Meanwhile, metastasis of breast and prostate cancer, for example, leads to further life-threatening complications that cause tens of thousands of deaths each year.

Building on studies showing that the matrix metalloproteinases are associated with cancer progression and metastasis in many types of cancers, Mobashery and Chang a few years ago discovered and

synthesized the first prototype selective mechanism-based inhibitor found to be effective in mouse models of prostate cancer metastasis to the bone, breast cancer metastasis to the lungs, and T-cell lymphoma metastasis to the liver. This work has progressed in the direction of compounds that can be used in additional in vivo models for disease, leading to second- and third-generation compounds. The researchers are now refining related compounds with the goal of developing selective inhibitors that can advance forward to preclinical development and ultimate entry into clinical trials for the treatment of cancer metastasis.



Development of antiemetics, palliative care, and doctor-patient relationships in clinical oncology

Rudolph Navari

Professor of Medicine

Assistant Dean and Director,
Indiana University School of
Medicine–South Bend

Clinical Director, Mike and
Josie Harper Cancer Research
Institute

Adjunct Professor of Chemistry
and Biochemistry, University of
Notre Dame

Rudolph Navari's research program involves several important issues aimed at improving quality of life of people living with cancer, including cancer-related anorexia (CRA), depressive symptoms in breast cancer patients, and the effect of religious practices and spiritual beliefs on end-of-life care decisions.

Navari's research has shown that the use of olanzapine, an antiemetic agent, and megestrol acetate appears to be an effective intervention for patients with CRA. Further clinical studies have revealed that olanzapine in combination with palonosetron can prevent chemotherapy-induced nausea and vomiting. In a Phase II research trial, the combination of olanzapine and palonosetron with dexamethasone given only

on the day of chemotherapy was safe and highly effective.

In another investigation, breast cancer patients had significant improvement in the completion rate of initial adjuvant treatment, quality of life, and depressive symptoms with the use of fluoxetine. Another of his studies, with 339 adults with advanced cancer, showed that those with advanced directives were more likely to be active in religious or spiritual practices, although they had little knowledge of their religion's recommendations on end-of-life care.



Prevention and therapy of prostate cancer

Morris Pollard

Professor Emeritus of
Biological Sciences

Coleman Foundation Chair of
Cancer Research, emeritus

Director of Lobund Institute

Morris Pollard develops and investigates models of cancers that are aimed at prevention of the advanced refractory that, at this time, resists all therapies. While prostate cancer occurs worldwide, the highest incidence of this disease occurs in developed countries. Records show that among new cases of prostate cancer among Americans, 90 percent of cases do not progress to the refractory stage, but about 10 percent die of the refractory disease. Familial prostate cancer, in which there are many cases per family, are frequently fatal, and African Americans develop the highest incidence and mortality by refractory prostate cancer in the world.

The Pollard group discovered the unique Lobund Wistar rat strain that is inherently predisposed to develop metastatic

refractory prostate cancer spontaneously in two stages: the first stage testosterone-dependent, is benign and reversible, and progresses at mid-life span (age 12 months) to the testosterone-independent refractory stage. The Pollard group developed a procedure that induces high incidences of refractory prostate cancers to study the role of stem cells in the development of refractory prostate cancer. In the sequence of events recorded, stem cells were activated to product putative cancer stem cells that induced small tumors that, in time, grew to large refractory prostate cancer cells.



Tumor cell metabolism and survival

Zachary Schafer

The Coleman Assistant
Professor of Cancer Biology

Zachary Schafer's laboratory in Biological Sciences studies how cancer cells can survive outside their natural niches and how changes in cellular metabolism can promote survival or induce cell death. The work is critical because the treatment and prevention of cancer requires the ability to selectively kill tumor cells without affecting non-cancerous cells. In order to obtain the necessary specificity in chemotherapeutic approaches, researchers must understand the basic biological processes governing normal and tumor cell survival, where little is now known.

