CANCER DISCOVERY

PURDUE UNIVERSITY

2013-2014

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INTRODUCTION

Purdue University is home to the Purdue University Center for Cancer Research. Established in 1978, the center was for 20 years the only NCI-designated Cancer Center in Indiana. The center's core mission and focus is basic cancer research. In 2005, the center established the Oncological Sciences Center, which serves as its Discovery Park arm.

The Center for Cancer Research (www.cancer.purdue.edu) brings together researchers from within Purdue University and beyond to study cancer. Using the combined expertise of scientists from disciplines as varied as engineering, veterinary medicine, nutritional science, biology, and chemistry, the Center for Cancer Research focuses on discovery of biological processes, new chemical entities, and novel therapeutics. To accomplish this mission, the center coordinates collaborative basic research and fosters the application of discoveries on enhancing cancer care through improving detection, prognosis, and treatment.

The Oncological Sciences Center (www.purdue.edu/dp/oncological) uses the interdisciplinary environment and strong infrastructure of Purdue's Discovery Park to initiate and enable large-scale, multi-investigator, cross-disciplinary cancer research. The center initiates new cancer-focused studies among faculty who historically have not focused on cancer research and fosters new programs for future integration into the Center for Cancer Research. Additionally, the Oncological Sciences Center engages the local community and IU Simon Cancer Center oncologists and health professionals in the translation of academic science to clinical settings and the cross-training of physical scientists, engineers, and clinicians.

Discovery Park was launched with $50 million in funding from Lilly Endowment Inc.; since its inception, the park has grown into a $500 million interdisciplinary research complex for large-scale projects. An arm of Purdue's research enterprise, Discovery Park brings scientists, researchers, engineers, and management experts together to make basic discoveries available to advance Indiana's economy and solve societal problems by developing new products and processes.

The Purdue University Center for Cancer Research, one of only seven basic science NCI-designated cancer centers, will begin its 32nd year of NCI funding in July 2010.

AREAS OF CANCER AND DRUG DISCOVERY RESEARCH

CANCER RESEARCH

Biomarker discovery

- Integrated OMIC analysis: metabolomics and proteomics
- Database development/Purdue Hub technology
- Predictive molecular signatures

Cancer cell biology

- Receptor signaling and cell cycle control
- Regulation of gene expression
- Animal models of cancer development
- Inflammation
- Cell imaging

Chemical and structural biology

- Intracellular networks
- Membrane proteins in cancer
- Chemical and biophysical tools

Drug delivery & cancer diagnostics

- Drug delivery – new molecules and materials
- In vitro and in vivo sensing, medium throughput screening
- Ex-vivo sensing
- Whole animal imaging

Drug design

- Synthetic medicinal chemistry
- In vitro molecular evaluation
- In vivo molecular evaluation

Cancer prevention

- Nutrition
- Epigenomics
- Communication

Systems engineering, modeling, physics

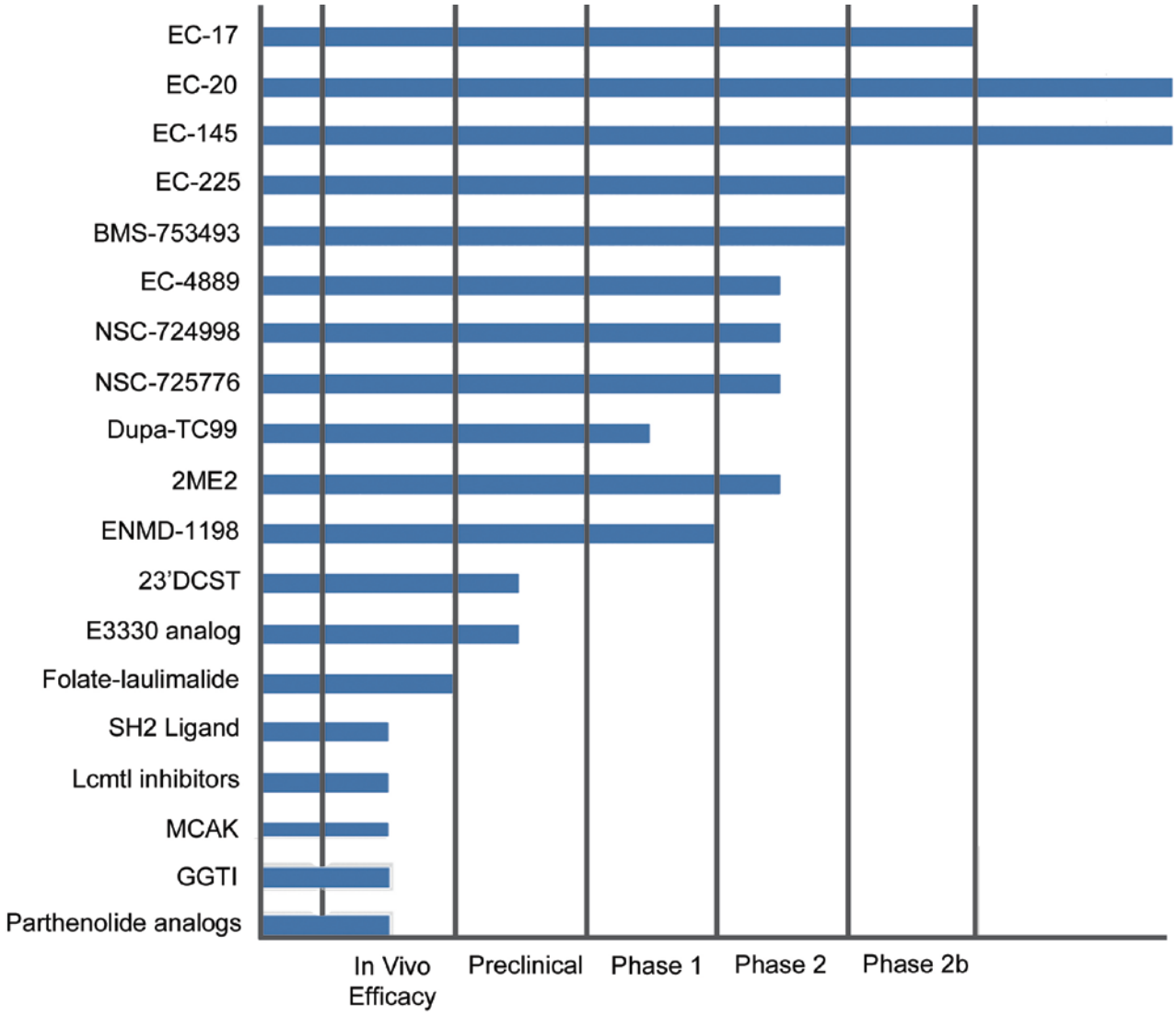
- Cancer care engineering
- Cross-training clinicians/physical scientists/engineers

CANCER DRUG DISCOVERY

- Drug design & delivery
- Detection technology
- Target development for drug discovery

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.



CANCER RESEARCH

ALPHABETICAL LIST OF CANCER RESEARCHERS

LAST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Biomarker Discovery	Cancer Cell Biology	Chemical & Structural Biology	Drug Delivery & Cancer Diagnostics	Drug Design & Discovery	Cancer Prevention	Systems Engineering Modeling, Physics
Adams	Robin	College of Engineering	Engineering Education						■	
Agnew	Christopher	College of Health and Human Sciences	Psychological Sciences						■	
Aguilar	Rubin Claudio	College of Science	Biological Sciences		■					
Alam	Muhammed Ashraful	College of Engineering	Electrical & Computer Engineering							■
Andrisani	Ourania	College of Veterinary Medicine	Basic Medical Sciences		■					
Bentley	R. Timothy	College of Veterinary Medicine	Veterinary Clinical Sciences							
Bolin	Jeffrey	College of Science	Biological Sciences			■				
Boling	Patricia	College of Liberal Arts	Political Science						■	
Borch	Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology				■	■		
Boushey	Carol	College of Health and Human Sciences	Nutrition Science (adjunct professor)						■	
Bouman	Charles	College of Engineering	Electrical & Computer Engineering				■			
Briggs	Scott	College of Agriculture	Biochemistry		■					
Buhman	Kimberly	College of Health and Human Sciences	Foods & Nutrition						■	
Burgess	Jay	College of Health and Human Sciences	Foods & Nutrition						■	
Camarillo	Ignacio	College of Science	Biological Sciences		■				■	
Chang	Chun-Ju (Alice)	College of Veterinary Medicine	Basic Medical Sciences		■		■		■	

LAST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Biomarker Discovery	Cancer Cell Biology	Chemical & Structural Biology	Drug Delivery & Cancer Diagnostics	Drug Design & Discovery	Cancer Prevention	Systems Engineering Modeling, Physics
Chang	Henry	College of Science	Biological Sciences		■					
Charbonneau	Harry	College of Agriculture	Biochemistry		■					
Chen	Jue	College of Science	Biological Sciences			■				
Cheng	Ji-Xin	College of Engineering	Biomedical Engineering		■		■	■	■	
Childress	Michael	College of Veterinary Medicine	Veterinary Clinical Sciences							
Chmielewski	Jean	College of Science	Chemistry			■		■		
Cho	Hyunyi	College of Liberal Arts	Communications						■	
Clifton	Chris	College of Science	Computer Science							■
Colby	David	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology					■		
Cooks	R. Graham	College of Science	Chemistry	■			■	■	■	
Craig	Bruce	College of Science	Statistics	■					■	■
Cramer	William	College of Science	Biological Sciences			■				
Cushman	Mark	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology					■		
Davisson	V. Jo	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology					■		
Delp III	Edward	College of Engineering	Electrical & Computer Engineering						■	
Doerge	Rebecca	College of Science	Statistics	■					■	
Dydak	Ulrike	College of Health and Human Sciences	Health Sciences	■			■			
Ebert	David	College of Engineering	Electrical & Computer Engineering							■
Fekete	Donna	College of Science	Biological Sciences		■					
Fleet	James	College of Health and Human Sciences	Foods & Nutrition		■				■	

LAST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Biomarker Discovery	Cancer Cell Biology	Chemical & Structural Biology	Drug Delivery & Cancer Diagnostics	Drug Design & Discovery	Cancer Prevention	Systems Engineering Modeling, Physics
Freeman	Jennifer	College of Health and Human Sciences	Health Sciences		■					
Friedman	Alan	College of Science	Biological Sciences			■				
Geahlen	Robert	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology	■	■				■	
Gelvin	Stanton	College of Science	Biological Sciences		■					
Ghosh	Arun	College of Science/ College of Pharmacy (j appointmer	Chemistry/ Medicinal Chemistry & Molecular Pharmacology					■		
Gibbs	Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology					■		
Golden	Barbara	College of Agriculture	Biochemistry			■				
Gruenbaum	Ellen	College of Liberal Arts	Anthropology							
Hall	Mark	College of Agriculture	Biochemistry		■	■				
Hannemann	Robert	College of Engineering	Biomedical Engineering							■
Harrison	Marietta	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■					■
Hazbun	Tony	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■			■		
Hrycyna	Christine	College of Science	Chemistry		■	■		■		
Hu	Chang-Deng	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■				■	
Hudmon	Karen	School of Pharmacy a Pharmaceut cal Sciences	Pharmacy Practice						■	
Irudayaraj	Joseph	College of Engineering	Agricultural and Biological Engineering	■	■		■		■	

LAST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Biomarker Discovery	Cancer Cell Biology	Chemical & Structural Biology	Drug Delivery & Cancer Diagnostics	Drug Design & Discovery	Cancer Prevention	Systems Engineering Modeling, Physics
Ivanisevic	Albena	College of Engineering	Biomedical Engineering				■			
Jiang	Qing	College of Health and Human Sciences	Foods & Nutrition		■				■	
Kim	Chang	College of Veterinary Medicine	Comparative Pathobiology		■					
Kim	Young	College of Engineering	Biomedical Engineering				■			
Kirchmaier	Ann	College of Agriculture	Biochemistry		■					
Kirshner	Julia	College of Science	Biological Sciences		■				■	
Knapp	Deborah	College of Veterinary Medicine	Veterinary Clinical Sciences	■				■	■	
Konieczny	Stephen	College of Science	Biological Sciences		■					
Kuang	Shihuan	College of Agriculture	Animal Sciences		■					
Kuhn	Richard	College of Science	Biological Sciences			■				
Leary	James	College of Veterinary Medicine	Basic Medical Sciences		■		■		■	
Lelièvre	Sophie	College of Veterinary Medicine	Basic Medical Sciences		■				■	
Lipton	Mark	College of Science	Chemistry					■		
Liu	Sandra	College of Health and Human Sciences	Consumer Sciences and Retailing						■	
Liu	Shuang	College of Health and Human Sciences	Health Sciences				■			
Liu	Wanqing	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology	■	■					
Liu	Xiaoqi	College of Agriculture	Biochemistry		■					
Lossie	Amy	College of Agriculture	Animal Science		■					
Low	Philip	College of Science	Chemistry		■		■	■		

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Mao	Chengde	College of Science	Chemistry							
McDonough	Meghan	College of Health and Human Sciences	Health and Kinesiology							
McMillin	David	College of Science	Chemistry							
Mendrysa	Susan	College of Veterinary Medicine	Basic Medical Sciences							
Miller	Margaret	College of Veterinary Medicine	Comparative Pathobiology							
Mittal	Suresh	College of Veterinary Medicine	Comparative Pathobiology							
Mobley	Amy	College of Health and Human Sciences	Foods & Nutrition							
Mobley	Stacey	College of Health and Human Sciences	Foods & Nutrition							
Mohammed	Sulma	College of Veterinary Medicine	Comparative Pathobiology							
Moore	George	College of Veterinary Medicine	Comparative Pathobiology							
Morgan	John	College of Engineering	Chemical Engineering							
Morgan	Susan	College of Liberal Arts	Communica-tion							
Nolte	David	College of Science	Physics							
Packer	Rebecca	College of Veterinary Medicine	Veterinary Clinical Sciences							
Park	Kinam	College of Pharmacy	Industrial & Physical Pharmacy							
Parker	Laurie	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology							
Peer	Wendy	College of Agriculture	Horticulture & Landscape Architecture (adjunct professor)							
Pekny	Joseph	College of Engineering	Chemical Engineering							

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Porterfield	D. Marshall	College of Engineering	Agricultural & Biological Engineering							■
Post	Carol	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology		■	■		■		
Ramachandran	P V	College of Science	Chemistry							■
Raman	Arvind	College of Engineering	Mechanical Engineering							■
Ramkrishna	Doraiswami	College of Engineering	Chemical Engineering					■		■
Ramos-Vara	Jose	College of Veterinary Medicine	Comparative Pathobiology		■					
Ratliff	Timothy	College of Veterinary Medicine	Comparative Pathobiology		■					
Regnier	Fred	College of Science	Chemistry	■			■			■
Reifenberger	Ronald	College of Science	Physics							■
Rickus	Jenna	College of Engineering	Agricultural & Biological Engineering							■
Robinson	J. Paul	College of Veterinary Medicine	Basic Medical Sciences		■		■			
Rossman	Michael	College of Science	Biological Sciences			■				
Rundell	Ann	College of Engineering	Biomedical Engineering		■					■
Sanders	David	College of Science	Biological Sciences			■				
Savinov	Sergey	College of Science	Chemistry			■				
Savran	Cagri	College of Engineering	Mechanical Engineering				■			
Shah	Kavita	College of Science	Chemistry		■	■				
Shields	Cleveland	College of Health and Human Sciences	Human Development & Family Studies						■	
Simpson	Garth	College of Science	Chemistry			■				
Smith	Al	College of Health and Human Sciences	Health and Kinesiology						■	

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Snyder	Paul	College of Veterinary Medicine	Comparative Pathobiology					■		
Stauffacher	Cynthia	College of Science	Biological Sciences		■	■				
Stein	Arnold	College of Science	Biological Sciences		■					
Story	Jon	College of Health and Human Sciences	Foods & Nutrition						■	
Sundararajan	Raji	College of Technology	Electrical & Computer Engineering Technology							■
Tao	Andy	College of Agriculture	Biochemistry	■	■	■				
Taparowsky	Elizabeth	College of Science	Biological Sciences		■					
Teegarden	Dorothy	College of Health and Human Sciences	Foods & Nutrition	■	■				■	■
Thompson	David	College of Science	Chemistry			■	■			
Tran	Elizabeth	College of Agriculture	Biochemistry		■	■				
Troped	Philip	College of Health and Human Sciences	Health and Kinesiology						■	
Waters	David	College of Veterinary Medicine	Veterinary Clinical Sciences	■				■	■	
Weaver	Connie	College of Health and Human Sciences	Foods & Nutrition						■	
Wei	Alexander	College of Science	Chemistry				■		■	
Wilker	Jonathan	College of Science	Chemistry						■	
Wirth	Mary	College of Science	Chemistry			■				
Won	You-Yeon	College of Engineering	Chemical Engineering				■			
Yeo	Yoon	College of Pharmacy	Industrial & Physical Pharmacy				■			
Yih	Yuehwern	College of Engineering	Industrial Engineering	■					■	■
Zhang	Dabao	College of Science	Statistics							■

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Zhang	Jian	College of Science	Statistics							
Zhang	Min	College of Science	Statistics							
Ziaie	Babak	College of Engineering	Electrical & Computer Engineering							
Zillich	Alan	College of Pharmacy	Pharmacy Practice							

ROBIN ADAMS

Dr. Adams' research seeks to empirically develop "languages for learning" in areas central to the practice of engineering – cross-disciplinarity and design – and to the practice of engineering education. A language of learning is a way of characterizing what it means to know, be able to do, or be as a professional and how this changes over time and through experience. It provides tools for students to self-assess their own progress, teachers to design and assess learning experiences, and leaders to take action in shaping engineering education programs and policies.

This research is concentrated in four interconnecting areas:
(1) building theories about learning and becoming "cross-disciplinary" (e.g., multi-, inter-, trans-disciplinary) in multiple contexts such as engineering, design, cancer research and engineering education;
(2) creating models for cross-disciplinary teaching and learning where educators share approaches to teaching, learn from each other and transfer new ideas for use in their own classrooms;
(3) in-depth studies into how beginning designers progress towards informed designing with a particular focus on the use of iterative design strategies, breadth and depth in framing and understanding complex problems, and an awareness of ambiguity and uncertainty in complex problems; and
(4) developing theories of engineering education transformation from cognitive and historical perspectives.

CHRISTOPHER AGNEW

Research interests of Dr. Agnew include (1) interpersonal relations, including commitment processes, dissolution processes, and social network interactions and influence; and (2) social psychological dimensions of health behaviors, including cancer-related behaviors such as smoking. At times, his research combines these two interests (e.g., how psychological commitment influences health; how relationships influence cancer-related behavior).

RUBIN CLAUDIO AGUILAR

It is well established that the processes of endocytosis and signaling are functionally linked. For example, abnormalities in the process of endocytosis are associated to malignant transformation due to deficient downregulation of signaling receptors.

However, endocytosis is also implicated in signaling activation. For instance, internalization is required for routing ligand-receptor complexes to endosomal compartments ("signaling endosomes") where they can initiate specific signaling events. Further, the Aguilar lab established that endocytic proteins can directly activate signaling pathways involved in cell polarity and cytoskeleton remodeling.

Currently, research in Dr. Aguilar's group is focused on the role played by the endocytic machinery in the activation of signaling pathways related to cancer cell invasion. Dr. Aguilar is particularly interested in the mechanisms linking endocytosis with epithelial-mesenchymal transition in fibrosarcoma and bladder carcinomas.

In order to pursue their research goals team members use genetic, biochemical and cell biological techniques in yeast and mammalian cells. They study protein-protein interactions by using biophysical, biochemical and genetic tools. The Aguilar lab also investigates the physiological relevance of these interactions in live cells by combining siRNA-mediated knock-down, functional assays (e.g., cell migration and invasion), time-lapse microscopy and Fluorescence Resonance Energy Transfer.

Also see p. 155.

MUHAMMAD ASHRAFUL ALAM

Dr. Alam is interested in theory, simulation, characterization, and compact modeling of semiconductor electronic, optoelectronic, and bio-electronic devices. He always looks for system-level technological bottlenecks as new research topics and tries to identify those problems whose solutions will illuminate the deeper physical principles involved and establish the limits of the technology for the particular system-level applications.

Currently Alam's team is working on four research topics that reflect their vision regarding continued evolution of semiconductor industry over the next 20-30 years. These topics are (1) Reliability physics of MOSFETs for microelectronic applications, (2) Possibility of novel DRAMs cells as memory elements beyond ITRS roadmap, (3) performance limits Nano-composite thin-films for macroelectronic applications (flexible, perhaps printable, large-area electronics), and (4) functionalized nano-bio sensor arrays for bio-medical and electro-chemical applications.

OURANIA ANDRISANI

Dr. Andrisani's laboratory investigates molecular mechanisms of mammalian cell growth and differentiation. The ongoing projects investigate the molecular mechanism of cancer pathogenesis and the development of strategies for mechanism-based therapy.

Project 1: Chronic hepatitis B virus (HBV) infection is a major risk factor for developing liver cancer, and the HBV X protein (pX) has been implicated as a cofactor in hepatocyte transformation. The goal of her laboratory is to determine how pX initiates hepatocyte transformation and identify new targets for therapy. Her team has shown that HBV replication as well as *in vitro* transformation by pX are associated with induction of the mitotic polo-like kinase 1 (Plk1) and down-regulation of the chromatin remodeling components Suz12 and Znf198. This inverse relationship between Plk1 and Suz12/Znf198 occurs in liver tumors from X/c-myc bitransgenic mice and woodchuck hepatitis virus (WHV)-infected woodchucks. Employing these animal models and HBV replication models the team identified a set of genes repressed by the Suz12/PRC2 remodeling complex. Specifically, CCND2, EpCAM and IGFII expression was elevated at the proliferative and preneoplastic stages in X/c-myc bitransgenic livers, whereas BAMBI and PLK1 were over-expressed in hepatic tumors from X/c-myc bitransgenics and WHV-infected woodchucks. Importantly, most of these genes were selectively up-regulated in HBV-induced HCCs. ***Conclusion:*** The distinct expression profile of the identified Suz12 repressed genes in combination with the proliferation genes hold promise as biomarkers for progression of chronic HBV infection to HCC.

Project 2: The team is investigating the molecular mechanisms involved in instructing pluripotent Neural Crest (NC) cells to differentiate to sympathoadrenal (SA) neurons and melanocytes. The goal of the work is to understand how the intensity of cAMP signaling in combination with hypoxia instructs NC toward these two cell fates. The research has determined key molecules involved in this differentiation process, with focus now on the protein NRSF/REST which suppresses neuronal gene expression in non-neuronal cells, while promoting melanocyte development. Intriguingly, a variety of human tumors, e.g., breast, ovary, lung and prostate, activate expression of neuron–specific genes.

Since embryonic development provides a context for understanding disease pathogenesis, the team members are exploring the link between NRSF/REST function and neuroendocrine cancers of the prostate. Understanding the pathogenesis of neuroendocrine prostate cancer is of significance because of its link to the aggressive, metastatic and life-threatening form of the disease. The team has identified a group of microRNAs as potential prognostic indicators of aggressive PCa.

Also see p. 156.

R. TIMOTHY BENTLEY

Dr. Bentley's cancer research interests are:

1) The use of spontaneously occurring brain tumors in dogs as a translational model for human disease, especially glial tumors such as glioblastoma multiforme. Spontaneously occurring canine gliomas successfully recapitulate the human disease, and offer promise as an improved model over rodent xenografts.
2) Novel therapeutics for intracranial neoplasia (human and veterinary). Assessment of improved surgical and chemotherapeutic treatment strategies.
3) Biomarkers of cancer and of angiogenesis. Improved prognostication for human and canine brain tumors, and identification of novel treatment targets.
4) Cancer cell primary culture and cancer stem cell culture: Proteomics and the effect of emerging therapies.
5) Brain Tumor neuroradiology

CANCER MODELS AVAILABLE:

1) Pet dogs presenting to the specialist veterinary hospital with intracranial neoplasia represent a ready source of diverse, real-life brain tumors for study of emerging therapies. Unlike traditional rodent models, cases enrolled in canine clinical trials have diverse subtypes of brain tumors in diverse locations, along with varying genetic mutations and levels of neurological impairment. In this respect, dogs with brain tumors represent much more accurate models of human glioma than immunodeficient laboratory animals harboring genetically identical xenografts. However, unlike humans, pets presenting with brain tumors can be included in treatment trials of agents that do not have FDA approval, offering a stepping stone between laboratory assessments and the design of human clinical trials.
2) Bentley's team is currently developing primary cultures and cancer stem cell cultures of multiple subtypes of canine glioma with collaborators in the Purdue Bindley Bioscience Building.

TECHNIQUES AVAILABLE:

1) Canine and feline patients: Brain tumor MRI; Neurosurgery including intracranial tumor resection, automated tumor resection device. The Purdue College of Veterinary Medicine also has on-site radiation therapy facilities and a medical oncology service.
2) Bentley is currently developing a quantitative assessment of canine angiogenesis with collaborators at the IU School of Medicine.

JEFFREY BOLIN

Dr. Bolin's research is in structural biology, a field that lies at the interface between molecular biology, biochemistry, and biophysics. The team studies relationships between the three-dimensional structures of proteins and their functions at atomic resolution through the application of X-ray crystallography in combination with other biophysical and biochemical methods.

One project targets enzymes involved in the biodegradation of aromatic compounds, a process that has potential applications in the bioremediation of many deleterious pollutants. For example, team members study several enzymes from a bacterial pathway that has a partially developed ability to degrade polychlorinated biphenyls, PCBs. These notorious, man-made chemicals have the potential to promote cancer and adversely affect neural development. They also contaminate the soils, rivers, and lakes of Indiana and other manufacturing states, as well as many other locations throughout the world.

By analyzing the structure and function of enzymes that can partially degrade PCBs, team members contribute to an international effort to develop a safe process that can be used to eliminate PCBs from storage sites and the environment. In addition, some of the enzymes they study have applications in biotechnology, such as in the synthesis of drugs and other chemicals. Understanding how the enzymes work also advances these applications.

PATRICIA BOLING

Dr. Boling's research deals with three major areas of political life: how problems rooted in private life (e.g., the family, sexuality, reproductive matters, intimate relationships) come to be understood as political issues; comparative family support policies in France, Germany, Japan, and the United States, focusing on how countries' political histories and processes shape outcomes; and food cultures and how they are shaped by national level agricultural, school lunch, and nutrition policies in France and the United States. She is interested in breast cancer as it relates to the politics of social welfare policymaking, especially health and nutrition policies.

RICHARD BORCH

Dr. Borch's laboratory has a longstanding interest in the development of new drugs for the treatment of cancer. Current efforts are focused on the design, synthesis, and activation mechanisms of novel prodrugs that undergo enzyme-catalyzed activation in the tumor cell to liberate a toxic phosphoramidate, phosphate, or phosphonate.

Several different targets are under investigation to exploit this approach. First, team members have applied this novel prodrug chemistry to the design and synthesis of novel phosphotyrosine peptidomimetic prodrugs that interfere with cell signaling pathways regulating cell proliferation. Cell-based assays have confirmed that the phosphotyrosine peptidomimetic prodrugs deliver the bioactive phosphate and inhibit tumor cell proliferation.

Second, the lab also has extended this chemistry to the synthesis of phosphatase-resistant phosphopeptidomimetics by incorporating a difluoromethylphosphonate group as a non-hydrolyzable phosphate surrogate. This provides technology for the design, synthesis, and intracellular delivery of long-lived phosphate-based antagonists and phosphatase inhibitors. Recent work in collaboration with the Geahlen laboratory has identified a novel kinesin target and led to the development of potent cell growth inhibitors that act via this target. In collaboration with the Gibbs lab, team members have developed a novel series of prodrugs designed to inhibit farnesyl transferase, an important enzymatic target in tumor cells. Although these prodrugs have minimal activity as single agents, in combination with the widely used statin drugs, they are nanomolar inhibitors of tumor cell proliferation and induce a potent G1 cell cycle arrest.

