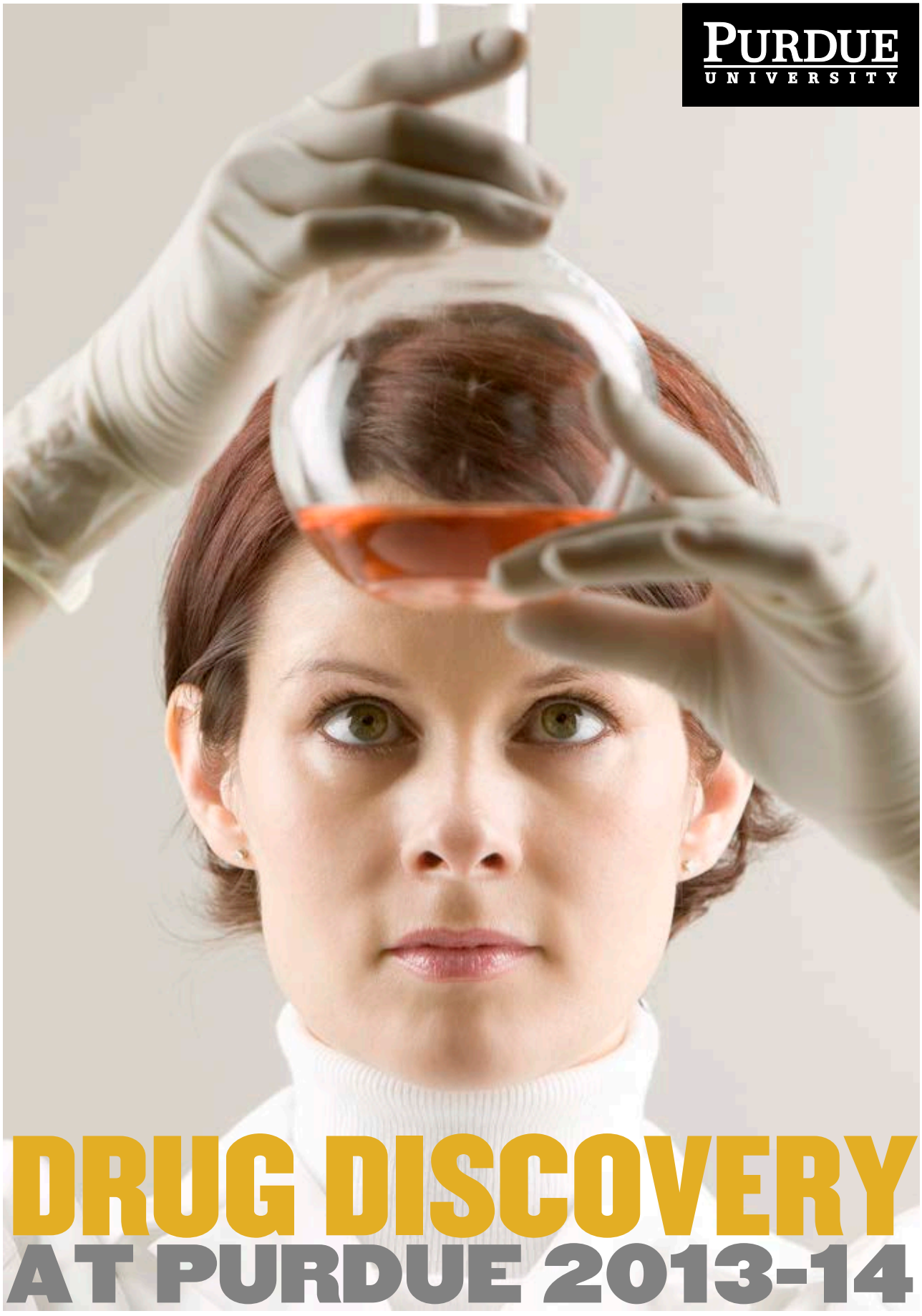
PURDUE
UNIVERSITY

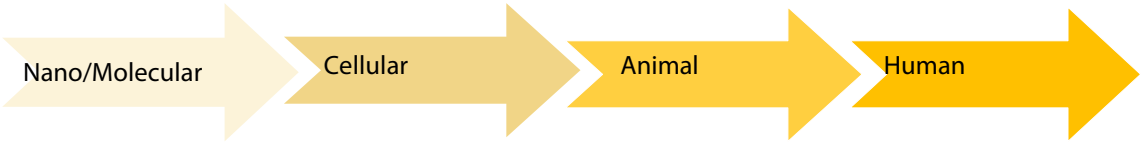


DRUG DISCOVERY
AT PURDUE 2013-14

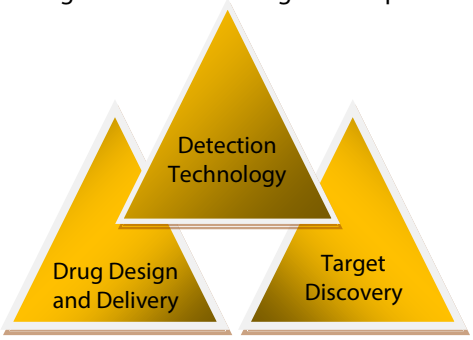
TABLE OF CONTENTS

INTRODUCTION

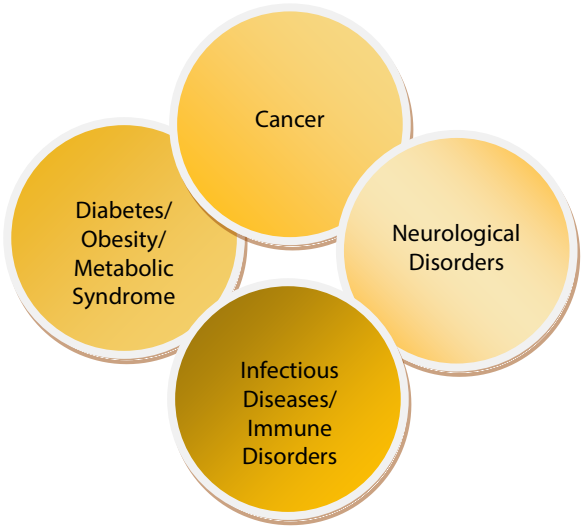
The drug discovery process at Purdue University begins at the nano level and ends with a viable human therapy that can reduce mortality and morbidity of disease. There is a considerable effort in enhancing our portfolio of novel and innovative drug candidates to treat chronic and acute illnesses.

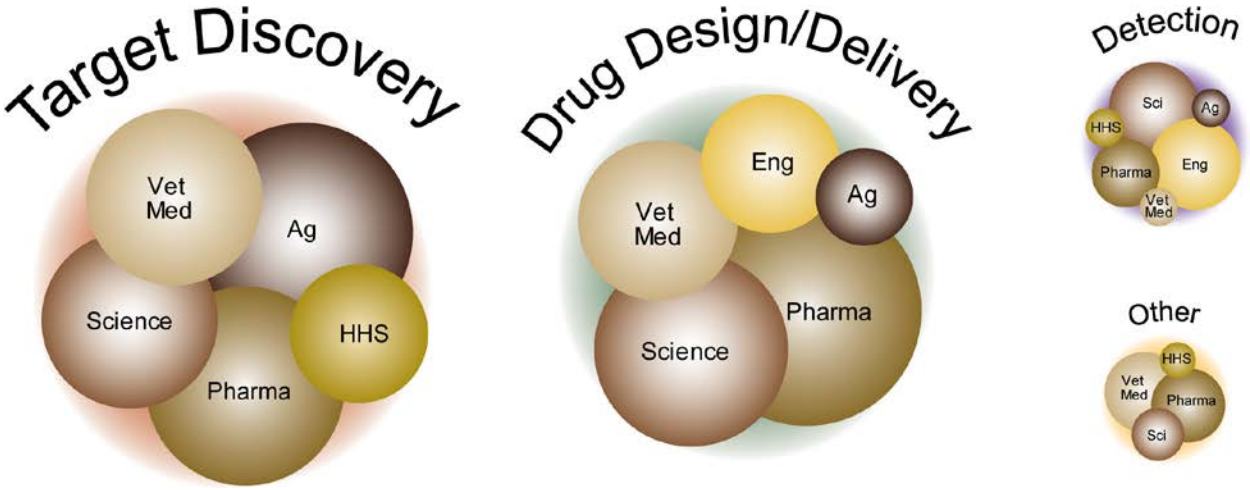


Our researchers also continue to be invested in various approaches to drug discovery, which include understanding of drug targets for future drug therapies, detection technology that will aid clinicians in early diagnosis or monitoring of therapies and design and delivery of drugs.



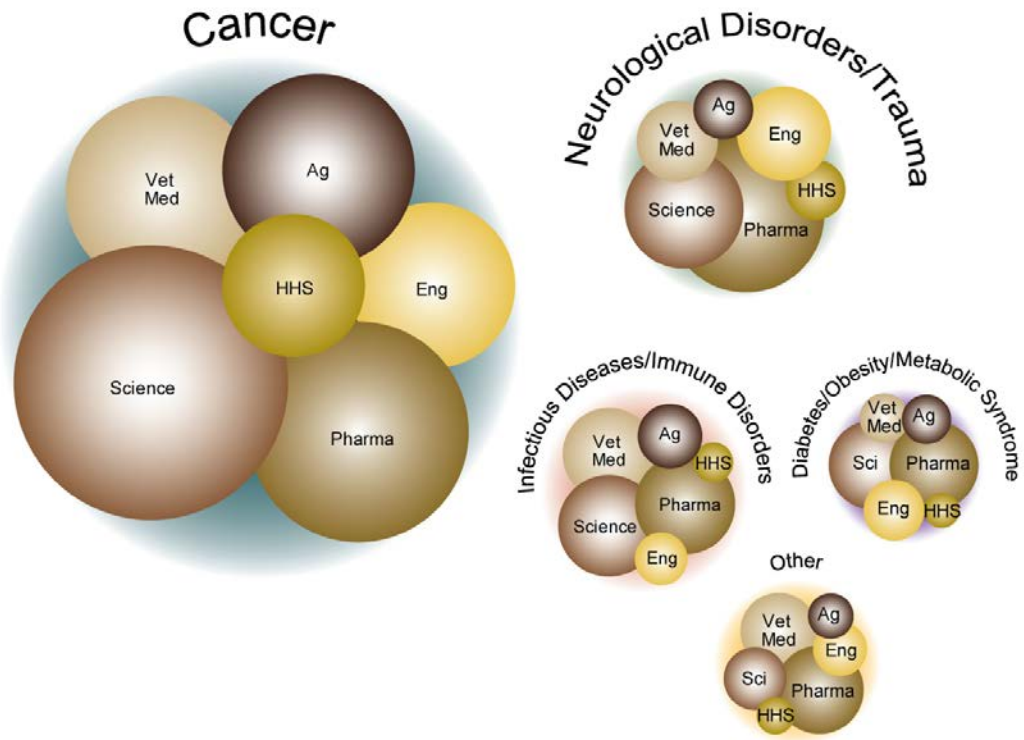
Collectively, our researchers are determined to leverage their great wealth of scientific expertise and collaboration in order to discover solutions for the public benefit. The following includes a summary of research interests.





