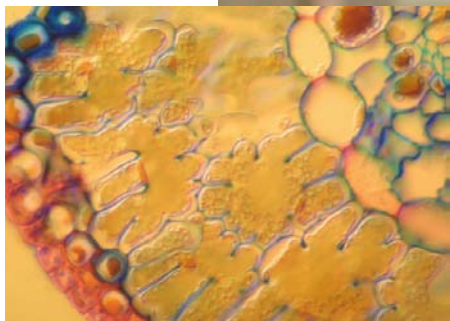
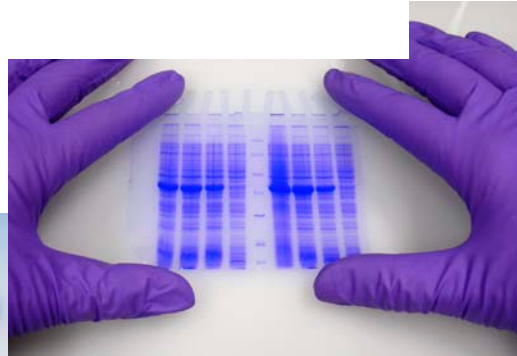


# *drug discovery* *at Purdue*

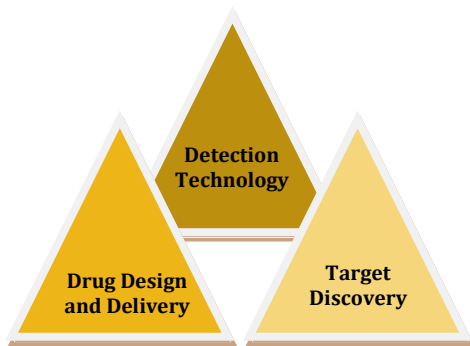
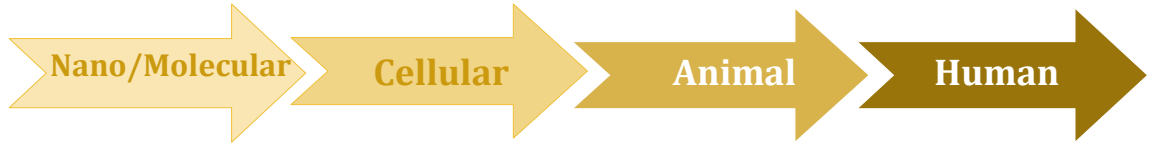


**PURDUE**  
UNIVERSITY



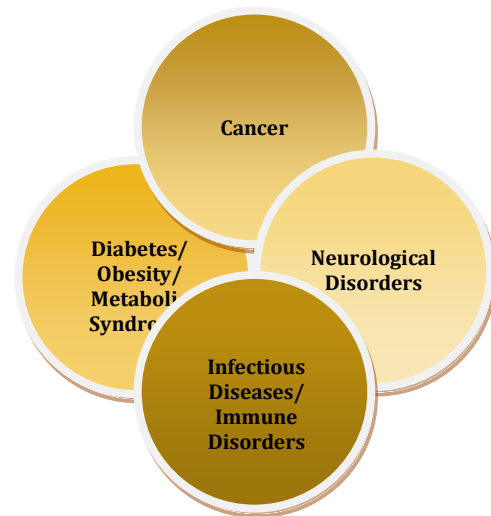
## Introduction

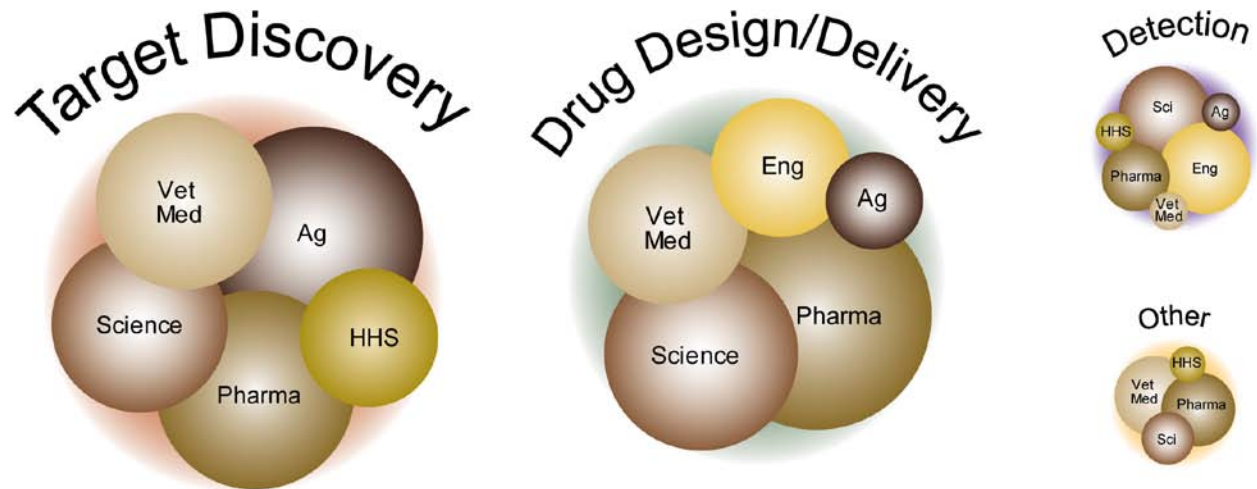
The drug discovery process at Purdue University begins at the nano level and ends with a viable human therapy that can reduce mortality and morbidity of disease. There is a considerable effort in enhancing our portfolio of novel and innovative drug candidates to treat chronic and acute illnesses.



Our researchers also continue to be invested in various approaches to drug discovery, which include understanding of drug targets for future drug therapies, detection technology that will aid clinicians in early diagnosis or monitoring of therapies and design and delivery of drugs.

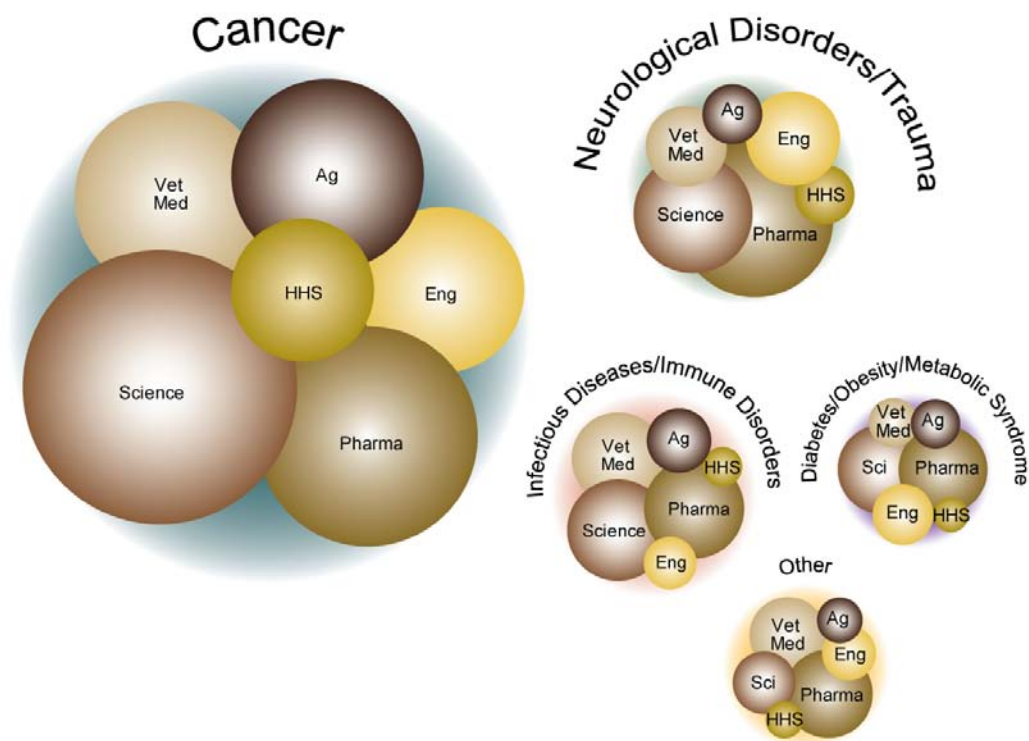
Collectively, our researchers are determined to leverage their great wealth of scientific expertise and collaboration in order to discover solutions for the public benefit. The following includes a summary of research interests.





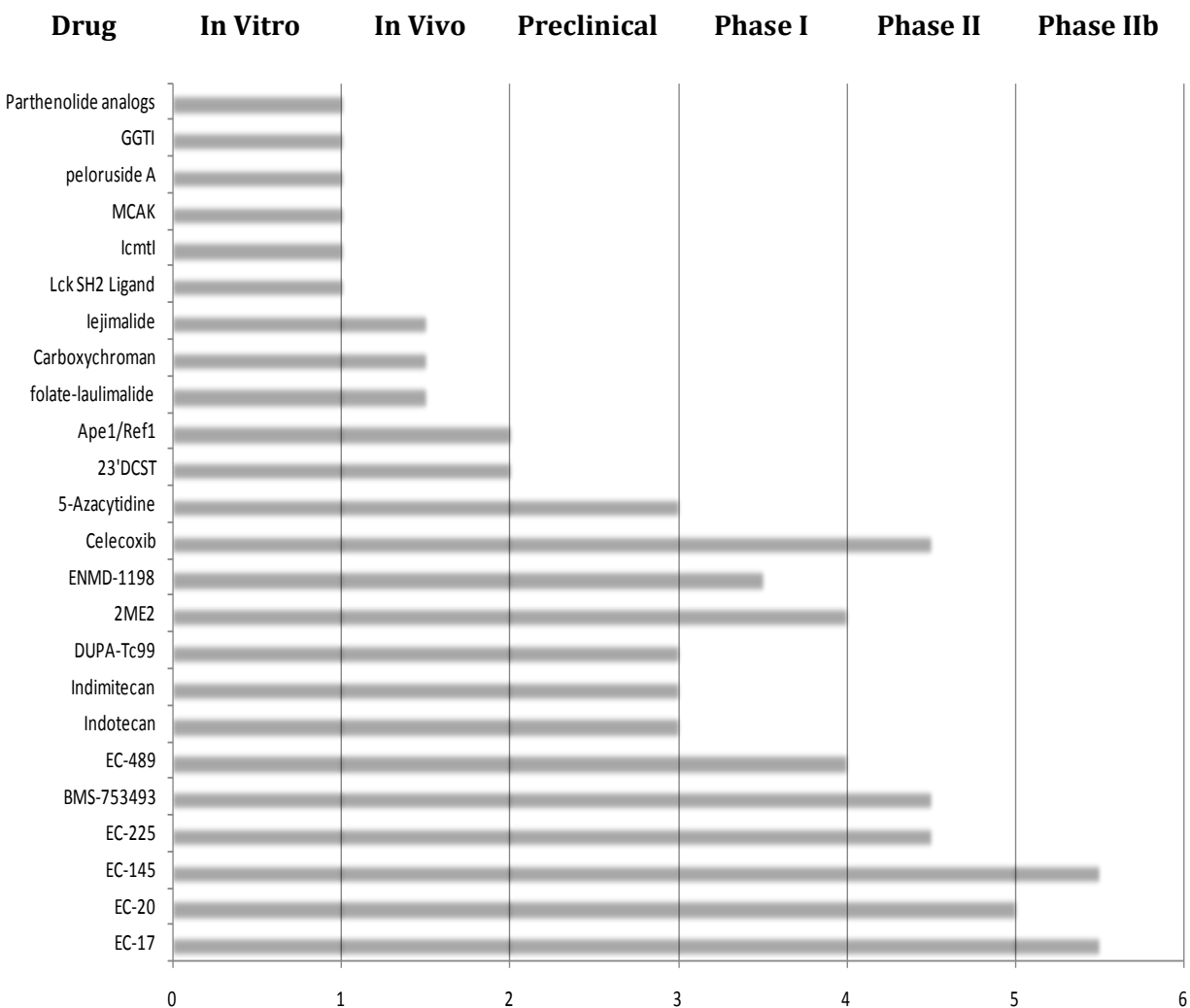
The diagram above illustrates various approaches to drug discovery, with proportionate representation by colleges and schools.

The diagram below illustrates proportionate study of major diseases.



## Compounds in Clinical Development for Cancer

Currently, our researchers are working on several classes of compounds and novel approaches to drug design. The figure below summarizes the active stages of drug discovery for cancer treatment.



## **NSF Engineering Research Center on Structured Organic Particulate Systems**

Launched in July 2006 with support from the National Science Foundation, the Engineering Research Center on Structured Organic Particulate Systems is a national hub for science-based development of structured organic particle-based products and their manufacturing processes. The center involves four universities: Rutgers University (which serves as administrator), Purdue University, New Jersey Institute of Technology and the University of Puerto Rico at Mayaguez. In addition to direct NSF support, the center has an industrial membership base of around 30 companies, including large pharmaceutical, equipment and instrument companies and small technology firms.

Working alongside researchers from the other institutions, the Purdue team — which is comprised of nine faculty members from chemical engineering, industrial pharmacy and mechanical engineering — focuses on aggregates of multiple solid organic materials. Designed to deliver active substances at pre-determined rates and in specific environments, this family of products is manufactured using similar processes across a number of industries, including pharmaceuticals, nutraceuticals, agricultural agents, detergents and foods. However, the largest and most valuable class is pharmaceuticals, especially solid oral dosage drugs.

Historically, engineering such products has been limited by technical issues such as:

- An incomplete understanding of intermolecular potentials and solid state physics
- Delicate materials that cannot withstand high shear and high temperature conditions
- The hierarchy of scales and substantial complexity of constitutive behavior

To date, manufacturing of these products has been largely carried out in batch mode, with limited online sensing and automation, and limited availability of reliable engineering predictive models to support product and process design, scale-up and manufacture. Center researchers aim to:

- Improve the understanding of active pharmaceutical ingredient and excipient material mechanical properties
- Enhance the understanding and prediction of nucleation and crystallization phenomena
- Predict drop formation and deposition phenomena
- Perfect particle-particle and particle surface adhesion
- Create predictive design, scale-up and mathematical modeling of key manufacturing operations, such as powder handling, blending, granulation, milling, compaction and coating;
- Develop online sensing (PAT) using various spectroscopic methods
- Create real-time process management, including supervisory control
- Develop knowledge management to support product development and manufacturing

In addition, the center is supporting development of three test beds specifically targeted for production of solid oral dosage pharmaceuticals: 1.) a continuous automated tableting line, 2.) production of gel strips with embedded drug nanoparticles, and 3.) products formed via precision deposits of drug solutions/melts on edible substrates. Through this work, researchers hope to accelerate the translation of ERC developed knowledge into commercial practice.