Finally, many of these prodrugs are highly lipophilic and therefore difficult to deliver. Borch's team has developed novel polyamidoamine (PAMAM) dendrimer technology in which intracellular prodrug activation simultaneously releases the bioactive phosphomimetic from the dendrimer. Thus, prodrugs having extremely high lipophilicity have been incorporated into dendrimers that are highly water soluble and in which the prodrugs retain bioactivity.

Also see p. 157.

CAROL BOUSHEY

Dr. Boushey's research interests include dietary assessment methods, adolescent dietary behaviors, school-based interventions, food insecurity, and applications of quantitative methods. She led two multi-site randomized school trials that resulted in the No Bones About It! and Eat Move Learn programs for middle schools.

Dr. Boushey's epidemiological research in the study of populations and what and how people eat has aided in identifying psychosocial factors influencing consumption of calcium-rich foods in adolescents and their parents, as well as influences on bone mass in early adolescent girls.

Dr. Boushey is collaborating with engineers to develop methods of dietary assessment that use advanced digital technology and concepts completely new to the field of dietary assessment.

CHARLES BOUMAN

Dr. Bouman's research focuses on the use of statistical image models, multiscale techniques, and fast algorithms in applications including medical, materials, and electronic imaging. A major technical focus of his research is in image reconstruction and formation for medical applications. In particular, his research in model-based image reconstruction is used in commercial CT scanners to reduce X-ray dosage and improve image quality.

SCOTT BRIGGS

Dr. Briggs focuses on epigenetics (changes in gene expression without altering the DNA sequence) and how histone methyltransferases and demethylases control gene expression profiles in a cell. In the eukaryotic cell, DNA is associated with protein factors to form chromatin. The fundamental repeating unit of chromatin is called the nucleosome, where 146 base pairs of DNA are wrapped around two copies of each histone protein (H3, H4, H2A, and H2B). An important role for histone proteins is to help in the compaction of the genome into the nucleus of the cell. However, this compaction of DNA can restrict nuclear factors from gaining access to the DNA template. Therefore, this inherently restrictive environment must be regulated and organized to allow permissive cellular processes such as gene transcription, replication, recombination, repair, and chromosomal segregation.

Posttranslational modifications on histones such as acetylation, phosphorylation, ubiquitination, and/or methylation play key roles in epigenetic gene regulation. Therefore, histone modifying complexes that epigenetically regulate gene expression are vital to biochemically and functionally understand. Team members are interested in studying the machinery that mediates these modification and how misregulation of these enzymes can alter signaling/metabolic pathways that lead to a disease state such as cancer.

Also see p. 158.

KIMBERLY BUHMAN

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.

JAY BURGESS

Oxidative stress, defined by the accumulation of reactive oxygen species (ROS), is implicated in the development of many chronic and degenerative diseases as well as some psychological disorders. ROS accumulation damages cellular macromolecules and can lead to loss of polyunsaturated fatty acids (PUFA) and endogenous antioxidants.

Dr. Burgess and his cohorts have been studying the role of oxidative stress and omega-3 fatty acid status in attention-deficit/hyperactivity disorder (ADHD) for a number of years. This work has involved studies in humans and animals. They have shown that a subpopulation of children with ADHD exhibit PUFA imbalances which may result from oxidative stress. Further work, in an animal model of ADHD, showed that supplemental treatment with the antioxidant nutrient vitamin E reversed brain PUFA deficits, elevated blood and brain antioxidant status to control levels, and improved behavior.

Burgess also has been studying whether flavonoid antioxidants exhibit this function in vivo. In this work, conducted in rodents, he has shown that although flavonoid compounds like naringenin and epigallocatechin gallate (EGCG) exhibit very good peroxyl-radical scavenging antioxidant activity in vitro, they are unable to compensate for deficiency of the essential antioxidant nutrients vitamin E and selenium. However, his studies with EGCG in vivo are suggestive of a synergy with vitamin E which has been previously proposed.

A current research effort is focused on the role of oxidative stress in the complications of diabetes and the potential for dietary antioxidants to ameliorate these complications. Studies are underway in a diabetes animal model and in cells representing peripheral neurons which are susceptible to the complications of diabetes. He also continues to pursue studies to determine the relationship between oxidative stress, antioxidant nutrient intake, and omega-3 fatty acid status in children and young adults with behavioral disorders.

IGNACIO CAMARILLO

Obesity is a major health concern and is associated with breast cancer incidence, tumor invasiveness, and higher cancer morbidity rates. Understanding of the mechanistic links between obesity and cancer progression is limited.

Furthermore, the epidemic of childhood obesity emphasizes a need to define the influence of early excess adiposity on cancer. In addressing these issues, Dr. Camarillo aims 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.

Towards these goals, team members have developed a rat model of early onset obesity and breast cancer. They have shown that Western diet-fed obese rats develop greater numbers of highly invasive mammary tumors, compared to Western-fed diet resistant lean rats. These results are in accord with the link between obesity and breast cancer aggressiveness in humans and support the rat model is a valuable system to identify biomarkers, and epigenomic and metabolomic signatures associated with dietary effects on tumor progression and on therapeutic response of tumors.

Camarillos' lab also has recently used proteomic and genomic methods to identify actions of the adipocytokine leptin on mammary tumor cell growth. The team has revealed leptin regulates the secretion of several growth factor and extracellular matrix proteins and that leptin regulates numerous genes including those involved in cell cycle and metastasis. Uncovering these factors provide valuable clues for defining mechanistic links between obesity, leptin, and tumor progression *in vivo*.

Furthermore, team members have developed a co-culture system that mimics the mammary gland 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, the team has demonstrated that adipose tissue, in the absence of exogenous growth factors or any other culture supplements, can support long-term mammary tumor cell growth. This is a valuable system to study the molecular interplay between microenvironment and mammary tumor cells and to identify cellular and secreted biomarkers for cancer progression.

Finally, the lab works with plant-derived proteins that are a structural homologs of adiponectin, an adipokine with antiproliferative, anti-diabetic, and anti-inflammatory activities. Similar to adiponectin, Camarillo has shown some of these molecules are antiproliferative, anti-migratory, and inhibit cell invasion in aggressive breast cancer cell lines. This demonstrates the potential for these proteins to serve as anti-tumor agents.

Collectively, these works are revealing new insights in the role of diet and obesity on breast cancer and laying a foundation for development of novel strategies for treatment and dietary prevention of aggressive cancers.

Also see p. 160.

CHUN-JU (ALICE) CHANG

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; and
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.

HENRY CHANG

Receptor and non-receptor tyrosine kinases (NTKs) regulate diverse cellular processes, including survival, proliferation, differentiation, and migration, and disruptions of these genes have been linked to numerous human disorders, including cancers. Among the NTKs, ACK1 represents a unique class, as it has the capability of directly interacting with the active form of Cdc42, a central regulator of actin cytoskeleton and cell polarity (Manser et al., 1993). Recent genome association studies have linked ACK1 to enabling metastasis, raising an intriguing possibility that ACK1 cooperates with Cdc42 to promote cell motility (van der Horst et al., 2005). Indeed, point mutations resulting in elevated ACK1 kinase activity have been detected in tumor samples, further strengthening an oncogenic role of ACK1 in cancer progression (Prieto-Echague et al., 2010). However, the biological processes regulated by ACK1 under normal conditions are not well understood. Furthermore, the functional relevance of its interaction with Cdc42, and the identity of upstream regulators and downstream substrates/effectors remain elusive. As several groups have designed ACK1 inhibitors to battle cancers, a better understand of ACK1 function under physiological condition is needed to evaluate the efficiency and safety of this approach.

We have used *Drosophila* to investigate the physiological roles of Ack family kinases. Mammals have two Ack-related genes, ACK1 and TNK1, and both are implicated in oncogenic processes. Like mammals, *Drosophila* contains two Ack-related genes, *dAck* and *dPR2*, with *dAck* bearing higher amino acid sequence similarity to ACK1. We have demonstrated that dAck is the functional homolog of ACK1 and its tyrosine kinase activity is essential for spermatogenesis in a cell autonomous manner (Abdallah et al., 2013). In addition, dAck forms a complex with Dock (dreadlocks, the *Drosophila* homolog of Nck), and its kinase activity is critical for Dock subcellular localization in differentiating male germ cells. Collectively, our results suggest that dAck-dependent phosphorylation generates specific phosphotyrosines, which recruits Dock via its SH2 domain and assembles multi-protein complexes with its SH3 domains to promote sperm morphogenesis. Taking advantage of our progress, we will use genetic and biochemical approaches to identify additional relevant regulators and downstream effectors/substrates, which will be critical to further understand the role of Ack family kinases.

HARRY CHARBONNEAU

Dr. Charbonneau's research focuses on the Cdc14 phosphatases, a conserved group of enzymes that play important roles in controlling protein phosphorylation during mitosis. In collaboration with Dr. Mark Hall's group (*Biochemistry*), the Charbonneau lab has recently discovered new details about the substrate specificity of the Cdc14 phosphatases.

For many years, Cdc14 phosphatases have been thought to act in opposition to cyclin-dependent kinases (Cdks) by dephosphorylating either phosphoserine (pSer) or phosphothreonine (pThr) residues in its protein substrates. We discovered that yeast Cdc14 actually possesses a strong preference for pSer over pThr at Cdk sites. We showed that this substrate specificity is conserved among all Cdc14 phosphatases and identified key structural features of the active site that account in part for the ability of the enzyme to discriminate between pSer and pThr residues. These unexpected findings require a refinement in the current dogma and reveal that Cdc14 phosphatases act only on a subset of Cdk sites.

Mechanisms governing the timing and order of Cdk site dephosphorylation are crucial for proper coordination of late mitotic events and the maintenance of genome stability. The unique substrate selectivity of Cdc14 may provide a mechanism for setting the order and timing of Cdk substrate dephosphorylation. We will examine the role of Cdc14 in setting the order in which Cdk sites are reversed during exit from mitosis. The strict selectivity of Cdc14 can be used in identifying novel substrates and will be employed in studies to elucidate the role of yeast Cdc14 in cytokinesis and in efforts to delineate the function of human Cdc14 isoforms by identification of their targets.

JUE CHEN

Dr. Chen's lab is interested in studying the structure and function of membrane proteins, specifically, in understanding how ATP-binding-cassette (ABC) transport systems exert their functions. Many cancer cells are resistant to drugs or become resistant during chemotherapy. This phenomenon is largely caused by the over-expression of a number of ABC transporters in tumor cells, such as the multidrug transporter P-glycoprotein (P-gp) and the multidrug resistance associate proteins (MRP). P-gp or MRP confers the drug resistance by pumping the drugs out of the cells and thus reducing their cytotoxicity. Therefore elucidating the structural and function of the transporter is essential for identifying agents to reverse the multidrug resistance in cancer.

JI-XIN CHENG

Dr. Cheng's lab is tackling several key questions, including

1) Lipid metabolism in aggressive prostate cancer and breast cancer
3) Effective nanomedicine for cancer elimination

Team members are developing

1) multimodality nonlinear optical microscopy for imaging of human cancer tissues
3) an endoscope for label-free diagnosis of prostate cancer
4) adaptable micelles for anti-cancer drug delivery without premature drug release in the blood

Also see p. 161.

MICHAEL CHILDRESS

Dr. Childress's primary research interest is canine lymphomas, particularly regarding the use of these naturally-occurring cancers in pet dogs as a preclinical research model for non-Hodgkin's lymphomas (NHL) in man. Naturally occurring lymphomas in pet dogs represent a largely untapped resource for developing new diagnostic and therapeutic modalities for humans with NHL. Canine lymphomas are remarkably similar to human NHL in their biology, histology and molecular pathology. Some of the genetic perturbations specific to certain types of human NHL have been documented in the canine counterpart. For example, the *MYC:IgH* gene translocation characteristic of Burkitt's lymphoma in man has been identified in Burkitt-like lymphoma in dogs. In contrast to induced lymphomas in immune-deficient laboratory animals, canine lymphomas occur spontaneously in an outbred host species with an intact immune system. Thus, lymphomagenesis in the dog may better recapitulate the same process in man than does the forced induction of this cancer in laboratory species.

In addition to the biologic similarity between canine lymphoma and human NHL, there are also many logistical advantages to studying lymphoma in dogs. First, lymphoma is among the most common spontaneous tumors to occur in dogs, with an incidence rate similar to, or possibly higher than, the incidence rate in humans. Therefore, affected dogs may be accrued rapidly into clinical trials. Dogs are physically larger than most laboratory species; this allows collection of large tissue and body fluid samples, and facilitates use of standard diagnostic imaging modalities such as radiography, ultrasonography, CT, MRI, and PET. Standards of care for canine lymphomas are poorly defined, allowing ethical enrollment of pet dogs into therapeutic clinical trials in the absence of previous (often multiple) treatment failures which precede the enrollment of most human patients into similar trials. Finally, owners of pet dogs with cancer are usually enthusiastic to participate in clinical trials — clinical trials may provide treatment that would otherwise be financially unaffordable or may be perceived to generate new knowledge that will benefit humans or other dogs with cancer.

In the United States, non-Hodgkin's lymphoma is the sixth-most commonly diagnosed cancer and is also the sixth-leading cause of cancer-related death. In 2013, NHL will be diagnosed in approximately 70,000 people in the United States, and will claim approximately 20,000 lives. Although therapeutic advances over the last two decades have dramatically improved the curability of NHL, clearly there is continued need for new and better treatments. For the reasons mentioned above, naturally-occurring lymphomas in pet dogs may serve as an important preclinical model which will help accelerate the development of new treatments for humans with NHL.

Childress's team is currently pursuing several projects in canine lymphoma (for more information, go to http://www.vet.purdue.edu/pcop/). He would welcome communication from any investigators interested in collaborating in the study of these cancers.

JEAN CHMIELEWSKI

Research in drug discovery focuses on developing agents and strategies to improve the brain penetration of anti-cancer therapies. For instance, potent inhibitors of multidrug resistance transporters present at the blood-brain-barrier, such as P-glycoprotein and ABCG2, have been developed that effectively reverse drug resistance in cell culture and show efficacy in a brain capillary model.

Research efforts in bionanotechnology focus on the development of collagen-based materials for the spatial and temporal release of protein therapies, such as growth factors, and the development of scaffolds to allow delivery of therapeutics into specific cells. Cell penetrating polyproline scaffolds have promoted the facile entry of small molecules, biopolymers, and gold nanoparticles into cells, whereas folate-conjugated hydrogel nanoparticles displayed specific toxicity for cancer cells displaying the folate receptor.

Also see p. 162.

HYUNYI CHO

Hyunyi Cho has conducted research on skin cancer prevention. Research has investigated media portrayals of tanning, skin cancer, and prevention, media effects on tanning and skin cancer related beliefs and intentions, and the processes underlying media effects on beliefs and intentions relevant to tanning and skin cancer. Cho's overall program of research focuses on risk communication and health communication. Current program of research investigates effects of communication on judgments and actions relevant to environmental risk and health risk and the role of messages and the media in social change and behavior change processes.

CHRIS CLIFTON

Dr. Clifton's research interests are in the areas of computer science and information security. He works on challenges posed by novel uses of data mining technology, including privacy-preserving data mining, data mining of text, and data mining techniques applied to interoperation of heterogeneous information sources.

Fundamental data mining challenges posed by these applications include extracting knowledge from noisy data, identifying knowledge in highly skewed data (few examples of "interesting" behavior), and limits on learning. He also works on database support for widely distributed and autonomously controlled information, particularly information administration issues such as supporting fine-grained access control. He has recently been applying this work to protecting privacy in healthcare data used in research settings, particularly anonymization techniques and methods for analysis of anonymized and encrypted data.

DAVID COLBY

The emergence of drug-resistant diseases has contributed to a growing need to develop innovative treatments. Dr. Colby's research interests are directed toward key therapeutic areas, such as cancer, which is one of the most prominent and deadly diseases when drug-resistance is present.

Natural products have traditionally provided a rich source of drugs for many diseases, including cancer. Specifically in the laboratory, team members seek to use natural products as potential leads for drug discovery in drug-resistant cancer. In order to accomplish these objectives, team members will blend the science of medicinal chemistry and synthetic organic chemistry through the use of natural product synthesis and the design of structurally-related analogues for structure-activity investigations.

Also see p. 163.

R. GRAHAM COOKS

Mass spectrometry is the major interest in Dr. Cooks' lab, including its potential applications in clinical diagnostics and in intra-surgical analysis. In pursuing these applications, the group is involved in developing small hand held mass spectrometers that can be used in the diagnostic lab, in the clinic and in the operating room. These small mass spectrometers — Mini MS systems — are capable of tandem mass spectrometry so that complex materials can be examined directly in air and without the usual extensive separation and sample work-up.

Simplifying the complex procedures that are involved in most biological analyses requires ambient ionization methods – methods of creating ions in the ambient environment without pretreating the samples. The first of these methods, desorption electrospray ionization (DESI), this is now in use with Mini MS to create a powerful method for examination of biological tissue in situ.

Tissue examination by DESI provides information on the wide variety of lipids in tissue. When the spray used in DESI is allowed to impinge on a point on the sample a mass spectrum is recorded and as the sample is moved under the spray, a chemical image of the tissue section is recorded. The data provide information on the spatial distribution of particular lipids, information that can be compared with standard histological and histochemical data. In bladder, testes, kidney, brain, and other tissues, correlations are emerging between DESI chemical images and the independently determined disease state of the tissue.

Also see p. 164.

BRUCE CRAIG

Dr. Craig's areas of interest include:

1) Diagnostic testing (sensitivity, specificity and test calibration)
2) Healthcare outcomes and utilization
3) Population modeling
4) Protein Structure Determination via small-angle x-ray scattering
5) Bayesian hierarchical modeling to address various problems in the biological sciences
6) Markov chain Monte Carlo and other simulation-based estimation techniques
7) Statistical Education
8) Design and analysis of genomic experiments
9) Spatial statistics

WILLIAM CRAMER

Dr. Cramer's research is on the structure-function of membrane proteins. Specific research focuses on:

1) Structure-function of energy-transducing proteins
2) Receptor function in the import of cytotoxins, antibiotic resistance.
3) Crystallization of receptors to guide vaccine development for disease mediated by gram-negative bacteria.
4) Discrete ion channel formation by alpha-synuclein; Parkinson's Disease

MARK CUSHMAN

Dr. Cushman's research group is engaged in the design and synthesis of a variety of molecules that interact with specific enzymes and membrane-bound receptors. This effort involves the integration of basic concepts in organic reaction mechanisms, synthetic organic chemistry, structural biology, biochemistry, computational chemistry, and pharmacology. At the present time, potential anticancer agents and antibiotics are being designed, synthesized, and tested.

In the anticancer drug development area, team members are focusing on novel indenoisoquinoline inhibitors of topoisomerase I. Work in this area has led to the synthesis of indenoisoquinolines containing amine side chains that confer exceptional potency as topoisomerase I inhibitors and as cytotoxic agents in human cancer cell cultures. Two indenoisoquinoline topoisomerase I inhibitors (LMP400 and LMP776) synthesized by the Cushman group have entered phase I clinical trials for treatment of cancer patients at the National Cancer Institute, and definite plans are being formulated to commence phase II clinical trials. The results of these clinical trials have been very promising, with no "show stoppers" involving bad ADME properties, lack of effects on biomarkers, or severe toxicities. In fact, the shrinkage of lung nodules in one cancer patient with colon cancer metastasis that was unresponsive to an array of established anticancer drugs, including irinotecan, after only one course of treatment with LMP400, is very encouraging. Recent work on the indenoisoquinolines has focused on synthesizing dual inhibitors of topoisomerase I and tyrosyl-DNA phosphodiesterase I. Since topoisomerase I inhibitors cause DNA breaks and tyrosyl-DNA phosphodiesterase I is involved in repairing them, the dual inhibitors my act synergistically to produce very potent anticancer activity. Strategies are also being investigated that are intended to target indenoisoquinolines specifically to prostate cancer cells and not normal cells in order to minimize undesirable systemic toxicity and improve efficacy.

Aromatase inhibitors are widely used in the treatment of breast cancer. However, they have significant side effects, including reduction in bone density leading to increase incidence of fractures, severe musculoskeletal pain leading to reduced patient compliance, and increase frequency of cardiovascular events. These undesirable effects are thought to be due to global estrogen depletion directly resulting from inhibition of aromatase. Cushman's research group is presently synthesizing aromatase inhibitors that also bind to estrogen receptors in normal cells and are designed to produce estrogenic effects in non-tumor tissues. The overall goal of this project is to design and synthesize compounds that inhibit estrogen production, block estrogen receptors in breast cancer cells, and stimulate estrogen receptors in normal cells. This is expected to result in an anticancer drug that would effectively treat breast cancer while greatly improving the quality of the lives of patients undergoing breast cancer chemotherapy.

Cancer prevention obviously offers distinct advantages over cancer treatment. A number of receptors that are involved in carcinogenesis are therefore being targeted by the Cushman group, including quinone reductases 1 and 2, NFκB, retinoid X receptor, inducible nitric oxide synthase, the estrogen receptor, cyclooxygenases 1 and 2, MAPKs (p38 and Jun N-terminal kinase), and p21.

Also see p. 165.

V. JO DAVISSON

Dr. Davisson's research is in the following areas:

(1) *Emerging biomolecular targets and pathways*: Focus on non-druggable protein interactions to modulate specific binding partners or allosteric modulation of target proteins; V-ATPase in tumor microenvironment and metastatic progression, mitochondrial regulation by functional agonists of Bax, selective modulation of DNA replication/repair systems by functional antagonism of PCNA assembly and regulation

(2) *Potential biomarkers for early-stage cancer*: The use of advanced proteomic/genomic detection to pursue quantification of post-translational modifications as early indicators

(3) *Compounds or combinations with novel tumoristatic activities*: Role of polyunsaturated fatty acid ligands in tumor targeting; Re-purposing statins for selective tumor down-regulation through lipid conjugation; Drug conjugates of V-ATPase antagonists

(4) *Tumor targeting and sub-cellular localization* : Receptor ligand discovery efforts for several families relevant to cancers; Drug-conjugate chemistry and sub-cellular localization; Ligands for specific vesicle transport systems to mitochondria and nucleus

(5) *Screening and development assays:* Innovative proteomic and genomic assay systems for target-pathway specific pharmacodynamics; Multi-parameter/high content and phenotypic cell-based screens; High content phenotype screens genome-wide screening based upon model organisms or RNAi; Animal models for testing anti-metastatic drugs; in vitro 3D tumor models for predictive high content screening platform;

Collaborative efforts with J. Paul Robinson

(i) *Diagnostics*: Cutting-edge development and application of the molecular cytomics for early detection and prognosis in cervical cancer, Cytometric detection and informatics systems for blood disorders and early disease prognosis

(ii) *Screening and development assays*: Platform development using multi-parameter, high content screening technologies for lead discovery and lead optimization; Predictive in vitro and in vivo animal models for risk of mitochondrial toxicity; Image-based screening technologies; Therapeutic classification systems for predictive pharmacology

Also see p. 166.

EDWARD DELP

Dr. Delp's research interests are in the following areas:

1) image and video compression
2) multimedia systems
3) image processing
4) parallel processing
5) computer vision
6) medical imaging
7) communication and information theory

REBECCA DOERGE

Dr. Doerge's research lies on the interdisciplinary boundaries of many fields (mathematical and statistical sciences, biological and plant sciences, genomics and epigenomics) that are currently involved in assessing genomic based questions.

Statistical bioinformatics brings together many scientific disciplines to ask, answer, and disseminate biologically interesting information in the quest to understand the ultimate function and control of DNA. Toward this end, her research program encompasses four broad areas as applied to both diploids and polyploids:

1) the development of statistical methodology for quantitative trait loci (QTL) mapping and transcriptomics (microarrays and next-generation sequencing)
2) the analysis of genetic mapping and (expression) QTL experimental data
3) the analysis of the epigenome
4) the development of methodology to combine data and/or results from genomic and epigenomic investigations.

ULRIKE DYDAK

Dr. Dydak's research interest is in the area of *in vivo* Magnetic Resonance Imaging (MRI) and focuses on the investigation of human *in vivo* metabolism by means of Magnetic Resonance Spectroscopy (MRS). She has expertise in the development of new MRI and MRS acquisition and reconstruction techniques, and in the design and implementation of clinical and pre-clinical MRI/MRS studies.

One focus of her group is to develop and validate novel phosphorus-31 (^{31}P) Magnetic Resonance Spectroscopic Imaging (MRSI) techniques, aiming at improving early treatment monitoring in liver cancer and understanding the metabolic response to radiation treatment. A novel and so far unique dual-tuned ^{1}H/^{31}P phased-array coil has recently been devised, that allows both clinical imaging and measuring the liver's energy metabolism at the same time, being sensitive to the whole human liver. Using this novel coil, ^{31}P MRSI has shown promising pilot data to distinguish tumors responding versus non-responding to radiation treatment within six weeks, i.e. months earlier than the RECIST imaging criteria used conventionally in the clinic. Dr. Dydak's group currently investigates the utility of ^{31}P MRSI as a treatment monitoring tool in liver cancer patients treated with ^{90}Y radioembolization or with Stereotactic Body Radiation Treatment (SBRT).

Due to the extreme radiation sensitivity of the liver, understanding the direct response of both healthy and malignant liver tissue to ionizing radiation is of utmost importance. Dr. Dydak's group continues to develop and optimize a high spatial resolution 3D protocol for ^{31}P MRSI and apply it in patients with hepatocellular cancer to assess spatially resolved changes in energy metabolism in correlation with radiation dose maps within 24-72 hours after radiation treatment.

DAVID EBERT

Dr. Ebert's cancer care engineering research has focused on both macro and micro-scale cancer engineering problems. At the macro level, team members have focused on creating tools and systems to analyze cancer incidence and mortality rates. Relative grouping of cancer statistics for analysis and summary reporting is an important task for public health officials. Unfortunately, summary statistics of cancer data are either provided only by geographic unit (county, state, etc.), or by population demographic unit (age, ethnicity, etc.). In the case of summarizing cancer statistics on a county by county basis, the disparity between data collected in rural and urban counties is often detrimental in the appropriate analysis of cancer care statistics. Low counts drastically affect the incidence and mortality rates of the data, leading to skewed statistics. One common method of handling this is to simply summarize the cancer data by population demographics within a state, ignoring the spatial data components. The team's work has focused on developing a system that allows analysts to create demographic clusters of their data while maintaining the spatial data constraints. Their scheme increases the stability of the reported cancer rates by aggregating areas with similar demographics through interactive spatial clustering. Interactive selection of demographic groupings allows analysts to ask questions of their data and see reports displayed on an interactive map. Users may scroll through time and use a novel dual time slider control to compare changes in rates with a variable lag time.

At the micro level, team mebers have focused on developing tools for researchers to more effectively explore gas chromatography data. To this end, they have developed a system that enables interactive comparative visualization and analytics of metabolomics data obtained by two-dimensional gas chromatography-mass spectrometry (GCxGC-MS). The key features of this system are the ability to produce visualizations of multiple GCxGC-MS data sets, and to explore those data sets interactively, allowing a user to discover differences and features in real time. Their system provides statistical support in the form of mean and standard deviation calculations to aid users in identifying meaningful differences between samples. They combine these with multiform, linked visualizations in order to provide researchers with a powerful new tool for GCxGC-MS exploration and bio-marker discovery. This system provides several features not currently available in other GCxGC-MS analysis systems including a comparative visualization window that allows multiple samples to be displayed simultaneously, data exploration tools for exploring mass spectra and filtering and comparing TIC images in real-time, the grouping of samples and statistical analysis tools for advanced data comparison, the application of mean and standard deviation TICs to the colormapping of difference measures, and a dynamic color scale adaptation tool for discovering sample differences.