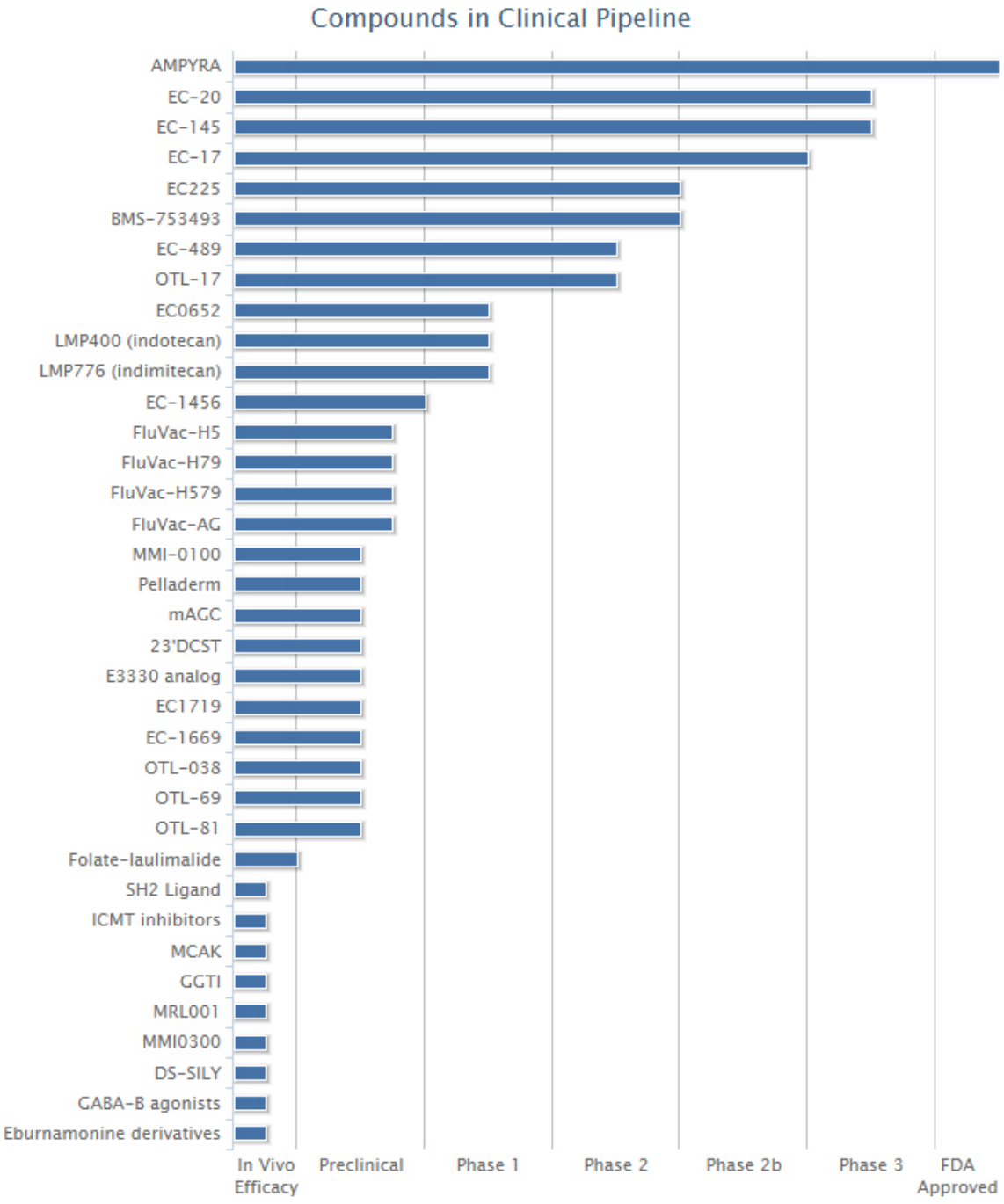
The diagram above illustrates various approaches to drug discovery, with proportionate representation by colleges and schools.

The diagram below illustrates proportionate study of major diseases.



COMPOUNDS IN CLINICAL DEVELOPMENT

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.



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

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

			CATEGORY				DISEASE				
Researcher	College/ school	Department	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		■			■				
Chang, Chun-Ju	College of Veterinary Medicine	Basic Medical Sciences		■	■		■				
Cheng, Ji-Xin	College of Engineering	Biomedical Engineering	■			■	■			■	■
Childress, Michael	College of Veterinary Medicine	Dept. of Veterinary Clinical Sciences				■	■				
Chmielewski, Jean	College of Science	Chemistry			■		■		■		■
Colby, David	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			■		■			■	
Cooks, Graham	College of Science	Chemistry	■				■				
Cushman, Mark	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			■		■		■		
Dai, Mingji	College of Science	Chemistry			■		■	■	■	■	
Davisson, Vincent Jo	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			■	■	■			■	
Dykhuizen, Emily C	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■			■				
Foster, David	Pharmacy	Pharmacy Practice				■			■		■
Freeman, Jennifer	College of Health and Human Sciences	Health Sciences		■			■			■	

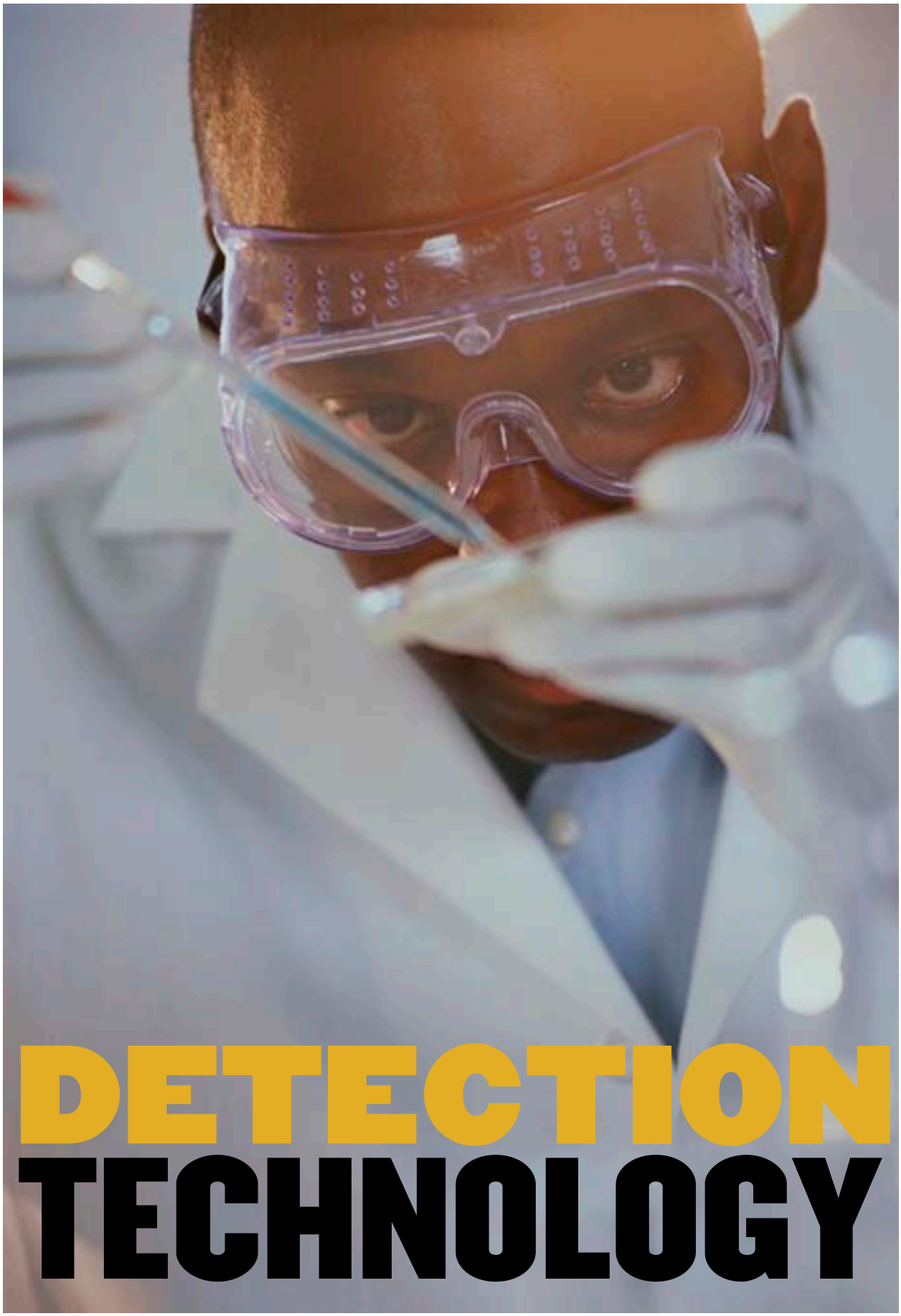
			CATEGORY				DISEASE				
Researcher	College/ school	Department	Detection Technology	Target Discovery	Drug Design/ Delivery	Other	Cancer	Diabetes/ Obesity/ Metabolic Syndrome	Infectious Diseases/ Immune Disorders	Neurological Disorders/ Trauma	Other
García, R. Edwin	College of Engineering	Materials Engineering			■						
Geahlen, Robert	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■			■				
Ghosh, Arun	College of Science	Chemistry			■		■		■	■	
Gibbs, Richard	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology			■		■				
Gore, Jay	College of Engineering	Mechanical Engineering	■				■	■			
Hall, Mark	College of Agriculture	Biochemistry		■			■				
Han, Bumsoo	College of Engineering	Mechanical Engineering	■		■		■				
Harrison, Marietta	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■			■				
Hazbun, Tony	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■			■		■	■	
Hill, Catherine	College of Agriculture	Entomology		■	■				■		
Hockerman, Gregory	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■				■		■	
Hogan, Daniel	College of Veterinary Medicine	Veterinary Clinical Sciences			■	■					■
HogenEsch, Harm	College of Veterinary Medicine	Comparative Pathobiology		■					■		
Hrycyna, Christine	College of Science	Chemistry			■		■				
Hu, Chang-Deng	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■		■	■	■			
Iradayaraj, Joseph	College of Engineering	Agricultural and Biological Engineering	■				■			■	
Janle, Elsa	Health and Human Sciences	Nutrition Science				■					■

			CATEGORY				DISEASE				
Researcher	College/ school	Department	Detection Technology	Target Discovery	Drug Design/ Delivery	Other	Cancer	Diabetes/ Obesity/ Metabolic Syndrome	Infectious Diseases/ Immune Disorders	Neurological Disorders/ Trauma	Other
Jiang, Qing	Health and Human Sciences	Nutrition Science		■			■				■
Kappock, T.J. (Joe)	College of Agriculture	Biochemistry		■					■		
Kasinski, Andrea	College of Science	Biology				■	■				
Kim, Chang	College 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	College of Veterinary Medicine	Veterinary Clinical Sciences				■	■				
Knipp, Gregory	College of Pharmacy	Industrial and Physical Pharmacy				■		■	■	■	■
Ko, Jeff	College of Veterinary Medicine	Veterinary Clinical Sciences		■				■		■	■
Konieczny, Steve	College of Science	Biological Sciences		■			■				
Krusemark, Casey J.	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology									
Kuang, Shihuan	College of Agriculture	Animal Sciences		■			■				
Leary, James	College of Veterinary Medicine	Basic Medical Sciences			■		■				
Lelièvre, Sophie	College of Veterinary Medicine	Basic Medical Sciences		■			■				
Leung, Yuk Fai	College of Science	Biological Sciences		■		■	■			■	■
Li, Jianming	College of Veterinary Medicine	Basic Medical Sciences									
Lill, Markus	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■	■	■	■			■	

			CATEGORY				DISEASE				
Researcher	College/ school	Department	Detection Technology	Target Discovery	Drug Design/ Delivery	Other	Cancer	Diabetes/ Obesity/ Metabolic Syndrome	Infectious Diseases/ Immune Disorders	Neurological Disorders/ Trauma	Other
Litster, James	College of Engineering	Chemical Engineering				■					■
Liu, Julie C.			■								■
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		■	■				■		
Mesecar, Andrew	College of Science	Biological Sciences (primary) Chemistry (courtesy)			■		■		■		
Mittal, Suresh	College of Veterinary Medicine	Comparative Pathobiology			■		■				
Mohammed, Sulma	College of Veterinary Medicine	Comparative Pathobiology		■			■				
Murphy, Angus	College of Agriculture	Horticulture			■		■				■
Nagy, Zoltan	College of Engineering	Chemical Engineering				■	■	■	■	■	■
Nauman, Eric	College of Engineering	School of Mechanical Engineering	■		■		■		■	■	■
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			■	■	■				