The laboratory has uncovered evidence that oxidative stress can be tumor suppressive by killing cells that are not in their natural environment. Also, the lab has discovered that oncogenes promote anchorage-

independent survival of tumor cells by altering their metabolism in a manner that reduces oxidative stress. The research has revealed that antioxidants may promote the survival of tumor cells in certain contexts. The laboratory now is using both 2D and 3D cell culture models to expand upon those antioxidant studies with the goal of better understanding the relationship between oxidative stress and the survival of tumor cells outside their natural niche.



Analysis of axon guidance genes: the intersection of nervous system development and cancer

Molly Duman Scheel

Assistant Professor, Medical and Molecular Genetics, Indiana University School of Medicine–South Bend

Adjunct Assistant Professor of Biological Sciences, University of Notre Dame

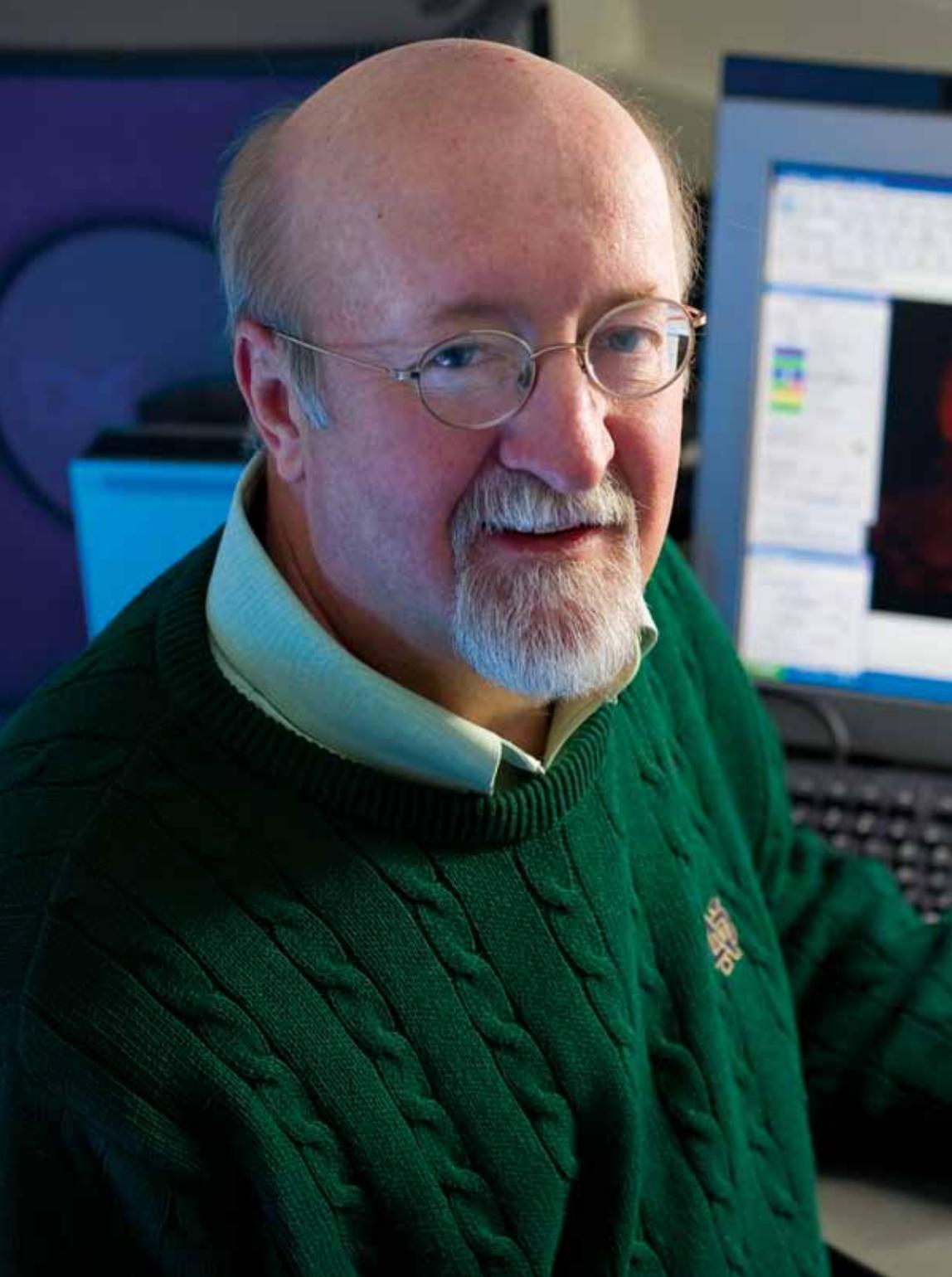
In recent years, a number of nervous system development genes, such as the Netrin, DCC, Semaphorin, and Plexin axon guidance regulators, have been linked to many different types of human cancer. However, the cellular processes by which these genes regulate nervous system development and cancer are still being elucidated. A more detailed understanding of how guidance molecules function to regulate development will provide insight into their roles in oncogenesis.