DONNA FEKETE

Dr. Fekete's laboratory is interested in the regulation of cell proliferation and the specification of cell types during development of the vertebrate inner ear. The Wnt signaling pathway has emerged as playing a signficant role in these processes. While Wnts serve to promote cell proliferation of the inner ear epithelium at early stages, proliferation then ceases to allow cell differentiation to proceed. Excessive Wnt signaling gives rise to colorectal cancer in humans via the dysregulation of cell proliferation. In contrast, while forced activation of the Wnt signaling pathway during inner ear development indeed increases cell proliferation, the cells can nonetheless override such a perturbation to pull out of division and differentiate into enlarged sensory organs. Experiments are being conducted to ask whether this cessation of cell division occurs through the action of negative feedback loops that utilize microRNAs to repress the translation of Wnt signaling components as a feature of normal development.

The Fekete lab is using several different approaches to look for interactions between microRNAs and the Wnt signaling pathway. In one set of experiments, organ cultures of the developing mouse cochlea are established and treated with Wnt activators or inhibitors. Chicken embryos are used as a second model system, where it is possible to manipulate either the Wnt pathway or microRNAs as the animal develops in ovo, thus permitting changes in cell numbers, cell fates and gene expression to be monitored over a longer time window. In both cases, transcriptome profiling will be used to identify genes and microRNAs that are regulated by Wnt signaling, and to ask whether different Wnt ligands activate different downstream pathways. Candidate genes identified by these screens will then be tested for their ability to influence distinct aspects of cell differentiation, such as the cessation of cell proliferation, the differentiation of different sensory cell types or the sources of axonal innervation. Of particular interest will be a search for evidence that Wnt signaling can alter levels of specific microRNAs and that these microRNAs can in turn target and repress Wnt-related transcripts.

The results of these studies may offer strategies for the design of biological-based therapeutic treatments for the regenerative repair of hearing loss by directing stem cells along specific differentiation pathways. Another possible outcome is that these data may offer insights into why cancers of the epithelium of the inner ear do not exist, perhaps by identifying molecular mechanisms that keep Wnt-mediated cell proliferation in check as this tissue develops.

JAMES FLEET

Dr. Fleet's research group is focused on the mechanisms underlying the development of cancer and the evaluation of environmental conditions that modulate that process. Epithelial cell cancers result from accumulation of gene mutations or chromosomal aberrations in cells, leading to unrestrained cellular proliferation that is the basis for tumor formation. Development of cancer can be accelerated by conditions that cause DNA damage such as tissue inflammation.

A number of dietary factors have been proposed to reduce cancer risk either directly or by inhibiting cancer causing inflammation. For example, evidence suggests that high circulating levels of the nutrient vitamin D reduce the risk for certain cancers and that this protection is due to events regulated by the vitamin D metabolite 1,25 dihydroxyvitamin D or "calcitriol." While many studies show that calcitriol can suppress cellular proliferation and promote development of mature epithelial cells, recent genomic research from the Fleet lab suggests that calcitriol may also enhance DNA repair mechanisms, increase expression of proteins that protect cells from DNA-damaging oxidative stress, and limit the effects of inflammation mediated through cytokines.

Dr. Fleet's group is testing these hypotheses with a focus on how they relate to prostate and colon cancer. In addition, his group develops animal models for cancer research and conducts preclinical studies to translate basic research findings into the complex physiology the whole animal.

Also see p. 167.

JENNIFER FREEMAN

Dr. Freeman's research interests are in molecular and environmental toxicology, cytogenetics, genomics, and epigenomics. Current research efforts in the Freeman laboratory are 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 dysfunction, and neurodegenerative disorders.

Dr. Freeman has also been involved in the cytogenetic mapping of the zebrafish genome in efforts to establish an accurate and comprehensive genome sequence. She also developed the first array comparative genomic hybridization platforms for the zebrafish that were applied to investigate copy number aberrations in zebrafish developmental mutant and disease models including numerous cancer models (e.g., melanoma, T-ALL, and rhabdomyosarcoma). In addition, these platforms were applied to define and characterize copy number variants (CNVs) in the zebrafish genome.

Also see p. 168.

ALAN FRIEDMAN

Dr. Friedman's research seeks to understand biological structure and its relationship to function by employing a combination of experimentation (structural biology/biophysics) and computation (computational biology/bioinformatics) to answer questions that neither can answer alone. Questions include elucidating structural information from challenging systems and interpreting the interactions that are revealed by structure elucidation to understand function.

In elucidating structural information, team members use the unique ability of computational methods to simulate outcomes and sift through enormous numbers of possibilities in order to plan the most informative experiments to conduct. They then employ traditional biophysical and biochemical techniques (e.g. crystallography, solution X-ray scattering, ultracentrifugation, cross-linking, site-directed mutagenesis) particularly in variant and hybrid methodologies that they are developing (e.g. planned disulfide-trapping, planned stability mutagenesis and decomposition of X-ray scattering from heterogeneous solutions) to probe the real behavior of these systems. The data is then analyzed also with the help of computational methods of the own devising.

In interpreting structure to explain function, team members have developed a series of methods for making and using chimeras of homologous proteins to probe the interactions between protein units. These methods also employ computation to design the most informative sets of chimeras. Chimeras are then created robotically using the recently-developed gene assembly planning and robotic control software and analyzed for stability and activity by well-established means. Here, too, computational models and analyses help them interpret the experimental data.

The model biological systems that team members employ for both kinds of studies are drawn from the longstanding interests in the damage that results to macromolecules upon aging and their repair by cellular processes and by the interaction of organisms as they form symbiotic, mutualistic or parasitic relationships. These are both questions in which macromolecular structure intersects with important evolutionary strategies to determine the health and longevity of organisms and ecosystems.

ROBERT GEAHLEN

Dr. Geahlen's current work is directed in several areas:

STRUCTURE-FUNCTION ANALYSIS OF SYK IN HEMATOPOIETIC CELLS: B cells fail to develop properly in mice lacking the gene for Syk due to the inability of pre-B cell antigen receptors to signal in the absence of the kinase. How Syk mediates signaling through B cell antigen receptors is a major question being investigated. The team has mapped multiple sites of phosphorylation on Syk that are important for its ability to function in B cells. By site-directed mutagenesis and expression studies, they are exploring the role of these phosphorylations in the ability of Syk to complement signaling in Syk-deficient cells. The team also has identified regions of Syk required for its translocation into and out of the nucleus. The role that Syk's nucleocytoplasmic translocation plays in modulating the properties of cells is actively under investigation. In collaboration with Dr. Chang Lu, Geahlen is investigating the use of electroporative flow cytometry as a tool for the analysis of protein translocations in cancer cells.

INTERACTIONS OF SYK WITH INTRACELLULAR PROTEINS: Through the use of genetic and biochemical screens, team members are identifying and characterizing novel Syk-interacting proteins that may be involved both in signal transduction pathways operating downstream of activated Syk and in the subcellular localization of the kinase. In collaboration with Dr. Andy Tao, the lab is using proteomic approaches to identify novel Syk-interacting proteins and phosphoproteomic approaches to identify novel Syk substrates. In collaboration with Dr. Carol Post, team members are examining the structural bases for protein-protein interactions involving Syk.

SYK IN BREAST EPITHELIAL CELLS: In addition to hematopoietic cells, Syk also is expressed in many other cell types including mammary epithelial cells. In breast cancer cells, the expression of Syk is inversely correlated with invasiveness. Team members are exploring the role of Syk in regulating the growth properties of breast epithelial cells. Proteomic approaches are being used to identify the substrates of Syk that mediate its effects on breast cancer cell motility and survival.

INHIBITORS OF PROTEIN-TYROSINE KINASES: In collaboration with Dr. Richard Borch, team members are developing and characterizing chemical probes that target the SH2 domains of protein-tyrosine kinases that mediate protein-protein interactions. We have expanded these collaborations to include additional phosphopeptide-binding domains.

Also see p. 170.

STANTON GELVIN

Dr. Gelvin's research investigates how a soil bacterium, Agrobacterium tumefaciens , genetically engineers plants. Agrobacterium transfers a piece of bacterial DNA, the T-(transferred) DNA, to wounded plant cells where it makes its way through the cytoplasm to the nucleus. Once in the nucleus, T-DNA integrates into the host genome and expresses genes.

Under normal circumstances, these genes cause the tumorous disease Crown Gall on plants. However, scientists have learned to manipulate T-DNA, replacing disease genes with genes of benefit to the plant. Many genetically engineered crop plants with desirable traits (disease resistance, herbicide tolerance, and enhanced nutritional value) were generated using Agrobacterium. Unfortunately, many important crop plants, including those important to Indiana farmers (corn, soybeans, and wheat) remain highly recalcitrant to Agrobacterium-mediated genetic transformation.

In Gelvin's lab, research focuses on understanding the role of host genes and proteins in this natural genetic engineering process. Team members have identified host genes involved in bacterial attachment to plant cells, T-DNA and Virulence protein transfer to and cytoplasmic trafficking within plants, T-DNA nuclear targeting, and T-DNA integration. Recently, they have been able to manipulate some of these genes to improve Agrobacterium transformation efficiency. Team members are currently working with agricultural biotechnology companies to improve the genetic engineering of crops, including those important for Indiana's economy.

Implicit in this basic research is an understanding of how protein/nucleic acid complexes assemble within a cell, how they traverse the cytoplasm and target the nucleus, and how the nucleic acid eventually targets chromatin for integration. The types of sub-cellular trafficking studied in their laboratory have obvious parallels with those of viruses, especially viruses that integrate into host genomes.

ARUN GHOSH

Dr. Ghosh is involved in multidisciplinary research projects in the areas of synthetic organic, bioorganic and medicinal chemistry. Current research interests are in the following areas:

1) synthesis and biological studies of bioactive natural products
2) design and synthesis of molecular probes for bioactive peptides and proteins
3) structure-based design of enzyme inhibitors for Alzheimer's disease and AIDS
4) development of asymmetric methodologies (catalytic and stoichiometric)

The total synthesis and exploration biology of various medicinally important natural products are important parts of his group's research. In this context, group members are investigating the chemistry and biology of anticancer agents laulimalide, peloruside A and jasplakinolides. The team has shown that both laulimalides and pelorusides are potent against paclitaxel and epothiolone resistant cell lines. Furthermore, they have shown synergistic effect with taxol. Ghosh's investigation revealed that both these natural products bind at a site on the tubulin that is distinct from the taxoid site. Team members are now designing novel molecular probes based upon laulimalide and peloruside A. Also, they are planning to locate the drug binding site of laulimalide and peloruside.

Another important research area is the design and synthesis of molecular probes and nonpeptidal turn-mimics for biologically active peptides and proteins. Team members currently are studying critical ligand-binding site interactions of various proteolytic enzymes. This includes memapsin 2, a very significant target for Alzheimer's disease as well as HIV protease, whose clinical effectiveness for the treatment of AIDS has been well recognized.

Also see p.171.

RICHARD GIBBS

Dr. Gibbs employs chemical biology approaches to address two key questions in the field of protein prenylation. His team explores the substrate specificity of FTase, with the goal of developing potential isoprenoid-based inhibitors or modulators of protein prenylation. Secondly, team members use synthetic isoprenoid analogues and labeled derivatives as probes of the biological function of protein prenylation. In more recent work, they are using the synthetic knowledge in the area of isoprenoids to develop inhibitors of the proteolytic cleavage and methylation steps.

The team has developed a new stereospecific route 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. The team has demonstrated that certain farnesol analogues are potent inhibitors of the growth of certain human tumor cells *in vitro*. In a collaborative effort with Dr. Richard Borch's laboratory, team members are synthesizing 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. Efforts to determine their mechanism of action are underway, in collaboration with Dr. Marietta Harrison's laboratory.

A second active area of interest concerning protein prenylation has been the function of this modification — how does it target the attached protein to the appropriate cellular location? The team has used the farnesylated a-factor mating peptide produced by Saccharomyces cerevisiae as a model system to evaluate the role of the prenyl group in the targeting of the prenylated protein to the proper position inside the cell and thus its biological activity. The team has demonstrated that a) a-factor analogues with modified farnesyl groups exhibit a wide range of biological activities and b) the biological activities of these peptides do not correlate with their affinity for model lipid bilayers. These investigations are now being expanded into the realm of mammalian prenylated proteins. Specifically, they are now looking at the ability of prenylcysteine derivatives to bind to rhoGDI, and thus block the interaction of this protein with Rho proteins, which are key mediators of metastatic tumor growth. This work, along with other biological studies, is carried out with collaborators at Wayne State University.

The laboratory has developed a general synthetic route to carbon-13 labeled farnesyl derivatives. In collaborative studies, team members are using solid-state NMR methods and the carbon-13 labeled farnesyl analogues as probes for the conformation of the farnesyl moiety bound in various protein and membrane environments. Understanding the conformations of the prenyl moiety in different environments will help them to design better inhibitors of FTase and other related enzymes and receptors, and will also provide a deeper understanding of the biological function of protein prenylation. The team also has synthesized prenylated peptides that have been used in structural studies by the collaborators at Scripps to develop a deeper understanding of the interaction of prenylated Rab proteins and the prenyl-binding protein RabGDI.

Most recent efforts have been directed toward the development of inhibitors of the enzymes Icmt and RCE1. These two enzymes process Ras after its farnesylation by FTase, and very recent evidence has indicated that they are also potential anti-cancer targets. These studies are in collaboration with Dr. Christine Hrycyna's laboratory in the Chemistry Department here at Purdue.

Also see p. 172.

BARBARA GOLDEN

The focus of Dr. Golden's research is the structure and folding of functional RNAs.

Unlike proteins, RNAs have a highly charged backbone, only four different monomeric units (compared to the 20 amino acids that make up proteins) and functional groups that are largely sequestered within the major and minor grooves of the double helix.

Yet, in the presence of magnesium ion, many RNA molecules have stable, globular, tertiary structures that support biological catalysis. To understand how these molecules fold and function, team members are investigating the structure and function of these RNA molecules using biochemistry, molecular biology, and X-ray crystallography.

ELLEN GRUENBAUM

Dr. Gruenbaum is a culturally-oriented medical anthropologist who has done ethnographic research with a special focus on women's health issues, gender, religious practices, and development in Africa and the Middle East. She has conducted research in Sudan and Sierra Leone on the practice of female genital cutting and the social movements against "harmful traditional practices." Her research interests extend to the development of self-perpetuating cultural discussions of public health strategies through the use of cultural practices, imagery, narratives, and media to promote health knowledge, attitude change, and practical actions applicable to a broad range of health issues.

MARK HALL

Dr. Hall's research focuses on the role of proteolysis in regulating cell division. All cancers arise from loss of control over the cell division cycle. Dr. Hall's lab is interested in basic mechanisms that eukaryotic organisms use to regulate the cell division process and ensure genome stability. The mechanisms of interest to him include proteolysis, the irreversible destruction of proteins, and phosphorylation, a highly dynamic post-translational modification controlled by the opposing activities of kinases and phosphatases. These regulatory processes are essential for proper execution of the cell division cycle in all eukaryotes, and his studies are conducted in a simple eukaryotic model organism, budding yeast.

Much of the team's focus has been on a large ubiquitin ligase called the anaphase-promoting complex (APC), which triggers anaphase onset, mitotic exit, and establishment of a G1 phase by targeting specific cell division proteins for destruction via the ubiquitin proteasome pathway. The Cdh1 protein, one of two activators of APC, is a tumor suppressor and cells lacking Cdh1 function exhibit various types of genome instability. This is not surprising since Cdh1-APC targets several important cell cycle regulators for destruction, including mitotic cyclins, POLO kinases, Aurora kinases, F-box proteins, and regulators of DNA replication that have all been implicated in or associated with human cancers. Hall's studies of Cdh1 regulation also has spurred his team's interest in temporal control of mitotic events by phosphorylation and dephosphorylation, specifically by cyclin-dependent kinase and its opposing phosphatase Cdc14.
Some of his ongoing projects are focused on:

1) How Cdh1-APC activity during the cell cycle is regulated by pseudosubstrate inhibition
2) Regulation of cell cycle proteins by ubiquitin-independent proteolytic mechanisms
3) Regulation of the APC and its activators by phosphorylation and dephosphorylation
4) Mechanisms that regulate the timing of Cdk substrate dephosphorylation during mitosis
5) Development of quantitative mass spectrometric methods for studying phosphorylation and other post-translational modifications

Also see p. 173.

ROBERT HANNEMAN

Dr. Hannemann's research interests are in the following areas:

1) aerosols in medical practice
2) surfactants in respiratory distress syndrome treatment
3) non-invasive diagnostic techniques
4) serum bilirubin determination by skin reflectance
5) application of engineering data analysis to cancer research, specifically childhood leukemia and multiple myeloma

MARIETTA HARRISON

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

Dr. Hazbun studies functional genomics, systems biology, and chemical genetics. Chromosomal instability due to aberrant chromosome segregation is a hallmark of cancer, suggesting that a more detailed and mechanistic understanding of the molecular processes that control the faithful segregation of chromosomes will lead to new therapeutic strategies to control cancer. An example of this promise is evident in the Aurora kinases, which are important regulators of chromosome segregation. Several specific Aurora kinase inhibitors have demonstrated anti-proliferative activities and are proceeding to clinical trials even though team members do not understand the multiple roles of this kinase.

Our research involves the development of functional genomics approaches in baker's yeast, Saccharomyces cerevisiae, to focus on the kinase-signaling network of the yeast Aurora kinase, Ipl1. The downstream effects these phosphorylated substrates have on protein-protein interactions will be determined using an integrated approach relying on a phosphomutant scanning approach in conjunction with two-hybrid technology and systematic genetic studies. Identification of phosphomodulated genetic interactions and phosphomodulated protein-protein interactions related to Ipl1 and its control of mitosis and chromosome segregation in yeast, should serve as a guide toward the analysis of — and ultimately, intervention in — the abnormal mitotic pathways that propagate cancer cells.

Also see p. 174.

CHRISTINE HRYCYNA

Dr. Hrycyna's laboratory takes a multidisciplinary approach to study important integral membrane proteins involved in cancer and cancer treatment. The two major cancer research areas in her 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, her laboratory is investigating the mechanisms of activity and assembly of these membrane-associated proteins as well as developing drugs that inhibit their activities.

ICMT: Mutations in the *K-Ras* oncogene are the key causative agents in >85% of human pancreatic cancers. Isoprenylcysteine carboxyl methyltransferase (Icmt) catalyzes the posttranslational methylesterification of the K-Ras protein. Recent biological studies have demonstrated that inhibition of Icmt results in the mislocalization and loss of transforming ability of K-Ras. Therefore, Icmt provides an attractive and novel anti-cancer target. The goals of her research, in collaboration with the Gibbs and Harrison laboratories, are to develop potent and efficacious Icmt inhibitors to be used in the treatment of pancreatic cancer. *In vitro* biochemical and cellular assays have been developed in their laboratories to assess Icmt inhibition by their novel compounds. Furthermore, experiments are currently underway with Dr. Stephen Konieczny's laboratory to determine the efficacy of these agents 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 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. Their laboratories have synthesized novel compounds and developed *in vitro* biochemical and cellular assays for P-glycoprotein and ABCG2 inhibition. In collaboration with Dr. David S. Miller (NIEHS/NIH), they are testing the 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.

Also see p. 175.

CHANG-DENG HU

Prostate cancer is the second leading cause of cancer death in men in developed countries. Although the majority of prostate cancer patients with localized and low grade tumors can be cured by surgery or radiotherapy, prostate cancer patients with high grade tumors may experience recurrence after surgery or radiotherapy. For example, 30-50% of prostate cancer patients with high grade tumors experience biochemical recurrence within five years after radiotherapy. In addition, patients with metastasized tumors and most recurrent tumors after surgery or radiotherapy are generally treated with hormonal therapy, the most effective, but temporal, control of the disease. Unfortunately, almost all patients are refractory to the treatment within an average of two years, a state called as castration-resistant prostate cancer (CRPC). Patients with CRPC tumors are treated with chemotherapy, but there is no effective treatment available. The focus of the Hu lab is "Molecular Mechanisms and Targeting of Therapy-resistant Prostate Cancer."

1. Regulation and targeting of neuroendocrine differentiation in prostate cancer. Neuroendocrine (NE) cells are present in normal prostate and represent a mall subset of prostatic epithelial cells. Interestingly, a number of stimuli including androgen deprivation therapy (ADT) can induce prostate cancer cells to differentiate into NE-like cells and increase the number of NE-like cells, a process known as prostate cancer neuroendocrine differentiation (NED). NE-like cells are androgen receptor negative, highly resistant to apoptosis, and can also secrete a number of peptide hormones and growth factors to support the growth of surrounding prostate cancer cells. Thus, an increased number of NE-like cells in prostate cancer tissues is linked to poor prognosis. Recently, we have discovered that ionizing radiation (IR) treatment also induces prostate cancer cells to differentiate into NE-like cells. Interestingly, IR-induced NED is reversible and IR-resistant clones derived from the dedifferentiated NE-like cells resume the ability to proliferate and are cross-resistant to IR, the chemotherapeutic agent docetaxel and androgen depletion treatments. These findings suggest that radiotherapy-induced NED may represent a novel pathway by which prostate cancer cells survive treatment and contribute to recurrence. The current effort in the lab is to evaluate the clinical significance of radiation-induced NED. The ultimate goal is to elucidate the molecular mechanisms underlying radiation-induced NED and to develop novel NED-based targeting therapy. In addition, the availability of isolated radiation-resistant sublines will also allow us to determine the molecular pathways in these cells and to identify therapeutic targets for clinically recurrent tumors.

2. Regulation of the androgen receptor signaling by AP-1 proteins. Activator protein 1 (AP-1) belongs to the basic region leucine zipper (bZIP) family of transcription factors and functions as homodimers or heterodimers formed among members of the Fos, Jun, ATF2, and Maf family of proteins to regulate gene expression. AP-1 activity can be induced by both physiological stimuli and environmental stresses, thereby regulating a wide range of cellular processes including cell proliferation, differentiation, death, and stress responses. Deregulated AP-1 activity is implicated in many human diseases including cancer. Furthermore, AP-1 proteins also interact with many other transcriptional regulatory proteins, such as the Rel family, SMADs family, hormone receptors, and coactivators CBP/p300. We are currently investigating how AP-1 proteins crosstalk with the androgen receptor and regulate the androgen signaling in the context of prostate cancer development and the progression to CRPC.

3. Screening of novel protein-protein interaction inhibitors for cancer therapy. We have developed several bimolecular fluorescence complementation (BiFC)-based assays to directly visualize protein-protein interactions in living cells and animals. These assays have enabled identification of several novel and specific interactions (e.g. AP-1 and NF-□B interaction) involved in therapy-resistance. We are also developing BiFC-based high throughput screening assays to screen for inhibitors of protein-protein interactions in living cells. The ultimate goal of these efforts is to identify drugs that specifically disrupt the protein-protein interactions involved in cancer development, progression and therapy-resistance.

Also see p. 176.

KAREN HUDMON

Dr. Hudmon's career goals are directed toward expanding the preventive medicine component of health care delivery and utilization and broadening the clinician's role as an advocate for positive health outcomes through disease prevention, as well as treatment. The approaches that she applies in attaining these goals are transdisciplinary, collaborative, and participatory. For the past 15 years, her primary clinical and cancer-related research focus has been tobacco cessation.

Her work in the area of tobacco research encompasses

1) the identification of predictors of tobacco use, including genetics and environment

2) evaluation of interventions for cessation among various patient populations

3) the development, evaluation, and dissemination of effective tobacco cessation training programs for health-care providers.

Perhaps her most significant scholarly contribution is the creation of a comprehensive, evidence-based tobacco cessation curriculum available for health professional students and licensed health-care providers — Rx for Change: Clinician-Assisted Tobacco Cessation (**http://rxforchange.ucsf.edu**).

JOSEPH IRUDAYARAJ

Dr. Irudayaraj is focused on developing ultrasensitive tools based on nanoscale imaging and nanomaterials to detect dynamic events (phosphorylation, drug diffusion, and nuclear targets), proteins, microRNA, and epigenetic modifications in single cells. His team has developed technologies based on fluorescence and nanoplasmonics to detect epigenetic modifications, alternative splice variants, and phosphorylation in single cells at single molecule resolution in collaboration with PCCR scientists. A significant effort is in place to develop nanomaterials for targeted drug delivery. These single cell studies are now being extended to tissue biopsies and blood samples for cancer screening and early detection. Their group has also fabricated polymeric particles targeting epigenetic modifications for regulation and treatment.

The biological engineering and biophysics laboratory is equipped with pico and femto second lasers for single molecule fluorescence spectroscopy and lifetime imaging, Plasmon hyperspectral imaging with ability to detect a single copy of m/miRNA in single cells, and Raman chemical imaging, stimulated Raman spectroscopy, and second harmonic super-resolution microscopy for intracellular mapping and structure identification of protein interactions relevant for cell function.

Also see p. 177.

ALBENA IVANISEVIC

Dr. Ivanisevic's efforts are centered on using surface techniques to immobilize biomolecules on inorganic and tissue surfaces. Her research utilizes a broad perspective on problems in chemistry, materials and biomedical engineering and is aimed to address the need to understand how to manipulate and tailor the properties of surfaces for the fabrication of better sensor and tissue platforms.

Ivanisevic's group has been working on three distinct projects:

1) fabrication and characterization of III-V semiconductor surfaces composed of lithographically defined biomolecular structures
2) massively parallel manufacturing of nanoscale wires with magnetic and metallic properties
3) high-resolution and -throughput AFM characterization and lithographic tools for tissue engineering applications

QING JIANG

Chronic inflammation constitutes one of the major etiologies of degenerative diseases including cancer. Dr. Jiang's laboratory has demonstrated that natural metabolites of vitamin E forms, long-chain carboxychromanols, inhibit cyclooxygenase- and 5-lipoxygenase-catalyzed reactions, which are key regulators of inflammation and carcinogenesis. Her laboratory is investigating the role of natural forms of vitamin E and their metabolites and polyphenols in berries in chemoprevention and therapy for various types of cancer.

Also see p. 178.

CHANG KIM

Dr. Kim is interested in studying trafficking, differentiation, and effector function of immune cells and their progenitor cells. Current studies in the lab include:

1) roles of gut commensal bacterial metabolites in regulation of cancer and autoimmune diseases
2) roles of effector T cells (Th1 and Th17 cells) and regulatory T cells (FoxP3+ T cells) in regulation of immune responses in normal, inflammatory, or cancerous states
3) regulation of inflammatory bowel diseases and inflammatory cancers in the intestine

Also see p. 179.

YOUNG KIM

Dr. Kim's research interests are in understanding light propagation in biological tissue, developing advanced biophotonics techniques for the quantification of physiological conditions and diseases such as cancer, and further translating these techniques to clinical settings and epidemiological studies. His research includes development of i) novel tissue spectroscopy/imaging techniques for early cancer detection, risk-stratification, treatment assessment, and intraoperative surgical guidance and ii) novel light-based treatment modalities for cancer prevention. In particular, his research group has recent developed mesoscopic (i.e. between microscopic and macroscopic) imaging methods to visualize detailed carcinogenic alterations in a relative large tissue area. In collaboration with the Indiana University of School of Medicine, this imaging approach has been applied to study experimental carcinogenesis and clinical studies.

ANN KIRCHMAIER

Research in Dr. Kirchmaier's lab focuses on epigenetics and how genetic and environmental factors perturb epigenetic processes, and thereby contribute to oncogenesis, by altering gene expression and genome integrity. Team members investigate how the formation, maintenance, and inheritance of heterochromatin and other complex chromatin structures are regulated by the cell cycle and influence or are influenced by DNA damage, chromosome segregation, and DNA replication. Team members are defining how histone and DNA modifications and histone variants are combined into patterns to act as instructions for biological processes at the single nucleosome level at defined sites on chromosomes.