			CATEGORY				DISEASE				
Researcher	College/ school	Department	Detection Technology	Target Discovery	Drug Design/ Delivery	Other	Cancer	Diabetes/ Obesity/ Metabolic Syndrome	Infectious Diseases/ Immune Disorders	Neurological Disorders/ Trauma	Other
Porterfield, D. Marshall	College of Engineering	Agricultural and Biological Engineering	■				■	■		■	
Pressler, Barrak	College of Veterinary Medicine	Veterinary Clinical Sciences				■			■		■
Raftery, M. Daniel	College of Science	Chemistry	■				■				
Ramachandran, P. V.	College of Science	Chemistry			■		■			■	
Ramkrishna, Doraiswami	College of Engineering	Chemical Engineering			■		■				
Ratliff, Timothy	College of Veterinary Medicine	Comparative Pathobiology		■	■		■				
Reklaitis, G.V.	College of Engineering	Chemical Engineering			■		■	■	■	■	■
Robinson, J. Paul	College of Veterinary Medicine	Basic Medical Sciences	■	■		■	■		■	■	■
Rochet, Jean-Christophe (Chris)	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■						■	
Savaiano, Dennis	Health and Human Sciences	Nutrition Science			■						■
Savran, Cagri	College of Engineering	Mechanical Engineering									
Seleem, Mohammed	College of Veterinary Medicine	Comparative Pathobiology		■					■		
Shah, Kavita	College of Science	Chemistry		■			■			■	
Shi, Riyi	College of Veterinary Medicine	Basic Medical Sciences				■				■	
Simpson, Garth	College of Science	Chemistry			■		■	■	■	■	
Smith, Daniel	College of Pharmacy	Industrial and Physical Pharmacy				■				■	
Sowinski, Kevin	College of Pharmacy	Pharmacy Practice				■			■		■
Stauffacher, Cynthia	College of Science	Biological Sciences		■			■				
Tao, Andy	College of Science	Chemistry		■			■	■			

			CATEGORY				DISEASE				
Researcher	College/ school	Department	Detection Technology	Target Discovery	Drug Design/ Delivery	Other	Cancer	Diabetes/ Obesity/ Metabolic Syndrome	Infectious Diseases/ Immune Disorders	Neurological Disorders/ Trauma	Other
Taparowsky, Elizabeth	College of Science	Biological Sciences		■			■				
Taylor, Lynne	College of Pharmacy	Industrial and Physical Pharmacy			■		■	■	■	■	■
Thompson, David	College of Science	Chemistry			■		■				■
Tisdale, James	College of Pharmacy	Pharmacy Practice				■					■
Topp, Elizabeth	College of Pharmacy	Industrial and Physical Pharmacy			■		■	■	■		■
Varma, Arvind	College of Engineering	Chemical Engineering			■						■
Van Rijn, Richard	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■						■	
Watts, Val	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology		■							■
Wei, Alexander	College of Science	Chemistry			■		■		■		
Wirth, Mary	College of Science	Chemistry	■				■				
Wilker, Jonathan	College of Science	Chemistry				■					■
Yang, Jer-Yen	College of Veterinary Medicine	Basic Medical Sciences		■			■				
Yuan, Chongli	College of Engineering	Chemical Engineering	■	■			■			■	
Zhang, Guanjun	College of Veterinary Medicine	Comparative Pathobiology		■			■				
Zhang, Yer-Jen	College of Veterinary Medicine	Basic Medical Sciences									
Zheng, Wei	College of Health and Human Sciences	Health Sciences				■					■
Zhou, Daoghu	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 cords.
- 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, brain and bladder carcinomas

Developmental Stage
- Intermediate

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 are 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.

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.cascademetrix.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 to understand localization and trafficking. We use gold nanoparticles and more recently liposomal and polymeric nanostructures for targeted delivery. Our targeted drug delivery with polymeric particles for epigenetic regulation and release methods have been applied to evaluate the efficacy of delivery and kinetics of release at single molecule resolution in live 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.

JULIE C. LIU

Category of Research

- Detection Technology

Disease

- Cancer

Developmental stage

- Early

Research Interest and Expertise
In collaboration with Dr. Chongli Yuan, my laboratory is working on a technology for identifying and detecting epigenetic biomarkers for early stage cancer. These biomarkers would be potential targets for therapeutic treatments with drugs.

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 have 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. I have become one of the leaders in using 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}Tc-3P-RGD_2 was selected for clinical evaluation. Preliminary clinical data clearly indicate that ^{99m}Tc-3P-RGD_2 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

I am director of the Human Injury Research and Regenerative Technologies (HIRRT) laboratory, and my 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 modulates 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 leukemia, 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

Adjunct Professor

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
- Signaling Pathway Analysis

Diseases

- Cancer
- Infectious Diseases/Immune Disorders
- Cardiovascular

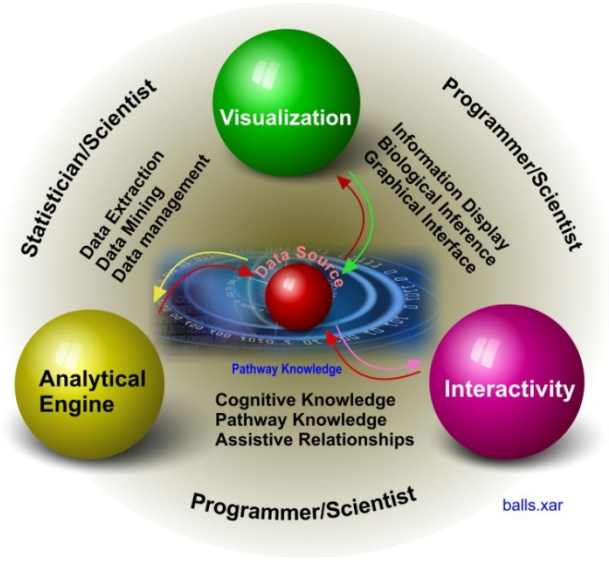
Developmental Stage

- Early
- Intermediate
- Late

Research Interest and Expertise

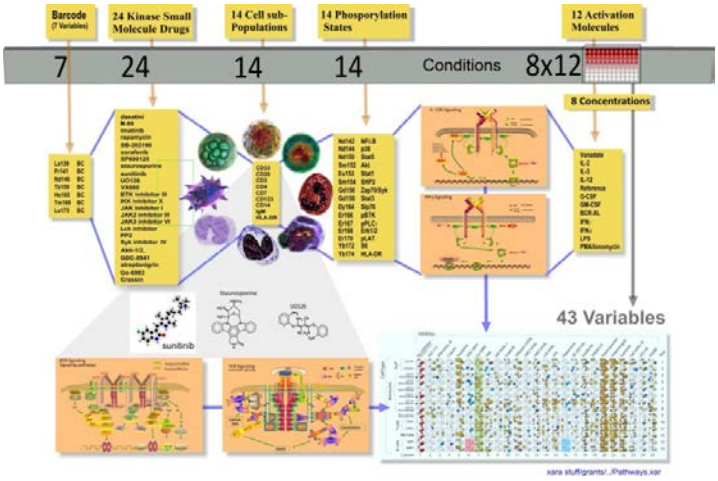
We have been developing advanced research strategies for high throughput screening (HTS) using both current tools and tools under development. This includes new detection systems for multiparametric detection as well as very sophisticated analytical toolsets. We have now developed a fully robotic assay technology that allows us to screen drugs, cellular products or molecules of interest. Systems are focused on two technologies: automated imaging driven by a robotically managed system to screen analysis plates delivering comprehensive information regarding cellular integrity, targeted molecule locations or other phenotypic changes of importance. A second technology that has become transformation in the single cell analysis arena is advanced high throughput flow cytometry, whereby we have the capacity to collect up to 11 parameter analyses from 384 well plates at a rate of one plate every 10 minutes. This allows us to potentially run as many as 20,000 multiparameter flow cytometry samples per day. This technology can be used for both primary and secondary screening as the data content achieved with this technology is very high indeed.

To facilitate the analysis of this system, we have also developed a highly advanced system for 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. The drug screening systems we have designed focus on live cell functional analysis that has great relevance to drug discovery for both functional verification and toxicological analysis. The use of complex multifactorial flow cytometry has not previously been considered in the drug screening environment because of the slow collection and overburdening task of data processing that cannot be accomplished using previously available tools. Our group has solved this

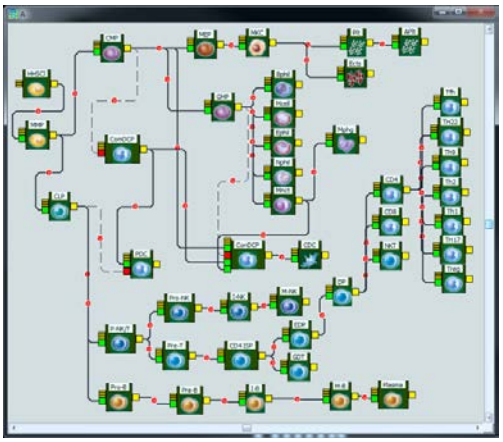


problem and continues to advance screening capabilities that have been previously impossible. This has involved developing highly complex but very fast analytical engines that are specifically designed for the biologist for direct interaction to avoid the typical informatics constriction.

A new approach we have developed recently may become transformation in identification of signaling pathways. Recently, Nolan et al. developed a systems approach to bone marrow screening using antibodies linked to heavy metals and detected by time-of-flight mass spectroscopy — a technology call mass cytometry. Our group has developed a tool called *ImmunoAnalyzer* that uses logic maps to develop analytical pathways to determine for example, phosphorylation sites, activation states and expression profiles for 14 to 20 different cell populations (particularly in bone marrow) simultaneously. Reducing these data using advanced algorithms can provide signaling profiles for cells under different drug influences in near real-time as shown in the figure below.

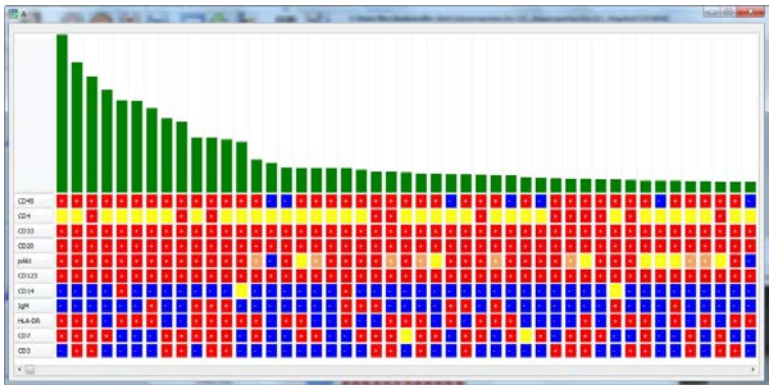


The drug screening technology developed in our lab for signaling pathway analysis is the most comprehensive yet developed and demonstrates the power of high content flow cytometry to place itself into the systems biology environment in line with current proteomic and genotypic tools most commonly used. Cytomic tools now provide potentially the most comprehensive evaluation of drug-cell interactions. The combination of our advanced interactive informatics tool-kit and the latest biochemical and analytical tools such as mass cytometry will be revolutionary in drug discovery and therapeutic intervention.



The latest development of this program is the incorporation of a knowledgebase of ontogeny of hematopoietic cells. In the case shown at left, the concept is to utilize automated analytical tools to correctly identify any cell based on its unique phenotype. This requires significant computing power since the system uses a data mining technique to evaluate every cell in the dataset. This powerful technology allows the experimenter to visually select any cell type and find all cells in a file that would be recognized by that phenotype. In addition, a new display has been developed that shows the phenotype as a combinatorial set. In this display shown below, each cell has been classified by the phenotype component of the application and the total number of cells so classified is also displayed.

This new technology has the possibility of rapid classification of patient phenotype in the clinical pathology environment. With the increased complexity of flow cytometry data now being in the vicinity of 9-10 color as standard in the clinical laboratory, it is necessary to develop new methods for rapid identification of abnormal cells.



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.

CHONGLI YUAN

Category of Research

- Target Discovery
- Detection Technology

Disease

- Cancer, Neurological Disorders

Developmental Stage

- Early

Research Interest and Expertise

Our research group focuses on using fluorescence spectroscopy to examine the effects of different epigenetic modifications on chromosome structure and activity. The following three directions are currently being pursued:

1) Evaluate the effects of anti-cancer drug molecules on chromosome conformation and gene activity.
2) Identify DNA methylation biomarkers affiliated with cancers.
3) Engineer molecular probes for the detection of early-stage cancer bio-marker in collaboration with Dr. Julie Liu.


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 and Suz12/PRC2 target genes as prognostic biomarkers for classification of HCC .
2) Plk1 inhibitors as antivirals for HBV replication, using the HepaRG cell line that supports HBV replication, in collaboration with Dr. Fabien Zoulim, INSERM, France.
3) Plk1 inhibitors as therapy targets of HBV pX-mediated HCC, using c-myc/X bitransgenic mice, in collaboration with Dr. P. Merle, INSERM, France.
4) Plk1 inhibitors as therapy targets of HBV pX-mediated HCC, using the woodchuck hepatitis virus/woodchuck animal model, in collaboration with Dr. Stephan Menne, Georgetown Medical School, USA.