In particular, although the majority of cancer fatalities are due to the ability of late stage tumors to metastasize, relatively little is known about the genetic alterations that cause noninvasive tumors to become metastatic. Since both nervous system development and metastasis involve changes in

cell polarity which accompany invasive growth, analysis of the functions of axon guidance molecules may lead to a better understanding of tumor metastasis.

The Scheel lab exploits the advantages of the *Drosophila* system in ongoing research studies, which include:

(1) Characterization of the impacts and targets of axon guidance protein signaling on cellular growth during development, (2) Characterization of invasive phenotypes resulting from genetic alterations in axon guidance molecules, and (3) Discovery of genetic suppressors of growth and metastasis resulting from genetic lesions in axon guidance genes.



A genetic model for research on leukemia

Robert Schulz

The Notre Dame Professor of Biological Sciences

Robert Schulz's laboratory is investigating blood cell formation, a key to understanding the uncontrolled proliferation of blood cells known as the cancer leukemia. Distinct types of leukemia are classified based on the maturity of cells affected, lineage type and differentiation stage of abnormal cells, and rate of aberrant cell growth. The specific cellular, genetic, and molecular events underlying the initiation and progression of various leukemias have not been fully elucidated.

As hematopoiesis is an evolutionarily conserved developmental process, the genetic control of blood cell production is being investigated in an expedient and relevant manner using the *Drosophila* model organism. A hematopoietic stem cell niche has been discovered in the fruit fly, with its cellular

organization and molecular signaling therein shown to be remarkably similar to that observed in the hematopoietic stem cell niches of mammals. The Schulz lab has initiated a systematic screen of the *Drosophila* genome to discover genes that are essential for hematopoietic stem cell maintenance. They are also determining the mechanisms through which these genes function in stem or support cells. Research findings obtained from these innovative studies will provide a wealth of information on the genetic and molecular mechanisms at work within a hematopoietic stem cell-niche microenvironment. Such knowledge will be beneficial to the study and understanding of abnormal hematopoiesis, including leukemia, in humans.



Imaging tumors and determining the efficacy of anticancer therapies in the early stages of treatment

Bradley Smith

Director, Notre Dame Integrated Imaging Facility

Emil T. Hofman Professor of Chemistry and Biochemistry

Bradley Smith's laboratory in Chemistry and Biochemistry is developing molecular imaging probes that can measure the apoptotic index for cell and tissue samples ranging from biopsy to non-invasive in vivo imaging. The work aims to meet the need for rapid, post-treatment tests to see if anticancer therapies, including a wide variety of cancer chemotherapeutic agents, are inducing their intended apoptotic effect for any specific patient. This monitoring strategy is part of the growing field of personalized medicine.

The researchers are developing novel fluorescent probes for in vitro and in vivo optical imaging. They have discovered that small, synthetic zinc dipicolylamine coordination complexes have advantages compared to an earlier targeting ligand.

Structurally, the probes, designed for maximum tissue penetration, are composed of two components, a very bright organic fluorophore that is attached to a targeting ligand with selective affinity for the surface of apoptotic cells. The probes can target the necrotic core of implanted human tumors (breast and prostate) in living mice and rats. The imaging signal increases when the animals are treated with targeted radiation or anticancer drugs.