Team members apply complementary biochemical, molecular biology, genetic, and single molecule approaches to dissect the relationship between chromatin modifications, transcription, gene silencing, DNA replication and repair, chromatin composition, and genome maintenance. The team investigates evolutionarily conserved proteins, including histone acetyltransferases and deacetylases, chromatin assembly factors, and replication proteins participating in epigenetic processes in cell culture and in the model organism *Saccharomyces cerevisiae*.

Also see p. 180.

JULIA KIRSHNER

Dr. Kirshner's long-term research objective is to answer the fundamental questions in cancer stem cell biology. Her lab is actively investigating the role of the microenvironment in maintaining the balance between self-renewal and differentiation of cancer stem cells. Answering this question will provide information on how to keep the cancer stem cell from initiating tumors and their re-growth.

Patients suffering from both hematological malignancies and solid tumors often see their disease relapse because of the inability of the currently available therapies to target successfully cancer stem cells. Thus, determining which characteristics of the cancer stem cells can be therapeutically exploited is of utmost importance. Kirshner's lab studies the properties of cancer stem cells using two model systems: multiple myeloma, a cancer of the bone marrow plasma cells, and breast cancer, representing hematological and solid malignancies respectively. Team members use 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.

The team's working hypothesis is that cancer stem cells are found in a specialized microenvironment niche which keeps the cells in a non-proliferative and drug-resistant state. Altering the conditions in favor of differentiation and proliferation leads to tumor re-growth.

Studies in the Kirshner lab are underway to: 1) determine the phenotype of the multiple myeloma cancer stem cell; 2) define the niche within the bone marrow microenvironment capable of supporting self-renewal of the multiple myeloma cancer stem cells; 3) determine how bone marrow microenvironment regulates differentiation of multiple myeloma cancer stem cells; 4) dissect the signal transduction pathways guiding breast cancer colonization of bone during metastatic spread; and 5) identify new compounds with specificity and selectivity against cancer stem cells.

DEBORAH KNAPP

Dr. Knapp directs the Purdue Comparative Oncology Program (PCOP), in which veterinary clinical and basic scientists study specific forms of naturally-occurring cancer in pet dogs, which serve as relevant models of human cancer. Veterinarians in the PCOP examine several hundred pet dogs and cats with cancer each year. Many of these animals (with informed consent of the pet owner) enter clinical trials evaluating new diagnostic and therapeutic techniques. Collaborating basic scientists perform mechanistic studies in parallel with clinical investigations.

STUDIES IN INVASIVE URINARY BLADDER CANCER: Urinary bladder cancer is diagnosed in more than 65,000 people, and causes more than 14,000 deaths yearly in the United States. The invasive form of urinary bladder cancer is especially problematic because of its propensity to metastasize and to resist chemotherapy. Naturally-occurring canine urinary bladder cancer closely resembles human invasive bladder cancer in regards to histopathologic characteristics, molecular features, biological behavior including sites and frequency of metastasis, and response to therapy.

Knapp and her colleagues are conducting several studies in dogs with urinary bladder cancer. These studies provide benefit to the pet dogs while also generating new information that could improve the outlook for humans and dogs with this cancer. Examples of recent and ongoing work include studies of:

1) further characteristics of spontaneous canine urinary bladder cancer to confirm its utility as a model of human invasive urinary bladder cancer
2) heritable factors that contribute to the development of urinary bladder cancer, made possible through strong breed-associated risks
3) environmental factors associated with bladder cancer development
4) proteomic and genomic analyses
5) novel therapy approaches
6) development of nanoparticle therapy agents

Also see p. 181.

STEPHEN KONIECZNY

Dr. Konieczny's research involves defining the molecular mechanisms that regulate gene expression in pancreatic epithelial cells during development and in cases of disease and tumor initiation and progression. His team focuses on two transcription factor families - basic helix-loop-helix (bHLH) and SRY-related HMG-box (SOX) transcription factors since these proteins are essential to controlling both developmental and cell proliferation events. Alterations in bHLH and SOX factor activity, or in gene expression patterns, often correlate with the development of pancreatic disease, including pancreatic tumors.

His laboratory has utilized a number of genetically altered mouse models to study the earliest stages of pancreatic disease including pancreatitis and pancreatic cancer. Using Cre/Lox systems, Konieczny's team has identified acinar cells as the cell of origin for preneoplastic lesions called PanINs. Upon KrasG12D expression, acinar cells convert to PanIN lesions which then progress to pancreatic ductal adenocarcinoma, the fourth leading cause of cancer deaths in the U.S. Their research has also identified a key bHLH transcription factor (MIST1) that is expressed in pancreatic acinar cells and which serves as a gate-keeper to maintaining normal acinar cell homeostasis, even when acinar cells obtain a KrasG12D mutation. MIST1 is one of the first genes that is silenced in patients that present with pancreatic PanIN lesions and a similar phenomenon occurs in mouse models of pancreatic cancer. Interestingly, forced expression of MIST1 protects acinar cells from undergoing rapid transformation upon KrasG12D mutation, suggesting the MIST1 may be an excellent therapeutic target to protect acinar cells from progressing to ductal adenocarcinoma. In contrast, the lab has shown that the SOX9 transcription factor is induced in pancreatic cancer cells and that deletion of SOX9 completely prevents tumor formation in KrasG12D expressing cells. Thus, SOX9 is a critical driver of tumorigenesis. Current studies are focused on employing a novel 3D culture system that can be used to model PanIN lesions in vitro and to test the importance of these two transcriptional networks to pancreatic disease. The development of this system will permit a unique approach to validate therapeutic agents prior to entering into Phase I clinical trials.

Also see p. 182.

SHIHUAN KUANG

ADULT STEM CELL BIOLOGY: A precise balance between self-renewal and differentiation is crucial for stem cell maintenance, tissue homeostasis, and prevention of cancer. Dr. Kuang investigates the molecular mechanisms underlying stem cell fate choices using satellite cells in the skeletal muscle as a model. Accumulating evidence strongly suggest that imbalanced self-renewal and differentiation of cancer-initiating stem cells often result in cancer. Consistent with this notion, deregulated proliferation of muscle satellite cells has been shown to result in rhabdomyosarcoma (RMS), the most common soft tissue cancer in children. Kuang further investigates how stem cell niche regulates satellite cell differentiation and how satellite cells interact with their niche. Such information is also pertinent to cancer biology, as cancer stem cells can to drive new tumor growth in response to cues from their niche.

NOTCH SIGNALING IN STEM CELL FUNCTION AND MUSCLE REGENERATION: Kuang's team recently has shown that the satellite cell niche contains heterogeneous subpopulations of committed myogenic progenitors and non-committed stem cells. This hierarchical composition of readily differentiating progenitors and self-renewable stem cells assures the extraordinary regenerative capacity of skeletal muscles while maintaining a sustainable pool of satellite cells. Ongoing studies in his lab now explore how Notch signaling differentially regulates subpopulations of satellite cells and how such mechanisms are employed in muscle regeneration. To this end, his lab has identified Dlk1 as a novel regulator of satellite cells. Interestingly, Dlk1 has recently been shown to be a critical regulator of stem cell pluripotency and its aberrant expression is associated with, and a prognostic marker for, many types of cancer including acute myeloid leukemia, hepatoblastoma, pancreatic cancer, and neuroblastoma. Therefore, understanding how Dlk1 regulates downstream genes may lead to novel therapeutic targets in cancer prevention and treatment.

STEM CELL THERAPY TO TREAT DEGENERATIVE DISEASES: Stem cell therapy is a promising treatment for many devastating degenerative diseases. One such affliction, Duchenne Muscular Dystrophy (DMD), is an inheritable, degenerative and lethal muscle disorder that affects young boys. However, several limitations, including poor survival rates, poor migration, and host rejection, have hampered the clinical usage of satellite cells to treat DMD. To address these issues, Dr. Kuang aims to develop degradable bioactive scaffolds that mimic the natural niche of skeletal muscle in order to promote the survival and proliferation of the transplanted satellite cells.

Also see p. 183.

RICHARD KUHN

Dr. Kuhn's research focuses on understanding the biology of viruses that infect humans. Specifically, his lab is interested in viruses that contain a lipid bilayer membrane and contain plus strand RNA as their genetic material. These viruses are grouped in the Togaviridae and Flaviviridae families; some representative members include Sindbis, Ross River and Venezuelan equine encephalitis virus for Togaviruses, and yellow fever, Dengue, West Nile and hepatitis C virus for the Flaviviruses. Hepatitis C virus is a significant contributor toward hepatocellular carcinoma.

Viruses within these two groups pose significant risks to large segments of the population, and methods for controlling infection and disease are few. His goal is to understand all aspects of their replication cycle at the molecular level by integrating techniques from molecular genetics, biochemistry, and structural biology. His laboratory is also developing viral vectors that are targeted to cancer cells for therapeutic purposes.

JAMES LEARY

Cancer research in Dr. Leary's laboratory is in two main areas:
1) isolation of rare circulating tumor cells or cancer stem cells for cancer cell diagnostics and therapeutics
2) development of new nanomedical systems for next-generation cancer therapeutics especially applied to breast and prostate cancer.

The rare cancer cell detection and isolation systems (high speed flow or magnetic cytometry/sorting) are being designed for very early diagnosis/therapeutics, e.g. minimal residual disease monitoring of breast or prostate cancer, when the tumor cells are still very rare, including when patients are clinically in remission. In addition to rare cell frequency, clonal isolation of these rare tumor cells can allow for molecular characterizations including development of mutations and other genetic changes that may have prognostic importance in choosing subsequent therapies.

Multilayered nanoparticle systems, providing programmable multi-step targeting and drug/gene delivery to tumor cells, are being constructed using magnetic nanoparticle cores which will also allow for magnetic focusing, in-vivo heating, and MRI in-vivo imaging.

One method of drug/gene delivery being explored is the construction of nanofactory templates for in-situ manufacture of therapeutic genes as an alternative to conventional drug/gene delivery. Multilayered structures, including peptide and antibody targeting components, are being built on ferric oxide superparamagnetic nanoparticle cores for guided nanoparticle drug/gene delivery in-vivo that permit simultaneous diagnostics and therapeutics (theragnostics). In-vivo animal studies are in progress.

Also see p. 184.

SOPHIE LELIÈVRE

ORGANIZATION OF THE CELL NUCLEUS AND CANCER: An altered nuclear organization is a hallmark of cancer cells. However, the functional link between alterations in nuclear organization and abnormal cell behavior is poorly understood. Dr. Lelièvre and her team are working on the concept that the way nuclear proteins are organized determines how the nucleus will respond to incoming signals and, hence, regulate nuclear and cellular functions. Projects aim at deciphering the mechanisms that control the organization and function of nuclear proteins, notably as it pertains to the regulation of gene expression, in normal and cancer cells, in order to develop strategies for better detection and control of cancer initiation and progression.

A fusion protein made of the nuclear protein NuMA and retinoic acid receptor has been shown to 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 systems, team members have identified a link between the distribution of NuMA, chromatin organization, and the maintenance of breast epithelial differentiation. Current hypotheses are that NuMA controls cell phenotype by influencing chromatin structure, specifically by targeting chromatin remodeling complexes (CRCs) to different nuclear sites, and that alteration of NuMA function at the chromatin level participates in cancer behavior.

Recent data show that NuMA interacts with members of different CRCs. Team members are now collaborating with biophysicist Joseph Irudayaraj to study the interaction of NuMA and CRCs in live cells. Team members also are working with Dr. Cynthia Stauffacher, a structural biologist, in order to unravel a previously unexplored, yet highly conserved, sequence that NuMA shares with other chromatin-associated proteins. Moreover, in collaboration with Dr. David Knowles (Lawrence Berkeley National Laboratory), they have developed an imaging analysis that identifies cells with different phenotypes involved in cancer progression based on NuMA distribution. NuMA organization is being investigated to help earlier diagnosis and/or prognosis of breast cancer and to 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. Lelièvre's hypothesis is that apical polarity controls epigenetic mechanisms of gene expression that are essential to prevent tumor development. Using the DNA Sequencing Resource, team members have identified, via microarray analyses performed in collaboration with Dr. Rebecca Doerge, 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 genes (and other genes in the list of candidates) as markers of preneoplastic alterations and targets for cancer prevention strategies is being assessed. Particularly, team members 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, team members are developing nanotechnology-based tools to diagnose and reverse apical polarity alterations. The team is also developing three-dimensional tissue culture models of high breast cancer risks for high throughput screening of preventive agents.

Also see p. 185.

MARK LIPTON

Dr. Lipton's team has recently developed two new reagents for the guanylation of amines, an important and underdeveloped reaction. His team also has developed a novel, cyclic dipeptide catalyst for an asymmetric variant of the Strecker amino acid synthesis. This has led to a broad effort directed toward the use of cyclic dipeptide catalysts in asymmetric carbon-carbon bond forming reactions. The team has initiated another broad effort in the area of reactions on solid supports. They began with the synthesis of cyclic dipeptides 1 and 2 for the catalysis studies.

Recent projects involve the synthesis of peptidomimetics (e.g., 3) and macrocyclic lactams on solid supports.

Ongoing projects include the synthesis of inhibitors of the enzymes cyclophilin A and HIV-1 protease (both essential for the replication of the HIV-1 virus and the pathogenesis of AIDS), and novel DNA-cleaving agents for the treatment of cancer. Projects of this type usually are designed using molecular modeling and tested in house after synthesis.

SANDRA LIU

Dr. Liu's research interests include consumerism in healthcare delivery, sales management in a knowledge era, and customer capital and structural capital in healthcare industry. She also is currently working on several projects that relate to obesity prevention as a way of reducing cancer risk.

SHUANG LIU

Dr. Liu's research interests include (1) discovery and development of new target-specific radiotracers for early diagnosis of cancer, (2) development of new techniques for the radiolabeling of small biomolecules, (3) evaluation of cationic metal complexes as radiotracers for cardiac perfusion imaging, and (4) fundamental coordination chemistry of radiopharmaceuticals.

NEW INTEGRIN A_VB_3-SPECIFIC RADIOTRACERS: There is a tremendous effort in development of target-specific radiotracers for early tumor detection. This effort relies heavily on identification and the use of receptor ligands as carriers for a radionuclide to localize in tumor tissues. Imaging with radiolabeled small biomolecules allows Liu to monitor the tumor biological changes at the molecular level rather than simple morphological or functional characterization. Over the last 10 years, Liu has become one of the leaders in radiolabeled RGD peptides as SPECT and PET radiotracers for imaging integrin expression $\alpha_v\beta_3$ in rapidly growing and metastatic tumors. Liu's group has clearly demonstrated that multimerization of cyclic RGD peptides enhances their integrin $\alpha_v\beta_3$ binding affinity and improves the radiotracer tumor uptake. Among more than 30 radiotracers evaluated in different tumor bearing animal models, ^{99m}Tc-3PR-GD_2 has been selected as a clinical candidate for tumor imaging in humans. Successful development of a clinically useful integrin $\alpha_v\beta_3$-specific radiotracer not only for the early cancer detection but also for monitoring tumor growth and metastasis will definitely help physicians to (1) detect the tumors (location, size and metastatic status), (2) determine therapeutic options (chemotherapy, radiation therapy, antiangiogenic therapy or combination thereof), (3) select the patients who will benefit most from a specific therapeutic regiment, and (4) optimize the dose and schedule of antiangiogenic treatment in an individual patient.

NEW MYOCARDIAL PERFUSION IMAGING AGENTS: Another research area of Liu's group is the development of new cationic ^{99m}Tc radiotracers that have fast liver clearance with very high heart/liver ratios. Rapid liver clearance will shorten the duration of imaging protocols and allow for much early acquisition of clinically useful diagnostic images of the heart with very high quality. Recently, Liu's group has identified a new cationic radiotracer, ^{99m}TcN-MPO. Preliminary clinical data clearly indicate that ^{99m}TcN-MPO is particularly useful for rapid image acquisition (within 10 – 15min post-injection) in patients with suspected coronary artery diseases. The development of such an excellent myocardial perfusion radiotracer is of considerable benefit in diagnosis and treatment of heart diseases in clinics (particularly in the emergency rooms).

NEW RADIOTRACERS FOR IMAGING MULTIDRUG RESISTANCE: Liu's group recently discovered that ^{64}Cu-labeled phosphonium cations were able to localize in MDR- and MRP-negative tumors (e.g. U87MG glioma) with very high tumor selectivity. His group also found that the ^{64}Cu-labeled phosphonium cations have significantly reduced uptake in the MDR and MRP-positive tumors (e.g. MDA-MB-435 breast tumor). The ^{64}Cu-labeled phosphonium cations are much better radiotracers than ^{99m}Tc-Sestamibi with respect to the tumor-to-background ratios and their ability for non-invasive imaging of the tumor MDR Pgp transport function. Since high negative mitochondrial potential is prevalent in tumor cell phenotype, the ^{64}Cu-labled phosphonium cations are useful for the early detection of most cancer types, if not all. Successful development of a tumor-specific PET radiotracer will help physicians (1) to detect the location of tumor(s) at early stage; and (2) to select the right patients for a specific therapeutic regiment based on the presence or lack of MDR Pgp.

Also see p. 186.

WANQING LIU

The long-term interest of Dr. Liu's lab is focused on human cancer genomics and personalized medicine towards discovering genetic markers integral to human cancers and therapeutic treatments, as well as translating these markers into clinical practice. His current research involves the use of integrated "omics" and systems approach to identifying susceptibility genetic variants for cancer as well as molecular targets for cancer therapy. Ongoing projects in the lab include:

Genetics and genomics of somatic mutations in lung cancer. Somatic mutations in EGFR gene is highly correlated with clinical outcome of EGFR-targeted treatment. Lung cancer with EGFR mutations is an unique disease. We are designing both candidate gene and genome-wide association studies (GWAS) towards identifying germline alleles conferring risk to the occurrence of these somatic mutations.

Genetic mechanism underlying genes/alleles contributing to cancer risk. Although GWAS has been successfully identifying a number of genetic alleles increasing risk for cancers, little is known regarding the biological function of these alleles and the underlying mechanism how these alleles mediating the development of cancer. We use both genomic and mechanistic approaches studying a few genetic loci associated with lung cancer.

Pharmacogenetics of anti-cancer agents. Personalized treatment is a promising avenue to cancer treatment in coming decades. Our study uses systems biology approach to discover important genetic factors affecting both pharmacodynamics and pharmacokinetics of anti-cancer agents.

Also see p.187.

XIAOQI LIU

It is now widely accepted that cancer arises at least partly due to the perturbation of normal cell cycle progression, in which reversible protein phosphorylation plays an important regulatory role. In addition to the well-documented cyclin-dependent kinases, the Polo-like kinase (Plk) family has emerged as a key player in many cell cycle-related events.

Genetic and biochemical experiments with several different organisms have demonstrated that polo kinases are involved in many aspects of mitosis, such as mitotic entry, sister chromatin separation and cytokinesis. Using a yeast two-hybrid system, Dr. Liu has identified a battery of potential Plk1-interacting proteins, and the significance of these interactions during cell cycle progression has been analyzed. So far, his team has analyzed the functional significance of Plk1 phosphorylation towards its substrates in three critical cellular processes: Topoisomerase IIα, HBO1 and TRF1 in chromosome dynamics; CLIP-170 and SGT1 in kinetochore function; Topors and GTSE1 in p53 regulation.

In terms of the roles of Plk1 in chromosome dynamics, team members showed that Plk1-associated phosphorylation is essential for the functions of TopoIIα in both S phase and mitosis. Moreover, team members provided first evidence to show that Plk1 phosphorylation of HBO1 (histone acetyltransferase binding to Orc1) is required for pre-replicative complex formation and DNA replication licensing. TRF1 (telomere binding factor 1) phosphorylation by Plk1 is essential for its interaction with telomeres during mitosis to maintain chromosome stability.

Involvement of Plk1 in kinetochore function is well established, its substrates have not been identified, however. Liu's team showed that Plk1 phosphorylation of SGT1 (suppressor of G2 allele of Skp1) is required for kinetochore assembly and that Plk1 phosphorylation of CLIP-170 (cytoplasmic linker protein) is critical for the establishment of kinetochore-microtubule attachments during prometaphase.

Finally, they also identified Topors (DNA topoisomerase I-binding protein) and GTSE1 (G2 and S phase expressed protein), two negative regulators of p53, as two Plk1 substrates. While Pk1 phosphorylation of Topors regulates p53 stability, Plk1-associated kinase activity towards GTSE1 is critical to control p53 nucleo-cytoplasmic shuttling during the G2 DNA damage recovery process.

Also see p. 188.

AMY LOSSIE

EPIGENETIC GENE REGULATION: Epigenetics can be thought of as the punctuation that the cellular machinery uses to 'read' the meaning encoded within the DNA sequence. Even though every cell in the body contains the same sequences of letters and words, the story is very different in brain compared with the heart, and the location of the punctuation can change the meaning of the sentence entirely. For example, the sentence, "Eats shoots and leaves." evokes an image of a panda bear. However, altering the punctuation to, "Eats, shoots and leaves." changes the meaning completely. Epigenetic marks perform analogous functions within each and every cell in the body. The placement of these marks dictates if, where and when a gene will be turned on in any given cell or tissue.

SIGNALING AND CANCER: Cancer can be described as development gone awry, as signaling pathways that are important for embryonic development are often severely misregulated in cancer. Misregulation of these signaling pathways is almost always accompanied by alterations in epigenetic processes, such as DNA methylation and non-coding RNAs. Dr. Lossie's research focuses on understanding the involvement of these two epigenetic processes in gene regulation of key signaling pathways (Notch, Wnt, p53 and Odz4) during early embryonic development. Mistakes in these pathways lead to multiple different phenotypes that include cell death, embryonic lethality or increases in pluripotency. By identifying the altered epigenetic punctuation in these pathways, the Lossie group is identifying potential genetic and epigenetic targets for therapies for treating cancer.

TECHNOLOGY DEVELOPMENT: Dr. Lossie is also developing single molecule tools to identify and quantify epigenetic marks in single cells. These studies focus on understanding the mechanisms by which epigenetic marks are erased and re-established during the earliest stages of mammalian development. By understanding how epigenetic marks are laid down, Dr. Lossie is helping to document and understand the epigenetic punctuation during these timepoints in development, which can be used to design epigenetic-based strategies to control gene expression during tumorigenesis.

PHILIP LOW

Dr. Low's laboratory is working in three areas that stem from a basic interest in finding application of membrane biology in medicine. First, lab members are developing methods to target therapeutic and imaging agents specifically to pathologic cells, thereby avoiding the undesirable consequence of uptake by healthy cells. Because the receptor for the vitamin, folic acid, is over-expressed on many human cancers (e.g. cancers of the ovary, lung, kidney, endometrium, breast and colon), team members are attaching folic acid to drugs in order to facilitate their binding and uptake by malignant cells. Molecules targeted to tumors with folate to date include: 1) radioimaging agents, 2) chemotherapeutic drugs, 3) gene therapy constructs, 4) liposomes with encapsulated drugs, 5) protein toxins, 6) immunotherapeutic agents, 7) radiotherapeutic complexes, 8) MRI contrast agents, 9) nanoparticles, 10) optical imaging agents, 11) oligonucleotides, and 12) various therapeutic proteins. In general, the folate conjugates have proven to be nontoxic to normal tissues, but very effective in killing cancer cells. Six folate targeted drugs are currently in human clinical trials for the aforementioned cancers.

Encouraged by the successful use of folate to deliver attached drugs to cancer cells, the Low lab has more recently undertaken to identify novel targeting ligands that will deliver attached drugs selectively to cancers that do not over-express a folate receptor. This effort has led to the discovery of very specific homing molecules that can be exploited to carry attached drugs to cancers of the prostate, lung, colon, pancreas, thyroid, and brain. The targeted drug for imaging and treatment of prostate cancer is currently in early clinical trials.

During the course of the above cancer targeting research, the Low lab observed that folate-drug conjugates also targeted activated macrophages. Because activated (but not resting) macrophages either cause or worsen a variety of autoimmune and inflammatory diseases, including rheumatoid arthritis, atherosclerosis, ulcerative colitis, Crohn's disease, psoriasis, osteoarthritis, multiple sclerosis, graft versus host disease, glomerulonephritis, systemic lupus erythematosis, and osteoporosis, team members have undertaken to develop targeted therapies for these diseases also. Preclinical data that have resulted in soon-to-be initiated clinical trials in osteoarthritis have demonstrated that the strategy is highly effective and is accompanied by little or no toxicity.

In the hematology field, team members are investigating the function and molecular organization of the human red blood cell membrane. Included in this research are projects aimed at characterizing: 1) the interactions between the membrane and its underlying cytoskeleton, 2) the signal transduction pathways that control cell shape and flexibility, 3) the causes and therapies for hematologic diseases such as malaria, sickle cell anemia, and β-thalassemia.

Also see p. 189.

CHENGDE MAO

Dr. Mao's research lies at the interface between chemistry, biology, nanotechnology and materials science. It falls into two general themes: 1) developing nanotechnology with biochemical approaches and 2) applying nanotechnology to address fundamental problems in chemistry and biology. Following are some examples:

BIOCHEMICAL NANOTECHNOLOGY: Fabrication of desired nanostructures is the key for nanotechnology. It promises great potential for technological applications and a necessary platform for basic nanoscience. Currently there is no general method for parallel fabrication of structures with feature sizes of 5-100 nm. To meet this challenge, team members will use self-assembled DNA structures as templates and use soft lithography as the primary tool to develop novel nanofabrication methods, such as the general fabrication of nanowire networks.

HIGHER ORDERED DNA STRUCTURE: How is DNA duplex organized in the cell? The understanding of this issue is far from complete. There are at least three features about DNA organization: 1) DNA is highly condensed to allow long linear DNA molecules to reside in a very tiny space, the nucleus, 2) DNA adopts dynamic structure to facilitate DNA replication, RNA transcription, and the like, and 3) DNA is highly ordered to avoid random tangling between DNA molecules. To address this problem, team members will fabricate nano/microstructured systems to mimic the nuclear environment of the cell and develop experimental and theoretical methods for structural analysis.

GENETIC RECOMBINATION INTERMEDIATE: Genetic recombination is essential for all living systems. Although a great amount of work has been devoted to characterizing its intermediate (Holliday junction), some key questions are still unanswered. What are the effects of DNA sequence on the structure, formation, isomerization, and resolution of Holliday junction? Mao's team hopes to answer such questions by imaging and chemical/enzymatic probing of in vitro model systems.

Major techniques in the group include DNA/RNA manipulation (gel electrophoresis, labeling, hybridization, PCR and footprinting), soft lithography, atomic force microscopy (AFM), electron microscopy (EM), fluorescence spectroscopy, microfluidics and chemical synthesis.

MEGHAN MCDONOUGH

Dr. McDonough's research focuses on social relationships, stress and coping, motivation, and self-perceptions in physical activity. Her work in cancer explores how social relationships and physical activity among cancer survivors contribute to their well-being and how they cope with stress related to cancer and survivorship. She has documented how breast cancer survivors involved in team sport experience enhanced social support and changes in body image and athletic identity through their participation, and how these changes may facilitate post-traumatic growth (positive psychological growth following a traumatic event such as cancer diagnosis and treatment).

She has also published work supporting the use of body image and posttraumatic growth measures for use with breast cancer survivors, and documented links between survivorship-related stress, cancer treatments, and physical and global self-worth. McDonough and Tarra Hodge (Clinical Assistant Professor in Health and Kinesiology) are currently working on a study examining the psychosocial and fitness outcomes of participating in a community-based group physical activity program for cancer survivors, offered through the local YWCA. McDonough is a core committee member of the International Breast Cancer and Nutrition Project, and an affiliated member of the Oncological Sciences Center at Purdue University.

Selected publications:

McDonough, M.H., Sabiston, C.M., & Ullrich-French, S. (2011). The development of social relationships, social support, and posttraumatic growth in a dragon boating team for breast cancer survivors. *Journal of Sport & Exercise Psychology, 33,* 627-648.