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 and 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:
    - Developing 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.
    - Developing and optimizing 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 and reduce atherosclerosis

Developmental Stage

- Early

Research Interest and Expertise

The long-term goal of the Buhman laboratory is to identify novel factors that regulate dietary fat sensing, metabolism or absorption that may be exploited for preventive and therapeutic interventions for obesity, diabetes, and heart disease. Research in the Buhman laboratory focuses on trafficking and metabolism of digestive products of dietary fat within the absorptive cells of the small intestine, enterocytes. Projects in the Buhman laboratory are currently addressing how diet, drugs and genetics affect chylomicron synthesis and secretion, cytoplasmic lipid droplets synthesis and metabolism, and fatty acid oxidation by enterocytes. Recent publications from the Buhman laboratory highlight important functions of diet, drugs, and genetics in regulation of dietary fat processing within enterocytes that results in effects related to metabolic diseases such as body weight, blood lipid concentrations, and hepatic steatosis.

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 in order 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.

CHUN-JU CHANG

Category of Research
- Target Discovery
- Drug Design and Delivery

Disease
- Cancer

Developmental Stage
- Early

Research Interest and Expertise
I have a broad background in the fields of pharmacy/pharmacology, stem cell biology and cancer biology. My research is focused on revealing critical molecular mechanisms by which tumor microenvironment regulates the epigenetic status of breast cancer stem cells. Cancer stem cells are thought to account for cancer initiation, progression and recurrence, and they are highly resistant to chemotherapy and radiation.

My previous studies show epigenetic modifiers, such as histone methyltransferase and microRNAs, which play an important role in regulating stemness and cancer progression, can be regulated in response to metabolic changes in the tumor microenvironment. Currently I am interested in:

1) Determining the involvement of metabolic influences (e.g. dietary factors) in the regulation of epigenetic status of breast cancer stem cells;
2) Exploring novel therapeutic interventions targeting crucial epigenetic regulation of cancer stem cells.

Future studies in this field are expected to open a new avenue by elucidating the link between metabolism, epigenetics and cancer stem cells. We seek to exploit suitable cellular and animal models in combination with nanomedicine tools to uncover novel therapeutics for eradicating the genesis of cancer and prevent cancer recurrence/progression.

EMILY DYKHUIZEN

Category of Research

- Target Discovery

Diseases

- Cancer

Developmental Stage

- Early

Research Interest and Expertise

Recent sequencing efforts have determined that over 20% of human cancers have mutations in one or more subunits of the BAF (SWI/SNF) chromatin remodeling complex. Our research focuses on biochemically defining the role of the BAF complex in tumor suppression and on identifying how mutation of the complex leads to oncogenesis. From the information gleaned from the biochemical analysis, we are developing screening strategies in order to identify drugs that can treat this class of cancers.

JENNIFER FREEMAN

Category of Research
- Target Discovery

Diseases
- Cancer
- Neurological Disorders

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

Developmental Stage
- Early

Research Interest and Expertise
The Freeman laboratory is an environmental molecular toxicology laboratory with current research efforts focused on investigating the adverse health effects of exposure to environmental stressors on human and environmental health using the zebrafish model system. The zebrafish is a prominent model system in a variety of biological disciplines and has become one of the preferred vertebrate models in biomedical research. Similarities between the zebrafish and human genome permits investigations into the molecular pathways found to play a role in the mechanisms of toxicity in the zebrafish and translation to humans. Ongoing research projects in the Freeman laboratory are defining the underlying genetic and epigenetic mechanisms of toxicity of environmental stressors with current focus on pesticides, metals, and radiation. These projects are identifying genetic biomarkers and molecular pathways of the immediate adverse impacts of a developmental exposure, the lasting impacts of this developmental exposure throughout the lifespan, and the analysis of subsequent generations linking genetic, epigenetic, and phenotypic assessments. These studies are investigating a developmental origin of adult disease pathogenesis with a specific focus on cancer, reproductive function, and neurodegenerative disorders.

The Freeman laboratory has expertise in the application of the zebrafish model system and with genomic and targeted genetic and epigenetic technologies including array comparative genomic hybridization (CGH) to detect copy number variants and aberrations; transcriptomics including gene expression microarrays and sequencing to identify genetic biomarkers (i.e., gene targets) and molecular pathway alterations; and epigenetic analysis specifically with a focus on microRNA deregulation. All equipment and analysis platforms needed for microarray experiments are available in the Freeman laboratory.

ROBERT GEAHLEN

Category of Research

- Target Discovery

Disease

- Cancer

Therapeutic Outcome

- Developing understanding of biomolecular targets and pathways, diagnostics and compounds with novel activities, with particular interests in leukemia/lymphoma and breast carcinomas.

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 leukemia/lymphoma and carcinomas where Syk functions as both a pro-survival factor and an anti-metastatic factor. We use a variety of cellular, biochemical, structural (in collaboration with Dr. Carol Post) and proteomic (in collaboration with Dr. Andy Tao) approaches.
- *Compounds with novel activities:* In collaboration with Dr. Richard Borch, we are evaluating the ability of metabolically activated prodrugs targeted toward phosphopeptide-binding 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.

MARIETTA HARRISON

Category of Research
- Target Discovery

Disease
- Cancer

Therapeutic Outcome
- Early

Research Interest and Expertise
Along with Joseph Pekny (Chemical Engineering Purdue) and Patrick Loehrer (IU Simon Cancer Center), I co-direct the multi-disciplinary Cancer Care Engineering (CCE) project. Early detection and personalized treatment are critical to dramatically reducing death from cancer. The Cancer Care Engineering (CCE) project seeks to discover molecular signatures (biomarkers) that are predictive of early disease onset and effective treatment response. The uniqueness of the CCE project lies in the integration of newly identified, discrete biomarkers from diverse classes of bio-molecules including: proteins, lipids, metabolites and genes. The linking of multiple types of informative biological data from a single patient provides a powerful approach for identifying robust predictive, biomarker patterns to inform clinical care.

CCE is an innovative, interdisciplinary, multi-institutional project that holds great promise for advancing the translation of cancer research to impact clinical care. The initial phase of the CCE project focuses on colorectal cancer and since sample collection was launched in April 2009, over 500 tissue and blood samples have been collected from healthy, polyp bearing, and cancer patients. The samples undergo multiple discrete molecular analyses in multiple laboratories at Purdue, Indiana University and the MD Anderson Cancer Center. The resulting massive datasets along with extensive sample annotation and lifestyle data are stored in a cloud computing environment built to enable the CCE project and support the necessary complex data integration that the project requires. This cyberinfrastructure (cceHUB) is based on Purdue's innovative HUBzero™ technology where stored data can be queried, mined, modeled and uniquely visualized in a single, easily accessible environment. cceHUB provides instant access to all data for all CCE investigators and enables rapid communication among the clinicians, scientists, statisticians, mathematicians, engineers and staff that compose the CCE team. The CCE goal is to develop novel screening and risk assessment tools to prevent cancer and decision making tools to personalize cancer therapy for optimal response.

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 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

Our lab specializes in 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^{2+} channels

HARM HOGENESCH

Category of Research

- Target Discovery

Disease

- Infectious Diseases/Immune Disorders

Developmental Stage

- Early

Research Interest and Expertise

Dr. HogenEsch is a board-certified veterinary pathologist with 20 years of experience in immunology and pathology. His research focuses on vaccine development and the immunopathology of chronic inflammation. Dr. HogenEsch is an expert on aluminum-containing adjuvants, the only adjuvants allowed for use in human vaccines in the US. The HogenEsch lab investigates mechanisms by which aluminum-containing adjuvants enhance the immune response and develops methods to optimize the formulation of aluminum-adjuvanted vaccines. The research on chronic inflammation focuses on the role of the protein SHARPIN in inflammation. Dr. HogenEsch discovered the cpdm mouse mutant which is caused by a mutation in the Sharpin gene. The mutant mice develop a severe chronic eosinophilic dermatitis, systemic inflammation and defects in the development of lymphoid organs and in the Th1 immune response.

CHANG-DENG HU

Category of Research

- Target Discovery and biomarker identification
- Development and applications of novel technologies in cancer research
- Development of imaging-based high throughput screening assays for drug discovery

Diseases

- Cancer
- Diabetes, neurodegenerative diseases and autoimmune diseases

Therapeutic Outcome

- Molecular mechanisms underlying therapy-resistant prostate cancer and identification of druggable targets
- Development of BiFC-based high throughput screening assays for identification of small molecule inhibitors of 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 Purdue and outside Purdue 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 inhibitors of protein-protein interaction and to develop novel BiFC-based biosensors to imaging signaling pathways in cancer cells.

QING JIANG

Category of Research
- Target Discovery

Diseases
- Cancer
- Inflammatory diseases

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 cyclooxygeenases (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
- 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 immune cell migration and differentiation in an organ-specific manner, with particular interests in breast, lymphoma and colorectal carcinomas.

Developmental Stage
- Middle

Research Interest and Expertise
We are studying immune cell development and migration to tumor in an organ-specific manner. The main focus is on cancer in the intestine.

Another topic is the roles of gut commensal bacterial metabolites and hormones in regulation of innate and adaptive immune responses. We study how organ-specific factors, cytokines, and hormones regulate T cell differentiation in inflammation and 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 maligancies 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-pulmonary 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 pancreatitis and pancreatic ductal adenocarcinoma (PDAC). The transcription factors MIST1 and SOX9 may serve as novel therapeutic targets for the earliest stages of these diseases.

Developmental Stage

- Early to intermediate

Research Interest and Expertise
Although activating mutations in the KRAS protooncogene (KrasG12D) are thought to initiate a PDAC cascade, our knowledge is grossly deficient in defining how KrasG12D 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.

We also have studied the importance of the SRY-related HMG-box (SOX) transcription factor SOX9 to driving exocrine pancreas disease, including pancreatitis and pancreatic cancer. Utilizing the Mist1 and Sox9 loci and KrasG12D mouse models, our studies have shown that MIST1 plays a critical role in preventing preneoplastic lesions upon KrasG12D expression while SOX9 is absolutely essential to generating a transformed cell. Thus, both MIST1 and SOX9 and their downstream networks are excellent candidates for therapeutic target development for each of these diseases. Interests: early stages of pancreatic cancer, pancreatitis, 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**.**

YUK FAI LEUNG

Stages of Drug Discovery

- Preclinical
- Target Discovery
- Traditional Chinese medicine
- Naturally-derived chemicals

Disease Category

- Cancer
- Neurological disorders
- Eye diseases
- Retinal degeneration
- Animal model: zebrafish

Research Interest and Expertise

Our group at Purdue University studies zebrafish models of human retinal degeneration to expedite discovery of novel treatments. The zebrafish has a number of advantages that are particularly suitable for eye disease research. For example, it is a vertebrate model that has a good color vision, rapid embryonic development and large clutch size. Together with a much cheaper maintenance cost compared with other established animal models, zebrafish has a unique competitive edge to be a sustainable research model in the years to come.

We have established behavioural-based assays to evaluate potential drug therapies to improve retinal degeneration. As there is currently no good drug therapy for retinal degenerative diseases, we are particularly interested in screening traditional Chinese medicines (TCMs) and other naturally-derived compounds for better vision. To this end, we are collaborating with a number of prominent centers in Hong Kong and China and have acquired pure compounds, extracts and herbal formulas that are good for vision and/or have been used to treat Chinese retinal degeneration patients successfully. Together with our unique approaches for studying disease-causing gene networks, we can effectively deduce the molecular pathways through which the drug candidates exert their therapeutic effects.

Other Relevant Information

Faculty page (www.bio.purdue.edu/development_disease/directory.php?refID=596)
Lab website (www.bio.purdue.edu/lab/leung/index.html)

MARKUS LILL

Category of Research

- Target Discovery
- Drug Design and Delivery
- Computer-Aided Drug Discovery

Diseases

- Cancer
- Neurological Disorders

Developmental Stage

Early

Research Interest and Expertise

My research has been dedicated to the development of computational methods to gain insight into the processes associated with protein-ligand and protein-protein binding and their applications to drug discovery. Current research activities are focused on addressing serious shortcomings of present computational approaches for modeling protein-ligand and protein-protein association: protein flexibility, entropic contributions, solvation effects, and kinetics of binding. Besides several collaborative projects for designing and optimizing chemical probes interacting with target proteins, the modeling of the biochemical processes associated with enzyme-catalyzed drug metabolism has been of particular interest for my research group.