Investigating lipids in cancer etiology

Robert Stahelin

Assistant Professor,
Biochemistry and Molecular
Biology, Indiana University
School of Medicine-South Bend

Adjunct Assistant Professor of
Chemistry and Biochemistry,
University of Notre Dame

Robert Stahelin's laboratory aims to advance understanding of how the mechanisms of lipid signaling are controlled in different types of cancers. His laboratory uses an interdisciplinary research approach focused on biological membranes as signaling and trafficking platforms for processes fundamental to life. These membranes composed mainly of lipids hold the key to cell division, growth, and metabolism necessary for cancer cell growth and metastasis. Thus, there is a need to comprehensively understand molecular events occurring within and on membranes as a means of grasping disease etiology and identifying viable targets for drug development. Currently, the cancer foci of the lab are lung, breast, and kidney cancers.

Briefly, the Stahelin lab is investigating:

- (1) The Molecular Basis of Oncovirus Replication. Fifteen to 20 percent of human cancers are caused by viruses which have no cures. The Stahelin lab is investigating how these viruses replicate in human cells and designing new drugs to inhibit their spread and cancer-inducing potential.
- (2) Discovery of New Drugs. The integration of computational biology, bioinformatics, structural biology, biochemistry, biophysics, and cell biology will aid in discovering new lipid binding proteins in the cancer genome.
- (3) Metals in Medicine. The Stahelin lab has discovered a number of pro-survival factors in cancer that are regulated by copper.
- (4) Lipid-Mediated Regulation of Inflammatory Enzymes. The role of inflammation in tumor growth and metastasis is the basis of these studies.



Tissue vaccines for cancer treatment

Mark Suckow

Director, Freimann Animal Care Facility

Research Associate Professor of Biological Sciences

Mark Suckow's laboratory is working to develop and define cancer vaccines which are produced from harvested tumor tissue and therefore include an enormous menu of relevant targets for the immune system. The research aims to overcome barriers to the success of vaccination (immunotherapy) as a therapeutic option for cancer that avoids the adverse side effects of chemotherapy. Present limits to immunotherapy likely are related to the limited antigenic targets included in most vaccines, allowing tumors to evolve resistance.

Using "tissue vaccines" produced from tumor tissue, the researchers have demonstrated in animal models that it is possible to prevent 90 percent of prostate cancer and reduce the incidence of metastasis by 70 percent. They have demon-

strated similar results for treatment of melanoma and started developing a tissue vaccine for ovarian cancer. One mouse model experiment demonstrated that a vaccine produced from a rat-derived tumor inhibited the growth of tumors from a human prostate cancer cell line. Future work aims to identify particularly immunogenic components of the vaccine so vaccine preparations can be standardized.



Cancer chemotherapeutic agents inspired by biosynthesis

Richard Taylor

Professor of Chemistry and
Biochemistry

Associate Dean of Research

Richard Taylor's laboratory has identified a number of chemical entities with significant anti-cancer activity and is working to evaluate these leads in pre-clinical animal models to determine their potential for clinical studies. The laboratory uses a combination of synthetic, computational, and molecular biological studies. Researchers are particularly interested in the correlation between unique natural product structures and their corresponding biological activities.

The research is significant because, despite the advent of combinatorial chemistry and high-throughput screening during the past decade, the number of new biological targets that have emerged from the pharmaceutical industry is remarkably small. Natural products are especially impor-

tant because evolution has created these compounds to transport and modulate biological function. The detailed study of natural products with unknown or unique modes of action represents a paradigm with the ability to identify new biological targets.

The laboratory aims to generate new sources of chemical diversity based upon the modification of polyketide scaffolds and explore their chemotherapeutic potential. Researchers will design, synthesize, and biologically evaluate structurally unique derivatives of polyketide natural product.