Sabiston, C.M., Rusticus, S., Brunet, J., **McDonough, M.H.**, Hadd, V., Hubley, A., & Crocker, P.R.E. (2010). Invariance test of the multidimensional body self-relations questionnaire: Do women with breast cancer interpret this measure differently? *Quality of Life Research, 19,* 1171-1180.

Hadd, V., Sabiston, C., **McDonough, M.H.**, & Crocker, P.R.E. (2010). Sources of stress for physically active breast cancer survivors: Examining associations with treatment characteristics and indicators of psychological well-being. *Journal of Women's Health, 19,* 1345-1353.

Brunet, J., **McDonough, M. H.**, Hadd, V., Crocker, P. R. E., & Sabiston, C. M. (2010). The posttraumatic growth inventory: An examination of the factor structure and invariance among breast cancer survivors. *Psycho-Oncology, 19*, 830-838.

McDonough, M.H., Sabiston, C.M., & Crocker, P.R.E. (2008). An interpretative phenomenological examination of psychosocial changes among breast cancer survivors in their first season of dragon boating. *Journal of Applied Sport Psychology, 20*, 425-440.

Sabiston, C.M., **McDonough, M.H.**, & Crocker, P.R.E. (2007). Psycho-social experiences of breast cancer survivors involved in a dragon boat program: Exploring links to positive psychological growth. *Journal of Sport & Exercise Psychology, 29,* 419-438.

DAVID MCMILLIN

Cationic porphyrins that bind to DNA and RNA molecules are of interest in connection with photodynamic therapy which uses light to initiate drug action in a selective fashion. The electronic excited states of transition metal complexes, especially late transition metal complexes of porphyrins, are a major research interest of Dr. McMillin's group. Because late transition metal systems typically have vacant coordination sites, exciplex (excited state complex) formation is an important process, and the excited states are quite sensitive to the local environment. The McMillin group exploits luminescence spectroscopy to map out DNA- and RNA-binding interactions.

SUSAN MENDRYSA

The research in Dr. Mendrysa's laboratory takes a multidisciplinary approach, combining molecular biology, genetics, and protein biochemistry in conjunction with a variety of biological systems including genetically modified mice, mammalian cell culture and yeast, to identify and study the function of new cellular oncogenes. Understanding which genes are mutated in human cancer is important as these genetic alterations can significantly alter the cellular response to some cancer therapeutics. Therefore, by identifying new genes involved in human cancer, team members may improve the ability to predict which cancer therapy will be the most effective for a specific tumor.

Current projects in the laboratory are focused on two main lines of inquiry. First, team members are investigating the signaling pathways that contribute to the formation of medulloblastoma (MB), a tumor of the cerebellum most frequently seen in young children. Team members are specifically investigating the role of MDM2 in in cerebellar granule neuron precursors (GNPs), the presumed cell of origin for some subtypes of MB. The team members have determined that MDM2 plays a critical role in negatively regulating p53 tumor suppressor function in the normal and tumorigenic cerebellum. Moreover, the same growth factor signaling pathways that regulate MDM2 during cerebellar development have been show by team members to also regulate MDM2 in MB formation. Team members have demonstrated using both genetic and pharmacological approaches that MDM2 is required for MB tumor cell survival suggesting that MDM2 may be a potent therapeutic target for the treatment of human MB.

Second, team members are investigating the function of the novel nucleolar oncogene, LYAR. Recent studies have demonstrated that the nucleolus may act as a critical sensor of cellular stress; however, the details of which nucleolar proteins are involved in mediating the stress response are not well understood. The team has developed both knockout and transgenic mice to investigate the function of this novel oncogene in development and cancer. The team has determined that while mice lacking either LYAR or p53 are viable, those embryos lacking both LYAR and p53 die during development and exhibit neural tube defects (NTDs). These studies provide new insight into the type of genetic events that contribute to NTDs that are among the most serious congenital malformations in humans. Moreover, the discovery by team members that the loss of LYAR is lethal only in combination with loss of p53 suggests that LYAR may be an important therapeutic target in cancer cells harboring mutant p53.

MARGARET MILLER

Dr. Miller's research interests are in the areas of:

1) toxic lung and olfactory injury
2) diagnostic pathology
3) canine mammary neoplasia
4) equine pituitary dysfunction
5) urinary bladder transitional cell carcinoma

SURESH MITTAL

Dr. Mittal's research focuses on:

1) human and nonhuman adenoviral vectors
2) gene therapy
3) circumvention of adenoviral vector immunity and toxicity
4) targeted adenoviral vectors for cancer gene therapy
5) Immunotherapy
6) Cancer prevention

Also see p. 190.

AMY MOBLEY

Dr. Mobley's research interests are the ecological approaches to preventing obesity, health behavior theory and motivational factors related to diet and exercise, and social marketing, with a special focus on limited resource audiences and youth.

STACEY MOBLEY

Dr. Mobley's research interests are:

1) multidisciplinary clinical and basic science approaches for optimal bone health and body weight in children and young adults
2) individualized diet and nutrition prescriptions based on genetics or behavior to prevent chronic diseases such as obesity and osteoporosis
3) obesity as related to body composition and calcium metabolism

SULMA MOHAMMED

Dr. Mohammed's laboratory is interested in understanding the molecular, genetic, epigenetic, and functional changes involved in the earliest steps of breast disease. Her goal is to identify molecules intrinsic to the breast premalignant lesions and normal-looking adjacent tissues to typify lesions destined to progress to become invasive cancer and to elucidate the causative pathways of carcinogenesis and to use this information to improve clinical management of patients who at high risk of developing breast cancer.

Mohammed's team has devoted much effort to characterization of a unique animal model which develops spontaneous pre-malignant lesions very similar to humans' lesions in all morphological, molecular, and clinical diversity. Team members have shown that spontaneous canine mammary premalignant lesions such as atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) are similar to those of the human breast in term of developing spontaneously before mammary tumors, histologic diversity, and immunohistochemical profile of ER-α, PR, and HER-2. In addition, clustered micro-calcifications and other radiographic lesions, corresponding to BI-RAD criteria for human breast cancer screening, can be detected in the canine mammary glands. This will allow non-invasive evaluation of drug efficacy in prevention clinical trials. Team members are using their dog model to shed the light on the evolution of ADH and DCIS to malignancy and to identify breast cancer progression features that distinguishes indolent from aggressive disease.

A major recent focus of Mohammed's laboratory is 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; the group has an ongoing study in collaboration with Indiana University School of Medicine to collect lymph from women with metastatic breast cancer. Team members have successfully grown the lymph tumor circulating cells isolated from lymph collected from an animal model in vitro. The study has the 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.

Mohammed also is interested in identifying the reasons for ER-negative tumors and what contribute to their aggressiveness. Her laboratory has special interest in African women living in Africa and African women living in the United States. A published work her laboratory indicated that the majority of breast cancers in women from Africa and living in Africa were ER-negative, a pattern similar to breast cancer in African American women. The team is studying the similarities and differences in breast cancer epigenetic and proteomic profiles and effect of race and the environment.

Also see p. 191.

GEORGE MOORE

Dr. Moore focuses on clinical epidemiology, particularly the following:

1) companion animal disease epidemiology
2) zoonotic diseases
3) pharmacoepidemiology
4) use of large medical databases
5) evidence-based medicine

JOHN MORGAN

Dr. Morgan's research group is interested in engineering metabolic pathways towards increased production of chemicals as well as novel biologically active metabolites. Team members are combining molecular biology with mathematical modeling of metabolism that enables the rational design of modifications to existing pathways. The approaches they employ span scales from manipulating the molecular structure of enzymes to bioreactor design and operation strategies.

SUSAN MORGAN

Dr. Morgan's research largely focuses on the construction of persuasive messages to strengthen health communication campaigns. She uses theory and formative research to tailor health messages to the specific needs of multicultural populations (especially African Americans) and youth.

Dr. Morgan focuses both on message variables (such as figurative language) as well as on features of receivers that demand that messages be constructed in specific ways. The features of receivers that she examines are culture, sensation seeking, and figurative language processing ability.

A secondary area of interest is intercultural communication. Her research in intercultural communication heavily informs her research and teaching in health communication since it helps her understand how health-related messages should be tailored to particular groups. However, she also conducts research on intercultural interactions independently of her interest in health communication. She is interested in people's motivations for seeking out others who are culturally different from themselves, and has been working toward building a theory of the motivations that affect intercultural communication behaviors.

DAVID NOLTE

The Adaptive Optics and Biophotonics group, directed by Dr. Nolte, applies bio-interferometry to a broad spectrum of problems in biology and medicine. Their applications range from BioCDs (Biological Compact Disks) that perform high-throughput label-free immunoassays for cancer biomarker detection, to biodynamic imaging of living tissue for early screening in drug discovery and for personalized cancer care.

The BioCD uses high-speed spinning-disc interferometry (SDI) to measure antibody capture of cancer biomarkers with surface height sensitivities down to a picometer (one thousand times smaller than a nanometer). These silicon discs are antibody microarrays that have the ability to screen for hundreds of biomarkers across hundreds of patient samples [1] at a sensitivity level of 1 ng/ml. The detection uses laser interferometry to measure molecular density directly in a process that is known as label-free detection, without the need for extra markers like fluorescent molecules. The BioCD can also be used for molecular interferometric imaging (MI2) applications to study the affinity and activity of surface-immobilized molecules by observing molecular binding in real time across broad areas and for multiple analytes [2]. The technique has higher throughput that conventional label-free biosensors based on surface plasmon resonance, because it is easy and inexpensive to fabricate in large-area formats that can support large protein microarrays.

Biodynamic imaging (BDI) is a novel tissue-level imaging approach that uses the functioning motion within cells as its imaging contrast [3]. BDI is an alternative drug screening technology that has higher throughput and provides higher content than conventional tissue-based assays. MCI is a three-dimensional imaging technology that uses digital holography for tissue-based, label-free functional imaging to capture the behavior of cells embedded in their native three-dimensional environment, far from surface effects. The ability to image cells in such an environment provides data that are more representative of cellular and tissue response to applied drugs [4] than traditional high-throughput, high-content methods, and subcellular dynamics provides phenotypic profiling for drug discovery [5]. The Nolte team is currently extending biodynamic imaging into .

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REBECCA PACKER

Dr. Packer's research focuses on acute spinal cord injury, minimally-invasive neurosurgical techniques, and novel therapies for the treatment of brain tumors. The goal of these efforts is to develop treatments that will benefit veterinary patients, and also provide potential translation to human patients. Her primary research goal is to develop more effective brain tumor treatments, while minimizing surgical invasiveness and chemotherapeutic side effects.

As part of her cancer-related research, Dr. Packer has previously described and published a minimally-invasive procedure for resecting brain tumors and administering brachytherapy in dogs. This technique allows resection of brain tumors deep within the brain tissue, through a small 6-mm burr hole in the skull. The next phase of work is to implement the technique in clinical patients with brain tumors. Additional minimally-invasive procedures are currently under investigation.

Together with the Department of Chemistry, she is developing interstitially-delivered, targeted, nanoparticle chemotherapy for treatment of gliomas. Such treatments hope to maximize the effectiveness of chemotherapy by targeting the tumor cells directly and minimizing side effects to other tissues in the body. Funding has been obtained for the first phase of this study, and additional funds are being sought to continue this research based on preliminary success.

In addition to direct treatment approaches, in collaboration with Purdue's biomedical engineering researchers, she also has contributed to the development of computer models that use each patient's MRI properties to predict tumor diffusion properties, which may lead to individualized treatment protocols for each patient, through optimizing the drug dosage and drug diffusion properties for each individual's tumor.

KINAM PARK

Dr. Park's main research focus is drug delivery systems including:

1) Microparticles for long-term delivery of anticancer drugs:

Conventional methods of making microparticles for drug delivery are based on double emulsion methods. But the drug loading is low and the drug release kinetics cannot be controlled. Professor Park has developed a new microfabrication technique that can produce homogeneous microparticles with predefined size and shape. The microparticles can be made of multilayers with high drug loading and controllable drug release kinetics. Various anticancer drugs, ranging from small hydrophobic drugs to peptide and protein drugs, can be loaded for sustained release for months after a single administration.

2) Tumor-Microenvironment-On-Chip (TMOC) system to study anticancer drugs

The current targeted drug delivery to tumors is based on an observation that nanocarrier systems accumulate around the tumor more efficiently as compared with non-particular drug delivery systems. To better understand the drug accumulation at the tumor site, Professor Park works with Professor Bumsoo Han who developed the TMOC systems using his expertise in microfluidic systems. The TMOC system is designed to simulate the tumor environment on a chip. The new model system is able to provide mechanical understanding of the critical steps that lead to failures of test drug delivery systems. This new versatile model system is capable of rapidly and efficiently screening various anticancer drugs and delivery systems for the in vivo efficacy.

3) Targeted Drug Delivery to Tumors:

The nanosized drug carriers (nanocarriers) have received significant attention for the last decade for their ability to increase the efficiency of drug delivery to target tumors. While the nanocarriers are better than the conventional delivery systems, the main limiting factor is that only a small fraction (<5%) of the drug loaded in the nanocarriers are actually delivered to the target site mainly due to the elimination by the reticuloendothelial system and the instability of most nanocarriers in the blood. Professor Park, in collaboration with Professor Ji-Xin Cheng, has been developing new nanocarriers that release the drug at the target site using adaptable nanocarriers. Professor Park also collaborates with Professor Tonglei Li for developing anticancer drug crystal formulation for targeted delivery to tumors.

4) Drug-eluting stents and drug-eluting balloons:

Restenosis and late thrombosis are two major problems occurring after implantation of cardiovascular stents. The new generation of drug-eluting stents is designed to deliver multiple drugs that not only control the restenosis but also the late thrombosis. Professor Park collaborates with Professors Alyssa Panitch and Michael Sturek (at IUSOM) to develop more efficient drug-eluting stents based on biodegradable polymer coating. Recently, the team is also developing drug delivery directly from balloons using a very thin drug layer.

Also see p. 192.

LAURIE PARKER

Dr. Parker's research interests focus on developing biosensors for intracellular phosphorylation signaling. Her team uses chemical biology, nanotechnology and synthetic peptide chemistry to design probes for multiplexed analysis of cancer-related signaling proteins e.g. Abl (important in chronic myeloid leukemia), other Src-family kinases, receptor tyrosine kinases, etc. In the Parker lab and in collaboration with other members of the Center for Cancer Research, they are exploring multidisciplinary analytical methods including mass spectrometry, fluorescence microscopy and Raman spectroscopy to develop novel techniques for monitoring these signaling proteins and their activities.

The Parker lab's technology development is leading to new methods for asking complex questions about multiple signaling activities, their disruption in cancer, and response of signaling profiles to cancer treatment. Current studies in the lab aim to monitor these signaling activities in basic cell culture models and patient samples.

Also see p. 193.

WENDY PEER

TARGETS OF FLAVONOID SIGNALING: Flavonoids are antioxidants and scavenge reactive oxygen species (ROS), thereby potentially regulating the pathways induced by ROS. Flavonoids also are kinase and phosphatase inhibitors. As such, they can modulate signal transduction within the cell. Likely targets are PTEN, PID, RCN1 (PP2a), and ABCBs. A major target of ROS is PTEN, a tumor suppressor implicated in breast cancer. Flavonoids (like xanthohumol from hop) can reduce stimulate PTEN and reduce tumor proliferation.

FLAVONOID REGULATION OF ABCBS AND M1 METALLOPROTEINASES: ATP Binding Cassette family B (ABCB) transporters are involved in pumping chemotherapeutic drugs out of cells in human cancer patients. Cancer cells have more ABCBs than healthy cells. In order for chemotherapy drugs to be effective, the drugs must stay within the cancer cells. Flavonoids inhibit the activity of ABCBs, so more of the drug stays in the cells. This decreases the effective dose of chemotherapy drugs given to a patient, thereby reducing the adverse effects of the drugs on the patient. Co-therapies with either flavonoid-rich whole foods, specific flavonoids alone, or drugs based on sites of flavonoid activity on the ABCB are being developed. For example, cancer patients undergoing chemotherapy may be instructed to drink grapefruit juice (hesperidin is the active flavonoid) prior to their treatment; however, consumption of grapefruit juice is contraindicated for some drug treatments. The flavonoid EGCG (epigallocatechin gallate) from green tea also modulates ABCB activity, reverses ABCB drug resistance, and reduces ABCB gene expression.

FLAVONOIDS MODULATE THE UPTAKE OF OTHER FLAVONOIDS: The use of herbicides on food has been linked to cancer. M1 proteinase activity in food crops reduces the toxicity of the herbicide to the plants, but can increase the carcinogenicity of the herbicides to humans.

FLAVONOID/HORMONE INTERACTIONS WITH REACTIVE OXYGEN SPECIES SIGNALING: Flavonoids are phytoestrogens and are active compounds, and flavonoid consumption improves human health and may act as protectants against breast cancer. One of the best known activities of flavonoids is their antioxidant activity as they scavenge reactive oxygen species (ROS). ROS can act as a signal within the cell and the ROS-induced pathway can produce cell damage and disease, most likely through activating/deactivating kinases/phosphatases. Flavonoids scavenge ROS and can potentially regulate the pathways induced by ROS to reduced damage, as flavonoids potent kinase inhibitors. A major target of ROS is PTEN (phosphatase and tensin homolog) that has been implicated in breast cancer. PTEN is a tumor suppressor, but is inactivated in some forms of breast cancer. Flavonoids (like xanthohumol from hop) can reduce the proliferation of breast cancer cells and stimulate PTEN. Food-based flavonoids are also anti-inflammatory and are an alternative to prescription non-steroidal anti-inflammatory drugs.

JOSEPH PEKNY

Dr. Pekny and his students work at the interface between engineering, computer science, mathematics, management science, and information technology to develop improved methods for the scheduling, planning, design, and optimization of manufacturing, business, and research pipeline processes. Many of the opportunities and challenges addressed by the research effort are emerging from the breathtaking changes in the information infrastructure of the process industries and the increasingly competitive nature of the global economy.

Inexpensive means of producing, transporting, storing, and processing large quantities of data is placing a premium on the development of more sophisticated methods for generating knowledge. In fact a significant aspect of generating knowledge is an ability to use data to make discrete process management decisions that arise in virtually all applications. Thus, a major thrust of Pekny's research group is the study of model combinatorial optimization problems and the development of software research platforms for process combinatorics problems.

Another closely related research area arising naturally out of applications is understanding the implications of uncertain data and the formulation of appropriate risk management strategies to mitigate uncertainty. This research area involves investigating mixed integer linear programming sensitivity analysis, the coupling of simulation and optimization methods, and developing methods that quantitatively and qualitatively incorporate risk preferences.

D. MARSHALL PORTERFIELD

Dr. Porterfield's teaching and research focus is on advanced physiological sensing technologies for research applications in biology, agriculture, and medicine. Specific projects include scanning probe sensor technology, biosensors, bioMEMS, bionanotechnology, and lab-on-a-chip systems. He also is working with plant systems in bioregenerative life support systems for spaceflight. His work in this area includes cell signaling, biophysical limitations in microgravity, nutrient delivery technology, and biomimetic sensors.

CAROL POST

The research in Dr. Post's group seeks to understand the regulation and function of protein-protein interactions associated with cell signaling and viruses. Multi-dimensional solution-state NMR methods are used to characterize intermolecular association and to determine the 3-dimensional structure of protein complexes. Computational methods are used to define the molecular mechanism for phosphotyrosine control of protein function in signal transduction, and the mechanism of action of antiviral compounds.

How tyrosine phosphorylation regulates enzymatic activity and protein-protein association is a central question of cell signaling and the transduction of chemical information outside of the cell to control intracellular processes that govern cell growth and differentiation. Protein tyrosine kinases are targets of high interest for cancer therapeutics. An integrated approach of NMR structural studies and computational methods is used to determine how tyrosine phosphorylation controls conformational activation of Src-family kinases, and the regulation of protein-protein interactions of Syk kinase. The energetics of conformational activation is being explored computationally using a new method this research group developed to exploit adaptively biased sampling of a conformational transition path. Recent results defined a major factor contributing to the energy barrier between the active and inactive forms of the kinase domain and that this factor appears to be present across the human kinome. NMR studies are also underway on Src catalytic domain and on the Src-substrate complex.

Another area of research interest for the Post group is the study of viral capsid processes using computational biology. Viral capsids are large assemblies that are known to undergo large-scale concerted motions as a vital part of their life cycle including cell entry and the release of RNA and protein from inside of the capsid. These concerted motions are sensitive to small-molecule binding to the capsid; antiviral compounds inhibit these motions and prevent the release of RNA, as well as stabilize the capsid with increasing temperature. Computational studies have recently identified correlated fast time-scale motions of viral capsids that could be the initial steps in this process, or contribute entropically to uncoating. The lab also uses NMR methods to probe binding of antiviral compounds, and seeks to develop these efforts on a larger scale for screening small molecules.

P. V. RAMACHANDRAN

Dr. Ramachandran's interests are firmly rooted in the application of organoborane and fluoro-organic chemistry. His team develops novel methods and reagents to facilitate the synthesis of a variety of complex molecular targets, particularly for the treatment of cancer, inflammation, and central nervous system disorders. They also focus on the mechanistic aspects of the methodologies.

The collaborative research setting encompasses biological aspects as well. At present, team members have a number of compounds that are ligands for a variety of targets. For example, the fluorinated dictyostatin molecules are being examined for tubulin poylmerization and several of the novel g-butyro- and d-valerolactones are being examined for both COX- and NFkB Inhibition in collaboration with the Indiana University School of Medicine.

The team has developed new procedures and reagents for allylboration of imines for the one-pot synthesis of optically active amines and amino acids including GABA analogs. Team members currently are investigating the properties of these de novo molecules generated by the initiatives by screening them for biological activity on ion channels and dopamine receptors through collaborations with the Department of Medicinal Chemistry and Molecular Pharmacology and the National Institute of Drug Abuse. Development of novel set of racemic and chiral GABA analogs will be assayed for activity as potential lead compounds for development as drugs for the treatment of epilepsy, neuropathic pain, and addiction.

ARVIND RAMAN

Dr. Raman's research interests span theoretical and experimental nonlinear dynamics with applications to micro and nanoscale device dynamics, and on flow-structure interactions with applications to the vibrations of data storage and manufacturing systems.

DORAISWAMI RAMKRISHNA

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 circadium 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.

JOSE RAMOS-VARA

Dr. Ramos-Vara studies immunohistochemical characterization of neoplastic diseases, focusing on development of diagnostic tests for infectious and neoplastic diseases using immunohistochemistry and other in situ techniques.

TIMOTHY RATLIFF

Dr. Ratliff's laboratory focuses on understanding immune regulation and the development of alternative approaches to treating urologic cancers, primarily bladder and prostate cancers, through the modulation of anti-cancer immunity. Current studies focus on prostate inflammation, its immune regulation and its impact on prostate stem cells, gene expression in prostate tissue, and cancer development. The intent is to develop a better understanding of the inflammatory factors contributing to cancer development and to use the information gained to develop novel approaches to treating prostate cancer through modulation of the immune response. Genetically modified mouse models are used to probe inflammation, immune regulation, the development of autoimmunity, and anticancer effector mechanisms. Regulatory cells termed myeloid-derived suppressor cells have been linked to regulation of prostate inflammation and are observed early in genetically modified mouse spontaneous prostate tumor models. Determining how to control myeloid-derived suppressor cell function is a focus that is anticipated to provide a new approach to augmenting antitumor immunity. Recent studies have identified genes and pathways associated with myeloid derived suppressor cell function that may provide targets for controlling their activity. In addition, understanding the impact of inflammation on prostate stem cells is anticipated to advance knowledge about the mechanisms of prostate growth and cancer development.

Studies to better understand the biological impact of cholesterol metabolism in prostate cancer are in progress. Cholesterol sulfonating and esterification enzymes have been shown to mediate important regulatory process in prostate cancer. Understanding the biological implications on prostate cancer development and progression will form the foundation for development of new therapeutics for the disease.

Studies to improve the treatment of bladder cancer through the development of nano-delivery approaches for intravesical therapy are in progress. The fibronectin binding protein, previously identified as an important attachment protein for mycobacteria, was observed to mediate antitumor activity in a bladder tumor model and alter the bladder inflammatory process. The fibronectin binding protein's capacity to deliver nanoparticles to bladder cancer cells is being tested as a new approach for delivery of therapeutic agents for the treatment of superficial bladder cancer. The approach has the potential to not only treat superficial bladder cancer but also to treat a bladder inflammatory condition termed interstitial cystitis.

More basic studies focus on the impact of platelet-derived immunomodulatory molecules on the adaptive immune response. Precursor frequency of antigen specific T and B lymphocytes is very low before antigenic recognition and clonal expansion of the reactive cells. Control of pathogenic microbes early in the infection period is linked to innate immunity prior to clonal expansion of antigen specific adaptive immunity. Studies in the Ratliff laboratory implicate platelet-derived ligands as mediators of the early amplification of the adaptive immune compartment. Ratliff's team hypothesizes that platelet-derived ligands are the earliest signals to the adaptive immune compartment that enables rapid and ultimately optimal expansion of the adaptive immune response to the invading microbe. Studies are in progress to fully characterize the role of platelets in the modulation of adaptive immunity.

FRED REGNIER

The current objective of Dr. Regneir's laboratory is to develop integrated analytical systems for the analysis and characterization of complex protein mixtures using multidimensional separation systems (1,2) and mass spectrometry. The current initiative is to develop an automated, one-pass system that would identify proteins from cellular extracts that are in regulatory flux. A wide variety of stimuli are being examined ranging from cancer to specific diseases. Both conventional and chip based separation systems are being developed for this purpose.

The chips based systems use micromachining to fabricate in situ all the components of multiple multidimensional separation systems on a single quartz wafer. This includes millions of micron size collocated monoliths support structures (COMMOS), fluid distributors, mixers, sample inlets, a solvent formation system, chemical reaction vessels, and detector flow cells. Through deep reactive ion etching, channels ranging down to 1.5 x 10 mmm in cross section have been fabricated. Subsequent to sample introduction into the chip, reduction and alkylation, proteolysis, reversed phase chromtography, and transport to a mass spectrometer will all be carried out within channel systems in the chip. The broad objective of the ongoing research is to optimize these new miniaturized systems for protein characterization.

RONALD REIFENBERGER

Dr. Reifenberger's nanophysics lab uses innovative experimental techniques to examine the physical properties of objects in the nanoscale size range, that is, a bit larger than the size of individual atoms. Some interesting physical properties that team members measure include the electronic conductivity of small numbers of atoms and molecules, the forces arising between nanoscale objects, and the transition between the quantum behavior exhibited by a few atoms and the bulk properties of a large number of atoms.

Reifenberger's lab focuses primarily on scanning probe techniques. The first scanning probe microscope was built in 1986. Since then, team members have built a number of scanning tunneling and scanning force microscopes. These instruments are the eyes that allow the study of nanometer-scale objects.

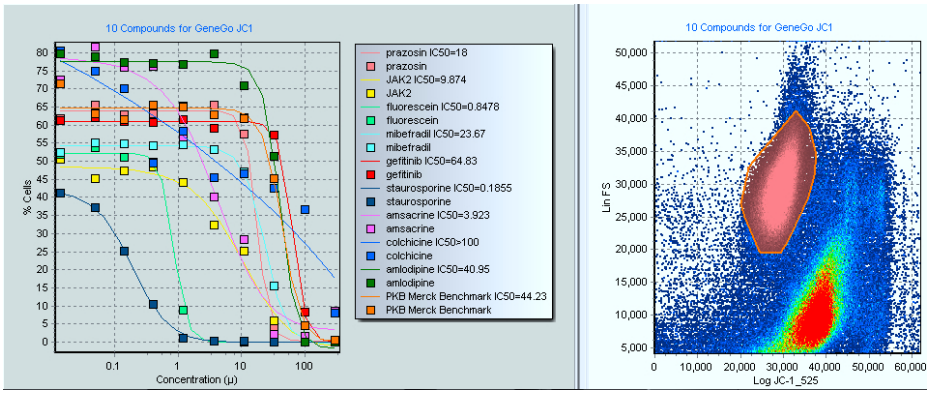
JENNA RICKUS

Dr. Rickus' research group is focused on the design of new materials to measure, control, and mimic living cells. Materials are designed in the context of specific biological problems.