## Alphabetical List of Drug Discovery Researchers

Researcher	College/school	Department	CATEGORY				DISEASE				
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other
Adams, Stephen	School of Veterinary Medicine	Veterinary Clinical Sciences			✓				✓		
Aguilar, Ruben Claudio	College of Science	Biological Sciences		✓			✓	✓		✓	
Andrisani, Ourania	School of Veterinary Medicine	Basic Medical Sciences		✓			✓				
Barker, Eric	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology	✓	✓						✓	
Ben-Amotz, Dor	College of Science	Chemistry	✓				✓	✓	✓	✓	✓
Bergstrom, Donald	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓		✓				
Bhunia, Arun	College of Agriculture/ School of Veterinary Medicine (joint appointment)	Food Science/ Comparative Pathobiology	✓	✓	✓				✓		
Borch, Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓		✓				
Borgens, Richard	School of Veterinary Medicine/ College of Engineering (joint appointment)	Basic Medical Sciences/Biomedical Engineering				✓				✓	
Bowman, Keith	College of Engineering	Materials Engineering/ Engineering Education (joint appointment)									
Briggs, Scott	College of Agriculture	Biochemistry		✓			✓				

Researcher	College/school	Department	CATEGORY				DISEASE					
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other	
Buhman, Kimberly	College of Health and Human Sciences	Foods and Nutrition		✓			✓	✓				✓
Byrn, Stephen	College of Pharmacy	Industrial & Physical Pharmacy				✓					✓	
Cabot, Ryan	College of Agriculture	Animal Sciences		✓				✓	✓			
Camarillo, Ignacio	College of Science	Biological Sciences		✓			✓	✓				
Cheng, Ji-Xin	College of Engineering	Biomedical Engineering	✓		✓		✓			✓		✓
Childress, Michael	School of Veterinary Medicine	Dept. of Veterinary Clinical Sciences				✓	✓					
Chmielewski, Jean	College of Science	Chemistry			✓		✓		✓	✓		
Colby, David	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓		✓				✓	
Constable, Peter	School of Veterinary Medicine	Veterinary Clinical Sciences				✓		✓	✓			✓
Cooks, Graham	College of Science	Chemistry	✓				✓					
Cushman, Mark	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓		✓		✓			
Davisson, Vincent Jo	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓	✓	✓				✓	
Fleet, James	College of Health and Human Sciences	Foods and Nutrition		✓			✓					
Freeman, Jennifer	College of Health and Human Sciences	Health Sciences		✓			✓				✓	
García, R. Edwin	College of Engineering	Materials Engineering			✓		✓	✓	✓	✓	✓	

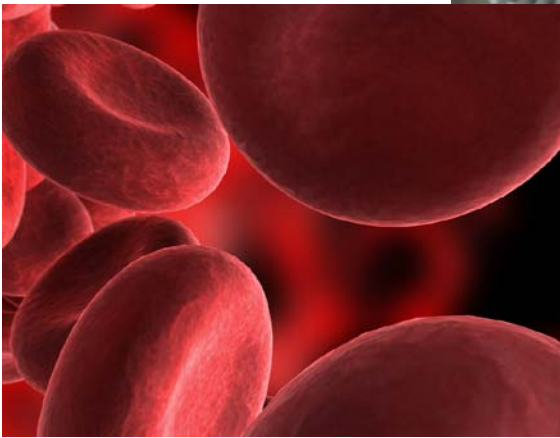
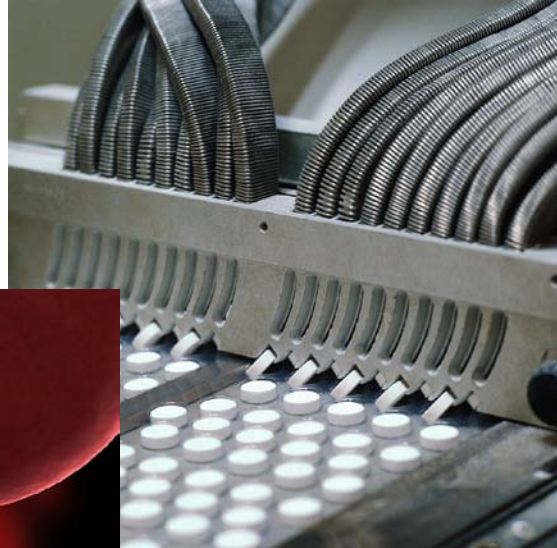
Researcher	College/school	Department	CATEGORY				DISEASE					
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other	
Garner, Joseph	College of Agriculture	Animal Sciences	✓								✓	✓
Geahlen, Robert	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓			✓					
Ghosh, Arun	College of Science/ College of Pharmacy (joint appt)	Chemistry/ Medicinal Chemistry & Molecular Pharmacology			✓		✓		✓	✓		
Gibbs, Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓		✓					
Gore, Jay	College of Engineering	Mechanical Engineering	✓				✓	✓				
Hall, Mark	College of Agriculture	Biochemistry		✓			✓					
Han, Bumsoo	College of Engineering	Mechanical Engineering			✓		✓					
Hazbun, Tony	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓			✓		✓	✓		
Hill, Catherine	College of Agriculture	Entomology		✓	✓				✓			
Hockerman, Gregory	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓				✓		✓		
Hogan, Daniel	School of Veterinary Medicine	Veterinary Clinical Sciences			✓							✓
Hrycyna, Christine	College of Science	Chemistry			✓		✓					
Hu, Chang-Deng	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓			✓	✓		✓		
Irudayaraj, Joseph	College of Engineering	Agricultural and Biological Engineering	✓				✓			✓		
Jiang, Qing	College of Health and Human Sciences	Foods and Nutrition		✓			✓		✓			

Researcher	College/school	Department	CATEGORY				DISEASE				
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other
Kappock, T.J. (Joe)	College of Agriculture	Biochemistry		✓			✓		✓		
Kim, Chang	School of Veterinary Medicine	Comparative Pathobiology		✓			✓		✓		
Kirchmaier, Ann	College of Agriculture	Biochemistry		✓			✓				
Kirshner, Julia	College of Science	Biological Science		✓			✓				
Kissinger, Peter T.	College of Science	Chemistry	✓		✓	✓	✓	✓	✓	✓	✓
Knapp, Deborah	School of Veterinary Medicine	Veterinary Clinical Sciences			✓		✓				
Knipp, Gregory	College of Pharmacy	Industrial and Physical Pharmacy				✓		✓	✓	✓	✓
Ko, Jeff	School of Veterinary Medicine	Veterinary Clinical Sciences		✓				✓		✓	✓
Konieczny, Steve	College of Science	Biological Sciences		✓			✓				
Kuang, Shihuan	College of Agriculture	Animal Sciences		✓			✓				
Leary, James	School of Veterinary Medicine	Basic Medical Sciences			✓		✓				
Lelièvre, Sophie	School of Veterinary Medicine	Basic Medical Sciences		✓			✓				
Liu, Shuang	College of Health and Human Sciences	Health Sciences	✓				✓				
Liu, Xiaoqi	College of Agriculture	Biochemistry		✓			✓				
Lipton, Mark	College of Science	Organic Chemistry/Chemical Biology			✓		✓	✓	✓		
Low, Philip	College of Science	Chemistry			✓		✓				
Luo, Zhao-Qing	College of Science	Biological Sciences		✓	✓				✓		
Mittal, Suresh	School of Veterinary Medicine	Comparative Pathobiology			✓		✓		✓		
Mohammed, Sulma	School of Veterinary Medicine	Comparative Pathobiology		✓			✓				

Researcher	College/school	Department	CATEGORY					DISEASE				
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other	
Murphy, Angus	College of Agriculture	Horticulture			✓		✓					✓
Nauman, Eric	College of Engineering	School of Mechanical Engineering	✓		✓		✓		✓	✓		✓
Nichols, David	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			✓						✓	
Overholser, Brian	College of Pharmacy	Pharmacy Practice		✓								✓
Park, Chiwook	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology	✓	✓								
Park, Kinam	College of Pharmacy	Industrial & Physical Pharmacy			✓		✓	✓				✓
Parker, Laurie	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology	✓				✓				✓	
Pinal, Rodolfo	College of Pharmacy	Industrial & Physical Pharmacy			✓		✓					
Porterfield, D. Marshall	College of Engineering	Agricultural and Biological Engineering	✓				✓	✓			✓	
Pressler, Barrak	School of Veterinary Medicine	Veterinary Clinical Sciences				✓			✓			✓
Raftery, M. Daniel	College of Science	Chemistry	✓				✓					
Ramachandran, P. V.	College of Science	Chemistry			✓		✓				✓	
Ratliff, Timothy	School of Veterinary Medicine	Comparative Pathobiology		✓	✓		✓					
Robinson, J. Paul	School of Veterinary Medicine	Basic Medical Sciences	✓	✓			✓		✓	✓	✓	✓
Rochet, Jean-Christophe (Chris)	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓							✓	
Rossie, Sandra	College of Agriculture	Biochemistry		✓			✓				✓	
Shah, Kavita	College of Science	Chemistry		✓			✓				✓	

Researcher	College/school	Department	CATEGORY				DISEASE					
			Detection Technology	Target Discovery	Drug Design/Delivery	Other	Cancer	Diabetes/Obesity/Metabolic Syndrome	Infectious Diseases/Immune Disorders	Neurological Disorders/Trauma	Other	
Shi, Riyi	School of Veterinary Medicine	Basic Medical Sciences				✓					✓	
Simpson, Garth	College of Science	Chemistry			✓		✓	✓	✓	✓	✓	
Smith, Daniel	College of Pharmacy	Industrial & Physical Pharmacy				✓					✓	
Stauffacher, Cynthia	College of Science	Biological Sciences		✓			✓					✓
Tao, Andy	College of Agriculture	Biochemistry		✓			✓	✓				
Taparowsky, Elizabeth	College of Science	Biological Sciences		✓			✓					
Taylor, Lynne	College of Pharmacy	Industrial and Physical Pharmacy			✓		✓	✓	✓	✓	✓	✓
Thompson, David	College of Science	Chemistry			✓		✓					
Topp, Elizabeth	College of Pharmacy	Industrial & Physical Pharmacy			✓		✓	✓	✓	✓		✓
Watts, Val J.	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		✓					✓	✓	✓	✓
Wei, Alexander	College of Science	Chemistry			✓		✓		✓			
Wilker, Jonathan	College of Science/College of Engineering	Chemistry/School of Materials Engineering				✓						✓
Wirth, Mary	College of Science	Chemistry	✓				✓					
Zheng, Wei	College of Health and Human Sciences	Health Sciences				✓					✓	
Zhou, Daoguo	College of Science	Biological Sciences		✓	✓				✓			





# *detection technology*



## **Eric Barker**

### **Category of Research**

- Detection Technology
- Target Discovery

### **Disease**

- Neurological Disorders

### **Therapeutic Outcome**

- Screening strategies for identification of potential therapeutics for Niemann Pick Type C, Anxiety disorders

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Molecular pharmacology of neurotransmitter transporters, intracellular transport of lipid signalling molecules, lipidomics, systems biology

## **Dor Ben-Amotz**

### **Category of Research**

- Detection Technology

### **Diseases**

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Obesity/Metabolic Syndrome/Diabetes
- Cardiovascular
- Spectral imaging of biological tissue, cells, and arrays

### **Developmental Stage**

- Intermediate

### **Research Interest and Expertise**

We specialize in spectral imaging of biological tissue, cells, arrays, and pharmaceuticals using Raman scattering and/or fluorescence. We also work with optical instrument development for rapid chemical sensing and imaging, along with biomarker discovery, drug delivery and pharmaceutical formulation analysis.

## Arun Bhunia

### Category of Research

- Detection Technology
- Drug Design and Delivery
- Target Discovery

### Diseases

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Intermediate

### Research Interest and Expertise

- Pathogen and toxin detection:
  - Develop biosensor based rapid high throughput screening methods for detection of pathogens and toxins in food. Biosensors include laser light scattering, mammalian cell-based, microfluidic biochip and fiber optic.
  - Develop and optimize reagents including antibodies, receptors, ligands, microbiological growth media, etc. for biosensor applications.
- Pathogenic mechanism of enteric pathogens and control strategies using probiotics:
  - Understanding the molecular and cellular mechanism of intracellular *Listeria monocytogenes* colonization and translocation through epithelial barrier during intestinal phase of infection.
  - Prevention and control strategies using probiotic bacteria and antimicrobial peptide loaded biocompatible nano-carrier.

## **Ji-Xin Cheng**

### **Category of Research**

- Drug Carriers
- Detection Technology

### **Diseases**

- Cancer
- Multiple Sclerosis
- Traumatic Spinal Cord Injury

### **Therapeutic Outcome**

- Development of detection of circulating tumors cells, oxidized lipids and polymer micelles for drug delivery, with particular interests in breast and prostate carcinomas, multiple sclerosis, and traumatic spinal cord injury.

### **Developmental Stage**

- Early to intermediate

### **Research Interest and Expertise**

Developing new methods for enhancing drug penetration into a solid tumor.

Developing new carriers for delivery of drugs to lesions in the central nervous system and to injured spinal cord.

Developing a fiber-optic flow cytometer for intravital detection of circulating tumor cells (CTCs). By sampling a large blood volume in vivo, this method will provide accurate measurement of CTCs to assess the effectiveness of chemotherapies.

Using coherent Raman microscopy to study the role of lipids in various human cancers. We have observed the accumulation of oxidized lipid in prostate cancer, which can potentially be used as a molecular marker for prostate cancer staging.

## **R. Graham Cooks**

### **Category of Research**

- Detection Technology

### **Disease**

- Cancer

### **Therapeutic Outcome**

- Developing tissue imaging technology in order to detect and monitor cancer, with particular interests in prostate and bladder carcinomas

### **Developmental Stage**

- Intermediate to late

### **Research Interest and Expertise**

We are interested in the use of mass spectrometry (MS) to identify markers for diseases such as prostate cancer. We are particularly interested in tissue imaging using MS to supplement standard histological methods. These experiments would be best conducted on site, during surgery, and our attempts at building high-performance handheld mass spectrometers are consistent with this aim.

Desorption electrospray ionization (DESI) is a new MS ionization method that is applicable in the ambient environment. We are interested in extending its use to problems of in situ disease diagnosis as well as clinical analysis.

## Joseph Garner

### Category of Research

- Detection Technology

### Diseases

- Neurological Disorders
- Psychiatric Disorders

### Developmental Stage

- Early
- Intermediate
- Late

### Research Interest and Expertise

Dr. Garner's lab uses an integrated interdisciplinary approach, best described as developmental neuroethology, to address issues in human and animal well-being. The lab has a particular focus on two closely related issues:

- 1) Developing methods and underlying psychobiological principles to predict and prevent abnormal behavior (in animals) and mental disorder (in humans);
- 2) Identifying the general reasons why animal models often fail to predict human outcomes, and providing solutions to improve the efficacy and well-being of animal models.

Both these issues reflect the interface between animal-based medical research, and animal well-being. The medical research community has long recognized that good well-being is good science — the lab's work is directed at exploring this interface, while providing tangible deliverables for the well-being of human patients and research animals.

## Jay P. Gore

### **Category of Research**

- Detection Technology

### **Diseases**

- Cancer
- Diabetes/Obesity/Metabolic Syndrome

### **Therapeutic Outcome**

- Critical care blood analysis technology being used by [www.cascadematrix.com](http://www.cascadematrix.com).

### **Developmental Stage**

- Critical care blood analysis technology is in commercialization stage.
- Preventive blood analysis technology is in intermediate development stage.
- Cancer detection technology is early stage.

### **Research Interest and Expertise**

- Sensors and models of fluid flow and chemical reaction processes in metabolic and other biological activities

## Joseph Irudayaraj

### Category of Research

- Detection Technology

### Diseases

- Cancer
- Neurological Disorders

### Therapeutic Outcome

- Our primary effort constitutes the development of single cell diagnostics and drug quantification strategies in cellular compartments in live cells.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

We have developed nanoscale platforms to quantify drug compartmentalization and localization in different cellular organelles in live cells upon delivery. We use single molecule spectroscopy and imaging tools to quantify drug distribution in live single cells. We use gold nanoparticles and more recently liposomal and polymeric nanostructures for targeted delivery. Our targeted drug delivery and release methods have been applied to evaluate the efficacy of delivery and kinetics of release at single molecule resolution in live single cells.