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-α, 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 is 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). The 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

Our 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.

Our laboratory also uses genetically modified mice to study the mechanisms by which tumor cells escape recognition by the immune response. Genetically modified mice also provide a model for better understanding the role of inflammation in the development and progression of prostate cancer. Recent studies have identified a number of genes and pathways that may provide targets for modulating tumor immunosuppressive activity. Bladder cancer studies focus on targeting bladder cancer cells with a specific protein known to be an important binding protein. Targeting studies will incorporate nanotechnology for the delivery of therapeutic agents.

J. PAUL ROBINSON

Category of Research

- Detection Technology
- Target Discovery
- Signaling Pathway Analysis

Diseases

- Cancer
- Infectious Diseases/Immune Disorders
- Cardiovascular

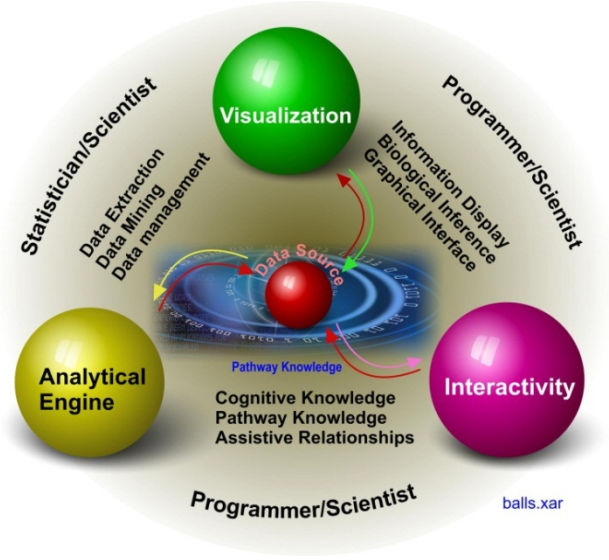
Developmental Stage

- Early
- Intermediate
- Late

Research Interest and Expertise

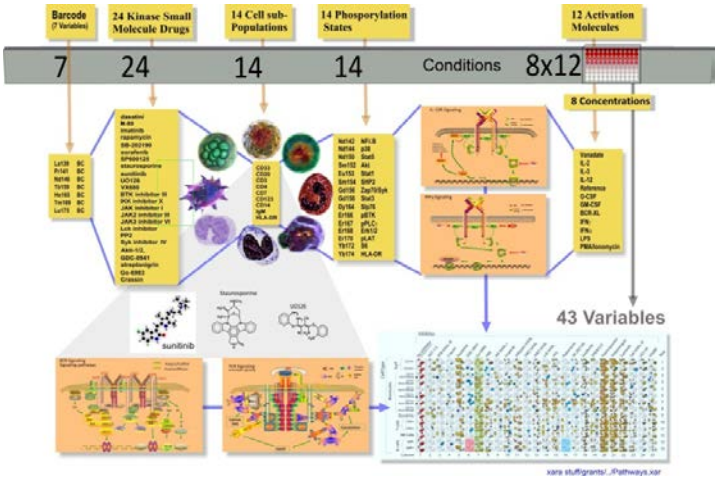
We have been developing advanced research strategies for high throughput screening (HTS) using both current tools and tools under development. This includes new detection systems for multiparametric detection as well as very sophisticated analytical toolsets. We have now developed a fully robotic assay technology that allows us to screen drugs, cellular products or molecules of interest. Systems are focused on two technologies: automated imaging driven by a robotically managed system to screen analysis plates delivering comprehensive information regarding cellular integrity, targeted molecule locations or other phenotypic changes of importance. A second technology that has become transformation in the single cell analysis arena is advanced high throughput flow cytometry, whereby we have the capacity to collect up to 11 parameter analyses from 384 well plates at a rate of one plate every 10 minutes. This allows us to potentially run as many as 20,000 multiparameter flow cytometry samples per day. This technology can be used for both primary and secondary screening as the data content achieved with this technology is very high indeed.

To facilitate the analysis of this system, we have also developed a highly advanced system for 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. The drug screening systems we have designed focus on live cell functional analysis that has great relevance to drug discovery for both functional verification and toxicological analysis. The use of complex multifactorial flow cytometry has not previously been considered in the drug screening environment because of the slow collection and overburdening task of data processing that cannot be accomplished using previously available tools. Our group has solved this

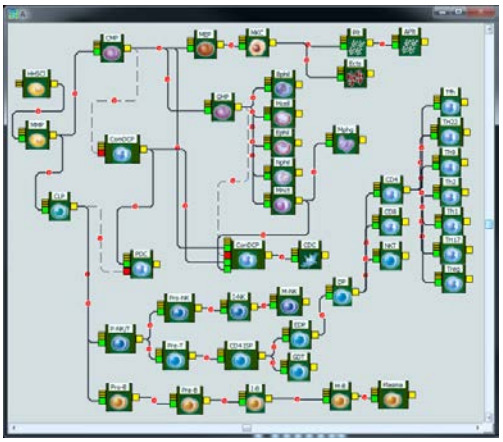


problem and continues to advance screening capabilities that have been previously impossible. This has involved developing highly complex but very fast analytical engines that are specifically designed for the biologist for direct interaction to avoid the typical informatics constriction.

A new approach we have developed recently may become transformation in identification of signaling pathways. Recently, Nolan et al. developed a systems approach to bone marrow screening using antibodies linked to heavy metals and detected by time-of-flight mass spectroscopy — a technology call mass cytometry. Our group has developed a tool called *ImmunoAnalyzer* that uses logic maps to develop analytical pathways to determine for example, phosphorylation sites, activation states and expression profiles for 14 to 20 different cell populations (particularly in bone marrow) simultaneously. Reducing these data using advanced algorithms can provide signaling profiles for cells under different drug influences in near real-time as shown in the figure below.

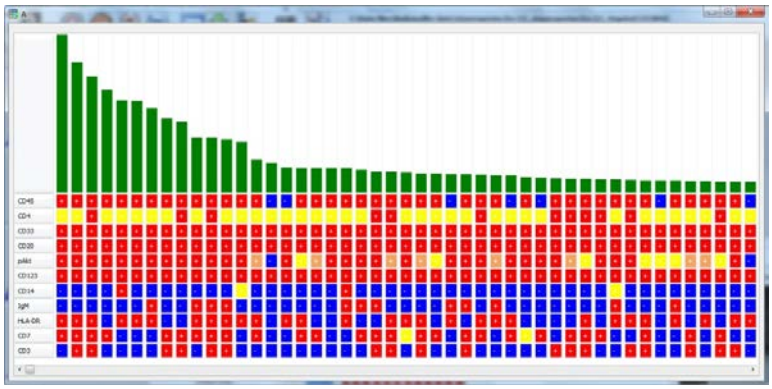


The drug screening technology developed in our lab for signaling pathway analysis is the most comprehensive yet developed and demonstrates the power of high content flow cytometry to place itself into the systems biology environment in line with current proteomic and genotypic tools most commonly used. Cytomic tools now provide potentially the most comprehensive evaluation of drug-cell interactions. The combination of our advanced interactive informatics tool-kit and the latest biochemical and analytical tools such as mass cytometry will be revolutionary in drug discovery and therapeutic intervention.



The latest development of this program is the incorporation of a knowledgebase of ontogeny of hematopoietic cells. In the case shown at left, the concept is to utilize automated analytical tools to correctly identify any cell based on its unique phenotype. This requires significant computing power since the system uses a data mining technique to evaluate every cell in the dataset. This powerful technology allows the experimenter to visually select any cell type and find all cells in a file that would be recognized by that phenotype. In addition, a new display has been developed that shows the phenotype as a combinatorial set. In this display shown below, each cell has been classified by the phenotype component of the application and the total number of cells so classified is also displayed.

This new technology has the possibility of rapid classification of patient phenotype in the clinical pathology environment. With the increased complexity of flow cytometry data now being in the vicinity of 9-10 color as standard in the clinical laboratory, it is necessary to develop new methods for rapid identification of abnormal cells.



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.

MOHAMED SELEEM

Category of Research
Target Discovery

Disease
Infectious Diseases

Developmental Stage
Early to Intermediate

Research Interest and Expertise

- Antimicrobials for treatment of Infectious diseases caused by multidrug resistant bacterial pathogens
- Molecular target identification of new antimicrobials
- Drug delivery and targeting of intracellular bacterial pathogens
- Animal model for infectious diseases
- Repurposing of existing drugs to find new uses (antibiotics) outside the scope of the original medical indication

KAVITA SHAH

Category of Research

- Target Discovery and Validation, Synthesis of small molecules

Diseases

- Cancer
- Neurological Disorders

Therapeutic Outcome

- Understanding the role of oncogenic kinases and their oncogenic targets as potential clinical targets. Specific interests are breast, ovarian, pancreatic and prostate carcinomas.
- Understanding the mechanism of neurodegeneration in Alzheimer's Disease with the goal to identify novel therapeutic targets and retrospective biomarkers

Developmental Stage

- Early

Research Interest and Expertise

Our long term goal is to identify effective therapeutic targets for cancer, particularly for breast, prostate, pancreatic and ovarian cancer. Our current research is focused on dissecting the roles of Aurora A and LIMK2 kinases in promoting oncogenesis using chemical, genetic and chemical-genetic approaches. Aurora A is overexpressed in several types of cancers. MLN8237, a highly selective Aurora A inhibitor, has shown significant efficacy in Phase II clinical trials, however, the adverse side effects due to ubiquitous Aurora A expression in all dividing cells have limited its potential effectiveness. One of the goals in our laboratory is to identify, characterize and validate substrates that are phosphorylated and regulated by Aurora A in cancer tissues, but not in their normal counterparts. Selective inhibition of these targets in cancer tissues will specifically abrogate Aurora A's oncogenic signaling, without disturbing its physiological roles in normal cells, thus avoiding collateral toxicity.

We have developed a tailored chemical genetic approach to identify the direct targets of Aurora kinases. 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, ovarian, pancreatic and breast cancer. We have documented that the ablation of LIMK2 kinase, 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. The 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 live 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.

RICHARD M. VAN RIJN

Category of Research
- Target Discovery

Disease
- Neurological Disorders

Developmental Stage
- Intermediate

Research Interest and Expertise
We are interested in discovering new targets to treat neurological disorders including addiction, anxiety disorders and depression. Our work is focused on novel attributes of G-protein coupled receptor functionality including protein-protein interactions a.k.a. heteromerization and biased signal transduction.
We combine high throughput in vitro assays with in vivo behavioral rodent models for drug screening.

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.

JER-YEN YANG

Category of Research
- Target Discovery

Diseases
- Cancer

Developmental Stage
- Intermediate

Research Interest and Expertise
Deficiency in the process of embryo development will lead to birth defects and severe diseases such as cancer. The Hedgehog (Hh) pathway is a conserved signaling system essential for embryonic development. Our group is interested in understanding how Hh signaling regulates early neuronal development in zebrafish, mouse and humans. Up ligand stimulation, Hh pathway promotes cell proliferation, differential and migration. However, by which and how the positive and negative regulators modulate signals still remains unknown.

Mutations that deregulate Hh signalling are directly implicated in basal cell carcinoma and medulloblastoma in mice and humans. The mechanisms of Hh pathway activation in cancers in which no pathway mutations have been identified are less clear, but of great translational significance. Using CHIP/CHIP, CHIP/seq, siRNA library screening and proteomics approach, we have identified several important hits for Hh regulation. Now we are investigating these candidates and trying to figure out how those genes impact on Hh pathway in chromatin and genes level- transcriptional regulation and protein-post-translational modification.