Investigating Rho GTPases in breast cancer

Tracy Vargo-Gogola

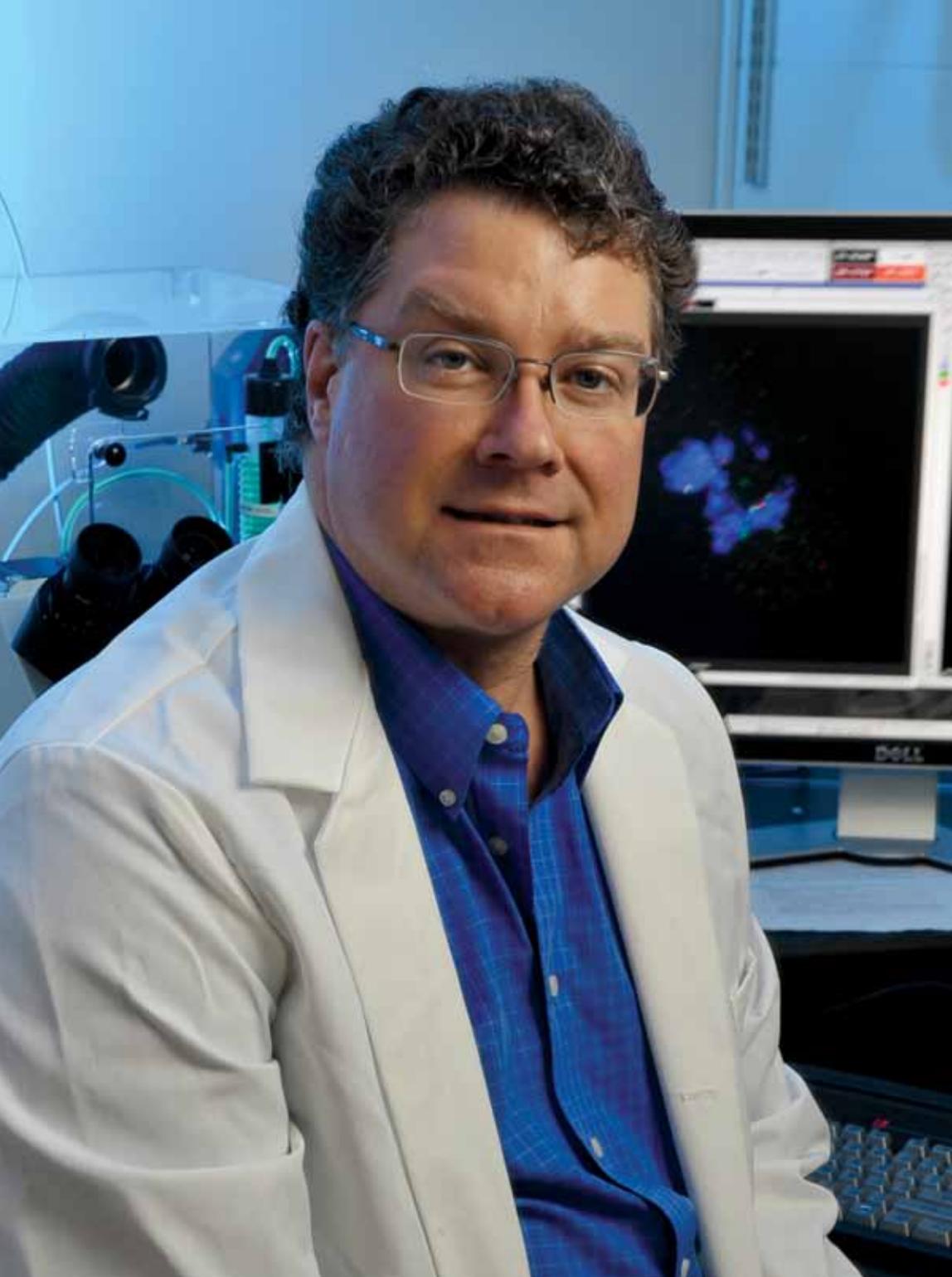
Assistant Professor,
Biochemistry and Molecular
Biology, Indiana University
School of Medicine–South Bend

Adjunct Assistant Professor of
Biological Sciences, University
of Notre Dame

Tracy Vargo-Gogola's laboratory has developed a mouse model to investigate the role of a major inhibitor of the Rho GTPases in mammary gland development and breast cancer. Altered expression of Rho GTPases has been detected in many types of cancer, including breast cancer. Many of these genes are essential, which means that loss of gene function in genetically engineered (transgenic) mice results in death of the animals during embryonic development. Understanding how Rho signaling regulates these processes in the context of the complex environment of a developing tissue will help determine how to most effectively target these pathways within the tumor microenvironment.