We have also developed microRNA and mRNA detection strategies in single cells. Preliminary proof of concept has been shown to detect splice variants of BRCA1 in live single cells using our nanoruler concept. We expect that this approach can be used to detect proteins and protein networks and RNA in single cells and tissues at ultrahigh sensitivity.

We have a significant thrust in single cell epigenetic-based screening, and we have the ability to detect histone modifications and DNA methylation in single cells. Currently we are developing approaches for epigenetic drug-delivery and treatment efficacy methods.

## Peter T. Kissinger

### Category of Research

- Detection Technology
- Drug Design and Delivery
- Pharmacokinetics/pharmacodynamics

### Diseases

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Obesity/Metabolic Syndrome/Diabetes

### Developmental stage

- Intermediate
- Late

### Research Interest and Expertise

My interests are in intact mammalian pharmacology and the process of drug development as related to improved protocols for animal work and the related bioanalytical chemistry for drugs, their metabolites and biomarkers. I have unique experience with several contract research organizations and instrument companies in the drug development space from mice to humans. I endeavor to connect drug developer interests with unique Purdue resources as well as other commercial firms that can help achieve an optimum solution to problems of drug formulations design and resulting mammalian responses — both pharmacological and physiological. My enthusiasms are not disease specific and have ranged from cancer to neuroscience, diabetes and HIV. Tissue imaging with mass spectrometry, processing dried blood spots with mass spectrometry, LC/MSMS, automated sampling of biological fluids from conscious freely moving animals, electrochemical biosensors (glucose), in vivo microdialysis sampling devices and Phase I/IIa clinical trials all remain areas of interest.

## Shuang Liu

### Category of Research

- Detection Technology

### Disease

- Cancer

### Therapeutic Outcome

- Developing imaging radiotracers for diagnosis of primary tumors and diagnostic measurement of tumor and their metastatic potential. Particular interests are in glioma, breast, colorectal, lung, and prostate carcinomas.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

I worked at DuPont Medical Imaging Division (new Lantheus Medical Imaging Inc) for nine years, and has extensive experiences in developing new molecular imaging probes (PET, SPECT and optical). Since joining Purdue, my research interest has been directed towards the development of new receptor-based radiotracers for tumor imaging. In addition, I have become one of the leaders in radiolabeled multimeric RGD peptides as radiotracers for non-invasive imaging of integrin  $\alpha_v\beta_3$  expression in the rapidly growing and metastatic tumors. After evaluating >30 radiotracers in different tumor-bearing animal models established in my laboratory,  $^{99m}\text{Tc}$ -3P-RGD<sub>2</sub> was selected for clinical evaluation. Preliminary clinical data clearly indicate that  $^{99m}\text{Tc}$ -3P-RGD<sub>2</sub> is useful for the diagnosis of primary tumors (breast, esophagus, lung, and melanoma) and small metastatic lesions (< 5 mm) in breast cancer patients.

Currently, we are working on new molecular imaging probes (PET, SPECT and optical) for noninvasive diagnosis of metastatic tumors and their metastatic potential. We believe that early detection remains the best approach to improving the odds of curing cancer. Noninvasive measurement of metastatic potential is the key to the reduction of cancer mortality and the eventual eradication of cancer.

## **Eric A. Nauman**

### **Category of Research**

- Drug Design and Delivery
- Detection Technology

### **Diseases**

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Cardiovascular

### **Developmental Stage**

- Early
- Intermediate
- Late

### **Research Interest and Expertise**

Dr. Nauman is the director of the Human Injury Research and Regenerative Technologies (HIRRT) laboratory and his primary research interests are focused on biological problems in which the cellular and tissue level mechanical loading environments and the transport of bioactive molecules are relevant. We emphasize the development of well-defined experimental protocols with advanced statistical and computational simulations in order to evaluate cell function in response to various types of insults. Applications include the repair of vital organs, the development of novel cancer treatments, and the primary and secondary injury patterns of the central nervous system.

## Chiwook Park

### Category of Research

- Detection Technology
- Target Discovery

### Developmental Stage

- Intermediate

### Research Interest and Expertise

My laboratory is specialized in biophysics of protein folding, stability, and protein-ligand interactions. We develop various methodology to investigate protein folding, stability, and ligand binding on molecular levels and also systems levels in order to understand how drug binding modulate the conformational energy landscapes of proteins and also to identify drug targets and off-targets from crude cell lysates on a proteomic scale.

## Laurie Parker

### Category of Research

- Detection Technology

### Diseases

- Cancer
- Neurological Disorders

### Therapeutic Outcome

- Development of kinase activity sensors and assays to monitor drug mechanisms and dosage. A particular interest is in chronic myeloid leukemia.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

We develop in vitro and intracellular sensors and assays for kinase activity, using peptides and nanoparticles to make specific substrates for various cancer-related kinases that are either targeted directly by inhibitor drugs (e.g. Bcr-Abl and imatinib) or related to off-target drug resistance and other cancer-specific signaling. We use highly sensitive mass spectrometry readouts that can be multiplexed to analyze many substrates at once, and we also are developing imaging-based readouts that can be analyzed using plate readers or microscopy.

Our technologies could be applied to high-content secondary screening of kinase inhibitor drugs, or more importantly, for monitoring therapeutic response during treatment. This could be extremely useful for drug discovery, where drug mechanisms and dosage are not well characterized in vivo during drug development and where traditional pharmacokinetics don't necessarily tell the whole story about mechanistic inhibition (since serum levels don't always correlate to intracellular enzymatic inhibition). In particular for leukemias, our techniques should be sensitive enough to monitor mechanistic response in peripheral blood from animal models and human subjects. Other than drug response, our technologies also could be used to generate personalized kinase activation biomarker signatures that may inform diagnosis, prognosis or treatment decisions for individual patients.

## **D. Marshall Porterfield**

### **Category of Research**

- Detection Technology

### **Diseases**

- Cancer
- Diabetes/Obesity/Metabolic Syndrome
- Neurological Disorders

### **Therapeutic Outcome**

- Drug screening
- Diabetes diagnostics

### **Developmental Stage**

- Early-Intermediate

### **Research Interest and Expertise**

- Biosensors
- Cell signaling
- Cellular metabolism
- Lab-on-a-chip systems for cell physiology

## M. Daniel Raftery

### Category of Research

- Detection Technology

### Diseases

- Cancer

### Therapeutic Outcome

- Developing detection techniques for advanced metabolite profiling. Metabolite detection would be used in recurrence, therapy monitoring, therapy prediction and companion diagnostics. Particular interests are breast, colon, pancreatic, liver, lung, prostate and esophageal carcinomas.

### Developmental Stage

- Intermediate to late

### Research Interest and Expertise

Our lab is focused on the discovery and development of metabolite biomarkers for early cancer detection. We have identified biomarker candidates in a number of cancers, including breast, colon, pancreatic, liver and esophageal. For example, we have a profile consisting of 11 metabolite markers that can detect breast cancer recurrence more than a year before the oncologist's diagnosis. We use a combination of mass spectrometry (LC and GC) and nuclear magnetic resonance to discover and validate our marker panels. Metabolite biomarker candidates are identified, quantified and then mapped to their pathways to provide biological validation. Profiles are built with rigorous cross validation procedures. These profiles are quite sensitive to drug response and in some cases can be used to predict therapy response.

More broadly, we have a wide range of advanced metabolite profiling capabilities, including novel methods developed in our lab for the identification and quantification of hundreds of metabolites as well as the ability to identify the structure of unknown molecules that are present in small quantities and low concentration.

## J. Paul Robinson

### Category of Research

- Detection Technology
- Target Discovery

### Diseases

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Cardiovascular

### Developmental Stage

- Early
- Intermediate
- Late

### Research Interest and Expertise

We have been developing advanced research strategies for high throughput screening (HTS) using both current tools and tools under development. This includes new detection systems for multiparametric detection as well as very sophisticated analytical toolsets. We have been developing fully robotic assays that allow us to screen drugs or cellular products, or molecules of interest. Systems are focused on two technologies: automated imaging that uses robotically managed systems to screen analysis plates in an automated manner. A second technology is advanced high throughput flow cytometry whereby we have the capacity to collect up to 9 color analyses from 384 well plates at a rate of one plate every 11 minutes. This allows us to potentially run as many as 20,000 multiparameter flow cytometry samples per day.

To facilitate the analysis of this system, we have developed a very advanced system of automated analysis capable of producing IC50 results, or other statistical results in a few minutes as opposed to the current technology that would not be capable of addressing such a large number of samples. We have designed screening assays systems that focus on live cell functional analysis that have great relevance to drug discovery. The use of complex multiparameter flow cytometry is often not considered in the drug screening environment because of the slow collection and essentially impossible analytical processes required using today's tools. Our group has solved this problem and continues to advance screening capabilities that have been previously impossible. We also have correlated image data with flow cytometry data to allow extraction of correlated information that may be of particular interest to the understanding of drug-effect pathways.

## Mary Wirth

### **Category of Research**

- Detection Technology

### **Disease**

- Cancer

### **Therapeutic Outcome**

- We are using nanoparticles for a wide range of tools used for biomarker discovery and medical tests.

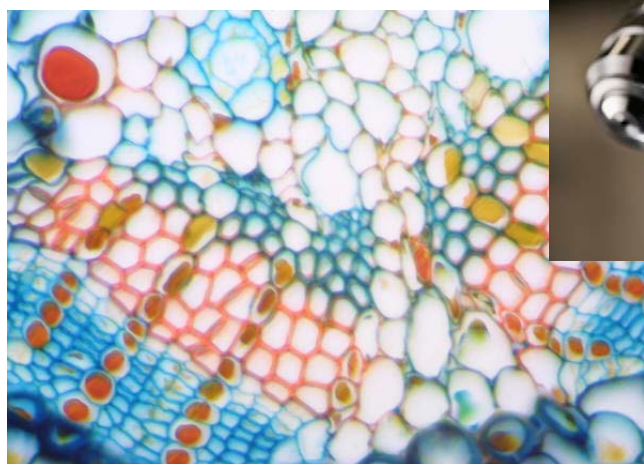
### **Developmental Stage**

- Early to intermediate

### **Research Interest and Expertise**

We are advancing the tools for protein biomarker discovery to increase the throughput and sensitivity. We use submicrometer silica particles to enhance lab supplies, including particles for quantitative immunoextraction and protein recovery at ng/mL levels, multiplexed microchannel isoelectric focusing with MALDI, and high resolution capillary chromatography.

# *target discovery*



## Ruben Claudio Aguilar

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Developmental Diseases
- Neurological Disorders

### Therapeutic Outcome

Our laboratory specializes in vesicle trafficking, particularly endocytosis. Currently, our research is focused on the role played by the endocytic machinery in the activation of signaling pathways related to cancer cell invasion and neurodegenerative diseases. We are particularly interested in the mechanisms linking endocytosis with epithelial-mesenchymal transition in lung, breast, and bladder carcinomas.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

- Identification of novel targets for cancer therapy (particularly anti-metastatics). Our emphasis is on counteracting novel cell invasion pathways. Based on a body of knowledge accumulated in the field, we predict that impairment of these pathways will decrease mesenchymal behavior and enhance drug sensitivity of malignant cells. In fact, preliminary evidence supports this hypothesis.
- Development of strategies to promote therapeutic agent uptake (via endocytosis). We are interested in designing strategies that would allow rapid and efficient internalization of therapeutics. Specifically, we are working on induction of receptor crosslinking (microaggregation) and on the effect of ligand multivalency.

## Ourania Andrisani

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Developing an understanding of targets for potential drug design. These include Plk1, SUZ12, and ZNF198.

### Developmental Stage

- Early

### Research Interest and Expertise

Primary liver cancer, hepatocellular carcinoma (HCC), is the fifth most common cancer world-wide. Chronic Hepatitis B virus (HBV) infection is the major etiologic factor in HCC pathogenesis; the viral protein pX acts a cofactor in HCC pathogenesis.

Our studies have found:

- 1) Polo-like-kinase1 (Plk1) activation as necessary for pX-induced hepatocyte transformation;
- 2) Plk1 as necessary for initiation of pX transformation;
- 3) SUZ12 and ZNF198 as two novel tumor suppressors of HBV-HCC. Specifically, human liver tumors exhibit increased Plk1 protein levels and reduced SUZ12 and ZNF198;
- 4) Increased Plk1 and reduced protein levels of SUZ12 and ZNF198 also occur in the context of HBV replication;
- 5) Inhibition of Plk1 suppresses viral titer in a mouse model supporting HBV replication; and
- 6) SUZ12, a component of a repressive chromatin remodeling complex (PRC2), directly suppresses expression of marker genes of hepatic cancer initiating cells.

We are exploring:

- 1) Use of Plk1, SUZ12 and ZNF198 as early prognostic biomarkers for classification of HCC;
- 2) Plk1 inhibitors as antivirals for HBV replication, using a xenograft mouse model that supports HBV replication;
- 3) Plk1 inhibitors as therapy targets of HBV pX-mediated HCC, using the c-myc/X bitransgenic and xenograft animal models; and
- 4) designing a prognostic biomarker gene signature comprised of genes regulated by SUZ12, for the early diagnosis of HBV-HCC.

## **Eric Barker**

### **Category of Research**

- Detection Technology
- Target Discovery

### **Disease**

- Neurological Disorders

### **Therapeutic Outcome**

- Screening strategies for identification of potential therapeutics for Niemann Pick Type C, Anxiety-disorders

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Molecular pharmacology of neurotransmitter transporters, intracellular transport of lipid signalling molecules, lipidomics, systems biology

## Arun Bhunia

### Category of Research

- Detection Technology
- Drug Design and Delivery
- Target Discovery

### Diseases

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Intermediate

### Research Interest and Expertise

- Pathogen and toxin detection:
  - Develop biosensor based rapid high throughput screening methods for detection of pathogens and toxins in food. Biosensors include laser light scattering, mammalian cell-based, microfluidic biochip and fiber optic.
  - Develop and optimize reagents including antibodies, receptors, ligands, microbiological growth media, etc. for biosensor applications.
- Pathogenic mechanism of enteric pathogens and control strategies using probiotics:
  - Understanding the molecular and cellular mechanism of intracellular *Listeria monocytogenes* colonization and translocation through epithelial barrier during intestinal phase of infection.
  - Prevention and control strategies using probiotic bacteria and antimicrobial peptide loaded biocompatible nano-carrier.

## Scott Briggs

### **Category of Research**

- Target Discovery

### **Disease**

- Cancer

### **Therapeutic Outcome**

Understanding the mechanism of how histone methyltransferases and demethylases function will provide key insights into designing small molecule inhibitors for potential novel chemotherapeutic drugs.

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

Several histone methyltransferases and demethylases are found either mutated, chromosomal translocated, or over-expressed when isolated from oncogenic cells, suggesting that they play an important regulatory role in the cell. Unique interactions have been identified that are being pursued to develop therapeutics. Currently, structural analyses are in progress to assist with targeting the interaction in an effort to disrupt in a specific manner.