CHONGLI YUAN

Category of Research

- Target Discovery
- Detection Technology

Disease

- Cancer, Neurological Disorders

Developmental Stage

- Early

Research Interest and Expertise

Our research group focuses on using fluorescence spectroscopy to examine the effects of different epigenetic modifications on chromosome structure and activity. The following three directions are currently being pursued:

1) Evaluating the effects of anti-cancer drug molecules on chromosome conformation and gene activity
2) Identifying DNA methylation biomarkers affiliated with cancers
3) Engineering molecular probes for the detection of early-stage cancer bio-marker in collaboration with Dr. Julie Liu.

GUANGJUN ZHANG

Category of Research

- Target discovery

Disease

- Cancer

Developmental Stage

- Early

Research Interest and Expertise

My research is mainly focused on cancer driver identifications. Currently, personalized targeted therapy holds promises for future cancer treatment. A major goal of current cancer research is to distinguish pathogenetically relevant genetic alterations (drivers) from the passive changes (passengers) in cancer genome, thus targeting therapy can be developed on human tumors. Our lab mainly uses zebrafish as a model to study human cancer biology and vertebrate developmental biology.

Specifically, we focus on two directions within cancer biology:

1) Identifying novel human cancer driver genes through zebrafish-human comparative oncogenomic analysis of copy number alterations. Following identification, novel genes' functions in cancer and vertebrate development will be extensively investigated in zebrafish adults and embryos.
2) Investigating the general biological consequences of aneuploidy and polyploidy, and their roles in cancer development.

In addition, we are also interested in small molecule screening on our newly identified cancer driver genes and aneuploid cells using zebrafish embryos as an *in vivo* screening platform.

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 systemic 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
AND 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. I am currently involved in research on 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. I would like to develop a delayed absorbable (7-10 days) vehicle for delivery of antimicrobial and anti-inflammatory drugs directly into infected joints. I am also doing research on needle insertion techniques that will minimize contamination of joints with tissue and hair debris following injections of drugs into the joints.

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 logP > 5 have been incorporated into dendrimers with logP ~ 0 in which the prodrugs retain bioactivity.

CHUN-JU CHANG

Category of Research

- Target Discovery
- Drug Design and Delivery

Disease

- Cancer

Developmental Stage

- Early

Research Interest and Expertise

I have a broad background in the fields of pharmacy/pharmacology, stem cell biology and cancer biology. My research is focused on revealing critical molecular mechanisms by which tumor microenvironment regulates the epigenetic status of breast cancer stem cells. Cancer stem cells are thought to account for cancer initiation, progression and recurrence, and they are highly resistant to chemotherapy and radiation.

My previous studies show epigenetic modifiers, such as histone methyltransferase and microRNAs, which play an important role in regulating stemness and cancer progression, can be regulated in response to metabolic changes in the tumor microenvironment. Currently I am interested in:

1) Determining the involvement of metabolic influences (e.g. dietary factors) in the regulation of epigenetic status of breast cancer stem cells
2) Exploring novel therapeutic interventions targeting crucial epigenetic regulation of cancer stem cells.

Future studies in this field are expected to open a new avenue by elucidating the link between metabolism, epigenetics and cancer stem cells. We seek to exploit suitable cellular and animal models in combination with nanomedicine tools to uncover novel therapeutics for eradicating the genesis of cancer and prevent cancer recurrence/progression.

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 drug-resistant cancers

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.

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 NFkB, 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 investigating a wide variety of chemotypes with antimicrobial activity against pathogenic microorganisms including viruses, protozoa, and bacteria.

Research Interest and Expertise

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

MINGJI DAI

Category of Research

- Drug Design/Delivery

Diseases

- Cancer
- Diabetes/Obesity/Cardiovascular
- Immune and Infectious Disease
- Neurological disorders/Trauma

Research Interest and Expertise

Our research focuses on innovating in both the strategy and methodology of chemical synthesis, and applying them to solve problems of biological and medical importance and ultimately impact human health. We work on both natural and unnatural molecules with particular potential for the treatment of cancer, CNS disorders and infectious diseases. We view the completion of a synthesis as the beginning of a larger and deeper scholarly inquiry. It would enable us to profile the biology of the selected natural products and rationally designed analogs, decipher their mechanism of actions/cellular targets, and optimize the lead compounds into useful chemical probe and novel therapeutics development. We also work on creating unconventional and diverse small-molecule libraries with the aim to target challenging but important disease targets, such as protein-protein interactions and transcription factors, and exploring reversible/irreversible covalent small molecule-protein interactions and their application in biology and drug discovery.

VINCENT JO DAVISSON

Category of Research

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

Diseases

- Cancer: 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

- None. Interested in basic science of drug fabrication and delivering Developmental Stage
-
- 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 and precipitation 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, Icmtl, 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.

We have 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, we have 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 and imaging agents have been developed, the efficacy of these agents is significantly limited because of various transport barriers of tumors. These barriers are associated with complex transport processes, which the therapeutic agents experience in vivo. My research focuses on the characterization and manipulation of these transport barriers, ultimately aiming to develop mechanistic strategies to deliver the therapeutic agents to targeted tumors.

Current research projects include:

1) development of tumor-microenvironment-on-chip to recapitulate the in vivo tumor microenvironment and to rapidly screen drugs and drug delivery systems;
2) enhancement of drug delivery for thermally treated tumors; and
3) early detection of epithelial-mesenchymal-transition. the concept of organ-on-chip is also being expanded to mimic liver and lung to test drug toxicity and inhalable drugs.

CATHERINE HILL

Category of Research

- Target Discovery
- Drug Design and Delivery

Diseases

- Infectious Diseases/Immune Disorders

Developmental Stage

- Early
- Intermediate

Research Interest and Expertise

We specialize in 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

Our research focuses on 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: Icmtl).

Development Stage

- Early to intermediate

Research Interest and Expertise

Icmt: Mutations in the *K-Ras* oncogene are the key causative agents in greater than 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 College 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. 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 is 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.

MARKUS LILL

Category of Research

- Target Discovery
- Drug Design and Delivery
- Computer-Aided Drug Discovery

Diseases

- Cancer
- Neurological Disorders

Developmental Stage

Early

Research Interest and Expertise

My research has been dedicated to the development of computational methods to gain insight into the processes associated with protein-ligand and protein-protein binding and their applications to drug discovery. Current research activities are focused on addressing serious shortcomings of present computational approaches for modeling protein-ligand and protein-protein association: protein flexibility, entropic contributions, solvation effects, and kinetics of binding. Besides several collaborative projects for designing and optimizing chemical probes interacting with target proteins, the modeling of the biochemical processes associated with enzyme-catalyzed drug metabolism has been of particular interest for my research group.

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

- Targeted Drug Design and Delivery

Diseases

- Cancer, autoimmune, inflammatory, and infectious diseases

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. (Drugs: folate-tubulysin, vintafolide, DUPA-^{99m}Tc, DUPA-tubulysin, EC-489, EC1669, EC-225, EC-145, EC-20, EC-17, EC1496)

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. malaria, influenza virus, Staphylococcus, Pseudomonas, etc.). Seven targeted drugs stemming from research in my lab are currently undergoing human clinical trials (mainly at Endocyte, Inc. and On Target Laboratories, two companies that I have 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, therapies for infectious diseases.

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

ANDREW MESECAR

Category of Research
- Drug Design

Disease
- Cancer
- Infectious Diseases

Therapeutic Outcome
- Developing an understanding of the roles of cytoprotective enzymes, induced by activation of the antioxidant responsive element (ARE) by Nrf2 by dietary and therapeutic agents, in cancer and neuroprotection. Ascertaining whether oncogenic deubiquitinating enzymes can be developed as therapeutic targets of anti-cancer agents for a variety of cancers. Developing coronaviral proteases as anti-viral drug targets.

Developmental Stage
- Early
- Intermediate

Research Interest and Expertise
We are currently studying the structure and function of enzymes involved in cancer chemoprevention, cancer cell proliferation and bacterial and viral pathogenesis. We are actively involved in the discovery of both natural and synthetic compounds that can be used as anti-cancer, anti-viral and anti-bacterial therapeutics, as well as compounds that can prevent cancer and promote cell longevity.

We are a gene-to-lead molecule discovery lab and therefore develop and utilize a number of research tools in the drug discovery process. We develop novel assays for our target enzymes and miniaturize these assays into 384-well plate format to preform high throughput screening for lead molecules. We utilize cheminformatics tools to establish structure-activity relationships (SAR) between our target enzyme and lead molecules as well as X-ray crystallography combined with computational docking to validate and refine our SAR models. Finally, we test the biological performance of our molecules in vitro and in vivo.

Our current projects in the lab include: (1) the roles of deubiquitinating enzymes (DUBs) in cancer and antagonism of the innate immune response and targeting DUBs for anti-cancer and antiviral drug development; (2) regulation of the Keap1-Cul3-Rbx1 E3 Ubiquitin ligase system in regulating the cellular concentrations of the transcription factor Nrf2 and hence activation of the anti-oxidant response element (ARE); (3) the structure, function and evolution of coronavirus papain-like and 3C proteases and developing therapeutics targeted at these enzymes; and (4) determining the structure and mechanisms of bacterial adenylyltrasferase enzymes in the CoA, NAD, FAD and menaquinone biosynthesis and evaluating these enzymes as potential drug targets.

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 *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. Following our demonstration that EphA2-EphrinA1 interaction inhibits tumor progression, we are exploring the link between the hematopoietic growth factor, FMS-like tyrosine kinase receptor ligand (Flt3L), and the expansion and mobilization of functional dendritic cells. We discovered that multiple inoculations of a human adenovirus vector (HAd) with Flt3L shows potent inhibition of tumor growth. Using the combination a human adenovirus vector expressing a secretory-form of EphrinA1 (HAd-EphrinA1-Fc) and a HAd vector expressing Flt3L (HAd-Flt3L), we observed an even greater increase in the inhibition of tumor growth. This vector pairing has the potential for an effective strategy for mammary tumor regression.

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 our 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 utilizes 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.

Our 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 our 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

I am director of the Human Injury Research and Regenerative Technologies (HIRRT) laboratory, and my 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.

KINAM PARK

Category of Research

- Drug Design and Delivery

Diseases

- Cancer
- Diabetes/Obesity/Metabolic Syndrome
- Cardiovascular

Therapeutic Outcome

- Delivery of anticancer agents from microparticle depot for weeks and months.
- Screening of anticancer drug and drug combinations using tumor-microenvironment on chip.
- Targeted delivery of anticancer agents using adaptable polymer micelles and drug nanocrystals.
- Particular interests are breast and brain carcinomas.

Developmental Stage

- Ready for clinical applications for microparticle formulations
- Intermediate for adaptable polymer micelles

Research Interest and Expertise

Long-term protein delivery systems using homogeneous microparticles: Peptide and protein drugs with anticancer activity 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 hydrophilic polymer template-based nanofabrication methodology to prepare microparticles for more efficient long-term delivery of protein drugs. The duration of protein delivery can range from weeks to several months.

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.

RODOLFO PINAL

Category of Research

- Drug delivery
- Bioavailability Enhancement
- Customization of drug exposure profile

Disease

- Cancer and metabolic diseases

Developmental Stage

- Intermediate (toward in vivo POC)

Research Interest and Expertise

- My laboratory has developed the 3D IP (3D Integrated Pharmaceuticals) technology.

Drug delivery systems are assembled from prefabricated working parts in a manner similar to which 3D integrated circuits are made. The a priori design and assembly construction method provide the ability to manipulate the rate, extent and multi-stage mode for drug release. The result is the ability to customize the drug release profile after administration.

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

DORAISWAMI RAMKRISHNA

Category of Research
- Drug Design and Delivery

Disease
- Cancer

Developmental Stage
- Intermediate

Research Interest and Expertise
Dr. Ramkrishna's research group is motivated by the application of mathematics to solving problems in chemical and biochemical reaction engineering, biotechnology, and biomedical engineering. Their research ideas arise from linear and nonlinear analysis of ordinary and partial differential equations, stochastic processes, and population balance modeling involving integro-partial differential equations.

In biotechnology, Dr. Ramkrishna, in collaboration with Dr. Morgan and Dr. Sherman, is investigating dynamic, cybernetic models of cyanobacteria for the elucidation of circadian rhythms, dynamic behavior in varying light and dark patterns, production of biofuels, and for application to metabolic engineering.