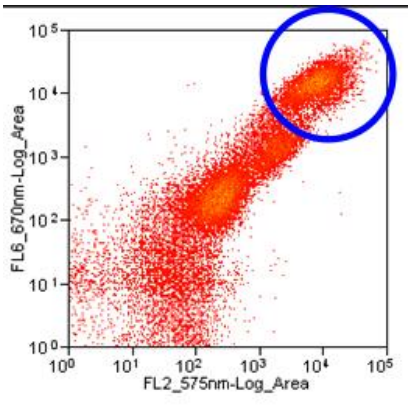
1) Hybrid biological/inorganic composite materials
2) Biological silica as a material platform for actuation and sensing of cells and tissues
3) Nanomaterial based biosensors for cell physiology
4) Integrating system biology and omics data into engineering design
5) Biomaterials to mimic and control cell fate and function

J. PAUL ROBINSON

The focus in the Robinson laboratory crosses typical faculty boundaries by integrating basic biology and engineering principles. We work on areas as broad as the role oxygen plays in disease, to models that may assist in diagnostics for HIV and cancer. The role oxygen radicals play in apoptosis has become an important area in Dr. Robinson's laboratory. This interest stems from mechanism of oxygen radical production in macrophages and neutrophils, which are heavily dependent upon the membrane bound enzyme NADPH oxidase. However, it has become increasingly clear for other cells that do not contain large amounts of membrane bound NADPH oxidase, the mitochondrial production of oxygen radicals via NADH oxidase is a vital link to understanding cancer cells resistance to oxygen radical damage.



We have previously shown that iodonium compounds such as diphenyleneiodonium (DPI) and diphenyliodonium (IDP), inhibit membrane bound NADPH oxidase, and also can also suppress ATP production by inhibiting mitochondrial complex 1. While these compounds decreased superoxide production via NADPH oxidase, they actually stimulated superoxide in HL60 mitochondria. Further, after six hours, they demonstrated that the mitochondrial membrane potential was reduced as measured by rhodamine 123 fluorescence using flow cytometry. This suggests a mitochondrial membrane permeability transition. Finally, team members determined that these same cells were induced into apoptosis, indicating that IDP itself may be able to induce apoptosis via induction of superoxide production within the mitochondria itself. The goal now is to study this mechanism in cells in cancer cells which appear to depend upon SOD to survive increased levels of oxygen radicals. We have shown that it is possible to transvect the HL60 cells with a vector that will increase either CUSOD or MN SOD to create a model system for the study of the impact of this enhanced scavenging system.



Expanding the interests in mitochondrial function, team members are trying to identify novel biomarkers for application in preclinical and eventually clinical studies linking mitochondrial dysfunction and oxidative stress as determinants of cell death. The primary physiological function of mitochondria, the powerhouse of the cell, is to generate ATP through oxidative phosphorylation via the electron transport chain. Reactive oxygen radicals generated from mitochondria have been implicated in several disease states and drug-induced tissue injuries. Mitochondrial dysfunction and oxidative stress is a commonly occurring biochemical consequence of drug administration that is a major component in the pathogenesis of many important drug-induced tissue injuries. Recent examples include those liabilities associated with PPAR agonists, kinases, antiretrovirals,

and antimalarials. Toxicities of major concern including hepatotoxicity, pulmonary toxicity, cataractogenesis, hemolysis, autoimmunity, inflammation, and carcinogenicity; all have direct links to oxidative stress. Understanding how to correlate the functional aberrations measured with causative agents is a goal of this program. The team has recently developed very high speed functional screens for mitochondrial function that will allow them to evaluate large numbers of drugs or compounds of interest in this area. These high throughput screens were developed by creating a fully automated flow cytometry system that allows the collection of around 1500 mutiparameter samples per hour on the team's specially designed screening flow cytometer system. However, without the unique analytical tools (above figure) developed in the group which can produce IC50 curves on multiple functional parameters almost instantaneously after samples are run, these high throughput systems would not be as advantageous. These tools have expanded the array of drug screening capacities and will almost certainly become fundamental tools in screening cancer drugs and potential candidates.

Another project in the laboratory is related to diagnostics in cervical cancer. In this NCI-funded program, team members are developing more accurate and faster diagnostics for high grade cervical cancer. Cervical cancer is second to breast cancer as the most common form of malignancy in both incidence and mortality for women worldwide. The population-wide utilization of screening cervical cytology (Pap tests) has been associated with a dramatic decrease in morbidity and mortality from cervical cancer in the United States and in other industrialized nations. Despite this success, the cytologic diagnosis of cervical lesions is plagued by a persistent problem of low specificity for clinically significant high-grade lesions in patients with low-grade cytologic abnormalities. As a result, more than four million women each year receive a cytologic diagnosis that requires further evaluation to rule out the possibility of high-grade dysplasia or cancer. In most cases, further evaluation does not identify underlying high-grade lesions in patients with low-grade cytologic abnormalities. Although HPV testing can play an important role for the triage of some patients, it is not useful for several cytologic diagnoses. Complicating the situation is that simple detection of high risk HPVs does not predict an underlying high grade lesion, since infections do not indicate clinically significant cervical lesions. The long-term goal of this project is to apply emerging technology to develop a high-throughput cell-based analysis with suitable specificity to identify high grade premalignant and malignant lesions of the cervical mucosa. The methods to be used in this project employ, test, and validate the approach of cytometry-based molecular diagnostics to detect false negative cervical specimens. Under the guise of the previous grant phase, an application of protein expression of p16INK4a and Mcm5 (cervical cancer biomarkers) with high-throughput flow cytometry and cell sorting has been used to identify and capture the rare cancerous cells in cervical specimens (see figure right). Furthermore, a multiplexed HPV genotyping assay has been implemented to analyze the rare cells isolated in this approach. Importantly, the work flow has been implemented using common sample preparation with current pathology testing protocols. The technology and methodology being applied in this application will be implemented using an integrated workflow, with substantial automation, to assess feasibility of further translation to accommodate clinical need and to improve the standard of care worldwide. The ultimate goal is to establish a primary assay with potential to supplant slide based cervical cytology with greater sensitivity, less subjectivity, and less labor intensiveness.

MICHAEL ROSSMANN

The central interest of Dr. Rossmann's laboratory is the determination of the three-dimensional, atomic resolution structure of viruses. However, it is not only the structure of the mature infectious virus that interests us, but all the structures that are involved in the assembly of the virus in a host cell, the interaction of viruses with host cells that initiates entry into the cell and infection, as well as the structures of viruses complexed with neutralizing antibodies or antiviral agents (potential drugs). In short, team members are investigating the way viruses interact with their environment. As many viruses can initiate tumor growth, investigations of mechanisms essential to viral functions are relevant to cancer studies.

The tools are X-ray crystallography for high resolution studies and electron microscopy for lower resolution studies of transient virus complexes, as well as all the tools of molecular biology. Viruses currently being studied include a variety of small RNA animal viruses, such as common cold viruses, polioviruses and coxsackieviruses. Team members are also looking at more complicated, lipid membrane enveloped RNA viruses, such as dengue virus and alphaviruses as well as the huge dsDNA Mimi virus whose functions and properties approach that of simple bacteria. Rossmann has long been interested in the small DNA parvoviruses. His team is also studying how viruses package their nucleic acid genomes in the analyses of a variety of bacterial viruses.

ANN RUNDELL

Dr. Rundell is devoted to developing effective quantitative approaches to design therapeutic and experimental strategies for the predictable manipulation of physiological and cellular processes in desired manners as well as refine the understanding of the underlying mechanisms. Her research approach integrates mathematical modeling, systems analysis, and control theory directly with experiments on biological and physiological systems.

Relating to cancer, she conducts research on personalizing the maintenance chemotherapy for Childhood Acute Lymphoblastic Leukemia and hematopoietic stem cell transplantation. The ultimate goal of her research is to lead to a new era in tissue engineering, therapeutic design, and personalized medicine based upon validated quantitative approaches that combine theory with experiments, link the controls community with physicians, biomedical engineering, and advance mathematical and systems biology.

DAVID SANDERS

Dr. Sanders has designed a set of novel viruses that show great promise for gene therapy. The viruses consist of retrovirus proteins on the interior and the proteins of other viruses on the surface. These pseudotyped viruses have been made with surface glycoproteins from a family known as the alphaviruses and from the Ebola virus. The retroviruses with the alphavirus glycoproteins, constructed in a collaboration with Dr. Richard Kuhn's laboratory, have properties that make them superior to any of the other retroviruses previously utilized and have been demonstrated to have strong capacities for gene transfer to the liver and the central nervous system.

The retroviruses with the Ebola virus glycoprotein have unique capabilities to enter the lung through the airway and may have utility for gene therapy for cystic fibrosis. Sanders has discovered a technique for greatly increasing the effectiveness of the retroviruses with the Ebola virus glycoprotein and also has acquired evidence indicating that the natural host of the Ebola virus may be a bird.

Recent research on cancer-causing retroviruses in the Sanders laboratory provides additional information on the association of the two subunits, SU and TM, of the retroviral envelope protein. Dr. Sanders had previous provided evidence that there is a disulfide bond between the two subunits that rearranges upon receptor binding. The new data indicate that the cleavage of the envelope protein precursor into the two subunits is necessary not only for envelope-protein-mediated membrane fusion but also for efficient incorporation of the envelope protein into viral particles. These findings provide an additional potential avenue for antiviral intervention.

SERGEY SAVINOV

Dr. Savinov is working on implementing computer-assisted technologies (small-molecule docking, molecular dynamics simulations, cheminformatic analysis, etc.) to discover and develop both anticancer and cancer-preventative agents in collaboration with experimental scientists. Current targets include: *i*) cholesterol sulfotransferase SULT2B1b upregulated in prostate cancer, *ii)* apurinic/apyrimidinic endonuclease (APE1) as a potential chemotherapy co-target, *iii*) folate receptor alpha, used for tumor-specific targeted chemotherapy, and *iv*) quinone reductase II linked to the generation of free-radicals and, thereby a potentially important target for chemoprevention of cancer.

CAGRI SAVRAN

Research interests of Dr. Savran include:

1) MEMS
2) Nanotechnology
3) BioMEMS
4) Biosensors
5) Protein detection
6) Aptamers (nucleic-acid-based receptor molecules)
7) Point-of-care diagnostics
8) Molecular cancer analysis technologies

Savran performs research in the interdisciplinary field of BioMEMS/Bionanotechnology. He develops novel biosensors that are not only sensitive but also robust and easy to fabricate and use. He has a special interest in applying his technology to detection of cancer markers and has active collaborations with non-engineering faculty who perform cancer research both within and outside of Purdue.

KAVITA SHAH

Dr. Shah's research focuses on the identification and validation of drug targets that are downstream of kinases and G Proteins in *cancer* and *neurodegeneration* using a combination of chemical, genetic and chemical-genetic approaches.

One of her areas of interest is Aurora A kinase, which 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 dividing cells have limited its effectiveness. One of the goals of the Shah 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. To this end, her laboratory has developed a tailored chemical genetic approach to identify the direct targets of Aurora A. 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. Her laboratory has identified several cancer-specific targets of Aurora A substrates in prostate, pancreatic, ovarian and breast cancer cells. One such target is LIMK2 kinase, which was identified as a direct Aurora A substrate in many different cancer cell lines. Ablation of LIMK2 in Aurora A-overexpressing breast cancer cells abrogates tumor formation in nude mice, suggesting that it is a critical oncogenic effector of Aurora A and a potential clinical target. Shah's team is exploiting this information for the development of pharmacodynamic biomarkers for Aurora A-targeted drugs, predictive biomarkers for breast, ovarian and prostate cancer progression and for unraveling the molecular mechanisms of tumorigenesis and metastasis. Aurora A substrates' that are highly associated with survival could supplement standard staging information in primary biopsy samples. The mechanism by which Aurora A functions in tumorigenesis and metastasis should reveal potential drug targets. Since Aurora A is an essential kinase, selective targeting of AA's oncogenic effectors is expected to show less toxicity. Results from these studies also have the potential to facilitate the development of combination therapies using both Aurora A and substrate-targeted drugs.

Guanine nucleotide binding Proteins (G-Proteins) constitute another large family of signaling proteins (>220 members) that are finely interwoven in every aspect of cellular signaling. Ras, the founding member of this superfamily, is deregulated in 30-40% of all known human cancers. Team members recently developed specific activators and inhibitors of engineered G Proteins for delineating their roles in various signaling cascades and for target validation. Using this approach, the team has identified several oncogenic effectors of Ras, including Nol1. Nol1 is overexpressed in a variety of tumors, including lung adenocarcinoma, prostate adenocarcinoma, breast cancer, oral carcinoma, follicular lymphoma, and human gliomas, and this overexpression is correlated with poor prognosis and shorter patient survival. Identification of Nol1 as a downstream effector of Ras thus suggests a novel mechanism by which Ras may influence malignancy.

Also see p. 194.

CLEVELAND SHIELDS

Dr. Shields' cancer related research examines the role of patient-centered communication in the assessment of cancer pain and management of end of life issues. He has found that physicians who explore and validate patients' concerns are more likely to discuss end of life issues as well as assess pain more thoroughly. In addition, his lab has found that physicians who express a greater certainty are less likely to assess pain thoroughly. He is currently conducting a multisite study to examine cancer pain management in a diverse group of physicians. He is also conducting an evaluation of the Affecting Cancer Together program, a cancer prevention program conducted through black barbershops that is sponsored by the Purdue Center for Cancer Research. He is also a faculty member of the Behavior Cooperative Oncology Group, a consortium of faculty from IUPUI, Michigan State, University of Michigan, and Ohio State University.

GARTH SIMPSON

New and remarkable interactions between light and matter arise in sufficiently intense optical fields, including the generation of new frequencies of light and the simultaneous absorption of multiple photons. At the core, Dr. Simpson's research group is devoted to the theoretical development and experimental application of new instrumental methods taking advantage of unique nonlinear optical interactions. Recent interests include detection and analysis of crystals formed from chiral molecules, building on a long-standing interest in understanding the role of chirality and polarization-dependent effects in nonlinear optics.

SENSITIVE AND SELECTIVE DETECTION OF PROTEIN CRYSTALS: Second harmonic generation microscopy is being explored for sensitive detection and characterization or protein crystals. High-resolution structures of proteins reveal insights into function and enable rational drug design. Crystal formation is a critical step in protein structure determination by X-ray or electron diffraction (see figure). The range of possible crystallization conditions to be explored is vast, while both time and protein are precious. Efforts are underway to dramatically reduce both the time and protein burden required for identification of conditions resulting in well-formed crystals amenable to diffraction analysis. These efforts take advantage of the unique symmetry properties of second harmonic generation (SHG) to enable early detection of protein microcrystals. Coherent SHG disappears completely in isotropic media, but is allowed by symmetry in ALL single-component crystals generated from chiral molecules, including crystals of proteins. As such, SHG microscopy provides exceptional selectivity for protein crystal formation. The Simpson group is working with numerous academic and commercial collaborators to further improve instrumentation for crystal detection and to apply the emerging methods to address key bottlenecks in protein crystal structure determination.

CRYSTALLIZATION OF ACTIVE PHARMACEUTICAL INGREDIENTS: The team is exploring applications of SHG microscopy for early detection of crystal formation to aid in optimizing pharmaceutical formulations. The shelf-life and bioavailability of a drug can be greatly impacted by the nature of the formulation. Often, formulations designed to prevent crystallization can improve bioavailability by speeding dissolution. In such cases, shelf-life can be substantially reduced by nucleogenesis. Preliminary experiments suggest detection limits of 1 part in 300 billion by volume for crystal formation, corresponding to a percent crystallinity of ~3´10-8. By comparison, the most common comparable analysis methods typically generate detection limits of a few % crystallinity.

AL SMITH

Dr. Smith studies the impact of physical activity involvement on youth psychosocial development as well as how social relationships are associated with sport and physical activity motivation. He is particularly interested in the structure of children's sport peer relationships and the interactive contribution of social agents (e.g., peers and parents) to youth sport and physical activity motivation. He also is interested in understanding physical activity as a means of addressing childhood attentional and behavioral problems. Recently completed projects have examined youth sport friendship quality, burnout in adolescent swimmers, self-presentational concerns in physical education settings, factors associated with adolescent physical activity behavior, and physical self-perceptions of children with ADHD.

PAUL SNYDER

Dr. Snyder's research interests include:

1) Immunopathology
2) Immunotoxicology
3) toxicologic pathology
4) developmental biology
5) environmental medicine
6) genetically engineered mouse models

Current research activities are related to collaborations involving colon, prostate, urinary bladder and skin cancer by providing immunology and pathology expertise to a number of cancer researchers within the College of Veterinary medicine and throughout Purdue University. Characterizing the phenotype of mice with targeted gene deletions in regulatory pathways involved of cell proliferation is an activity currently underway. These mice provide an opportunity to study the molecular mechanisms of cancer development. Dr Snyder is also director of the core facility, Purdue Histology and Phenotyping Laboratory (PHPL), that provides histology, immunohistochemistry and pathology services to researchers for soft tissues (paraffin sectioning) and hard tissues (plastic sectioning).

CYNTHIA STAUFFACHER

Dr. Stauffacher's laboratory is investigating the molecular modifications and their signaling consequences in the oncogene pair, HCPTP (human low molecular weight protein phosphatase) and EphA2 (ephrin A2) tyrosine kinase receptor. EphA2 receptor has been implicated in the metastatic transformation in a wide range of human cancers, with the phosphorylation state, controlled by HCPTP, a strong determinant of the transformed state of the cell. Using biophysical techniques ranging from mass spectroscopy to NMR and X-ray crystallography, team members 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.

Also see p. 195.

ARNOLD STEIN

Dr. Stein's laboratory studies the fine structure of chromosomes to understand how chromosome abnormalities and rearrangements arise. Chromosome structural variants, which are characteristic of cancer cells and cells associated with other diseases, arise in part due to chromosome structure. The Stein lab has found that DNA sequence is involved in specifying chromosome fine structure. Particular periodic motifs interact preferentially with the protein cores of nucleosomes, the fundamental building blocks of chromosomes. Long-range variations in these motifs influence chromosome structure through a previously unrecognized code in the DNA. In this work, computer bioinformatics methods are used in addition to biochemical, biophysical, and molecular biology techniques.

An additional interest of Stein's laboratory is in the area of biotechnology. In collaboration with Dr. Minou Bina of the Department of Chemistry, team members have developed and patented miniaturized disposable gels capable of sequencing DNA. Because of the small size and ultra-thin design, these gels run very fast. They are also inexpensive to make and convenient to use. This gel system has now been used successfully for several years in one of the teaching labs (BIOL 542) at Purdue to teach DNA sequencing and genotyping.

JON STORY

Diet has long been implicated as regulator of sterol metabolism and, as such, as a means of altering risk in humans for development of diseases related to sterol balance. In the case of cholesterol, control of levels of cholesterol in the blood has been suggested as a means of reducing risk for cardiovascular disease while modification of bile acid excretion as been related to risk for colon cancer. Regulation of cholesterol balance is a combination of regulation of synthesis of cholesterol and the regulation of synthesis of bile acids, the predominant mode of excretion of sterol from the body.

Dr. Story's interest has focused on the dietary regulation of bile acid metabolism. The balance among the amount of bile acids synthesized, the amount reabsorbed from the small intestine or excreted, and the relative amounts of the various bile acids making up the pool plays a pivotal role in regulation of cholesterol balance. His team has focused on the effects of dietary fiber on these determining factors in cholesterol balance. Some sources of dietary fiber reduce bile acid reabsorption (and thus increase excretion) by binding bile acids and as a result of the increased viscosity of intestinal contents. These changes not only alter sterol balance directly as a result of the increased excretion but also alter the relative amounts of bile acids returning to the liver by altering the balance of passive and active routes of absorption.

Team members have observed increased levels of mRNA for apical sodium dependent bile acid transporter (the active route of bile acid reabsorption) in the ileum of rats fed viscous stheces of dietary fiber. This change is suggested to be responsible for the changes in the hydrophobicity of bile also observed in response to these stheces of dietary fiber. Hydrophobicity of bile has been shown to be a regulator of cholesterol synthesis and bile acid synthesis, supported in the experiments by the observation of increased levels of mRNA for the rate limiting steps for these two processes (HMG CoA reductase and cholesterol 7alpha-hydroxylase, respectively). Similar changes in bile acid metabolism have been observed in humans in response to stheces of dietary fiber which reduce hypercholesterolemia.

Story has extended these efforts to an examination of the role played by diet in modification of colonic microflora, in addition to bile acids, and the effect these changes have in modifying risk for colon cancer. In this case, his team has focused on a much broader array of diet components as modifiers of bile acid metabolism.

RAJI SUNDARARAJAN

Dr. Sundararajan's expertise and research interests include:

1) Electrical pulse-mediated chemo/gene therapy
2) Characterization of biological tissues using state-of-the-art material diagnostic techniques, such as impedance spectroscopy, atomic force microscopy, Scanning Electron Microscopy, Transmission Electron Microscopy, and Raman and Infra-red Spectroscopy
3) Electrical modeling and simulation of biological systems
4) Design and development of smart apps for digital image processing applications, such as enhanced accuracy of mammograms.
5) Aging and degradation of electrical devices, including high voltage outdoor insulators, batteries, wind turbine blades.

ANDY TAO

The mission of Dr. Tao's research group is to bridge technology with biomedical/biochemical discovery. Mass spectrometry-based proteomics is the kind of research that is highly interdisciplinary, bringing together biology, chemistry, instrumentation, statistics, and bioinformatics. Proteomics thus holds significant promise for the discovery of diagnostic or prognostic protein markers, for the detection of new therapeutic targets and for the understanding of basic biological processes and mechanisms. The realization of these expectations relies on the development of novel chemistry and instrumentation.

Tao's group focuses on the development of novel strategies and reagents to efficiently target and discover proteins of important biological relevance as potential biomarkers. Such proteins of interest are typically low in abundance, dynamically expressed, and post-translationally modified. The subject, called targeted proteomics, therefore involves the integration of a number of technologies including the selective targeting of proteins with activities of interest, multi-step sample preparation, and mass spectrometry. Examining changes in these proteins within cells under different physiological conditions will offer insights into understanding cellular and molecular mechanisms that cannot currently be obtained through traditional biological studies that usually focus on the detailed analysis of individual biomolecules.

Current projects in his group are:

1) proteomic studies of dendrimer-based nanomedicines
2) biomarker discovery using Ossabaw swine as the animal model for metabolic syndrome and cardiovascular disease
3) profiling of protease substrates in apoptotic cells
4) molecular signaling in cancer cells: phosphoproteomics

Also see p. 196.

ELIZABETH TAPAROWSKY

Dr. Taparowsky is interested in proteins that regulate cell growth. Her team studies how alterations in the expression of these proteins influence mammalian development and contribute to the aberrant growth characteristics of cancer cells.

Currently, the team is focusing on the BATF family of basic leucine zipper transcription factors which function as inhibitors of cell growth. Two of these proteins (BATF and BATF3) are normally expressed in the cells of the immune system and team members are exploring how overexpression of these inhibitors, or loss-of-function of these inhibitors, impacts the development of B and T lymphocytes.

While team members can investigate some of these effects using isolated subsets of immune system cells grown in culture, they also are using genetically engineered mice to test how these inhibitors impact the global regulation of the immune system in vivo. The goal is to provide the basic observations necessary to assess the feasibility of using the BATF family proteins to design molecular strategies to control disease states such as cancer.

Also see p. 197.

DOROTHY TEEGARDEN

Dr. Teegarden's laboratory is investigating the role and the mechanism of vitamin D metabolites in regulation of proteins during cancer progression in breast cancer. Currently, the mechanism by which 1,25 dihydroxyvitamin D, the active form of vitamin D, regulates energy metabolism is being investigated in breast cell model systems. In addition, the signaling pathways and the role of the nuclear vitamin D receptor mediating its effects are being explored.

Team members also are investigating the independent roles of dietary calcium and vitamin D on muscle and insulin resistance particularly in cell models and animal models.

DAVID THOMPSON

Dr. Thompson's team has developed plasma-stable polymer- and liposome-based carrier systems 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 therapeutic agents such as siRNA, plasmid DNA, and conventional small molecule chemotherapeutics. Mechanistic evaluation of their performance in tissue culture and animal models is employed to develop novel delivery vehicles with improved anti-cancer activity *in vivo*. Specific areas of research focus include:

Self-assembling cyclodextrin polymers as non-viral vectors. Cyclodextrins are used as hosts to deliver hydrophobic drug guest molecules in over 45 F.D.A.-approved therapeutics. We are utilizing the rich knowledge base of cyclodextrin host:guest properties to design multivalent polymer systems that can readily condense nucleic acid therapeutics (e.g., siRNA, miRNA & pDNA) into nanoparticles using these interactions. Through appropriate design of the multivalent attachments to the polymer, these self-assembled nanoparticle vectors are controllably disassembled to release their nucleic acid drug cargo after specific binding and uptake by the tumor cell population. These materials, which show at least 1000-fold lower toxicity and equivalent activity to the current benchmark non-viral vectors, are under investigation in animal models of glioblastoma.

Fusogenic liposomes with programmable drug delivery activity. Many drug vehicles utilize poly(ethylene glycol) (PEG) coatings to enhance their circulation time in humans, with $t_{1/2} \sim 42$ h observed for liposomal drugs bearing a PEG2000 coronal coating. Unfortunately, the favorable long-circulation features contributed by PEG eventually inhibit the activity of the liposomal carrier once it has reached the target tumor site. We are developing PEG-lipid and PEG-lipopeptide conjugates that promote the fusion of the liposomal carrier with target cell membranes upon programmable removal of the PEG coating. These constructs are currently under investigation in tissue culture and animal models of bladder carcinoma *in situ*.

Affinity-capture materials for accelerated elucidation of protein structures. Nanostructured interfaces, soluble liquid crystals, brush polymers, and supported monolayer materials bearing high-affinity ligands for specific capture of protein targets are being developed to aid in the determination of protein structures that can help guide anti-tumor drug design. The performance of the materials we have made to date suggests that they possess promising capabilities for aiding medium- and high-resolution structure determinations of membrane protein and soluble protein targets.

Also see p. 198.

ELIZABETH TRAN

Dr. Elizabeth Tran studies the role of DEAD-box proteins in gene expression, a group of RNA helicase enzymes that control RNA: protein interactions *in vivo*. Multiple DEAD-box protein genes have been connected to cancer, suggesting that mis-regulation of DEAD-box protein function(s) is a general feature of tumorigenesis. The Tran laboratory is currently investigating the DEAD-box protein Dbp2 using the *Saccharomyces cerevisiae* model system. The human ortholog of Dbp2 in human cells (DDX5 or p68) acts as a potent oncogene, promoting tumor formation in prostate, breast and colon and resistance to cancer therapeutics. In normal cells, Dbp2/DDX5 acts as a transcriptional regulator of multiple genes that promote cell growth and differentiation; however, the function of this DEAD-box protein is not well understood. By utilizing a genetically tractable model system, Dr. Tran is uncovering novel mechanisms for regulating gene expression as well as providing key insights into the molecular basis for cancer development.

PHILIP TROPED

Dr. Troped's research interests are in three broad areas:
1) environmental and policy determinants of physical activity and obesity
2) novel approaches of assessing physical activity behaviors with accelerometers and global positioning system (GPS) units
3) the design, implementation, and evaluation of physical activity and disease prevention interventions

In a current observational study funded by the National Cancer Institute, Troped and colleagues from several other institutions are examining associations between objective built environment variables and both physical activity and weight-related outcomes in more than 25,000 older women living in Massachusetts, Pennsylvania, and California.