## **Kim Buhman**

### **Category of Research**

- Target Discovery

### **Diseases**

- Obesity/Metabolic Syndrome
- Atherosclerosis
- Cancer

### **Therapeutic Outcome**

- Reduce body weight, improve insulin sensitivity, lower blood glucose and triglyceride concentrations, improve postprandial triglyceridemic response, reduce atherosclerosis

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- My research interests and expertise are in the area of lipid metabolism, including neutral lipid (triglyceride and cholesterol ester) synthesis, storage and lipoprotein metabolism. The current focus of my laboratory is on understanding molecular mechanisms involved in the process of dietary fat absorption, which is important in regulating energy balance and blood triglyceride concentrations. We use genetic and dietary mouse models to understand the role of lipid metabolism genes and specific dietary components in these processes.
- One of the major projects in my laboratory is to investigate the role of diacylglycerol acyltransferases 1 (DGAT1), an enzyme that catalyzes the last step in triglyceride biosynthesis, and related enzymes in dietary fat absorption. We recently found that inhibiting this enzyme in the intestine, specifically, is important for its beneficial effects on energy balance. Several pharmaceutical companies are developing small molecule inhibitors towards this enzyme with the hope that these inhibitors will be helpful for treatment of obesity and type 2 diabetes.

## Ryan Cabot

### **Category of Research**

- Target Discovery
- Development of animal models

### **Diseases**

- Diabetes/Obesity/Metabolic Syndrome
- Infectious Diseases

### **Therapeutic Outcome**

- Animal model development, transgenic animals

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

I am a reproductive biologist with research emphasis on events that occur during the first week of development following fertilization. We use pig and sheep embryos as our research models. We have done some work in the area of transgenic animal production. We also investigate how specific stresses affect embryo and fetal development.

## Ignacio Camarillo

### Category of Research

- Target discovery

### Disease

- Cancer

### Therapeutic Outcome

- Understand the impact of diet and obesity on tumor microenvironment, tumor progression and therapeutic response, in particular, breast carcinoma

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

Obesity is a major health concern and is associated with breast cancer incidence, tumor invasiveness and higher cancer morbidity rates. Our understanding of the mechanistic links between obesity and cancer progression is limited. In addressing these issues, goals of our research are to 1) determine the relationship between diet, early onset obesity and breast cancer aggressiveness, 2) identify mechanisms of adipocyte-derived hormones on breast cancer progression and drug resistance and 3) better understand the impact of diet and obesity on mammary tissue and tumor microenvironment.

We have developed a rat model of early onset obesity to study the effects of a Western diet and obesity on breast cancer progression. We have shown that Western Diet fed Obese rats develop greater numbers of highly invasive mammary tumors with distinct extracellular matrix features, compared to Western fed Diet Resistant Lean rats. These results support the rat model as a valuable system to identify biomarkers, and epigenomic and metabolomic signatures associated with dietary effects on tumor progression and on tumor therapeutic response.

We have also developed a co-culture system that mimics the mammary gland/tumor microenvironment *in vitro*. This system provides an excellent transitional tool between *in vitro* (2D cell culture) and *in vivo* experiments for drug screening. Using this model, we demonstrate that adipose tissue, in the absence of exogenous growth factors or other culture supplements, supports long-term mammary tumor cell growth. This is an excellent system to study the molecular interplay between microenvironment and mammary tumor cells, to identify cellular and secreted biomarkers for cancer progression, and to evaluate therapeutic response in a physiological context — without extensive animal cost.

Finally, we work with plant-derived proteins that are structural homologs of adiponectin, an adipokine with antiproliferative, anti-diabetic and anti-inflammatory activities. We have revealed these molecules can act through mammalian adiponectin receptors and are antiproliferative, pro-apoptotic and anti-migratory in aggressive breast cancer cell lines. This demonstrates the strong potential for these proteins as anti-tumor agents.

## James Fleet

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Developing an understanding the role of inflammation, Vitamin D, stem cells, and the use of animal models relevant to colon cancer. There is also interest in prostate cancer.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

We have developed transgenic animal models for colon cancer that limits Cre-recombinase expression to the epithelial cells of the colon. We are currently making a version of this transgenic mouse that would allow inducible deletion of floxed transgenes. These animal models will permit production of adult mice with specific (and multiple) deletions to occur in the colon, making them more relevant to human colon cancer.

We are interested in the role that vitamin D, vitamin D metabolites, or vitamin D analogs have in the prevention or slowing of cancer. Our interest is in prostate and colon cancer.

We are examining the role of inflammation as a tumor promoter, and we are interested in whether vitamin D compounds suppress cancer by limiting local inflammatory responses.

We are interested in the stem-cell theory of cancer, and we are examining how various conditions alter the colon stem cell compartment (e.g. APC allele deletion, inflammation, vitamin D signaling).

## Jennifer Freeman

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Neurological Disorders

### Therapeutic Outcome

Identification genetic biomarkers and the molecular pathways involved in cancer initiation and progression.

### Developmental Stage

- Early

### Research Interest and Expertise

We are a molecular toxicology laboratory with interests in identifying DNA structure and gene expression alterations induced by chemical exposure and defining how these alterations influence disease onset. We have expertise with genomic technologies, including array comparative genomic hybridization (CGH) to detect genomic copy number imbalances and gene expression microarrays to identify genetic biomarkers (i.e., gene targets) and the molecular pathways involved in cancer initiation and progression. We have all equipments available to do the genomic analyses in our laboratory. In addition, we use the zebrafish model system for screening and investigating the genetic mechanisms of toxicity. Moreover, we have experience characterizing genetic signatures of leukemia, melanoma, and rhabdomyosarcoma using zebrafish cancer models.

## Robert Geahlen

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Develop understanding of biomolecular targets and pathways, diagnostics, and compounds with novel activities, with particular interests in leukemia/lymphoma and breast carcinomas (Drug: MCAK).

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

- *Biomolecular targets and pathways:* We are exploring the role of the Syk protein-tyrosine kinase in the regulation of signal transduction pathways in both immune cells where Syk functions as an oncogene product and in breast cancer cells where Syk behaves more as a tumor suppressor. We use a variety of cellular, biochemical, structural (in collaboration with Dr. Carol Post), and proteomic (in collaboration with Dr. Andy Tao) approaches.
- *Diagnostics:* In collaboration with Dr. Chang Lu (now at Virginia Tech), we are exploring the use of electroporative flow cytometry to monitor the translocation of proteins from the cytoplasm to the plasma membrane and from the cytoplasm into the nucleus. Such translocations are often indicative of growth promoting signals in tumor cells.
- *Compounds with novel activities:* In collaboration with Dr. Richard Borch, we are evaluating the ability of metabolically activated prodrugs targeted toward SH2 domains to alter the growth properties of cells by engaging novel targets that control replication and cytokinesis.

## Mark Hall

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Mechanisms of cell cycle regulation, which is defective in all types of cancers

### Developmental Stage

- Early

### Research Interest and Expertise

One of our interests is in developing mass spectrometric approaches for the sensitive and specific detection of molecules of interest in complex biological samples, such as bodily fluids or tissue homogenates. These approaches, using selected reaction monitoring mass spectrometry, are a potential method for detecting protein biomarkers.

Our own biological interests have led us to develop methods for the quantitative detection of post-translational modifications on proteins, and this could be applied to detection of certain cancer biomarkers. We are collaborating with the labs of Drs. Deborah Knapp and Cynthia Stauffacher to apply these methods to the detection and quantification of tyrosine phosphorylation on the EphA2 receptor in breast and prostate cancer cell lines.

There is some indication that EphA2 phosphorylation status may correlate with hormone response in certain types of breast cancers. We are currently involved in a collaborative project with Dr. Harry Charbonneau to explore contributions of the Cdc14 phosphatase to genome stability and cancer avoidance in human cells.

## Tony Hazbun

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Neurological Disorders
- Infectious Diseases/Immunological Disorders

### Therapeutic Outcome

We are using yeast as a model system to investigate therapeutic targets implicated in several disease areas. We are mapping protein and genetic interaction networks in yeast in an effort to delineate biological pathways and discover novel therapeutic targets. Using this technology, we are investigating and discovering non-oncogene dependencies related to the Aurora kinase signaling network, with particular interest in pancreatic cancer. These non-oncogene relationships are defined as genes that are essential only in the context of specific cancer-causing mutations, such as when the Aurora kinases are overexpressed in pancreatic cancer.

Another project uses yeast-based chemical genetics and high-throughput assays to identify small molecule modulators of Hsp90 and other cancer relevant pathways using isogenic and genomewide yeast strains.

We are also currently developing a yeast model to understand the biological activities of DJ-1, a protein implicated in Parkinson's disease. Development of this model will allow us to better understand the interplay between DJ-1 and alpha-synuclein and may be used as a tool for screening chemical libraries to identify small molecule modulators of this interaction.

### Developmental Stage

- Early

### Research Interest and Expertise

- Mitosis, Aurora kinase, Protein interaction and synthetic genetic interaction networks, functional genomics, high-throughput screening, yeast biology
- We are working to establish protein interaction networks in the yeast kinetochore, with a focus on the interactions of the yeast homologue of Aurora kinase.

## Catherine Hill

### **Category of Research**

- Target Discovery
- Drug Design and Delivery

### **Diseases**

- Infectious Diseases/Immune Disorders

### **Developmental Stage**

- Early
- Intermediate

### **Research Interest and Expertise**

Discovery and development of new, safer insecticides to control arthropod (mosquito and tick) vectors of human and animal disease. Research efforts focus on arthropod genome mining, target-based drug discovery and chemical compound screening against arthropod G-protein coupled receptor targets.

## **Gregory H. Hockerman**

### **Category of Research**

- Target Discovery

### **Diseases**

- Diabetes/Obesity/Metabolic syndrome
- Neurological Disorders

### **Therapeutic Outcomes:**

- Diabetes control
- Prevention of panic attacks in patients with post-traumatic stress disorder
- Prevention of relapse in recovering drug addicts and alcoholics

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Stimulation of insulin secretion from pancreatic beta cells in a glucose-dependent manner
- Discovery of agonists and modulators of GABA-A and GABA-B receptors
- Molecular pharmacology of L-type voltage-gated Ca<sup>2+</sup> channels

## Chang-Deng Hu

### Category of Research

- Target Discovery and biomarker identification
- Applications of novel technologies in cancer research

### Diseases

- Cancer

### Therapeutic Outcome

- Molecular mechanisms underlying therapy-resistant prostate cancer and identification of druggable targets
- Development of novel DNA nanotube-based antisense DNA delivery to treat cancer
- Identification of lead compounds for targeting protein-protein interactions involved in diseases
- Novel BiFC-based diagnostic tools

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

**1) Mechanisms and targeting of therapy-resistant prostate cancer.** We have discovered that ionizing radiation can induce neuroendocrine differentiation (NED) of prostate cancer cells. We are collaborating with researchers at the Indiana University School of Medicine to evaluate the clinical significance of this novel finding. Two potential projects are relevant to early-stage cancer intervention:

- Development of novel radiosensitizers by targeting radiation-induced NED.
- Serum chromogranin A (CgA) as a biomarker to monitor radiation-induced NED and to predict prognosis.

**2) Regulation and impact of ATF2 subcellular localization in human diseases.** We have been investigating the molecular mechanism underlying the regulation of ATF2 subcellular localization in the context of several human diseases. Results from this study will likely lead to identification of new molecular targets for drug development.

**3) Applications of BiFC-based technologies in cancer research.** We have developed several novel bimolecular fluorescence complementation (BiFC)-based technologies to visualize protein-protein interactions in living cells and animals. We are interested in applying these technologies to screen for protein-protein interaction disruptors and to develop novel BiFC-based biosensors to imaging signaling pathways in cancer cells.

**4) Development of novel drug delivery systems.** We have been collaborating with Dr. Chengde Mao to develop a novel DNA nanotube-based targeted delivery of antisense DNA to treat prostate cancer. The proposed novel delivery system is completely biodegradable and should overcome current limitations of nanoparticles using other nanomaterials.

## **Qing Jiang**

### **Category of Research**

- Target Discovery

### **Diseases**

- Cancer
- Infectious Diseases/Immune Disorders

### **Therapeutic Outcome**

- Developing understanding of the role of COX-1/2 and 5-LOX combined with use of long-chain carboxychromanols. In addition, we are studying vitamin E forms as chemoprevention agents. Particular interests are prostate, pancreatic, and colorectal carcinomas (Drug: Carboxychroman).

### **Developmental Stage**

- Early to intermediate

### **Research Interest and Expertise**

We have recently demonstrated that long-chain carboxychromanols, physiological metabolites from vitamin E forms, are potent competitive inhibitors of cyclooxygenases (COX-1/2) with the potency similar to ibuprofen. Even more interestingly, these compounds also potently inhibit 5-lipoxygenase (5-LOX) catalyzed reactions with a potency similar to zileuton.

Both COXs and 5-LOX catalyzed reactions are known to play key roles in inflammation and cancer development. Because long-chain carboxychromanols inhibit both COXs and 5-LOX, they may show stronger anti-inflammatory and anticancer activity while they may have reduced adverse effects compared with specific COX inhibitors (which have been consistently shown to reduce the risk of various types of cancer but increase the risk of cardiovascular diseases). We are in the process of synthesizing some long-chain carboxychromanols (in collaboration with the lab of Dr. Richard Gibbs) and testing both anti-inflammatory and anticancer effects in animal models.

Some non-traditionally studied vitamin E forms such as gamma-tocopherol and tocotrienols may be interesting chemoprevention agents, which are being tested in cell-culture studies and prostate and colon cancer models in mice.

## **T. J. (Joe) Kappock**

### **Category of Research**

- Target Discovery

### **Diseases**

- Cancer
- Infectious Diseases

### **Therapeutic Outcome**

- Antimicrobials
- Antimetabolites

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

We are interested in enzyme mechanisms and prokaryotic metabolism. Purine biosynthesis is a good target for anticancer and antimicrobial agents. The de novo purine biosynthesis pathway uses a different reaction sequence in animals and in yeast/bacteria/plants at the CAIR (carboxyaminoimidazole ribonucleotide) synthesis step. We use X-ray crystallography and mechanistic experiments to characterize these divergent routes to CAIR. We hope to help develop selective antimicrobial agents or antimetabolites that inhibit nucleotide synthesis/metabolism.

## **Chang Kim**

### **Category of Research**

- Target Discovery

### **Disease**

- Cancer

### **Therapeutic Outcome**

- Developing understanding of cell migration and cell differentiation in an organ-specific manner, with particular interests in breast, lymphoma and colorectal carcinomas.

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

We are studying immune cell migration to tumor in an organ-specific manner. The main focus is on cancer in the intestine versus other organs such as breast cancer and lymphoma.

Another topic is the changes in T cell differentiation in cancer and associated lymphoid tissues in an organ-specific manner. We study how organ-specific factors, cytokines, and hormones regulate T cell differentiation in cancer patients.

## Ann Kirchmaier

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Relevant applications include drug screening, cancer diagnosis and staging, identification of fungal-specific targets for drug design for secondary infections in cancer patients, and identification of rare sub-populations of cell in tumors based on epigenetic profiles.

### Developmental Stage

- Early

### Research Interest and Expertise

In collaboration with Dr. Joseph Irudayaraj (Department of Agricultural and Biological Engineering), we are developing and applying innovative, customizable, single-molecule strategies for detecting and quantifying epigenetic processes contributing to oncogenesis (histone modifications, DNA modifications, miRNAs, histone variants, chromatin modifying enzymes and gene expression patterns) in vitro, in single cells and in tissues.