An active research program in collaboration with Drs. Robert Hannemann (ChE), Ann Rundell of the Weldon School of Biomedical Engineering is under way in the application of mathematical and systems engineering principles to personalize the treatment protocol for cancer chemotherapy (leukemia). This work involves clinical data from the Riley Children's Hospital at Indianapolis through collaboration with Dr. Terry Vik. Recently, in collaboration with Dr. Jamie Renbarger of the Riley, an exploratory pharmaco-metabonomics based biomarker discovery work has been initiated to identify small molecules responsible for variable vincristine induced peripheral neuropathy observed in cancer patients. The central theme here is in identifying genetic and biomolecular traits specific to a patient, followed by quantitative clinical decision making based upon the patient's genetic and phenotypic make-up. With the mapping of the human genome and recent developments in 'omic' technologies, a deluge of patient-specific data have become available which can be used to characterize an individual patient. However, the elucidation of the molecular phenotype, and further in to cellular response, from the gene sequence involves numerous transcriptional and translational processes.

Consequently, a holistic approach, integrating many levels of biomolecular entities and events, provides superior information for clinical decision making. Given the complexity of biological processes and the amount of available quantitative data, it would be unreasonable to expect a simple deductive process to guide personalized treatment. Quantitative models, derived from first principles and suitably empowered by systems theoretic methodology, have had a history of demonstrated successes in many scientific and industrial applications. Such a quantitative approach has the potential to greatly enhance the decision making capabilities of the treating physicians and improve the quality-of-life among cancer patients.

In an effort to elucidate signal transduction and gene regulatory processes in drug resistance transfer, a collaborative work was initiated with Dr. Wei-Shou Hu at the University of Minnesota. A Population Balance Model (PBM) with stochastic intracellular gene regulation has been constructed for the drug resistance transfer of *Enterococcus faecalis* which clarified the importance of population interaction/cooperation. The next phase of the project aims to analyze the phenomenon of transfer of drug resistance in planktonic and biofilm environments featuring a mixture of donor and recipient bacterial populations.

TIMOTHY L. RATLIFF

Category of Research

- Drug Design and Delivery
- Target Discovery

Disease

- Cancer

Developmental Stage

- Early
- Intermediate

Research Interest and Expertise

Our 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.

Our laboratory also uses genetically modified mice to study the mechanisms by which tumor cells escape recognition by the immune response. Genetically modified mice also provide a model for better understanding the role of inflammation in the development and progression of prostate cancer. Recent studies have identified a number of genes and pathways that may provide targets for modulating tumor immunosuppressive activity. Bladder cancer studies focus on targeting bladder cancer cells with a specific protein known to be an important binding protein. Targeting studies will incorporate nanotechnology for the delivery of therapeutic agents.

G V REKLAITIS

Category of Research

- Drug Design and Delivery

Diseases

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

Developmental Stage

- Intermediate

Research Interest and Expertise

- Continuous and automated manufacture of solid oral dosage products with assured quality, including conventional tablet production methods as well as innovative drop on demand based, small batch dosage formation technologies.
- Management of data and predictive models associated with drug development and manufacture and knowledge extraction methodologies to support decisions associated with development of new drug products.
- Use of pharmacometric models and Bayesian estimation methods to develop individualized patient dosing regimens.

DENNIS SAVAIANO

Category of Research

- Drug Design and Delivery
  We have worked with the pharma industry to design specific non-digestible carbohydrates that can adapt colon bacteria to improve gastrointestinal symptoms from lactose intolerance and related disorders.

Diseases

- Gastrointestinal disorders/IBS/Lactose Intolerance

Developmental Stage

- Late

Research Interest and Expertise

Our research group has studied numerous factors which influence lactose digestion and tolerance including lactose load, gastric and intestinal transit, the use of lactose digestive aids, colon fermentation of lactose and the consumption of fermented dairy foods and lactic acid bacteria. The colonic flora readily adapts to lactose and other non-digestible carbohydrates. Thus, people with maldigestion who routinely consume lactose and related carbohydrates have fewer symptoms due to enhanced metabolism by the colon microflora. We have also characterized the ability of lactic acid bacteria including acidophilus and bifidus to improve lactose digestion in vivo in the gastrointestinal system. There are several drug development opportunities we are exploring regarding colon adaptation to non-digestible carbohydrates that could improve clinical outcomes for patients with lactose intolerant, irritable bowel and related digestive syndromes.

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 bioavailablility. 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
- Niemann-Pick Type C (NPC)
- Viral disease

Therapeutic Outcome

Research efforts in the Thompson group address problems in:

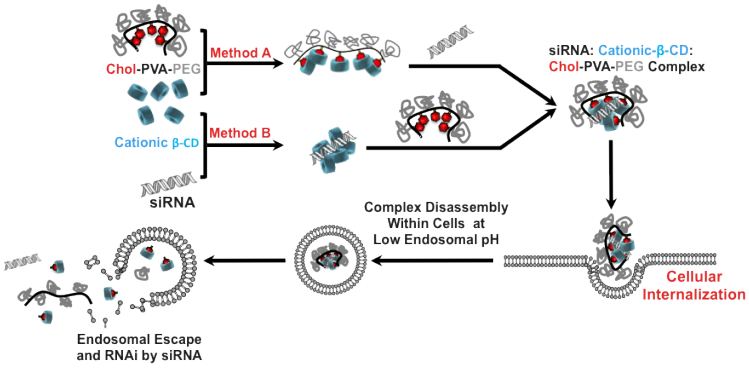
1) Self-assembling polymers & fusogenic liposomes with molecularly-engineered release properties
2) Cyclodextrin-based polymers for mobilizing stored cholesterol in NPC
3) Affinity-capture materials for accelerated elucidation of protein structures

Developmental Stage

- Early to intermediate

Research Interest and Expertise

Our materials design and synthesis team has developed plasma-stable polymer- and liposome-based carriers that display long-circulation properties in the blood, but rapidly and efficiently release their contents once they have reached their cellular target. These vehicles are designed to release their cargo within the cytoplasm of target cells, thereby greatly enhancing the efficacy of nucleic acid therapeutics and conventional small molecule drugs. Two different families of cyclodextrin polymers that degrade within acidic endosomes have been developed for delivery of pDNA, miRNA, or 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 bladder carcinoma in situ, breast cancer and glioblastoma intervention are under investigation using these carrier systems.



Triblock copolymer and pendant polymer constructs that non-covalently bind β-cyclodextrin derivatives are being developed as potential Niemann-Pick Type C (NPC) therapeutics. These vehicles are designed to carry multiple copies of β-cyclodextrin derivatives and release them within the lysosomes of cells that have accumulated a large cholesterol burden due to mutation(s) in the NPC gene. The efficiency of these constructs toward cholesterol mobilization in $npc2^{-/-}$ fibroblasts and $npc1^{-/-}$ mice is under investigation.

Nanostructured materials bearing high-affinity ligands for specific capture of important protein targets for drug discovery are being developed to aid structure-based drug design efforts. The performance of these compounds suggests that they have promising capabilities for aiding medium- and high-resolution structure determinations of membrane protein and soluble protein targets.

ELIZABETH 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

Our 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.

ARVIND VARMA

Category of Research

- Drug Design and Delivery

Disease

- Optimum design and operation of batch and continuous-flow reactors for drug manufacture

Developmental Stage

- Late

Research Interest and Expertise

My expertise is in chemical and catalytic reaction engineering, including micro-reaction technology, for design, scale-up and operation of batch and continuous-flow reactors for optimum product selectivity and yield. I have a particular emphasis on experimental and modeling studies involving complex reaction networks, encountered in the synthesis of pharmaceutical products

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 AREAS OF RESEARCH

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 effects 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.

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.

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 cords.
- 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.

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.

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 a particular interest in drug-resistant cancers

Developmental Stage

- Early

Research Interest and Expertise

We are synthesizing derivatives of natural products to understand structure-activity relationships. Our goal 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.

VINCENT JO DAVISSON

Category of Research

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

Diseases

- Cancer: 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

DAVID FOSTER

Category of Research

- Drug therapy
- PK/PD

Disease

- Infectious Diseases/Immune Disorders
- Critical Illness
- Gastrointestinal Disorders

Developmental Stage

- Late

Research Interest and Expertise

My research is focused on the evaluation of changes in intestinal permeability in critical illness. Specifically, this research involves the investigation of natural anti-inflammatory compounds to attenuate inflammation-related changes in intestinal permeability. A related area of research is the investigation of alterations in intestinal drug and nutrient absorption by passive and active transport mechanisms, and the molecular mediators underlying these changes in burn injury and sepsis. Other interests include the study of the contribution of active transport processes to variability in drug disposition.

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

Our research focuses on cardiovascular therapeutics, including heart failure and antithrombotics. We have expertise in veterinary clinical trials, pre-clinical animal trials and animal modeling.

CHANG-DENG HU

Category of Research

- Target Discovery and biomarker identification
- Development and applications of novel technologies in cancer research
- Development of imaging-based high throughput screening assays for drug discovery

Diseases

- Cancer
- Diabetes, neurodegenerative diseases and autoimmune diseases

Therapeutic Outcome

- Molecular mechanisms underlying therapy-resistant prostate cancer and identification of druggable targets
- Development of BiFC-based high throughput screening assays for identification of small molecule inhibitors of protein-protein interactions involved in diseases
- Novel BiFC-based diagnostic tools

Developmental Stage

- Early to intermediate

Research Interest and Expertise

4) **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 Purdue and outside Purdue 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.
    -
5) **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.
6) **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 inhibitors of protein-protein interaction and to develop novel BiFC-based biosensors to imaging signaling pathways in cancer cells.

ELSA M. JANLE

Category of Research

- Bioavailability and tissue distribution

Disease

- All Diseases

Developmental Stage

- Intermediate

Research Interest and Expertise

In the Nutrition Science Department, I have led in vivo research on several grants with a bioavailability core, focusing on the pharmacokinetics, metabolism and tissue distribution of test materials. We use animal models including, rodents, pigs and sheep. For plasma pharmacokinetics in rodents, we have an automated blood sampling system that can remove blood and store it in a cooled fraction collector. Blood is automatically replaced by saline. If desired, the animal activity can be simultaneously recorded. Tissue distribution studies are conducted with membrane probes, which can be implanted in multiple tissues to determine a pharmacokinetic profile of the test materials in a number of tissues simultaneously.

ANDREA L. KASINSKI

Category of Research

- Assay Development and Primary Screening

Disease

- Cancer

Developmental Stage

- Late

Research Interest and Expertise

The labs overall focus explores the involvement of miRNAs in cancer. Specifically we are working to identify and understand the role of various miRNAs in the tumorigenic process and to use this knowledge to advance miRNA-based therapeutics. Many of our studies are currently in the early phases of assay development and small molecule screening with long-term goals that include secondary screens, cell-based validation, toxicological profiling, and pre-clinical *in-vivo* efficacy studies. The assay currently in the pipeline seeks to identify a small molecule inhibitor of a biologically relevant interaction between an RNA and a protein. When bound to the protein, LIN-28, processing the miRNA, *let-7*, to its mature active form is prevented. Disrupting this interaction allows processing to proceed which ultimately produces the tumor-suppressive form of *let-7*, which will subsequent target key oncogenes such as KRAS, MYC, and LIN-28.

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.

GREGORY KNIPP

Category of Research

- Biopharmaceutics
- Pediatric Formulations
- Preclinical Screening

Diseases

- Diabetes/Obesity/Metabolic Syndrome
- Effects of xenobiotics on pregnancy and fetal outcomes
- Infectious Diseases
- Cancer

Developmental Stage

- Preclinical lead candidate selection and optimization
- Intermediate pharmacokinetic and pharmacodynamic studies.

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 rodent and porcine models. 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. A recent interest has been in the development of dosing flexible formulations for pediatric populations, who often are "therapeutic orphans" based on the limited amount of research in this area.

YUK FAI LEUNG

Stages of Drug Discovery

- Preclinical
- Target Discovery
- Traditional Chinese medicine
- Naturally-derived chemicals

Disease Category

- Cancer
- Neurological disorders
- Eye diseases
- Retinal degeneration
- Animal model: zebrafish

Research Interest and Expertise

Our group at Purdue University studies zebrafish models of human retinal degeneration to expedite discovery of novel treatments. The zebrafish has a number of advantages that are particularly suitable for eye disease research. For example, it is a vertebrate model that has a good color vision, rapid embryonic development and large clutch size. Together with a much cheaper maintenance cost compared with other established animal models, zebrafish has a unique competitive edge to be a sustainable research model in the years to come.