DAVID WATERS

As a comparative oncologist, Dr. Waters focuses on the use of naturally occurring tumors in dogs as models of human cancer. Team members are utilizing canine osteosarcoma as a pre-clinical model to evaluate antimetastatic therapy and non-invasive imaging techniques. They are studying canine prostate cancer to further understand prostate carcinogenesis and the factors that regulate the progression to two lethal phenotypes: androgen-independence and skeletal metastasis. Their work with athymic mice is focused on in vivo testing of new anticancer agents and the development of metastatic models of human cancer.

CONNIE WEAVER

Dr. Weaver's lab focuses on building peak bone mass during adolescence and bone loss in postmenopausal women. Through her research, team members determine **c**alcium balance as well as calcium kinetics using stable isotopic tracers, total body calcium and bone mineral density using dual energy X-ray absorptiometry, and biochemical markers of bone turnover. Their goal is to determine the influence of diet, gender, and actual calcium retention and maximize development of peak bone mass. Team members are also studying the relationship between dairy and calcium intake and body fat maintenance in this population.

Dietary alternatives to estrogen replacement therapy for postmenopausal women are also being investigated in the laboratory by a novel approach of Ca-41 technology. Osteoporosis is a disease characterized by decreased skeletal mass and increased susceptibility to bone fractures. Health care costs related to hip fracture alone exceed $17 billion per year in the United States. Two strategies to prevent osteoporosis include increasing bone mass early in life and to prevent loss later. The team hopes to provide dietary and exercise advice to help women prevent osteoporosis later in life. Dr. Weaver is also leading a team to determine factors that affect coronary artery calcification using the Ca-41 technology and the Ossabaw pig model.

The chemical form of minerals in foods and bioavailability of minerals from foods has been a theme of study in the laboratory for many years. Her team uses isotopic tracer techniques to intrinsically label foods or salts of interest in order to study factors that enhance or inhibit absorption and their biological fate in animal models or humans. They have screened many food sources for calcium bioavailability. Team members have developed rat models for studying calcium kinetics and bone strength. Recently calcium tracers have been used to study soft tissue calcification in a pig model.

ALEXANDER WEI

Dr. Wei's research team blends creative organic synthesis with nanotechnology to produce exotic materials with unique physical or biomimetic function in the service of cancer research. Current activities involve the development of nanoprobes with hybrid plasmonic and magnetic function, to enhance biomedical imaging or therapeutic activity in combination with cancer-fighting chemotherapies. Other projects are driven by an interest to correlate the molecular structure of cell-surface carbohydrates with biological recognition and function, using organic synthesis and surface chemistry to develop well-defined models that mimic the function of the glycocalyx.

CANCER NANOTECHNOLOGY: Much of Wei's efforts have been focused on ligand-functionalized gold nanostructures with strong absorption or scattering at near-infrared (NIR) wavelengths, which can penetrate more deeply than visible light through biological tissues, These nanoparticles are chemically inert under physiological conditions, but can serve as multifunctional agents with combined diagnostic and therapeutic potential, often referred to as *theranostics*. Wei's biocompatible nanoparticles support plasmon resonances that are excited at NIR wavelengths to produce intense but localized photothermal effects. Nanosized vehicles based on gold nanorods and nanostars with magnetic cores have been engineered for tumor targeting, delivery, imaging, and release, using various photophysical and mechanical mechanisms.

CARBOHYDRATE-PROTEIN RECOGNITION: Wei is investigating structure-affinity relationships between various signaling proteins and carbohydrates presented on cell surfaces and in the extracellular matrix, particularly the glycosaminoglycans which are important in cell signaling, inflammation, and cancer. These include glycoforms whose biological activities are defined by specific post-glycosylation modifications, but whose precise structures remain poorly defined. Natural and unnatural carbohydrates have been synthesized to address questions relating structure to biological function, and also for identifying ligands with affinity toward heparin-binding proteins and cell-surface biomarkers. Research activities include methodologies for generating glycans with diverse sulfate patterns (sulfoforms) and stereochemistries, and their screening as affinity ligands against important heparin-binding proteins.

Also see p. 199.

JONATHAN WILKER

Dr. Wilker's research is in the following areas:

MARINE BIOLOGICAL MATERIALS: CHARACTERIZATION, SYNTHETIC MIMICS, AND APPLICATIONS: The oceans abound with a fascinating array of materials produced by nature. Barnacles cement themselves to rocks. Starfish use adhesives for locomotion. Oysters create aggregate reef structures. Mussels generate an impressive adhesive that can bond to nearly any surface, including Teflon (polytetrafluoroethylene, PTFE). Dr. Wilker's laboratory is working to understand how such biological materials function, design synthetic mimics, and develop applications for these new materials.

CHARACTERIZATION OF MARINE BIOLOGICAL MATERIALS: DISCOVERING HOW NATURE MAKES MATERIALS: Ongoing studies include characterizing the composition, bonding, and performance of these biomaterials produced by mussels, barnacles, oysters, and other species. Here the chemistry, biochemistry, and biology of adhesion are all being examined. In order to obtain chemical insights on specific bonding motifs in the materials, team members are using synthetic peptide models to obtain atom-by-atom level detail of the cross-links present in mussel adhesive. At a biochemical level they are extracting adhesive proteins, characterizing proteins, and exploring how such macromolecules can bring about bulk adhesion. Several methods including spectroscopy, reactivity, and microscopy are being used to provide direct observation of the bonding. More biological work with live animals includes changes made to the water chemistry and then quantifying the influences upon adhesion. With all of these studies they keep in mind mechanical performance of the materials. For example, the lab is uncovering links between protein cross-linking and adhesion strengths of the animals.

SYNTHETIC POLYMER MIMICS — NEW MATERIALS INSPIRED BY NATURE: As researchers learn how sea creatures stick, they can use this information to create new classes of synthetic materials. Bioinspired synthetic materials can have advantages over the natural versions such as the ability to tailor the material for a given property (e.g., adhesion, modulus, porosity, etc.) as well as provide access to large quantities of material. Team members have found that complex adhesive proteins can be mimicked with simple polymer backbones into which they incorporate biological cross-linking chemistry.

APPLICATIONS: DEVELOPING BIOMEDICAL MATERIALS, HIGH PERFORMANCE ADHESIVES, AND COATINGS:The underwater adhesion and high bonding strengths of marine biological materials bring to mind many applications ranging from wet-setting biomedical adhesives to new materials with tailored moduli. Current materials engineering efforts rely on their abilities to alter the polymer compositions and carry out the syntheses on large scales. As they incorporate more advanced functionalities into the polymers, they are tailoring the materials for specific uses. Perhaps most in demand are new adhesive materials for biomedical procedures and devices. At the moment there are no adhesives available that are simultaneously wet setting, strong bonding, and non-toxic. Marine biology may have already solved this problem, hence their exploration of these materials for biomedical applications.

MARY WIRTH

Dr. Wirth's team works at the interface of chemistry and medicine in order to create technology for earlier detection of diseases. The dream of 21st century medicine is that simple lab tests will reveal diseases well before the onset of symptoms, while the disease is easily curable.
Wirth's team has developed affinity beads that capture trace proteins from serum and release the intact proteins for biomarker discovery. They have coupled this with high throughput screening of glycoforms for cancer biomarker discovery.

Also see p. 200.

YOU-YEON WON

Dr. Won's laboratory is developing self-assembling block copolymers into nanosized carriers that can enable the simultaneous delivery of multiple therapeutic agents to cancer targets. Specifically, Dr. Won has developed a polymer micelle-based gene delivery system ("micelleplex") for the encapsulation of multiple types of therapeutic agents within its hydrophobic micelle core, thus enabling combination therapies (**Figure**).

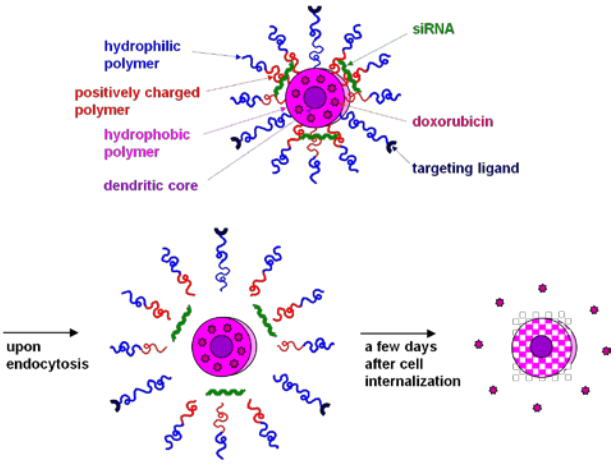


Figure. Self-assembling "micelleplexs" as delivery vehicles for combination drug therapies.

Recent studies include the co-delivery of an anticancer drug (doxorubicin) and siRNA for the treatment of drug-resistant cancers, and co-delivery with metal nanoparticles for the combination of hyperthermia and RNAi agents. Some of these micelleplex formulations have recently been evaluated for systemic toxicity using mice models. Dr. Won has also developed a novel polymeric carrier for gene delivery, one that is degradable upon exposure to mild UV irradiation. This photo-degradability can be used to precisely control the timing and location of the intracellular DNA/siRNA release. This photodegradable polymer vector is currently being examined for enhancing the transfection of refractory cell types, such as primary and stem cells.

YOON YEO

Dr. Yeo's research is focused on three main areas.

TUMOR TARGETED DRUG DELIVERY: Yeo's laboratory is developing new polymeric nanoparticulate drug delivery systems for tumor-specific chemotherapy in two ways. First, the nanoparticle surface is modified with various ligands that protect the nanoparticles during circulation but activate them in the tumoral extracellular environment. Team members use overexpressed matrix metalloproteinases or acidic pH, unique properties of tumoral tissues, as molecular cues to activate the nanoparticles. They anticipate that the activatable nanoparticles would remain inert during circulation but become interactive with cells upon tumor accumulation, thereby enhancing the tumor-specificity of drug delivery. The second approach is to decorate the nanoparticle surface with a ligand that can selectively interact with molecular markers overexpressed on the peritumoral endothelium. The rationale of this approach is that the increased interactions between nanoparticles and the peritumoral endothelium via this ligand-marker interaction would increase the chance nanoparticles can extravasate, a critical step for drug delivery to tumors. Yeo anticipates that the nanoparticles interactive with the peritoumoral endothelium would increase the accumulation of nanoparticles in the tumors beyond the level that has been possible with the enhanced permeability and retention effects alone.

INTRAPERITONEAL DRUG DELIVERY FOR POST-SURGICAL CHEMOTHERAPY OF OVARIAN CANCER: Ovarian cancer is currently managed by surgical debulking of the tumor followed by systemic chemotherapy. Recent clinical studies have recognized intraperitoneal (IP) chemotherapy, and its clinical application has been encouraged by the NCI. However, IP chemotherapy faces several challenges that limit its widespread adoption in practice. One of the challenges is the rapid clearance of a drug from the peritoneal cavity. Yeo's laboratory uses a combination of biocompatible hydrogels and nanoparticles to increase the IP residence time and the availability of a chemotherapeutic drug. Therapeutic efficacy of the new system delivering paclitaxel and/or platinum is currently tested in a murine model of IP cancer.

INHALATIONAL DRUG DELIVERY FOR CHRONIC PULMONARY DISEASES: The inhalable microparticle is an attractive treatment option for chronic pulmonary diseases such as cystic fibrosis, asthma, or chronic obstructive pulmonary disease, because it can provide efficient local medication with minimal systemic side effects, a prolonged therapeutic effect, and an easy method of administration. Recent advances in particle technology have overcome a number of hurdles in achieving microparticles with favorable aerodynamic properties. However, existing technologies do not adequately address biological barriers specific to the pulmonary diseases. The mucus layer on the lung epithelium is a significant barrier for pulmonary drug delivery, especially in therapy of cystic fibrosis and obstructive lung diseases. The rationale of this research is that if this barrier is overcome, the inhalational microparticles would more effectively deliver drugs to the target cells and achieve superior therapeutic effects. Team members have shown a proof of principle that simultaneous delivery of a drug along with a mucolytic agent can facilitate diffusion of the drug and enhance its efficacy and, consequently, reduce the dose requirement for inhaled particles. Their goal is to extend this principle to the development of inhalable gene delivery systems.

YUEHWERN YIH

Dr. Yih is involved in cancer prevention and control. Her research focuses on:

1) Design, monitor, and control of complex systems
2) Behavior-based dynamic control
3) Process/system model, analysis, and improvement
4) Machine learning and artificial intelligence
5) Healthcare system re-engineering

DABAO ZHANG

Dr. Zhang's research interests include:

1) High-dimensional data analysis
2) genome-wide association study (GWAS)
3) Bioinformatics and statistical genetics
4) Bayesian statistics
5) computational methods for statistical inference
6) data mining and machine learning
7) extreme values
8) genetic epidemiology
9) omics data analysis (including microarray data and mass spectrometry data)
10) quantitative trait loci (QTL) mapping
11) survival analysis (i.e., analysis of time-to-event data)
12) genomic selection

JIAN ZHANG

Dr. Zhang's research focuses on

1) Bayesian
2) Computational Methods for Statistical Inference
3) Computational Statistics
4) Data Mining
5) Information Retrieval
6) Machine Learning
7) Massive Data
8) Nonparametric Regression/Density and Models

MIN ZHANG

Dr. Zhang's research interests include:

1) bioinformatics and biologically related disciplines (genomics, nutrition, proteomics, statistical genetics)
2) statistical methods for genome-wide association studies
3) Bayesian methods for QTL mapping
4) Omics data modeling and integration
5) proteomics
6) statistical genetics
7) methods for systems biology

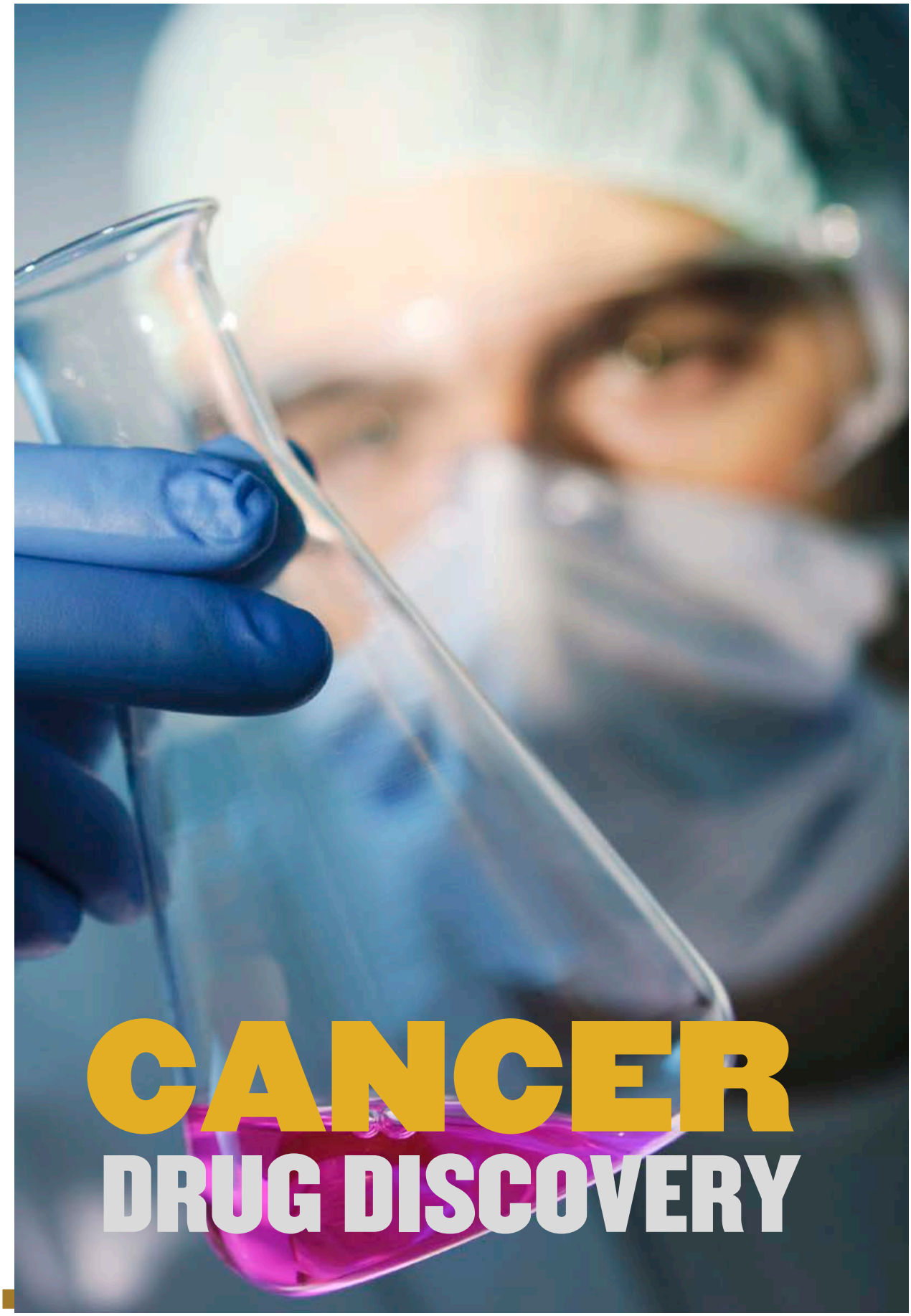
BABAK ZIAIE

Dr. Ziaie's research interests include:

1) biomedical micro and nanosystems
2) bioMEMS
3) implantable wireless Microsystems
4) micro and nanofabrication technology
5) biomimetics
6) soft condensed matter
7) analog circuit design for biomedical applications

ALAN ZILLICH

Dr. Zillich's research interests involve (1) the roles of professional collaborative relationships between pharmacists and other health care providers; and (2) the effectiveness of pharmacy-based services on improved medication prescribing, patient safety, and patient health outcomes, and (3) methods to improve prescribing and utilization of medications through systems redesign and health informatics.


CANCER
DRUG DISCOVERY

ALPHABETICAL LIST OF CANCER DRUG DISCOVERY RESEARCHERS

LAST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Drug Design & Discovery	Detection Technology	Target Development for Drug Discovery
Aguilar	Rubin Claudio	College of Science	Biological Sciences			
Andrisani	Ourania	College of Veterinary Medicine	Basic Medical Sciences			
Borch	Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Briggs	Scott	College of Agriculture	Biochemistry			
Buhman	Kimberly	College of Health and Human Sciences	Foods & Nutrition			
Camarillo	Ignacio	College of Science	Biological Sciences			
Cheng	Ji-Xin	College of Engineering	Biomedical Engineering			
Chmielewski	Jean	College of Science	Chemistry			
Colby	David	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Cooks	R. Graham	College of Science	Chemistry			
Cushman	Mark	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Davisson	V. Jo	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Fleet	James	College of Health and Human Sciences	Nutrition Science			
Freeman	Jennifer	College of Health and Human Sciences	Health Sciences			
Fuchs	Phil	College of Science	Chemistry			
Geahlen	Robert	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			

AST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Drug Design & Discovery	Detection Technology	Target Development for Drug Discovery
Ghosh	Arun	College of Science/ College of Pharmacy (joint appointment)	Chemistry/ Medicinal Chemistry & Molecular Pharmacology			
Gibbs	Richard	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Hall	Mark	College of Agriculture	Biochemistry			
Hazbun	Tony	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Hrycyna	Christine	College of Science	Chemistry			
Hu	Chang-Deng	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Irudayaraj	Joseph	College of Engineering	Agricultural and Biological Engineering			
Jiang	Qing	College of Health and Human Sciences	Nutrition Science			
Kim	Chang	School of Veterinary Medicine	Comparative Pathobiology			
Kirchmaier	Ann	College of Agriculture	Biochemistry			
Knapp	Deborah	College of Veterinary Medicine	Veterinary Clinical Sciences			
Konieczny	Stephen	College of Science	Biological Sciences			
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			
Liu	Shuang	College of Pharmacy, Nursing & Health Sciences	Health Sciences			
Liu	Wanqing	College of Pharmacy	Medicinal Chemistry and Molecular Pharmacology			

AST NAME	FIRST NAME	COLLEGE	DEPARTMENT	Drug Design & Discovery	Detection Technology	Target Development for Drug Discovery
Liu	Xiaoqi	College of Agriculture	Biochemistry			
Low	Philip	College of Science	Chemistry			
Mittal	Suresh	College of Veterinary Medicine	Comparative Pathobiology			
Mohammed	Sulma	College of Veterinary Medicine	Comparative Pathobiology			
Park	Kinam	College of Pharmacy	Industrial & Physical Pharmacy			
Parker	Laurie	College of Pharmacy	Medicinal Chemistry & Molecular Pharmacology			
Shah	Kavita	College of Science	Chemistry			
Stauffacher	Cynthia	College of Science	Biological Sciences			
Tao	Andy	College of Agriculture	Biochemistry			
Taparowsky	Elizabeth	College of Science	Biological Sciences			
Thompson	David	College of Science	Chemistry			
Wei	Alexander	College of Science	Chemistry			
Wirth	Mary	College of Science	Chemistry			

RUBIN CLAUDIO AGUILAR

THERAPEUTIC OUTCOME: Dr. Aguilar's laboratory specializes in vesicle trafficking, particularly endocytosis. Currently, the team's research is focused on the role played by the endocytic machinery in the activation of signaling pathways related to cancer cell invasion. Team members 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/EXPERTISE: Identification of novel targets for cancer therapy (particularly anti-metastatics). The team's emphasis is on counteracting novel cell invasion pathways. Based on a body of knowledge accumulated in the field, the team predicts 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): Team members are interested in designing strategies that would allow rapid and efficient internalization of therapeutics. Specifically, they are working on induction of receptor crosslinking (microaggregation) and on the effect of ligand multivalency.

Also see p. 18.

OURANIA ANDRISANI

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

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Project 1: 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.

The team's 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
6) SUZ12, a component of a repressive chromatin remodeling complex (PRC2), directly suppresses expression of marker genes of hepatic cancer initiating cells

The team is exploring:
1) Use of Plk1 and Suz12/PRC2 target genes as early 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.

Project 2: The team is testing a microRNA gene signature as prognostic for the active surveillance of low-risk prostate cancer by which to distinguish low-risk prostate cancers that will progress clinically to the aggressive, life-threatening form.

Also see p. 20.

RICHARD BORCH

THERAPEUTIC OUTCOME: Dr. Borch focuses on the 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: The team is 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. Team members also are exploring mitotic centromere-associated kinesin (MCAK) as a novel cancer target and have developed selective inhibitors.

Many of the team's most potent phosphomimetic prodrugs are highly lipophilic and thus are not suitable for further in vivo development. They 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.

Also see p. 24.

SCOTT BRIGGS

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/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.

Also see p. 27.

KIMBERLY BUHMAN

My research interests and expertise are in the area of lipid metabolism, including neutral lipid (triglyceride and cholesterol ester) synthesis, storage and lipoprotein metabolism. The major focus of my laboratory is on understanding molecular mechanisms involved in the process of dietary fat absorption, which is important in regulating energy balance and blood triglyceride concentrations. We use genetic and dietary mouse models to understand the role of lipid metabolism genes and specific dietary components in these processes.

In addition, my laboratory has an interest in how lipid metabolism is disrupted in tumors. We have found abnormal accumulation of lipids in cancer cell lines. We investigated the role of key enzymes and proteins involved in regulation of lipid metabolism contributing to proliferation and migration of cancer cells and found that the synthesis of cholesterol esters via acycoenzyme A cholesterol acyltransferase 1 (ACAT1) contributes to the tumor phenotype.

IGNACIO CAMARILLO

THERAPEUTIC OUTCOME: Develop understanding of the impact of diet and obesity on tumor microenvironment and tumor progression. Of particular interest to Dr. Camarillo is breast carcinoma.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Team members have been working with a plant protein that is a structural homolog of adiponectin, an adipokine with antiproliferative, anti-diabetic, and anti-inflammatory activities. Similar to adiponectin, team members have demonstrated this molecule is antiproliferative, anti-migratory, and inhibits cell invasion in aggressive breast cancer cell lines. This demonstrates the potential for this molecule to serve as an anti-tumor agent in cancer progression. This molecule is common in various fruits and vegetables and therefore offers decreased likelihood of side effects.

Team members have developed a co-culture system that mimics the mammary gland 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, team members have demonstrated that adipose tissue, in the absence of exogenous growth factors or any other culture supplements, can support long-term mammary tumor cell growth. This is a valuable system to study the molecular interplay between microenvironment and mammary tumor cells and to identify cellular and secreted biomarkers for cancer progression.
An ongoing concern with breast cancer therapies is the associated harsh side effects. Enhancing the ability of current drugs to permeate tumor cells can help alleviate these unwanted effects. Electropermeabilization technique has the potential to enhance cell membrane permeability to various chemotherapeutic compounds. Their in vitro studies have demonstrated electropermeabilization, in combination with standard breast cancer treatments, can enhance drug efficiency. This enhanced drug delivery system has been utilized with skin cancer patients and has improved outcomes dramatically. Development of this system with other forms of cancer will enhance current treatment options.

Obesity is a major concern and is associated with breast cancer incidence, tumor invasiveness, drug resistance and higher cancer morbidity rates. Team members have developed a rat model of diet-induced obesity to study the effects of a western diet and obesity on breast cancer progression. Their research shows that Western diet-fed rats develop greater numbers of highly invasive mammary tumors, compared to Western-fed diet resistant lean rats. These results support that this rat model is a valuable system to identify biomarkers and epigenomic and metabolomic signatures associated with dietary effects on tumor progression and on therapeutic response of tumors.

Also see p. 30.

JI-XIN CHENG

THERAPEUTIC OUTCOME: Development of detection of circulating tumors cells, oxidized lipids, and polymer micelles for drug delivery. Dr. Cheng's particular interests are breast and prostate carcinomas.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Team members are 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.

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

The team is developing shell-crosslinked polymer micelles for delivery of anti-cancer drugs (in collaboration with Dr. Kinam Park). Compared to currently used micelles, these shell crosslinked micelles avoid premature release of drugs during blood circulation.

Also see p. 35.

JEAN CHMIELEWSKI

THERAPEUTIC OUTCOME: Developing agents and strategies to improve the brain penetration of anti-cancer therapies.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Team members have developed potent inhibitors of multidrug resistance transporters present at the blood-brain-barrier that effectively reverse drug resistance in cell culture and show efficacy in a brain capillary model.

Also see p. 37.

DAVID COLBY

THERAPEUTIC OUTCOME: Synthesizing derivatives of natural products to selectively target cancer stem cells and aggressive drug-resistant cancers.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST AND EXPERTISE: The team is 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 drug-resistant cancer cells and populations of cancer cells, termed cancer stem cells. Colby's team also is developing new synthetic methodologies to modify the structure of complex natural products.

Also see p. 40.

R. GRAHAM COOKS

THERAPEUTIC OUTCOME: Developing tissue imaging technology in order to detect and monitor cancer. Particular interests are prostate and bladder carcinomas.

DEVELOPMENTAL STAGE: Intermediate to Late

RESEARCH INTEREST/EXPERTISE: Dr. Cooks' team is interested in the use of mass spectrometry (MS) to identify disease markers including prostate cancer markers. He and his team are particularly interested in tissue imaging using MS to supplement standard histological methods. These experiments would be best conducted on site, during surgery, and Cooks' 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. The team is interested in extending its use to problems of in situ disease diagnosis as well as clinical analysis.

Also see p. 41.