Our laboratory has a broad background in gene regulation, epigenetics, chromatin modification and chromatin assembly, tumor virology and human oncology, using genetic and biochemical approaches, cell culture and the model organism *Saccharomyce cerevisiae*.

## **Julia Kirshner**

### **Category of Research**

- Target Discovery

### **Disease**

- Cancer

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

Strong evidence in support of the cancer stem cell theory has been steadily accumulating over the last decade. In addition to tumorigenic potential, cancer stem cells possess characteristics of normal stem cells, including proliferative quiescence, self-renewal potential and multipotency. Upon receiving proliferation signal(s) from the microenvironment, cancer stem cells switch their program from quiescence to differentiation/proliferation, initiating tumor growth. Patients suffering from both hematological malignancies and solid tumors often see their disease relapse because of the inability of currently used therapies to target successfully cancer stem cells. Thus, determining which characteristics of the cancer stem cells can be therapeutically exploited is of utmost importance.

My lab studies the properties of cancer stem cells using two model systems: multiple myeloma, a cancer of the bone marrow, and breast cancer, representing hematological and solid malignancies respectively. The long-term research objectives of my laboratory are to investigate the fundamental question in cancer stem cell biology: What is the role of microenvironment in maintaining the balance between self-renewal and differentiation of cancer stem cells? Our working hypothesis is that cancer stem cells are found in a specialized microenvironment niche, which keeps the cells in a non-proliferative state. Altering the conditions in favor of differentiation and proliferation leads to tumor re-growth. To study these processes, we utilize tissue culture and in vivo approaches, using 3-dimensional tissue culture models to reconstruct human tissues in vitro and humanized mouse models to recapitulate the human microenvironment in an animal.

## Jeff Ko

### **Category of Research**

- Target Discovery

### **Diseases**

- Anesthesia and pain management
- Cardiovascular-pulmonary dysfunctions
- Obesity/metabolic syndrome animal models
- Spinal cord-CNS animal models

### **Therapeutic Outcome**

- Anesthesia and pain management

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

We specialize in anesthesia and pain management, obesity/metabolic syndrome animal models, cardiovascular-plumonyary dysfunctions, and spinal cord-CNS animal models, including:

- 1) animal models of anesthesia and pain management
- 2) inhalant and injectable anesthetics
- 3) pain management techniques and drug delivery
- 4) pain assessment and brain images with functional MRI
- 5) anesthesia equipment
- 6) anesthetic monitoring of cardiorespiratory and brain functions

## Steve Konieczny

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- We are interested in understanding the earliest molecular and signaling events involved in the development of pancreatic ductal adenocarcinoma (PDAC). Mist1 may serve as a novel therapeutic target for the earliest stages of this disease.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

Although activating mutations in the KRAS protooncogene (Kras<sup>G12D</sup>) are thought to initiate a PDAC cascade, our knowledge is grossly deficient in defining how Kras<sup>G12D</sup> expression leads to acinar-ductal metaplasia, in identifying transcriptional networks that are integral to advancing or repressing metaplasia, and in determining how cellular plasticity contributes to PDAC. To address these deficiencies, we have examined the importance of Mist1 — an acinar cell restricted basic helix-loop-helix transcription factor — to acinar-ductal metaplasia and pancreatic cancer. Utilizing the Mist1 locus and Kras<sup>G12D</sup> mouse models, our studies have shown that Mist1 plays a critical role in preventing preneoplastic lesions upon Kras<sup>G12D</sup> expression. *Interests:* early stages of pancreatic cancer; pancreatic cancer mouse models, histopathology, transcriptional gene regulation, signaling pathways, and in vitro culture models.

## Shihuan Kuang

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Understanding how Dlk1 regulates downstream genes may lead to novel therapeutic targets in cancer prevention and treatment. There is also interest in understanding cancer stem cells relative to new tumor growth. Particular interests are hepatocellular carcinoma and rhabdomyosarcoma.

### Developmental Stage

- Early

### Research Interest and Expertise

The primary focus of our research is the regulation of stem cells by Notch signaling. To this end, we have identified Dlk1 as a regulator of Notch and the proto-oncogene c-Myc. Importantly, elevated Dlk1 expression is associated with, and a prognostic marker for many types of cancer including acute myeloid leukemia, hepatoblastoma, renal carcinoma, pancreatic tumor, pituitary adenomas, neuroblastoma, and glioma.

## Sophie Lelièvre

### Category of Research

- Target discovery

### Disease

- Cancer

### Therapeutic Outcome

- Deciphering the mechanisms that control the organization and function of nuclear proteins, notably as it pertains to gene expression, in normal and cancer cells, in order to develop strategies for better detection and control of cancer initiation and progression. Identify targets involved in the control of apical polarity to be used to prevent cancer development.

### Developmental Stage

- Early

### Research Interest and Expertise

*NuMA as a controller of cell fate:* A fusion protein made of the nuclear protein NuMA and retinoic acid receptor can act as an oncogenic factor for leukemias, and alterations in NuMA gene have been proposed to be associated with higher risk of breast cancer development. Using 3D cell culture models, we have identified a link between the distribution of NuMA, chromatin organization and the maintenance of breast epithelial differentiation. NuMA might control cell phenotype by influencing chromatin structure, specifically by targeting chromatin remodeling complexes (CRCs) to different nuclear sites, such function, if altered, might participate in cancer behavior.

Recent data show that NuMA interacts with members of different CRCs. We are now collaborating with biophysicist Dr. Joseph Irudayaraj to study NuMA-CRCs interaction in live cells. We are working with Dr. Cynthia Stauffacher, a structural biologist, to unravel a previously unexplored, yet highly conserved, sequence that NuMA shares with other chromatin-associated proteins. In collaboration with imaging experts, we are using NuMA distribution to classify phenotypes involved in cancer progression to help prognosis and screen for preventive and risk factors.

*Link between tissue polarity and breast cancer development:* Apical polarity is essential for epithelial differentiation and is altered in very early stages of breast cancer. The team has shown that non-neoplastic breast epithelial cells that have lost apical polarity are primed to enter the cell cycle. Our hypothesis is that apical polarity controls epigenetic mechanisms of gene expression that are essential to prevent tumor development. Using the DNA Sequencing Resource, we have identified, via microarray analyses performed in collaboration with Dr. Rebecca Doerge (Department of Statistics), genes responsive to apical polarity. The link between the expression of two of the genes and early changes in breast epithelium has been confirmed in breast tissue samples. The usefulness of these and other genes as markers of preneoplastic alterations and targets for cancer prevention strategies is being assessed. Particularly, we are investigating the effect of apical polarity loss on the expression of genes involved in the control of cell quiescence and how dietary compounds impact apical polarity. With Dr. James Leary, we are developing nanotechnology-based tools to diagnose and reverse apical polarity alterations, notably via an intraductal approach.

## **Xiaoqi Liu**

### **Category of Research**

- Target Discovery

### **Disease**

- Cancer

### **Therapeutic Outcome**

- Developing an understanding of Plk1 and its role in cancer formation and for potential drug design. Particular interests are melanoma, prostate, and pancreatic cancers.

### **Developmental Stage**

- Early and late

### **Research Interest and Expertise**

We are studying the roles of the cell cycle in cellular transformation. In particular, we are focusing on Polo-like kinase 1 (Plk1), a critical regulator of many cell cycle events. The lab has identified several novel Plk1 substrates, whose phosphorylation by Plk1 likely contributes to early events of cancer formation. We are collaborating with colleagues in PCCR to test our hypotheses in animal models. Based on our biochemical and cell biology studies, we are proposing novel mechanisms to understand acquisition of resistance of chemotherapy. We will determine how Plk1-dependent DNA replication contributes to development of gemcitabine resistance in pancreatic cancer. We will also understand how Plk1-dependent p53 regulation affects acquisition of docetaxel and doxorubicin resistance in prostate cancer. The lab has extensive experience with various signal pathways, such as the MAP kinase pathway, the PI3K/AKT/mTOR pathway and different mitotic kinases.

## **Zhao-Qing Luo**

### **Category of Research**

- Drug Design and Delivery
- Target Discovery

### **Disease**

- Infectious Diseases/Immune Disorders

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Infectious disease and immunology

## Sulma Mohammed

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Determining progression markers for diagnostics, imaging probes, and intervention strategies, with particular interests in breast.

### Developmental Stage

- Early

### Research Interest and Expertise

We have characterized an animal model that develops spontaneous pre-malignant lesions similar to humans' lesions in all morphological, molecular, and clinical diversities. Spontaneous canine mammary premalignant lesions such as ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ (low grade, intermediate grade, and high grade type) are strikingly similar to those of the human breast. This similarity in histology and pattern of ER- $\alpha$ , PR, and HER-2 expression make the dog an ideal model to study human breast cancer, especially ER-negative (both HER-2-positive and -negative) breast cancer pre-malignancy as well as prevention and treatment. Not only that, X-ray studies performed on canine mammary glands show signs on X-ray images (e.g., clustered micro-calcifications) that are very similar to the BI-RAD criteria employed clinically for breast cancer screening. Therefore, our dog model provides a unique opportunity to examine breast cancer premalignancies and to elucidate the breast cancer pathogenesis. Clinical impact of this work is enormous, as it will assist in identifying breast cancer progression markers that can be developed as diagnostic tools, imaging probes, and as targets to test different intervention strategies to prevent the disease in asymptomatic women at risk of developing breast cancer, identify women diagnosed with DCIS risk of developing subsequent invasive cancer, and as therapeutic targets to treat the disease at its early stages.

Our lab also interested in identifying and characterizing, in term of receptors expression, stem cell-like properties, and pathway analysis, lymph tumor circulating cells compared to blood tumor circulating cells in human (we have an ongoing study in collaboration with Indiana University School of Medicine to collect lymph draining the breast tumor and before it enters the sentinel lymph node in women with metastatic breast cancer). This study has potential to identify metastasis-specific molecules to stratify women according to the risk of developing metastasis, provide targets to treat and prevent metastasis, and determine therapeutic efficacy.

Using breast cancer tissues from African women, African American women, and Caucasian women, our plan is to determine molecular markers (racial differences and environmental factors) that occur early and contribute to the tumor aggressiveness in African and African American women with breast cancer.

## **Brian R. Overholser**

### **Category of Research**

- Target Discovery

### **Diseases**

- Arrhythmias
- Cardiovascular

### **Therapeutic Outcome**

- Prevention of arrhythmias

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

My research is focused on identifying molecular targets that can be manipulated pharmacologically with the goal of preventing arrhythmias during disease states in which they are the most prevalent. Therefore, we use mechanistic models of various cardiovascular diseases to design treatment modalities that are tested in disease models and eventually clinical trials.

## Chiwook Park

### Category of Research

- Target Discovery
- Detection Technology

### Developmental Stage

- Intermediate

### Research Interest and Expertise

My laboratory is specialized in biophysics of protein folding, stability, and protein-ligand interactions. We develop various methodology to investigate protein folding, stability, and ligand binding on molecular levels and also systems levels in order to understand how drug binding modulate the conformational energy landscapes of proteins and also to identify drug targets and off-targets from crude cell lysates on a proteomic scale.

## **Timothy L. Ratliff**

### **Category of Research**

- Drug Design and Delivery
- Target Discovery

### **Disease**

- Cancer

### **Developmental Stage**

- Early
- Intermediate

### **Research Interest and Expertise**

Dr. Ratliff's research is directed toward the understanding of the role of the immune response in cancer. Studies are directed toward understanding inflammation and its role in cancer development and progression, and the development of effective immunotherapy treatments for prostate and bladder cancer. These studies address questions regarding activation of anti-tumor responses, characterization of immunological tumor killing mechanisms, and the regulation of anti-tumor immunity. The laboratory also uses genetically modified mice to study the mechanisms by which tumor cells escape recognition by the immune response. The genetically modified mice also provide a model for better understanding the role of inflammation in the development and progression of prostate cancer. The bladder cancer studies focus on targeting bladder cancer cells with a specific protein known to be an important binding protein. The targeting studies will incorporate nanotechnology for the delivery of therapeutic agents.

## Jean-Christophe (Chris) Rochet

### Category of Research

- Target Discovery

### Disease

- Neurological Disorders

### Therapeutic Outcome

- Inhibition of neurodegeneration, slowing of motor and/or cognitive decline in diseases such as Parkinson's disease or Alzheimer's

### Developmental Stage

- Early

### Research Interest and Expertise

A major focus of the Rochet lab is to discover and characterize potential drug targets in Parkinson's disease (PD). These targets typically belong to one of two categories:

- 1) Targets that increase the risk of PD by assuming abnormal, toxic functions. An example of such a target is the neuronal protein alpha-synuclein, which undergoes a structural change to produce harmful aggregates in the brains of PD patients.
- 2) Targets that increase the risk of PD by undergoing a loss of protective function. These targets are often identified because they are defective in some patients with genetic forms of PD. An example of such a target is DJ-1, a protein that normally protects neurons by carrying out antioxidant and molecular chaperone activities.

Another focus of the lab is to characterize small molecules for their ability to suppress neurodegeneration in cellular models of PD. Examples of small molecules of interest include anti-oxidant compounds (e.g. molecules in polyphenol-rich botanical extracts), compounds that modulate protein aggregation, and compounds that rescue intracellular trafficking defects. Our ultimate goal is to identify therapeutic leads that can be further developed into drugs for the treatment of PD patients.

## Sandra Rossie

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Neurological Disorders

### Therapeutic Outcome

- We study the regulation and function of serine/threonine phosphatase 5 (PP5). Protein phosphatase 5 is elevated in a number of human cancers and participates in several signaling pathways that are often activated in cancer. Specifically, we are investigating the role of PP5 in heat shock protein 90 (Hsp90) function and in cell responses to the monomeric G protein Rac1. Understanding this would lead to development of a more selective therapeutic target.

### Developmental Stage

- Early

### Research Interest and Expertise

Hsp90 and several Hsp90 substrates or clients are upregulated in cancer cells; in recent years, Hsp90 has become an important therapeutic target for cancer treatment. PP5 is a major component of Hsp90 chaperone complexes. Using phosphoproteomic analyses, together with biochemical and cell biological studies, we are trying to determine the function, regulation, and substrates for PP5 complexed to Hsp90. We hypothesize that PP5, which in contrast to Hsp90 is a nonessential protein, potentially represents a more selective therapeutic target for upregulated Hsp90 chaperone complexes in cancer cells.

Rac1 is involved in cancer cell metastasis. We have shown that active Rac1 directly binds and stimulates PP5 in vitro and recruits PP5 to cell membranes. We are investigating the potential role of PP5 in Rac1-dependent metastasis.

## Kavita Shah

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Neurological Disorders

### Therapeutic Outcome

- Understanding the role of oncogenic kinases and their oncogenic targets as a potential clinical target. Particular interests are breast and prostate carcinomas.
- Understanding the mechanism of neurodegeneration in Alzheimer's Disease

### Developmental Stage

- Early

### Research Interest and Expertise

Our research is focused on dissecting the roles of oncogenic kinases (Aurora A, Aurora B) using chemical, genetic and chemical-genetic approaches. Aurora A is overexpressed in several types of cancers. Many small molecule inhibitors against Aurora A are in clinical trials. Our goal is to identify the direct oncogenic targets of Aurora A in prostate and breast cancer tissues using a chemical genetic approach developed in our laboratory.