We have established behavioral-based assays to evaluate potential drug therapies to improve retinal degeneration. As there is currently no good drug therapy for retinal degenerative diseases, we are particularly interested in screening traditional Chinese medicines (TCMs) and other naturally-derived compounds for better vision. To this end, we are collaborating with a number of prominent centers in Hong Kong and China and have acquired pure compounds, extracts and herbal formulas that are good for vision and/or have been used to treat Chinese retinal degeneration patients successfully. Together with our unique approaches for studying disease-causing gene networks, we can effectively deduce the molecular pathways through which the drug candidates exert their therapeutic effects.

Other Relevant Information

Faculty page (www.bio.purdue.edu/development_disease/directory.php?refID=596)
Lab website (www.bio.purdue.edu/lab/leung/index.html)

MARKUS LILL

Category of Research

- Target Discovery
- Drug Design and Delivery
- Computer-Aided Drug Discovery

Diseases

- Cancer
- Neurological Disorders

Developmental Stage

Early

Research Interest and Expertise

My research has been dedicated to the development of computational methods to gain insight into the processes associated with protein-ligand and protein-protein binding and their applications to drug discovery. Current research activities are focused on addressing serious shortcomings of present computational approaches for modeling protein-ligand and protein-protein association: protein flexibility, entropic contributions, solvation effects, and kinetics of binding. Besides several collaborative projects for designing and optimizing chemical probes interacting with target proteins, the modeling of the biochemical processes associated with enzyme-catalyzed drug metabolism has been of particular interest for my research group.

JAMES LITSTER

Category of Research

- Particle design and formulation

Particle design is the production of novel particles with specific attributes, which are controlled by the size, morphology and surface properties of the particles that are produced. To control these attributes, both the particle formation processes and the feed formulation properties need to be controlled. The products of interest are many and varied, including proteins and other biological materials, pharmaceuticals, detergents and consumer goods, food, ceramics and high value materials, fertilizers and agricultural chemicals, and minerals.

Developmental Stage

- Early
- Intermediate
- Late

Research Interest and Expertise

My major research area is **granulation and agglomeration.** The research is targeted at several levels:

- Particle level — Prediction of the behavior of partially saturated bulk powders and granules from understanding of the particle-particle and particle-binder interactions in the granule;
- Rate process level — Mapping of regimes of operation for the key rate processes in granulation - wetting and nucleation, growth and consolidation, breakage and attrition and the development of mathematical models for these processes;
- Unit operation and granulation circuit level — Development of scale-up rules for granulation processes. This includes simulation, optimization and control of continuous granulation circuits.

Current research projects in this area are:

- Multiscale modeling of granulation processes;
- Regime mapping and quantitative modeling of wet granule breakage in granulators;
- Characterization of cohesive powder flows in a mixer granulator; and
- Design of regime separated granulators for continuous granulation.

ZOLTAN K. NAGY

Category of Research

- Other (Pharmaceutical process development and optimization)

Diseases

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

Developmental Stage

- Late

Research Interest and Expertise

- Development of pharmaceutical process intensification and optimization techniques to improve final product consistency and eliminate failures in production.
- Application of modern process analytical technologies, mathematical modeling and process control of batch and continuous pharmaceutical crystallization.
- Control of crystal size distribution, shape and polymorphic form to assure desired drug product performance (e.g. in vivo/in vitro dissolution).
- Development of automated intelligent decision support systems for drug development and manufacture.

RODOLFO PINAL

Category of Research

- Drug delivery
- Bioavailability Enhancement
- Customization of drug exposure profile

Disease

- Cancer and metabolic diseases

Developmental Stage

- Intermediate (toward in vivo POC)

Research Interest and Expertise

- My laboratory has developed the 3D IP (3D Integrated Pharmaceuticals) technology.

Drug delivery systems are assembled from prefabricated working parts in a manner similar to which 3D integrated circuits are made. The a priori design and assembly construction method provide the ability to manipulate the rate, extent and multi-stage mode for drug release. The result is the ability to customize the drug release profile after administration.

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.

J. PAUL ROBINSON

Category of Research

- Detection Technology
- Target Discovery
- Signaling Pathway Analysis

Diseases

- Cancer
- Infectious Diseases/Immune Disorders
- Cardiovascular

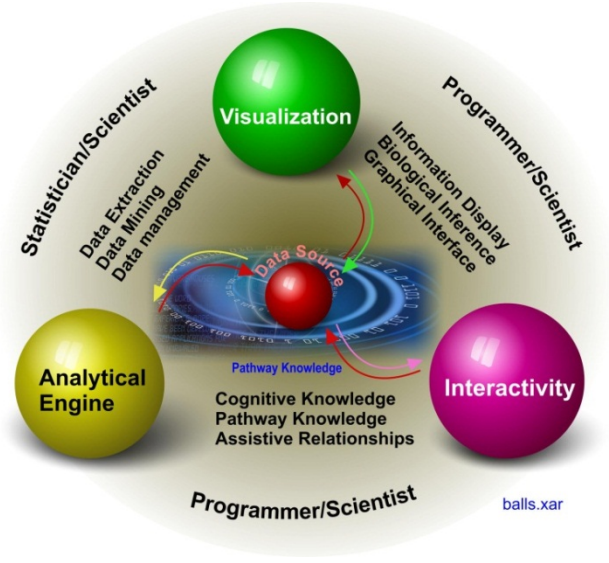
Developmental Stage

- Early
- Intermediate
- Late
-

Research Interest and Expertise

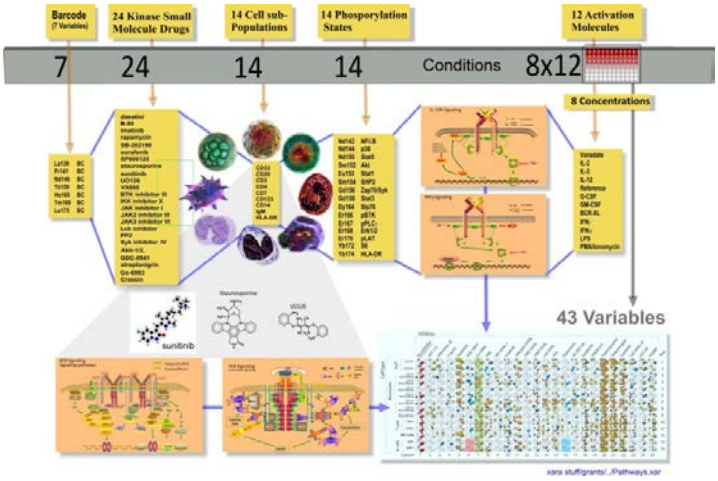
We have been developing advanced research strategies for high throughput screening (HTS) using both current tools and tools under development. This includes new detection systems for multiparametric detection as well as very sophisticated analytical toolsets. We have now developed a fully robotic assay technology that allows us to screen drugs, cellular products or molecules of interest. Systems are focused on two technologies: automated imaging driven by a robotically managed system to screen analysis plates delivering comprehensive information regarding cellular integrity, targeted molecule locations or other phenotypic changes of importance. A second technology that has become transformation in the single cell analysis arena is advanced high throughput flow cytometry, whereby we have the capacity to collect up to 11 parameter analyses from 384 well plates at a rate of one plate every 10 minutes. This allows us to potentially run as many as 20,000 multiparameter flow cytometry samples per day. This technology can be used for both primary and secondary screening as the data content achieved with this technology is very high indeed.

To facilitate the analysis of this system, we have also developed a highly advanced system for 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. The drug screening systems we have designed focus on live cell functional analysis that has great relevance to drug discovery for both functional verification and toxicological analysis. The use of complex multifactorial flow cytometry has not previously been considered in the drug screening environment because of the slow collection and overburdening task of data processing that cannot be accomplished using previously available tools. Our group has solved this

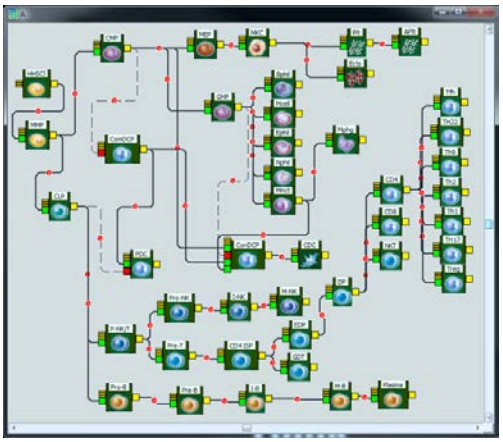


problem and continues to advance screening capabilities that have been previously impossible. This has involved developing highly complex but very fast analytical engines that are specifically designed for the biologist for direct interaction to avoid the typical informatics constriction.

A new approach we have developed recently may become transformation in identification of signaling pathways. Recently, Nolan et al. developed a systems approach to bone marrow screening using antibodies linked to heavy metals and detected by time-of-flight mass spectroscopy — a technology call mass cytometry. Our group has developed a tool called *ImmunoAnalyzer* that uses logic maps to develop analytical pathways to determine for example, phosphorylation sites, activation states and expression profiles for 14 to 20 different cell populations (particularly in bone marrow) simultaneously. Reducing these data using advanced algorithms can provide signaling profiles for cells under different drug influences in near real-time as shown in the figure below.

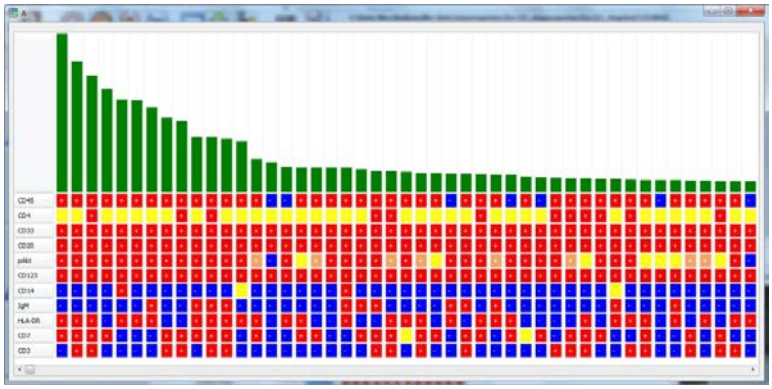


The drug screening technology developed in our lab for signaling pathway analysis is the most comprehensive yet developed and demonstrates the power of high content flow cytometry to place itself into the systems biology environment in line with current proteomic and genotypic tools most commonly used. Cytomic tools now provide potentially the most comprehensive evaluation of drug-cell interactions. The combination of our advanced interactive informatics tool-kit and the latest biochemical and analytical tools such as mass cytometry will be revolutionary in drug discovery and therapeutic intervention.



The latest development of this program is the incorporation of a knowledgebase of ontogeny of hematopoietic cells. In the case shown at left, the concept is to utilize automated analytical tools to correctly identify any cell based on its unique phenotype. This requires significant computing power since the system uses a data mining technique to evaluate every cell in the dataset. This powerful technology allows the experimenter to visually select any cell type and find all cells in a file that would be recognized by that phenotype. In addition, a new display has been developed that shows the phenotype as a combinatorial set. In this display shown below, each cell has been classified by the phenotype component of the application and the total number of cells so classified is also displayed.

This new technology has the possibility of rapid classification of patient phenotype in the clinical pathology environment. With the increased complexity of flow cytometry data now being in the vicinity of 9-10 color as standard in the clinical laboratory, it is necessary to develop new methods for rapid identification of abnormal cells.



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.

KEVIN M. SOWINSKI

Category of Research

- Pharmacokinetics and Pharmacodynamics

Disease

- Cardiovascular/Renal/Infectious Diseases

Developmental Stage

- Late

Research Interest and Expertise

The goal of my research is to use pharmacokinetics and pharmacodynamics and mathematical modeling to develop and evaluate rational approaches to optimize drug therapy regimens.

JAMES E. TISDALE

Category of Research
- Other

Diseases
- Cardiovascular

Developmental Stage
- Late

Research Interest and Expertise
My translational research program focuses on identification of therapeutic targets for prevention of atrial fibrillation, understanding mechanisms, risk factors, and prevention of drug-induced arrhythmias, and developing methods of risk assessment and prevention of specific drug-induced diseases

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

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