The goal of the research is to use mammary epithelial cells isolated from the mice in com-

ination with unique three dimensional culture methods that mimic mammary morphogenesis and invasion to determine the molecular mechanisms by which Rho signaling affects normal and tumorigenic processes in the mammary gland. These studies will help determine how best to target the Rho signaling pathway to develop therapies for breast cancer.



Cell division errors and cancer initiation

Kevin Vaughan

Associate Professor of
Biological Sciences

Kevin Vaughan's laboratory is deciphering the "spindle assembly checkpoint," a biochemical system that monitors chromosome segregation and reduces the frequency of mistakes in this process. The fidelity of this surveillance system is especially important for cells that divide frequently because errors lead to loss of tumor suppressor genes and tumor formation. Vaughan's research is focused on the molecular components of the checkpoint and the signaling pathways that regulate normal cell division.

Using mass spectrometry of proteins that mediate chromosome movement, the group has identified a novel set of proteins regulated by a molecular switch known as phosphorylation. These phosphorylation events are driven by proteins known as kinases and phosphatases, enzymes identified as the most promising targets for

chemotherapy drugs. Because work in the Vaughan laboratory reveals the molecular consequences of treatment with these chemotherapy drugs, cancer researchers are able to determine combinations of drugs that improve efficacy and reduce side effects. Furthermore, these studies justify the development of new generation drugs with increased specificity and potency.

The specific investigations in the laboratory include breast cancer, leukemia and occupational exposure to carbon nanofibers. The latter represents a developing industrial problem similar to asbestos exposure. A multifaceted approach is applied to these cancer problems, including biochemistry of phosphorylation, pharmacological manipulation of kinases and phosphatases, molecular genetics and sophisticated imaging of cell cycle progression.



Chronic inflammatory diseases and cancer

Peter Velázquez

Assistant Professor,
Microbiology and Immunology,
Indiana University School of
Medicine–South Bend

Adjunct Assistant Professor of
Biological Sciences, University
of Notre Dame

The intestine is unique from other organs in that it allows for the presence of billions of bacteria without causing the inflammation seen in other organs challenged with bacteria. However, in order to accomplish this, approximately 80 percent of the body's white blood cells are found in the gut. Many of these immune cells are pro-inflammatory cells. Nonetheless, homeostasis is maintained in the healthy individual.

Clinical observations indicate that individuals with chronic inflammatory disease are more likely to develop cancer in the inflamed organ. It is interesting that, despite the abundance of proinflammatory cells, tumors do not normally form in the intestine. However, recent evidence indicates that signals driven by the innate immune compartment actually contribute to tumor formation,

in a genetically susceptible individual. The Velázquez lab hypothesizes that a low chronic inflammatory state driven by innate sensors is a complexing factor in intestinal tumor genesis.

The lab is utilizing a genetic approach to better understand the role these innate sensors play in driving tumor formation. They are combining these studies with intravital microscopic approaches to better understand the role innate sensors play in modulating T-cell activation and T-cell-dendritic cell interactions during tumor formation in the intestine.



Isoform selective HDAC inhibitors as anticancer reagents

Olaf Wiest

Professor of Chemistry and Biochemistry

Olaf Wiest's laboratory has developed structural models for the different human histone deacetylases (HDACs) that can enable the identification of HDAC inhibitors (HDACi) that are to distinguish them. The research aims to overcome the major problem that hampers use of the promising HDAC inhibitors in fighting cancer. So far, they inhibit most or all of the 18 HDAC isoforms present in humans, leading to such side effects as cardiotoxicity or fatigue.

The laboratory's models have been exploited to design novel, potent, and selective HDAC, which have been synthesized and tested in collaborations with synthetic chemists and biochemists. Researchers were able to achieve high selectivity for the inhibitors. The laboratory also has designed several

metal binders of similar potency but higher selectivity than hydroxamates. Together, these studies can lead to the design of tailor-made HDACi for each individual isoform that can serve as drug leads or biochemical tool compounds in a variety of cancer studies. The discoveries also could help decipher the cellular and molecular processes connecting gene transcription to cancer and other diseases.