The power of this approach emanates from engineered Aurora A's ability to selectively tag its substrates in the context of the cellular milieu containing numerous other kinases and substrates. We have identified several direct Aurora A substrates in prostate and breast cancer. We have documented ablation of a novel Aurora A substrate using RNAi abrogates tumor formation in nude mice, suggesting that it is a critical oncogenic effector of Aurora A and a potential clinical target. We are using this information for unraveling the molecular mechanisms of tumorigenesis and metastasis.

Our research also focuses on Alzheimer's Disease (AD). AD is a debilitating neurological disorder. The only available drugs for AD are symptomatic agents, which enhance cognitive states, but do not confer neuroprotection. Our goal is to understand the molecular mechanisms of neurodegeneration in AD. Our focus is Cyclin Dependent Kinase 5 (Cdk5), which shows significantly higher activity in AD brains. Our studies have revealed multiple neurotoxic roles of Cdk5 in AD. Elucidation of the mechanism by which Cdk5 promotes neurodegeneration is expected to reveal new targets for preventing or delaying neuronal degeneration.

## Cynthia Stauffacher

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Developing an understanding of molecular modification and their signaling and development of phosphatase inhibitors that affect the metastatic potential of tumor cells.

### Developmental Stage

- Early

### Research Interest and Expertise

Our laboratory is investigating the molecular modifications and their signaling consequences in the oncogene pair, HCPTP (human low molecular weight protein phosphatase) and EphA2 (ephrin A2) tyrosine kinase receptor. EphA2 receptor has been implicated in the metastatic transformation in a wide range of human cancers, with the phosphorylation state, controlled by HCPTP, a strong determinant of the transformed state of the cell. Using biophysical techniques ranging from mass spectroscopy to NMR and X-ray crystallography, we are exploring the interactions of these molecules and are in the process of developing phosphatase inhibitors that can be used to modulate these interactions and affect the metastatic potential of tumor cells.

## Andy Tao

### Category of Research

- Target Discovery

### Diseases

- Cancer
- Diabetes/Obesity/Metabolic Syndrome

### Therapeutic Outcome

- Developing discovery of biomarkers for drug targeting and imaging. Particular interests are breast and liver carcinomas.

### Developmental Stage

- Early

### Research Interest and Expertise

We are developing proteomic technologies to identify intracellular drug targets and novel therapeutic and imaging reagents based on dendrimers. We also are developing a set of techniques and reagents for the analyses of protein modifications using mass spectrometry, in particular phosphorylation, prenylation and degradation.

*Biomarker discovery:* We are pursuing proteomic approaches to identify protein biomarkers in serum/plasma as potential biomarkers.

## Elizabeth Taparowsky

### Category of Research

- Target Discovery

### Disease

- Cancer

### Therapeutic Outcome

- Understanding emerging biomolecular targets and pathways (AP-1) for novel therapeutic approaches. Particular interests are leukemia, lymphoma, and lymphoproliferative disease.

### Developmental Stage

- Early

### Research Interest and Expertise

The goal of our research is to establish how regulation of the AP-1 transcription factor, through natural or artificial means, may be applied to controlling human disease. Our group has generated mouse models in which the level of AP-1 activity is modulated in the immune system by expressing Batf — a native, immune system specific, negative regulator of AP-1. Mice in which Batf is overexpressed show altered development of NKT cells, hypergammaglobulinemia and lymphoid tumors that consist of polyclonal outgrowths of T cells. These phenotypes mimic human autoimmune lymphoproliferative syndrome (ALPS).

Mice in which Batf expression has been eliminated do not develop Th17 cells, and both T cell-dependent and T cell-independent antibody production are blocked due to a failure in class-switch recombination (CSR). These phenotypes mimic a number of human syndromes in which the pro-inflammatory response is impaired and/or the immune system is unable to fight routine infection. Our mouse models 1) have provided proof of principle that AP-1 is an emerging biomolecular target for these (and other) diseases and 2) can be used for *in vivo* testing of novel therapeutic approaches to manage these diseases.

## Val J. Watts

### Category of Research

- Target Discovery

### Diseases

- Infectious Diseases
- Neurological Disorders
- Psychiatry

### Therapeutic Outcome

- Treatment and prevention

### Developmental Stage

- Early and Intermediate

### Research Interest and Expertise

*Signaling mechanisms of G protein-coupled receptors (GPCRs) and adenylyl cyclases:* Fluorescent approaches to visualize and localize protein-protein interactions in living cells.

*Development of high throughput screening assays for allosteric modulators of human dopamine receptors and biogenic amine receptors in invertebrates:* This work has been done in collaboration with the National Institutes of Health, Department of Defense, and Vanderbilt Screening Center for GPCRs, Ion Channels, and Transporters.

## Daoguo Zhou

### Category of Research

- Target Discovery
- Drug Design and Delivery

### Disease

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Early

### Research interest and expertise

My research focuses on the cell biology of infectious diseases, in particular human intestinal diseases caused by pathogenic *Salmonella* and *E. coli*. These pathogens cause intestinal diarrhea and may lead to more serious systematic infections in humans. Both pathogenic *Salmonella* and *E. coli* utilize the type III protein secretion/translocation system (TTSS) to inject bacterial “effector proteins” into host cells to exploit host cell functions to survive in the hostile environment and cause inflammatory responses. We aim to understand the molecular and cellular mechanism of how these effectors function to enable the pathogens to circumvent our host immune system to cause diseases.

We currently have projects studying the role(s) of actin dynamics in *Salmonella* and *E. coli* infections and how bacterial effectors exploit the host ubiquitination pathways to induce inflammatory responses. Results from our study will not only advance our understanding the fundamental principles of bacterial pathogenesis, but also may aid the design of pharmaceutical drugs to prevent and treat bacterial infections and inflammatory responses.

# *drug design & delivery*



## **Stephen B. Adams**

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Infectious Diseases/Immune Disorders

### **Developmental stage**

- Intermediate

### **Research Interest and Expertise**

My interests are in developing and testing novel methods of local antimicrobial delivery for treatment of orthopedic infections which include septic synovitis and osteomyelitis. Currently involved in drug delivery using absorbable gels and non-absorbable delivery vehicles, intravenous and intraosseous regional limb perfusion, and use of continuous infusion pumps to delivery drugs directly to site of infections. Would like to develop a delayed absorbable (7-10 days) vehicle for delivery of antimicrobial and anti-inflammatory drugs directly into infected joints.

## Donald Bergstrom

### Category of Research

- Drug design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- Develop alkyl substituents for appendage to oligonucleotides for use as biological tools and potential therapeutic agents.
- Establish the potential of multivalent peptides and peptide assemblies as potential therapeutic agents. Our work establishes a new way to control this assembly and the potential for combining targeting, diagnostic and therapeutic peptides on a single self-assembling platform.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

We have developed alkyl substituents to append to oligonucleotides for use as biological tools and potential therapeutic agents. We see efficient cell uptake of dsDNA with the conjugation of two alkyl groups positioned adjacent to each other, mimicking the adjacent post-translational lipidation of proteins in nature that directs proteins to lipid rafts, in addition to facilitating uptake the alkyl modifications confer resistance to exonucleases. The invention, therefore, consists of the reagents used to make the modified oligonucleotides and any oligonucleotides containing them (single-stranded DNA, double-stranded DNA, single-stranded RNA, double-stranded RNA and any modifications of these containing modified bases, modified linkages or modified saccharides).

We have found that the self-association of peptide nucleic acids can be controlled by choice of sequence to assemble either into nanorings or into linear tetramers. This assembly has been characterized by following spectral changes on heating and cooling using UV spectroscopy. Characterization with atomic force microscopy and transmission electron microscopy shows that discrete ring-type particles are formed. We have discovered that peptide sequences can be appended to the PNA to create biologically active peptide decorated nanoparticles on assembly.

Cell uptake studies show that these nanoparticles readily translocate into cells and are not trapped in endosomal vesicles like most other nanoparticles. There is an extensive body of work that establishes the potential of multivalent peptides and peptide assemblies as potential therapeutic agents. Our work establishes a new way to control this assembly and the potential for combining targeting, diagnostic and therapeutic peptides on a single self-assembling platform.

## Arun Bhunia

### Category of Research

- Detection Technology
- Drug Design and Delivery
- Target Discovery

### Diseases

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Intermediate

### Research Interest and Expertise

- Pathogen and toxin detection:
  - Develop biosensor based rapid high throughput screening methods for detection of pathogens and toxins in food. Biosensors include laser light scattering, mammalian cell-based, microfluidic biochip and fiber optic.
  - Develop and optimize reagents including antibodies, receptors, ligands, microbiological growth media, etc. for biosensor applications.
- Pathogenic mechanism of enteric pathogens and control strategies using probiotics:
  - Understanding the molecular and cellular mechanism of intracellular *Listeria monocytogenes* colonization and translocation through epithelial barrier during intestinal phase of infection.
  - Prevention and control strategies using probiotic bacteria and antimicrobial peptide loaded biocompatible nano-carrier.

## Richard Borch

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- Design and synthesis of prodrugs that provide intracellular delivery of small molecule phosphates and phosphomimetics for use as a cancer therapy. (Drug: GGTI, MCAK, Lck SH2 ligand, Ape1/Ref1)

### Development Stage:

- Early

### Research Interest and Expertise

We are interested in the design and synthesis of prodrugs that provide intracellular delivery of small molecule phosphates and phosphomimetics of potential therapeutic interest. Prodrugs currently available include phosphatase inhibitors, prenyl transferase inhibitors, and compounds that target SH2 domains. We are also exploring mitotic centromere-associated kinesin (MCAK) as a novel cancer target and have developed selective inhibitors.

Many of our most potent phosphomimetic prodrugs are highly lipophilic and thus are not suitable for further in vivo development. We have developed novel polyamidoamine (PAMAM) dendrimer technology in which intracellular prodrug activation simultaneously releases the bioactive phosphomimetic from the dendrimer. Prodrugs with  $\log P > 5$  have been incorporated into dendrimers with  $\log P \sim 0$  in which the prodrugs retain bioactivity.

## Jean Chmielewski

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Cancer, neurodegenerative disease, HIV, malaria

### **Therapeutic Outcome**

- Developing agents and strategies to improve the brain penetration of anti-cancer and anti-neurodegenerative therapies
- Limit the formation of HIV reservoirs
- Overcome drug resistance in malaria

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

We have developed potent inhibitors of multidrug resistance transporters present at the blood-brain-barrier and within *P. falciparum* that effectively reverse drug resistance in cell culture and show efficacy in a brain capillary model.

## David Colby

### Category of Research

- Drug Design and Delivery
- Neurological Disorders

### Disease

- Cancer

### Therapeutic Outcome

- Synthesizing derivatives of natural products to selectively target cancer stem cells, with particular interests in leukemia and multiple myeloma (Drug: parthenolide analogs)

### Developmental Stage

- Early

### Research Interest and Expertise

We are synthesizing derivatives of natural products to understand structure-activity relationships. The application of this interest to cancer is to develop molecules that will selectively target populations of cancer cells, termed cancer stem cells. We also are developing new synthetic methodologies to modify the structure of complex natural products. Currently, parthenolide analogs are a focus of our work.

## Mark Cushman

### Category of Research

- Drug Design and Synthesis

### Diseases

- Cancer
- Infectious Diseases

### Therapeutic Outcome

- Design and synthesis of potential anticancer and chemopreventive agents. We currently have two drugs (LMP400 and LMP776, which are indenoisoquinoline inhibitors of topoisomerase I) in Phase 1 clinical trials at the National Cancer Institute. Inhibitors and modulators of a wide variety of chemopreventive targets are also being designed and synthesized, including NF $\kappa$ B, aromatase, quinone reductases 1 and 2, retinoid X receptor, and inducible nitric oxide synthase.
- Design and synthesis of potential antiviral agents and antibiotics. We are currently targeting flaviviral envelope proteins and HIV-1 reverse transcriptase, as well as OSB-CoA synthetase, lumazine synthase, and riboflavin synthase.

### Research Interest and Expertise

- Design and synthesis of potential therapeutic agents using medicinal chemistry approaches, including computer graphics molecular modeling and computational chemistry.
- Synthesis of hypothetical drug metabolites to confirm drugs metabolism pathways and provide metabolites for investigation of their pharmacological activities.

## Vincent Jo Davisson

### Category of Research

- Drug Design and Delivery
- Drug discovery platform technology
- Disease marker development

### Diseases

- Cancers: breast, bone, colon, ovarian, and prostate carcinomas
- Neurological Disorders

### Therapeutic Outcome

- Novel ligands for tumor targeting
- Pharmacodynamic biomarkers
- Lead compounds

### Development Stage

- Early to intermediate drug targeting
- Intermediate translation of molecular marker
- Early molecular target testing/validation

### Research Interest and Expertise

- *Emerging biomolecular targets*: Molecular design and synthesis of ligands for non-druggable protein-protein interactions and allosteric modulation of signaling proteins; V-ATPase antagonists to control metastatic progression, mitochondrial regulation by functional agonism or antagonism of Bak-Bax, selective modulation of DNA replication/repair systems by functional antagonism of PCNA; selected heat shock protein interactions
- *Biomarker panels for early-stage cancers*: Integration of cytometric, proteomic, genomic analyses for biomarker panels useful in diagnosis
- *Development of screening platforms*: Innovative pharmacodynamic screens for hit to lead optimization and de-replication; multi-parameter/high content and high through put cell-based screens; proteomic and genomic assay systems for target-pathways and specific post-translational modifications; phenotype genome-wide screens; animal models for testing anti-metastatic drugs; in vitro 3D tumor models for predictive high content screening platform
- *Tumor targeting and cellular localization*: Synthetic ligand discovery for Eph and EGFR family receptors, ligands for targeting vesicle transport systems (mitochondria, ER, or nucleus); drug-conjugates for tumor and cell compartment localization
- *Compounds with novel tumoristatic or cytoprotective activities*: Selective effects of polyunsaturated fatty acids; statin cogeners for tumor down-regulation; protective agents to prevent mitochondrial damage and intrinsic apoptosis

## **R. Edwin García**

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Cancer
- Infectious Diseases
- Neurological Disorders
- Diabetes/Obesity/Metabolic syndrome

### **Developmental Stage**

- Intermediate

### **Research Interest and Expertise**

Our group is interested in the development, integration, and application of discrete and continuous analytical and numerical models to predict the processing-properties relationships and the mechanical reliability of pharmaceutical tablets. Of great interest is also the development of models and theories to design the dissolution kinetics of pharmaceutical materials.

## **Arun Ghosh**

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Cancer
- Infectious Disease/Immune Disorders
- Neurological Disorders

### **Therapeutic Outcome**

- We are carrying out synthesis and biological evaluation of structurally diverse natural product-based anticancer agents, with particular interest in ovarian, breast, colorectal, and prostate carcinomas (Drug: peloruside, folate-laulimalide).

### **Developmental Stage**

- Early to intermediate

### **Research Interest and Expertise**

Our work emphasizes structural modification, design of molecular probes, and investigation of biological mechanism of actions. At present, we are involved in the design and synthesis of laulimalide and peloruside-based molecular probes for locating drug-binding sites of these two very potent microtubule stabilizing agents on tubulin.

## Richard Gibbs

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- Employs chemical biology approaches to address key questions in the field of protein prenylation. This work has significant therapeutic potential, due to the necessity for protein prenylation in many crucial signaling proteins, with particular interest in pancreatic cancer (Drug: GGTI, IcmtI, Carboxychroman).

### Developmental Stage

- Early

### Research Interest and Expertise

Icmt is an enzyme that methylates the carboxyl terminus of Ras, a key oncogene product, and many other key signaling proteins. Mouse knockout studies provide evidence that Icmt is a promising anti-cancer drug target. In collaboration with Dr. Christine Hrycyna and Dr. Marietta Harrison at Purdue, the Gibbs laboratory has developed the most potent Icmt inhibitors yet developed, with nanomolar IC50 values. These compounds have exhibited promising preliminary anti-cancer activity, and we are in a uniquely strong position in this field.

The Gibbs laboratory has developed new stereospecific routes to isoprenoids to synthesize novel, specifically substituted analogues of FPP, the isoprenoid substrate of FTase. This program led to the development of a series of potent inhibitors of FTase. In a collaborative effort with Dr. Richard Borch's laboratory, the Gibbs laboratory has developed prodrug variants of these compounds, in an attempt to enhance their *in vivo* activity. There are preliminary indications that these analogues may exert their effects through a novel mechanism — the selective modulation of the prenylation of a subset of prenylated proteins — in combination with statin treatment. Efforts to determine their mechanism of action are underway, in collaboration with pharmacologists at Wayne State University.

The Gibbs laboratory has developed unique chemical tools and methods that allow for the quantitation of protein prenylation in drug-treated cells, and also for the determination of the identity of prenylated proteins in a drug-treated cell. These methods will be useful for pharmacodynamic evaluation of the agents developed as described in 1) and 2) above, and for the evaluation of the effects of other drugs (such as statins or bisphosphonates) on protein prenylation in cells or *in vivo*.

## **Bumsoo Han**

### **Category of Research**

- Drug Design and Delivery

### **Disease**

- Cancer

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

Although many potent anti-cancer drugs have been developed, the efficacy of these agents is significantly limited because of the drug resistance of tumor at both cellular and tissue levels. My research focuses on the characterization and manipulation of the drug transport within the interstitial space and across the cellular membrane in order to overcome the chemo-resistance.

Current research tasks include the enhancement of drug delivery for thermally treated tumors, and the development of drug carrier for enhanced drug transport in mucus. In addition to enhancing drug delivery, high-throughput screening and toxicity test platforms are being developed using microfluidic and microfabrication technologies.

## Catherine Hill

### Category of Research

- Target Discovery
- Drug Design and Delivery

### Diseases

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Early
- Intermediate

### Research Interest and Expertise

Discovery and development of new, safer insecticides to control arthropod (mosquito and tick) vectors of human and animal disease. Research efforts focus on arthropod genome mining, target-based drug discovery and chemical compound screening against arthropod G-protein coupled receptor targets.

## **Daniel F. Hogan**

### **Category of Research**

- Drug Design and Delivery
- Pre-clinical animal models

### **Diseases**

- Antithrombotic
- Cardiovascular
- Thrombosis

### **Developmental Stage**

- Intermediate

### **Research Interest and Expertise**

Cardiovascular therapeutics including heart failure and antithrombotics. We have expertise in veterinary clinical trials, pre-clinical animal trials, and animal modeling.

## Christine Hrycyna

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

The two major cancer research areas in our laboratory focus on:

- 1) the human isoprenylcysteine carboxyl methyltransferase (Icmt) and
- 2) the human ATP binding cassette (ABC) transporters ABCG2 and P-glycoprotein.

Using the tools of biochemistry, cell and molecular biology, organic synthesis and bioanalytical chemistry, we are investigating the mechanisms of activity, assembly, trafficking and cellular localization of these membrane-associated proteins as well as developing drugs that inhibit their activities. Particular interests are brain and pancreatic carcinomas (Drug: IcmtI).

### Development Stage

- Early to intermediate

### Research Interest and Expertise

*Icmt*: Mutations in the *K-Ras* oncogene are the key causative agents in >85% of human pancreatic cancers. Isoprenylcysteine carboxyl methyltransferase (Icmt) catalyzes the posttranslational methylesterification of the K-Ras protein. Recent biological studies have demonstrated that inhibition of Icmt results in the mislocalization and loss of transforming ability of K-Ras. Therefore, Icmt provides an attractive and novel anti-cancer target. The goals of our research, in collaboration with the Gibbs laboratory, are to develop potent and efficacious Icmt inhibitors for treatment of pancreatic cancer. We have developed in vitro biochemical and cellular assays for Icmt inhibition, and are currently collaborating with Dr. Stephen Konieczny on determining the efficacy of our compounds in 3D cell culture models and in a mouse model of pancreatic cancer.

*ABC Transporters*: The blood-brain barrier presents a major hurdle to delivering therapeutic molecules to the brain. The Hrycyna laboratory, in collaboration with the Dr. Jean Chmielewski laboratory, is investigating general approaches to increase the bioavailability of agents targeted against brain cancer by reversibly modulating the activity of P-glycoprotein and ABCG2 at the blood brain-barrier. We have developed in vitro biochemical and cellular assays for P-glycoprotein and ABCG2 inhibition. In collaboration with Dr. David S. Miller (NIEHS/NIH), we are testing our lead compounds for efficacy in a rat brain capillary transport assay as well as in a rat brain perfusion model. The ultimate goal of this research is to improve the penetration and concentrations of therapeutic drugs in the brains of humans to improve the clinical efficacy of these cancer treatments.

## Peter T. Kissinger

### Category of Research

- Drug Design and Delivery
- Detection Technology
- Pharmacokinetics/pharmacodynamics

### Diseases

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Obesity/Metabolic Syndrome/Diabetes

### Developmental stage

- Intermediate
- Late

### Research Interest and Expertise

My interests are in intact mammalian pharmacology and the process of drug development as related to improved protocols for animal work and the related bioanalytical chemistry for drugs, their metabolites and biomarkers. I have unique experience with several contract research organizations and instrument companies in the drug development space from mice to humans. I endeavor to connect drug developer interests with unique Purdue resources as well as other commercial firms that can help achieve an optimum solution to problems of drug formulations design and resulting mammalian responses — both pharmacological and physiological. My enthusiasms are not disease specific and have ranged from cancer to neuroscience, diabetes and HIV. Tissue imaging with mass spectrometry, processing dried blood spots with mass spectrometry, LC/MSMS, automated sampling of biological fluids from conscious freely moving animals, electrochemical biosensors (glucose), in vivo microdialysis sampling devices and Phase I/IIa clinical trials all remain areas of interest.

## Deborah Knapp

### Category of Research

- Pre-clinical (pre human) in vivo evaluation of agents to prevent and treat cancer

### Disease

- Cancer

### Therapeutic Outcome

- Our research in the Purdue University School of Veterinary Medicine involves a unique approach to studying the causes of cancer development and progression, and to investigating novel approaches for cancer prevention, early detection, and treatment. We study dogs with specific forms of naturally-occurring cancer in which the cancer closely mimics the human condition. Studies are conducted in the dogs that provide benefit to the dogs and that lead to translation of important findings into human trials. One of our major focus areas is invasive urinary bladder cancer. We also work with colleagues in our department, doing comparative research in brain cancer and with non-Hodgkin lymphoma.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

In our focus area of invasive urinary bladder cancer, we are defining heritable (through very strong dog breed-associated risk) and environmental risk factors for the cancer. This will facilitate cancer prevention research in a highly relevant model in a very timely fashion. Because prevention studies in dogs can be performed in 1-3 years, dog studies can be used to select the most promising approach for the longer-term (15+ years) human studies. Our group also studying cancer treatments including nanoparticles (in collaboration with Dr. James Leary), folate targeted therapy (in collaboration with Dr. Philip Low), demethylating agents (in collaboration with Dr. Noah Hahn, Indiana University School of Medicine) and with already established drugs (cyclooxygenase inhibitors, oral chemotherapies) being applied in a more effective dosing schedule.

## James Leary

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- We are developing multilayered, multifunctional, targeted nanoparticles with diagnostic and therapeutic (*theragnostic*) capabilities. We also are developing single cell analysis technologies, with particular interests in breast, prostate and bladder carcinomas.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

We design and build complex, multifunctional nanoparticles containing iron oxide cores for MRI contrast agents and near infrared fluorescent probes for fluorescent imaging for either diagnostics or for fluorescence-guided surgery. The nanoparticles generally contain either drugs (e.g., doxorubicin) or peptides (e.g. apoptosis-inducing peptides). We also design gene delivery systems with feed-back controlled molecular biosensors to provide steady-state control of cells for regenerative medicine.

For in-vitro and ex-vivo developmental steps in designing and testing nanomedical systems, our lab has world-class expertise in quantitative single cell analysis technologies, including high-speed, multicolor flow cytometry and interactive (laser ablation or laser-optoinjection) scanning image cytometry for high-throughput analysis of nanoparticle-tissue interactions. With our collaborator, Dr. Deborah Knapp, we are doing in-vivo experiments on animal systems, including a highly human-relevant bladder cancer model system in dogs. With collaborator, Dr. Sophie Lelievre, we are doing testing of magnetic field-directed nanomedical systems for human ductal breast cancer using 3D tissue engineering and cell-lined microfluidic channel models prior to future animal testing.

## Mark Lipton

### Category of Research

- Drug Design and Delivery

### Diseases

- Cancer
- Infectious Diseases/Immune Disorders
- Obesity/Metabolic Syndrome/Diabetes

### Developmental Stage

- Early

### Research Interest and Expertise

Our group's activities include the design, synthesis and testing of small molecules against select targets. Our tools include those of computerized molecular modeling, organic synthesis and in vitro testing. Our current targets include molecules that prevent HIV-1 infection and novel inhibitors of the enzymes quinone reductase II and HMG CoA reductase.

## Philip Low

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- Developing targeting ligands that will deliver attached therapeutic and imaging agents selectively to cells responsible for specific pathologies. Particular interests are breast, prostate, lung, ovarian, endometrial, kidney, and colorectal carcinomas. (Drug: folate-laulimalide, DUPA-Tc99, EC-489, BMS-753493, EC-225, EC-145, EC-20, EC-17)

### Developmental Stage

- Late

### Research Interest and Expertise

To date, we have developed targeted therapeutic and/or imaging agents for a variety of cancers (e.g. ovarian, lung, kidney, endometrial, breast, and prostate), several inflammatory diseases (rheumatoid arthritis, Crohn's disease, osteoarthritis, organ transplant rejection, psoriasis, etc.), diabetes, atherosclerosis, and a variety of infectious diseases (e.g. influenza virus, Staphylococcus, Pseudomonas, etc.). Six targeted drugs stemming from research in my lab are currently undergoing human clinical trials (mainly at Endocyte, Inc., a company that I founded).

*Interests include:* Imaging of malignant diseases; isolation and analysis of circulating tumor cells; fluorescence guided surgery using tumor-targeted fluorescent dyes; and personalized medicine.

## **Zhao-Qing Luo**

### **Category of Research**

- Drug Design and Delivery
- Target Discovery

### **Disease**

- Infectious Diseases/Immune Disorders

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Infectious disease and immunology

## Suresh Mittal

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

- Development of adenovirus vectors for gene therapy and immunotherapy, with a particular interest in breast cancer.

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

*Adenovirus vectors as a delivery vehicle for cancer gene therapy:* We are developing human, nonhuman, and chimeric adenovirus vectors for cancer gene therapy.

*Evaluation of the role of EphA2 activation or inhibition in breast cancer therapeutics using adenovirus vectors:* Overexpression of the receptor tyrosine kinase, EphA2, occurs in the majority of invasive breast cancers, and successful binding to its ligand Ephrin-A1 has been shown to restore normal cellular functions. In normal breast cells and other adult epithelial cells, EphA2 is expressed at considerably low levels and is associated with its ligand, whereas in breast cancer cells, EphA2 is overexpressed and its significant amounts are not associated with its ligand. Therefore, EphA2 provides a unique cancer cell target for breast cancer intervention by adenovirus vectors. We have demonstrated *in vitro* (human or murine mammary tumor cells) and *in vivo* (mouse models) systems that EphA2-EphrinA1 interaction results in apoptosis of tumor cells leading to suppression in tumor growth.

*Development of anti-tumor cytotoxic T cells by immunotherapy:* We also are working on a strategy to enhance anti-tumor cytotoxic T cells by immunotherapy using adenovirus vectors.

## Angus Murphy

### Category of Research

- Drug Design and Delivery

### Diseases

- Cancer
- Cystic Fibrosis

### Therapeutic Outcome

- Improved efficacy of existing therapeutics by limiting ABC-mediated drug efflux, discovery of improved CFTR correctors

### Developmental Stage

- Early

### Research Interest and Expertise:

The focus of research in the lab is on the structural characteristics that determine the specificity of substrate affinity in ABC transporters and the mechanisms that regulate folding and maturation of ABC transporters. Work on substrate specificity utilises comparisons of substrate-specific plant and fungal ABC transporters with promiscuous mammalian orthologs to identify amino acid motifs that associated with substrate specificity. This work includes screens of compounds that competitively or noncompetitively inhibit the transporters in plants and fungi, since such screening can take place more rapidly in these organisms.

The lab also investigates mutations and drugs that affect the folding and maturation of ABC transporters. The primary areas of investigation are interactions of the C-termini of ABC transporters with the FK506 binding immunophilins such as FKBP8/38/42 and mechanisms that regulate the sterol packing of ABCB transporters in the trans Golgi and plasma membrane. Several classes of compounds that impact these interactions have been identified in the lab.

## **Eric A. Nauman**

### **Category of Research**

- Detection Technology
- Drug Design and Delivery

### **Diseases**

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Cardiovascular

### **Developmental Stage**

- Early
- Intermediate
- Late

### **Research Interest and Expertise**

Dr. Nauman is the director of the Human Injury Research and Regenerative Technologies (HIRRT) laboratory and his primary research interests are focused on biological problems in which the cellular and tissue level mechanical loading environments and the transport of bioactive molecules are relevant. We emphasize the development of well-defined experimental protocols with advanced statistical and computational simulations in order to evaluate cell function in response to various types of insults. Applications include the repair of vital organs, the development of novel cancer treatments, and the primary and secondary injury patterns of the central nervous system.

## **David E. Nichols**

### **Category of Research**

- Drug Design and Delivery

### **Disease**

- Neurological Disorders

### **Therapeutic Outcome**

- Palliative symptom relief

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Medicinal chemistry
- Drug design
- Neuropharmacology

## Kinam Park

### Category of Research

- Drug Design and Delivery

### Diseases

- Cancer
- Diabetes/Obesity/Metabolic Syndrome
- Cardiovascular

### Therapeutic Outcome

- Developing micelles for tumor targeting and protein delivery systems using homogeneous microparticles. Particular interests are breast and brain carcinomas.

### Developmental Stage

- Intermediate

### Research Interest and Expertise

*Adaptable polymer micelles for tumor targeting:* Tumor targeting is one of the most important and extensively studied areas, but it is still poorly understood. One of the limiting factors in tumor targeting is that only a small fraction of the drug loaded in the nanocarriers is actually delivered to the target site because of the instability of most nanocarriers in the blood and elimination by the reticuloendothelial system. Our approach is to develop nanocarriers that hold the drug until they reach the target site, and — using adaptable nanoparticles, such as polymer micelles, elastic polymer particles and drug nanocrystals — only release drugs within the target when specific enzymes are present.

*Long-term protein delivery systems using homogeneous microparticles:* Protein drugs with anticancer activity (e.g., Avastin) have been essential in treating various tumors, and yet the long-term delivery ranging from weeks to months has not been easy. We use the newly developed hydrogel template-based nanofabrication methodology to prepare nano/micro particles for more efficient long-term delivery of protein drugs. The duration of protein delivery can range from weeks to several months.

## **Rodolfo Pinal**

### **Category of Research**

- Drug Design and Delivery

### **Disease**

- Cancer

### **Developmental Stage**

- Intermediate

### **Research Interest and Expertise**

- Methods for enhancing the bioavailability of poorly soluble drug candidates, especially those compounds that do not solubilize in water nor in oils
- Studies of the effect of formulation additives on exposure

## **P.V. Ramachandran**

### **Category of Research**

- Drug Design and Synthesis

### **Diseases**

- Cancer
- Neurological Disorders

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- Organic synthesis of simple and complex biologically active molecules, Enantioselective synthesis, synthesis of fluorinated medicinal molecules

## **Timothy L. Ratliff**

### **Category of Research**

- Drug Design and Delivery
- Target Discovery

### **Disease**

- Cancer

### **Developmental Stage**

- Early
- Intermediate

### **Research Interest and Expertise**

Dr. Ratliff's research is directed toward the understanding of the role of the immune response in cancer. Studies are directed toward understanding inflammation and its role in cancer development and progression, and the development of effective immunotherapy treatments for prostate and bladder cancer. These studies address questions regarding activation of anti-tumor responses, characterization of immunological tumor killing mechanisms, and the regulation of anti-tumor immunity. The laboratory also uses genetically modified mice to study the mechanisms by which tumor cells escape recognition by the immune response. The genetically modified mice also provide a model for better understanding the role of inflammation in the development and progression of prostate cancer. The bladder cancer studies focus on targeting bladder cancer cells with a specific protein known to be an important binding protein. The targeting studies will incorporate nanotechnology for the delivery of therapeutic agents.

## **Garth Simpson**

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Cancer
- Neurological Disorders
- Infectious Diseases
- Obesity/Metabolic Syndrome

### **Research Interest and Expertise**

Our contributions to drug design are based on providing enabling tools for structural biological efforts to better characterize the target. Specifically, nonlinear optical imaging of chiral crystals enables ultrasensitive detection and characterization of protein microcrystals to facilitate a key step in the protein structure determination pipeline. Our approach appears to address nicely a real and important bottleneck.

Our contributions to drug delivery are focused primarily on development of tools for characterizing drug formulations to enhance bioavailability. Approximately 40% of drug targets are abandoned due to poor solubility, which in turn can negatively impact bioavailability. Nonlinear optical imaging provides a ~8 order of magnitude improvement in the detection of crystal formation in powdered samples and a comparable linear dynamic range. These measurement capabilities enable substantial reductions in the timeframe required for shelf-life assessments and allow the development and validation of quantitative models for predicting the outcomes of preparations.

## Lynne Taylor

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Cancer
- Neurological Disorders
- Infectious Diseases/Immune Disorders
- Obesity/Metabolic Syndrome/Diabetes
- Cardiovascular

### **Developmental Stage**

- Early
- Intermediate
- Late

### **Research Interest and Expertise**

Formulation of poorly water soluble compounds to improve solubility in particular by making amorphous dispersions. General solid state characterization of new compounds. Formulation approaches based on solid state properties of compounds.

## David Thompson

### Category of Research

- Drug Design and Delivery

### Disease

- Cancer

### Therapeutic Outcome

Research efforts in the Thompson group address problems in:

- 1) high-throughput screening for membrane-associated methyl transferases
- 2) bioresponsive polymer and nanoparticle carriers of nucleic acid therapeutics
- 3) microfabricated particles for drug and gene delivery to glioblastoma and bladder tumor tissue

### Developmental Stage

- Early to intermediate

### Research Interest and Expertise

An interferometric method has been developed for detection of methyl transferase substrate turnover that exhibits low picomolar detection sensitivity. This batchwise method is currently undergoing evaluation for translation to two different high-throughput analysis platforms.

Two different families of pendant polymer and polyrotaxane materials that degrade within acidic endosomes have been developed for delivery of pDNA and siRNA to target cells. These materials deliver their nucleic acid cargo with high efficiency while displaying exceptionally low cytotoxicity in multiple cell lines. Several different RNAi strategies for oncologic intervention are under investigation.

Templated microfabrication of degradable nanoparticles bearing small molecule therapeutics and antitumor DNA vaccines are under investigation. Particles produced through this scalable method are being modified with target ligands that will promote their association with bladder tumor and glioblastoma cells in animal models of disease.

## **Elizabeth M. Topp**

### **Category of Research**

- Drug Design and Delivery

### **Diseases**

- Autoimmune Disorders
- Cancer
- Cardiovascular disease
- Diabetes/Obesity/Metabolic Syndrome
- Infectious Diseases

### **Therapeutic Outcome**

- Elimination of disease or amelioration of symptoms

### **Developmental Stage**

- Late

### **Research Interest and Expertise**

The group's primary interests are in the formulation and stability of protein drugs in solution and amorphous solids. Methods include a variety of chemical and biophysical techniques, including the mass spectrometric analysis of degradants and glycoforms and the application of hydrogen/deuterium exchange with MS analysis to assess protein structure.

## Alexander Wei

### Category of Research

- Drug Design and Delivery

### Diseases

- Cancer
- Infectious Diseases

### Therapeutic Outcome

- Developing nanoprobes that can be coupled with drug action or drug delivery, with particular interests in breast and ovarian carcinomas.
- Targeting ligands for pathogen detection and treatment, with particular interests in respiratory-tract and sexually transmitted infections.

### Developmental Stage

- (Cancer) Early/metastatic
- (Infectious Diseases) Rapid detection

### Research Interest and Expertise

We are developing nanoparticle-based systems that can be triggered to release localized thermal or acoustic responses that can be coupled with drug action or siRNA delivery. Combination therapies based on synergistic physical and chemical activities are intended to reduce loading requirements for therapeutic effects. We are also developing multifunctional nanoprobes to measure changes in the biomechanical properties of tumor cells and tissues. Biomechanical changes may be prognostic of tumor cell proliferation, EMT, and the onset of metastasis, and serve as a metric for early-stage tumor progression.

Low molecular weight compounds such as glycans are being developed as targeting ligands for pathogenic microorganisms that bind to cell-surface carbohydrates, often the first step toward infection. We have a particular interest in oligosaccharides with specific sulfation patterns, which are being synthesized and screened against heparin-binding proteins and pathogens.

## Daoguo Zhou

### Category of Research

- Target Discovery
- Drug Design and Delivery

### Disease

- Infectious Diseases/Immune Disorders

### Developmental Stage

- Early

### Research interest and expertise

My research focuses on the cell biology of infectious diseases, in particular human intestinal diseases caused by pathogenic *Salmonella* and *E. coli*. These pathogens cause intestinal diarrhea and may lead to more serious systematic infections in humans. Both pathogenic *Salmonella* and *E. coli* utilize the type III protein secretion/translocation system (TTSS) to inject bacterial “effector proteins” into host cells to exploit host cell functions to survive in the hostile environment and cause inflammatory responses. We aim to understand the molecular and cellular mechanism of how these effectors function to enable the pathogens to circumvent our host immune system to cause diseases.

We currently have projects studying the role(s) of actin dynamics in *Salmonella* and *E. coli* infections and how bacterial effectors exploit the host ubiquitination pathways to induce inflammatory responses. Results from our study will not only advance our understanding the fundamental principles of bacterial pathogenesis, but also may aid the design of pharmaceutical drugs to prevent and treat bacterial infections and inflammatory responses.

# *Other*

## **Richard Borgens**

### **Disease**

- Neurological Trauma

### **Therapeutic Outcome**

- Improved nerve conduction, improved quality of life

### **Developmental Stage**

- Early stage, pre-IND

### **Research Interest and Expertise**

The Center for Paralysis Research and Department of Industrial and Physical Pharmacy focus on neurological trauma, endeavoring to discover and develop drugs for the treatment of spinal cord injuries.

## **Keith J. Bowman**

### **Category of Research**

- Tablet processing, crystallization and amorphization

### **Disease**

- Any treated by oral solids

### **Developmental Stage**

- Late

### **Research Interest and Expertise**

- Mechanical processing and properties of active ingredients and excipients
- Thermal and mechanical affects on crystalline solids
- X-ray diffraction

## **Stephen Byrn**

### **Disease**

- Neurological Trauma

### **Therapeutic Outcome**

- Improved nerve conduction, improved quality of life

### **Developmental Stage**

- Early stage, pre-IND

### **Research Interest and Expertise**

The Center for Paralysis Research and Department of Industrial and Physical Pharmacy focus on neurological trauma, endeavoring to discover and develop drugs for the treatment of spinal cord injuries.

## **Michael Childress**

### **Category of Research**

- Use of naturally occurring cancers in dogs and cats as preclinical models with translational relevance to human cancers. This potentially encompasses all categories of research listed (target discovery, drug design/delivery, detection technology).

### **Disease**

- Cancer

### **Therapeutic Outcome**

- Establish proof-of-concept for novel therapies or diagnostics (i.e. demonstrate that a molecular pathway can be targeted in a canine or feline cancer and that this is relevant to equivalent human cancers)

### **Developmental Stage**

- Early

### **Research Interest and Expertise**

- My primary research interest is in canine and feline hematopoietic neoplasia, particularly canine lymphomas. I am a board-certified veterinary oncologist with extensive experience in the clinical management of canine and feline cancers.

## Peter Constable

### Category of Research

- Clinical studies in target species or animal models

### Diseases

- Cardiovascular Disease (in vivo toxicity and mechanism of action) in pigs, dogs, horses, and calves
- Gastrointestinal Disease (oral rehydration solutions for diarrhea, prokinetics for improving gastric emptying and gastrointestinal motility)
- Infectious Diseases (pharmacokinetics of antimicrobial drugs)
- Metabolic Syndrome in dairy cattle
- Shock (animal models)

### Therapeutic Outcome

- Effective treatment of infectious diseases
- Increased gastric emptying
- Shock resuscitation

### Developmental Stage

- Late

### Research Interest and Expertise

- GLP experience and studies with pharmaceutical companies
- Extensive experience with in vivo assessment of cardiovascular toxicity (FDA/USDA funded studies)
- Developed sensitive in vivo model for assessing prokinetic agents (increase gastric emptying rate)
- Biostatistics and experimental design
- Pharmacokinetic analysis/modeling
- Acid-base physiology

## Gregory Knipp

### Category of Research

- Biopharmaceutics

### Diseases

- Diabetes/Obesity/Metabolic Dyndrome
- Effects of xenobiotics on pregnancy and fetal outcomes
- Infectious Diseases
- Neurodevelopmental Disorders

### Developmental Stage

- Early
- Intermediate

### Research Interest and Expertise

Our laboratory's interest lies in the molecular and functional characterization of human intestinal oligopeptide transporters, the effect of xenobiotics on placental fatty acid homeostasis and fetal development, and the effects of processing induced dosage form variation on clinical performance in the porcine model. We have performed research at both the early developmental stages for lead candidate selection based on *in vitro* permeability to the intermediate stages, where we have investigated the *in vivo* preclinical impact of formulation factors on PK in animal models.

## Barrak Pressler

### Category of Research

- Toxicity and efficacy studies in laboratory animals or dogs and cats with naturally-occurring diseases

### Diseases

- Immunosuppressants
- Infectious Diseases
- Kidney and lower urinary tract diseases
- Pulmonary Diseases

### Developmental Stage

- Intermediate to late (Bench-top drug development has been completed, but toxicity or efficacy studies are required in laboratory animals or naturally-occurring domestic animal disease models prior to beginning trials in people.)

### Research Interest and Expertise

I am a veterinarian who has completed advanced training and am now a board-certified diplomate of the American College of Veterinary Internal Medicine (ACVIM) in the specialty of small animal internal medicine; there are currently only about 1,300 certified specialists in this field, with the majority practicing in the United States and Canada, and only eight in the entire state of Indiana. Board certification means that I am considered an expert in the diagnosis and treatment of endocrine, gastrointestinal, hematologic, immune-mediated, urinary tract, and infectious disease disorders of dogs and cats. When general practice veterinarians treat a pet dog or cat with a rare illness, encounter symptoms for which a cause cannot be found, or diagnose the pet with an illness for which highly specialized treatments are needed, have the option of either calling me here at Purdue for advice or sending their pets to me and my colleagues for further treatment.

Although I am considered an expert in all of these fields, I am one of only about 50 ACVIM specialists who have been inducted into the Society of Veterinary Nephrology and Urology based on my mastery of and original research in the area of kidney disease. My expertise in immune-mediated and infectious diseases is derived from my PhD in immunology, where in addition to dogs and cats I worked with several rodent models of human disease. In short, any investigators in the area of drug discovery who are in need of a consultant or collaborator prior to beginning toxicity or efficacy studies in laboratory animals, or who are in search of a naturally-occurring dog or cat model of disease and would like to set up a clinical trial using animals at the veterinary school, should feel free to contact me. Examples of previous and on-going drug discovery or related research areas include investigation of novel anti-fungal delivery systems for treatment of Candida bladder infections; early diagnosis of kidney damage via use of novel laboratory assays or instruments in both laboratory animals with induced kidney disease or client-owned animals with naturally-occurring diseases; collaboration on optimization of immunosuppressive protocols in dogs with naturally-occurring immune-mediated hemolytic anemia and idiopathic thrombocytopenic purpura.

## **Riyi Shi**

### **Disease**

- Neurological Trauma

### **Therapeutic Outcome**

- Improved nerve conduction, improved quality of life

### **Developmental Stage**

- Early stage, pre-IND

### **Research Interest and Expertise**

The Center for Paralysis Research and Department of Industrial and Physical Pharmacy focus on neurological trauma, endeavoring to discover and develop drugs for the treatment of spinal cord injuries.

## **Daniel Smith**

### **Disease**

- Neurological Trauma

### **Therapeutic Outcome**

- Improved nerve conduction, improved quality of life

### **Developmental Stage**

- Early stage, pre-IND

### **Research Interest and Expertise**

The Center for Paralysis Research and Department of Industrial and Physical Pharmacy focus on neurological trauma, endeavoring to discover and develop drugs for the treatment of spinal cord injuries.

## Jonathan Wilker

### Category of Research

- Surgical adhesives, bone cements, and dental glues

### Diseases

- Surgical materials and methods

### Developmental Stage

- Early
- Intermediate

### Research Interest and Expertise

New biomaterials are needed for developing robust surgical adhesives, dental glues and bone cements. No synthetic materials are currently available to provide simultaneous wet adhesion and strong bonds without toxicity. The adhesives and cements of marine organisms such as mussels, barnacles and oysters provide inspiration for such applications development. Our lab is characterizing these biological materials, developing synthetic mimics, and formulating new biomedical materials. Beyond adhesion, these bioinspired, cross-linking polymers may provide suitable matrices for drug delivery and tissue engineering.

## **Wei Zheng**

### **Category of Research**

- New category of drugs

### **Diseases**

- Manganism
- Parkinson's disease

### **Therapeutic Outcome**

- Relieve syndromes

### **Developmental Stage**

- Intermediate
- Late

### **Research Interest and Expertise**

- Metal chelation therapy
- Drug transport across the blood-brain barrier



**OFFICE OF THE VICE PRESIDENT FOR RESEARCH**

Hovde Hall  
610 Purdue Mall  
West Lafayette, IN 47907-2040  
OVPR@purdue.edu  
Phone: 765-494-9806  
Fax: 765-496-7474

EA/EOU  
Produced by the Office of the Vice President for Research, revised March 2011