MARK CUSHMAN

THERAPEUTIC OUTCOME: Dr. Cushman's laboratory is designing and synthesizing potential anticancer agents. The team currently has two drugs (indenoisoquinoline inhibitors of topoisomerase I) in Phase 1 clinical trials at the National Cancer Institute.(Drug: Indimitecan, Indotecan; assistance with drug metabolism/agent SAR with ENMD-1198, 2ME2)

DEVELOPMENTAL STAGE: Late

RESEARCH INTEREST/EXPERTISE: In the anti-cancer drug development area, Cushman's team is focusing on novel indenoisoquinoline inhibitors of topoisomerase I. One of the main goals of this project is to synthesize topoisomerase I inhibitors that will facilitate crystallization and X-ray structure determination of ternary complexes containing the enzyme, a DNA fragment, and the inhibitor. This will provide insight into the mechanism of action of the indenoisoquinolines as topoisomerase I inhibitors and it will shed light on how other topoisomerase I inhibitors work as well. Work in this area has led to the synthesis of indenoisoquinolines containing polyamine side chains that confer exceptional potency as topoisomerase I inhibitors and as cytotoxic agents in human cancer cell cultures. A second project in the anticancer drug design area involves the design and synthesis of brefeldin A prodrugs that induce apoptosis in cancer cell cultures.

Also see p. 44.

V. JO DAVISSON

THERAPEUTIC OUTCOME: Dr. Davisson is developing novel ligands for tumor targeting, re-purposing statins for tumor regulation, and identification of biomarkers and their pathways. Particular interests are breast, bone, colon, cervical, and prostate carcinomas. (Drug: Lejimalide)

DEVELOPMENT STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: *Compounds or combinations with novel tumoristatic activities:* Role of polyunsaturated fatty acid ligands in tumor targeting; Re-purposing statins for selective tumor down-regulation through lipid conjugation; Drug conjugates of V-ATPase antagonists.
Emerging biomolecular targets and pathways: Focus on non-druggable protein interactions to modulate specific binding partners or allosteric modulation of target proteins; V-ATPase in tumor microenvironment and metastatic progression, mitochondrial regulation by functional agonists of Bax, selective modulation of DNA replication/repair systems by functional antagonism of PCNA assembly and regulation

POTENTIAL BIOMARKERS FOR EARLY-STAGE CANCER: The use of advanced proteomic/genomic detection to pursue quantification of post-translational modifications as early indicators
Tumor targeting and sub-cellular localization: Receptor ligand discovery efforts for several families relevant to cancers; Drug-conjugate chemistry and sub-cellular localization; Ligands for specific vesicle transport systems to mitochondria and nucleus

SCREENING AND DEVELOPMENT ASSAYS: Innovative proteomic and genomic assay systems for target-pathway specific pharmacodynamics; Multi-parameter/high content and phenotypic cell-based screens; High content phenotype screens genome-wide screening based upon model organisms or RNAi; Animal models for testing anti-metastatic drugs; in vitro 3D tumor models for predictive high content screening platform

Also see p. 45.

JAMES FLEET

THERAPEUTIC OUTCOME: Developing an understanding the interactions among inflammation, Vitamin D, and normal tissue stem cells on the development of colon and prostate cancer.

DEVELOPMENTAL STAGE: Early to Intermediate

Research Interest/Expertise: Dr. Fleet is an expert on carcinogenesis, particularly the early stages that precede clinical diagnosis of cancer (i.e. molecular cancer prevention studies). He is interested in identifying molecular mechanisms that either enhance or suppress cancer development. In particular, his group examines the cancer chemoprotective actions of vitamin D compounds and they are currently testing whether vitamin D can inhibit precancerous inflammatory processes or whether it can protect the normal stem cell compartment from conditions that promote DNA damage. In addition, Dr. Fleet is an expert in the development and use of animal models for human prostate and colon cancer. He developed the first transgenic mouse model for colon cancer that limits it impact to the epithelial cells of the colon. His group is currently making an inducible version of this transgenic mouse that will permit production of adult mice with specific (and multiple) deletions to occur in the colon, making them more relevant to human colon cancer.

Also see p. 51.

JENNIFER FREEMAN

THERAPEUTIC OUTCOME: Identification of genetic biomarkers and the molecular pathways involved in cancer initiation and progression.

DEVELOPMENTAL STAGE: Early

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

Also see p. 52.

PHIL FUCHS

THERAPEUTIC OUTCOME: Synthesis of analogs of antineoplastic agents for cancer therapy. (Drug: 23'DCST)

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: The Fuchs research group is working on the synthesis of analogs of antineoplastic agents such as cephalostatin, apoptolidine, aplyronine A, Vitamin D3, and (+)-discodermolide. These analogs are screened at the Purdue Center for Cancer Research and are also submitted to John Beutler, a long-term collaborator at the NCI, for 60-cell line testing.

The team is currently supplying Peng Huang (MD Anderson Cancer Center) with a cephalostatin analog for animal studies. Fluorescent-tagged cephalostatin analogs have been prepared to serve as probes to monitor their cellular location (collaboration with J.J. LaClair of Xenobe).

Fuchs plans to collaborate with four biochemists at Purdue (Drs. Shah, Staiger, Suter, and Low) to systematically examine the physical, chemical, and biological interactions of aplyronides with actin and actin-binding "suspect" proteins that are up-regulated during carcinogenesis.

ROBERT GEAHLEN

THERAPEUTIC OUTCOME: Develop understanding of biomolecular targets and pathways, diagnostics, and compounds with novel activities. Particular interests are leukemia/lymphoma and breast carcinomas.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Biomolecular targets and pathways: The team is exploring the role of the Syk protein-tyrosine kinase in the regulation of signal transduction pathways in both immune cells where Syk functions as an oncogene product and in breast cancer cells where Syk behaves more as a tumor suppressor. The team uses a variety of cellular, biochemical, structural (in collaboration with Dr. Carol Post), and proteomic (in collaboration with Dr. Andy Tao) approaches.

DIAGNOSTICS: In collaboration with Dr. Chang Lu (now at Virginia Tech), Dr. Gehlen's team is exploring the use of electroporative flow cytometry to monitor the translocation of proteins from the cytoplasm to the plasma membrane and from the cytoplasm into the nucleus. Such translocations are often indicative of growth promoting signals in tumor cells.

COMPOUNDS WITH NOVEL ACTIVITIES: In collaboration with Dr. Richard Borch, the team is evaluating the ability of metabolically activated prodrugs targeted toward SH2 domains and other phosphopeptide-binding motifs to alter the growth properties of cells by engaging novel targets that control replication and cytokinesis.

Also see p. 54.

ARUN GHOSH

THERAPEUTIC OUTCOME: Dr. Ghosh's team is carrying out synthesis and biological evaluation of structurally diverse natural product-based anticancer agents. Particular interest is in ovarian, breast, colorectal and prostate carcinomas. (Drug: peloruside, folate-laulimalide)

DEVELOPMENTAL STAGE: Early to intermediate

RESEARCH INTEREST/EXPERTISE: The team's work emphasizes structural modification, design of molecular probes and investigation of biological mechanism of actions. At present, the team is 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.

Also see p. 56.

RICHARD GIBBS

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. Particular interest is 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 Drs. Christine Hrycyna and 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 the team is in a uniquely strong position in this field.

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

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

Also see p. 57.

MARK HALL

THERAPEUTIC OUTCOME: General interest is in mechanisms of cell cycle regulation, which is defective in all types of cancers.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: One of Dr. Hall's interests is in developing mass spectrometric approaches for the sensitive and specific detection of molecules of interest in complex biological samples, like bodily fluids or tissue homogenates. These approaches, using selected reaction monitoring mass spectrometry, are a potential method to detect protein biomarkers. His own biological interests have led him to develop methods for the quantitative detection of post-translational modifications on proteins, and this could be applied to detection of certain cancer biomarkers. The team is collaborating with the Knapp and Stauffacher labs to apply these methods to 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. Team members currently are involved in a collaborative project with Dr. Charbonneau to explore contributions of the Cdc14 phosphatase to genome stability and cancer avoidance in human cells.

Also see p. 60.

TONY HAZBUN

THERAPEUTIC OUTCOME: Dr. Hazbun is working to establish protein interaction networks in the yeast kinetochore, with a focus on the interactions of the yeast homologue of Aurora kinase. Using this technology, team members are investigating and discovering non-oncogene dependencies related to the Aurora kinase signaling network. Of particular interest to Hazbun is pancreatic cancer.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: These non-oncogene relationships are defined as genes that are essential only in the context of specific cancer-causing mutations such as when the Aurora kinases are overexpressed in pancreatic cancer. Team members have just submitted a manuscript on this work.

Hazbun's team is developing high-throughput assays to identify small molecule modulators of Hsp90 and other cancer relevant pathways using chemical genetic based relationships that are dependent on isogenic and genomewide set of yeast strains

Also see p. 63.

CHRISTINE HRYCYNA

THERAPEUTIC OUTCOME: The two major cancer research areas in her 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, her laboratory is investigating the mechanisms of activity, assembly, trafficking, and cellular localization of these membrane-associated proteins as The teamll as developing drugs that inhibit their activities. Particular interests are brain and pancreatic carcinomas. (Drug: Icmtl)

DEVELOPMENT STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE:
Icmt: Mutations in the K-Ras oncogene are the key causative agents in >85% of human pancreatic cancers. Isoprenylcysteine carboxyl methyltransferase (Icmt) catalyzes the posttranslational methylesterification of the K-Ras protein. Recent biological studies have demonstrated that inhibition of Icmt results in the mislocalization and loss of transforming ability of K-Ras. Therefore, Icmt provides an attractive and novel anti-cancer target. The goals of her research, in collaboration with the Gibbs laboratory, are to develop potent and efficacious Icmt inhibitors to be used in the treatment of pancreatic cancer. Team members have developed in vitro biochemical and cellular assays for Icmt inhibition and are currently collaborating with Dr. Stephen Konieczny on determining the efficacy of their 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 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. Team members have developed in vitro biochemical and cellular assays for P-glycoprotein and ABCG2 inhibition. In collaboration with Dr. David S. Miller (NIEHS/NIH), they are testing their 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.

Also see p. 64.

CHANG-DENG HU

THERAPEUTIC OUTCOME: Understanding of cancer cell survival in radiation therapy, understanding ATF2 transcription factor, nanotube targeted delivery of antisense DNA in prostate cancer, and developing several bimolecular fluorescence complementation (BiFC)-based assays to visualize protein-protein interactions in living cells. Particular interests are prostate, breast and melanoma carcinomas.

Developmental Stage: Early to Intermediate

Research Interest/Expertise: Team members have discovered that ionizing radiation can induce neuroendocrine differentiation (NED) of prostate cancer cells. Given that neuroendocrine-like cells are apoptosis resistant and can secrete peptide hormones and growth factors to support the growth of surrounding cancer cells and that radiation-induced NED is reversible, Dr. Hu hypothesizes that radiation therapy-induced NED for early-stage prostate cancer patients may allow cancer cells to survive treatment and contribute to recurrence and the development into late-stage of prostate cancer. Team members are evaluating the clinical significance of this novel finding in collaboration with Dr. Song-Chu Arthur Ko at IU Medical School. Two potential projects are relevant to early-stage cancer intervention:
1) Development of novel radio sensitizers by targeting radiation-induced NED. Team members have had some candidate pathways and genes in mind already and further pursuing of this direction is necessary.
2) Serum chromogranin A (CgA) can be used as a biomarker to monitor radiation-induced NED and to predict prognosis.

Dr. Hu has discovered that the transcription factor ATF2 is a nucleocytoplasmic shuttling protein. Team members have also demonstrated that ATF2 is a transcriptional repressor of NED. Importantly, increased cytopolasmic localization of ATF2 has been observed in several human diseases including melanoma, breast cancer, and prostate cancer and its cytoplasmic localization correlates to disease progression. These findings suggest that ATF2 may act as a novel tumor suppressor in these cancers. A better understanding of how ATF2 nuclear import is impaired in prostate cancer and breast cancer will likely identify novel pathways for development of targeted therapy. In addition, a better understanding of the consequences of increased ATF2 cytoplasmic localization could also lead to identification of new biomarkers for diagnosis and prediction of clinical outcomes.

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

Also see p. 65.

JOSEPH IRUDAYARAJ

THERAPEUTIC OUTCOME: Dr. Irudayaraj's primary effort constitutes the development of single cell diagnostics and drug quantification strategies for cancer research.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Team members have developed nanoscale platforms to quantify drug compartmentalization and localization in different cellular organelles [ACS NANO, 2009, 3(12):4071-4079], upon delivery. Their nanotechnology-based strategies for targeted drug delivery and release have been applied to evaluate the efficacy of delivery and kinetics of release at single molecule resolution in live single cells.

Team members have developed microRNA and mRNA detection strategies in single cells. Preliminary proof of concept has been shown to detect splice variants of BRCA1 in live single cells using their nanoruler concept. Irudayaraj expects that this approach can be used to detect proteins and rNA in single cells and tissues at ultrahigh sensitivity (Limit of detection is at atto Molar level).

Team members have a significant thrust in single cell epigenetic-based screening. Team members have the ability to detect histone modifications and DNA methylation in single cells. Approaches for epigenetic drug-delivery and treatment efficacy methods are in development.

Also see p. 67.

QING JIANG

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

Developmental Stage: Early to Intermediate

Research Interest/Expertise: Team members 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 the 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 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). Jiang's team is in the process of synthesizing some long-chain carboxychromanols (in collaboration with Dr. Richard Gibbs' lab) and then 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.

Also see p. 69.

CHANG KIM

THERAPEUTIC OUTCOME: Developing understanding of cell migration and cell differentiation in an organ-specific manner. Particular interests are breast, lymphoma and colorectal carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Dr. Kim's team is studying immune cell migration to tumor in an organ-specific manner. The main focus is on the cancer in the intestine versus other organs such as breast cancer and lymphoma.

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

Also see p. 70.

ANN KIRCHMAIER

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/EXPERTISE: In collaboration with Joseph Irudayaraj (Biological Engineering), Dr. Kirchmaier is 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, gene expression patterns) in vitro, in single cells and in tissues.

Her 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.

Also see p. 72.

DEBORAH KNAPP

THERAPEUTIC OUTCOME: Dr. Knapp's research involves a unique approach to study the causes of cancer development and progression, and to investigate novel approaches for the prevention (primary and secondary), screening, early detection, and treatment of cancer. Her focused work is invasive urinary bladder cancer; the team also works with colleagues in her department doing comparative research in brain cancer and with non-Hodgkin's lymphoma in dogs. (Drug: animal studies with 5-azacytidine, Celecoxib)

DEVELOPMENTAL STAGE: Early to intermediate

RESEARCH INTEREST/EXPERTISE: Team members have characterized specific forms of naturally-occurring cancer in pet dogs that serve as highly relevant models of human cancer. In the focus area of invasive urinary bladder cancer, Knapp's team is defining heritable (through very strong dog breed-associated risk) and environmental risk factors for the cancer. This will facilitate cancer prevention research in a highly relevant model in a very timely fashion. Because prevention studies in dogs can be performed in 6-24 months, dog studies can be used to select the most promising approach for the longer term (15+ years) and more expensive human studies. The team's group is also conducting research in cancer treatment with studies of new agents such as nanoparticles (in collaboration with Dr. J. Leary), targeted therapy (in collaboration with Dr. P. Low), demethylating agents (in collaboration with Dr. N. Hahn, IUSM), and with already established drugs (5-azacytidine, Celecoxib) being applied in a more effective dosing schedule.

Also see p. 74.

STEPHEN KONIECZNY

THERAPEUTIC OUTCOME: Dr. Konieczny is interested in understanding the earliest molecular and signaling events involved in the development of pancreatic ductal adenocarcinoma (PDAC). Mist1 may serve as a novel therapeutic target for the earliest stages of this disease.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Although activating mutations in the KRAS protooncogene ($Kras^{G12D}$) are thought to initiate a PDAC cascade, knowledge is grossly deficient in defining how $Kras^{G12D}$ 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, Konieczny's team has examined the importance of Mist1 — an acinar cell restricted basic helix-loop-helix transcription factor — to acinar-ductal metaplasia and pancreatic cancer. Utilizing the Mist1 locus and $Kras^{G12D}$ mouse models, their studies have shown that Mist1 plays a critical role in preventing preneoplastic lesions upon $Kras^{G12D}$ expression.

INTERESTS: early stages of pancreatic cancer; pancreatic cancer mouse models, histopathology, transcriptional gene regulation, signaling pathways, and in vitro culture models.

Also see p. 75.

SHIHUAN KUANG

THERAPEUTIC OUTCOME: Understanding how Dlk1 regulates downstream genes may lead to novel therapeutic targets in cancer prevention and treatment. Dr. Kuang also is interested in understanding cancer stem cells relative to new tumor growth, with particular interests in hepatocellular carcinoma and rhabdomyosarcoma.

DEVELOPMENTAL STAGE: Early

Research Interest/Expertise: The primary focus of Dr. Kuang's research is the regulation of stem cells by Notch signaling. To this end, team members 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.

Team members also are studying how microenvironment, or niche, regulates stem cell function. Understanding how stem cells interact with niche is particularly important in cancer research, as cancer stem cells are known to drive new tumor growth in response to cues from their niche.

Also see p. 76.

JAMES LEARY

THERAPEUTIC OUTCOME: Dr. Leary is developing multilayered, targeted nanoparticles with diagnostic and therapeutic (theragnostic) capabilities. His team also is developing single cell analysis technologies. Particular interests are breast, prostate, and bladder carcinomas.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: The team's current particles contain iron oxide cores for MRI contrast agents and near infrared fluorescent probes for fluorescent imaging for either diagnostics or for guided surgery. The nanoparticles contain either drugs (e.g. doxorubicin) or peptides (e.g. caspase 3 pathway inducing apoptosis). In conjunction with other laboratories, Leary's team is doing experiments on animal systems.

Leary's lab has world-class expertise in quantitative single cell analysis technologies including high-speed, multicolor flow cytometry, and interactive (laser ablation or optoinjection) scanning image cytometry for high-throughput analysis of nanoparticle-tissue interactions. Team members use these technologies for in-vitro or ex-vivo analysis of their nanomedical systems.

Also see p. 78.

SOPHIE LELIÈVRE

THERAPEUTIC OUTCOME: Deciphering the mechanisms that control the organization and function of nuclear proteins, notably as it pertains to the regulation of gene expression, in normal and cancer cells, in order to develop strategies for better detection and control of cancer initiation and progression.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: A fusion protein made of the nuclear protein NuMA and retinoic acid receptor has been shown to 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 systems, team members have identified a link between the distribution of NuMA, chromatin organization, and the maintenance of breast epithelial differentiation. Current hypotheses are that NuMA controls cell phenotype by influencing chromatin structure, specifically by targeting chromatin remodeling complexes (CRCs) to different nuclear sites, and that alteration of NuMA function at the chromatin level participates in cancer behavior.

Recent data show that NuMA interacts with members of different CRCs. Team members are now collaborating with biophysicist Joseph Irudayaraj to study the interaction of NuMA and CRCs in live cells. Team members also are working with Dr. Cynthia Stauffacher, a structural biologist, in order to unravel a previously unexplored, yet highly conserved, sequence that NuMA shares with other chromatin-associated proteins. Moreover, in collaboration with Dr. David Knowles (Lawrence Berkeley National Laboratory), they have developed an imaging analysis that identifies cells with different phenotypes involved in cancer progression based on NuMA distribution. This technique is being tested to help earlier diagnosis and/or prognosis of breast cancer and to 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. Lelièvre's hypothesis is that apical polarity controls epigenetic mechanisms of gene expression that are essential to prevent tumor development. Using the DNA Sequencing Resource, team members have identified, via microarray analyses performed in collaboration with Dr. Rebecca Doerge, 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 genes (and other genes in the list of candidates) as markers of preneoplastic alterations and targets for cancer prevention strategies is being assessed. Particularly, team members 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, team members are developing nanotechnology-based tools to diagnose and reverse apical polarity alterations.

Also see p. 79.

SHUANG LIU

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/EXPERTISE: Dr. Liu worked at DuPont Medical Imaging Division (new Lantheus Medical Imaging Inc) for 9 years, and has extensive experiences in developing new molecular imaging probes (PET, SPECT and optical). Since joining Purdue, Dr. Liu's research interest has been directed towards the development of new receptor-based radiotracers for tumor imaging. In addition, Dr. Liu has become one of the leaders in radiolabeled multimeric RGD peptides as radiotracers for non-invasive imaging of integrin $\alpha_v\beta_3$ expression in the rapidly growing and metastatic tumors. After evaluating >30 radiotracers in different tumor-bearing animal models established in my laboratory, ^{99m}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.

Recently, Dr. Liu's group is working on new molecular imaging probes (PET, SPECT and optical) for noninvasive diagnosis of metastatic tumors and their metastatic potential. Team members believe that early detection remains the best approach to improve 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.

Also see p. 82.

WANQING LIU

The long-term interest of Dr. Liu's lab is focused on human cancer genomics and personalized medicine towards discovering genetic markers integral to human cancers and therapeutic treatments, as well as translating these markers into clinical practice. His current research involves the use of integrated "omics" and systems approach to identifying susceptibility genetic variants for cancer as well as molecular targets for cancer therapy. Ongoing projects in the lab include:

Genetics and genomics of somatic mutations in lung cancer. Somatic mutations in EGFR gene is highly correlated with clinical outcome of EGFR-targeted treatment. Lung cancer with EGFR mutations is an unique disease. We are designing both candidate gene and genome-wide association studies (GWAS) towards identifying germline alleles conferring risk to the occurrence of these somatic mutations.

Genetic mechanism underlying genes/alleles contributing to cancer risk. Although GWAS has been successfully identifying a number of genetic alleles increasing risk for cancers, little is known regarding the biological function of these alleles and the underlying mechanism how these alleles mediating the development of cancer. We use both genomic and mechanistic approaches studying a few genetic loci associated with lung cancer.

Pharmacogenetics of anti-cancer agents. Personalized treatment is a promising avenue to cancer treatment in coming decades. Our study uses systems biology approach to discover important genetic factors affecting both pharmacodynamics and pharmacokinetics of anti-cancer agents.

Also see p. 83.

XIAOQI LIU

THERAPEUTIC OUTCOME: Developing an understanding of Plk1 and its role in cancer formation and for potential drug design. Particular interests are prostate, pancreatic, and breast carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Dr. Liu is studying the roles of the cell cycle in cellular transformation. In particular, Liu's team is 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. Team members are collaborating with colleagues in PCCR to test their hypotheses in animal models. Liu's lab
has developed several bimolecular fluorescence complementation (BiFC)-based assays to visualize protein-protein interactions in living cells. In particular, team members have developed a multicolor BiFC assay that allows visualization of two interactions simultaneously in the same cell. This multicolor BiFC assay has a great potential for high throughput screening of protein-protein interaction disruptors. This screening system does not have false positive, which is the limitation of many single pair of protein-protein interaction assays. More importantly, the assay can be set up in vitro, in cells and in living animals (e.g. C. elegans).

Also see p. 84.

PHILIP LOW

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

DEVELOPMENTAL STAGE: Late

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

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

Also see p. 86.

SURESH MITTAL

THERAPEUTIC OUTCOME: Dr. Mittal is developing adenovirus vectors for gene therapy and immunotherapy, with a particular interest in breast cancer.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Adenovirus vectors as a delivery vehicle for cancer gene therapy. Mittal's team is 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. Team members 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. Mittal's team also is working on a strategy to enhance anti-tumor cytotoxic T cells by immunotherapy using adenovirus vectors. Following their demonstration that EphA2-EphrinA1 interaction inhibits tumor progression, team members 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. They have 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), the team 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.

Also see p. 92.

SULMA MOHAMMED

THERAPEUTIC OUTCOME: Determining progression markers for diagnostics, imaging probes, and intervention strategies. Particular interests are breast and bladder carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Team members 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 comedo type) are strikingly similar to those of the human breast. This striking 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, Mohammed's 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.

Mohammed's lab also is 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* (Team members have an ongoing study in collaboration with Indiana University School of Medicine to collect lymph draining the breast tumor and before it enter the sentinel lymph node in women with metastatic breast cancer).

Team members have successfully grown the lymph tumor circulating cells isolated from lymph collected from an animal model in vitro. This study has potential to identify *metastasis-specific molecules* to stratify women according to the risk of developing metastasis, provide targets to treat and prevent metastasis, and determine therapeutic efficacy.

Using proteomics, Mohammed's lab has identified protein markers that are specifically expressed in human urinary bladder cancer and are in the process in validating these makers biologically.

Using breast cancer tissues (DCIS and Stage 1; luminal A and basal-like type) from African Women, African American women, and Caucasian women, Mohammed aims to determine molecular markers (racial differences and environmental factors) that occur early and contribute to the tumor aggressiveness in breast cancer among African and African American women.

Also see p. 95.

KINAM PARK

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

DEVELOPMENTAL STAGE: Intermediate

RESEARCH INTEREST/EXPERTISE: *Adaptable polymer micelles for tumor targeting:* Tumor targeting is one of the most important and extensively studied areas, but it is still poorly understood. One of the limiting factors in tumor targeting is that only a small fraction (<5%) of the drug loaded in the nanocarriers are actually delivered to the target site due to the instability of most nanocarriers in the blood and elimination by the reticuloendothelial system. Dr. Park's approach is to develop nanocarriers that minimizes drug release in blood until they reach the target site using adaptable nanoparticles, such as crosslinked polymer micelles, elastic polymer particles, and drug nanocrystals that release drugs in the presence of specific enzymes.

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

Also see p. 102.

LAURIE PARKER

THERAPEUTIC OUTCOME: Development of kinase activity sensors and assays to monitor drug mechanisms and dosage. A particular interest is in leukemia (chronic myeloid leukemia).

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Parker's lab is developing in vitro and intracellular sensors and assays for kinase activity. The team use 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. The team uses highly sensitive mass spectrometry readouts that can be multiplexed to analyze many substrates at once, and Parker's lab is developing imaging-based readouts that can be analyzed using plate readers or microscopy. Technologies could be applied to high-content secondary screening of kinase inhibitor drugs, or more importantly, for monitoring therapeutic response during treatment. This could be extremely useful for drug discovery, where drug mechanisms and dosage are not well characterized in vivo during drug development and where traditional pharmacokinetics don't necessarily tell the whole story about mechanistic inhibition (since serum levels don't always correlate to intracellular enzymatic inhibition). In particular for leukemias, their techniques should be sensitive enough to monitor mechanistic response in peripheral blood from animal models and human subjects. Other than drug response, the technologies could also be used to generate personalized kinase activation biomarker signatures that may inform diagnosis, prognosis, or treatment decisions for individual patients.

Also see p. 103.

KAVITA SHAH

THERAPEUTIC OUTCOME: Understanding the role of oncogenic kinases and their oncogenic targets as a potential clinical target. Specific interests are breast, pancreatic, ovarian and prostate carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Dr. Shah's research focus is on dissecting the roles of oncogenic kinases (Aurora A, LIMK2, v-Src) and G Proteins (Ras) using chemical, genetic and chemical-genetic approaches. One recent area of interest is Aurora A kinase, located in 20q13 amplicon, which is overexpressed in several types of cancers: prostate, breast, ovarian, colorectal, gastric, pancreatic, hepatocellular, gliomas, nonendometriod and aggressive non-Hodgkin's lymphoma to name a few. Several small molecule inhibitors against Aurora A and Aurora B are in clinical trials. The team's goal is to identify the direct oncogenic targets of Aurora A kinase in prostate, ovarian and breast cancer tissues using a chemical genetic approach developed in their laboratory. The power of this approach emanates from engineered Aurora A's ability to selectively tag its substrates in the context of the cellular milieu containing numerous other kinases and substrates.

Her laboratory has identified several cancer-specific targets of Aurora A substrates in prostate, ovarian and breast cancer cells. One such target is LIMK2 kinase, which was identified as a direct Aurora A substrate in many different cancer cell lines. Ablation of LIMK2 in Aurora A-overexpressing breast cancer cells abrogates tumor formation in nude mice, suggesting that it is a critical oncogenic effector of Aurora A and a potential clinical target. Shah's team is exploiting this information for the development of pharmacodynamic biomarkers for Aurora A-targeted drugs, predictive biomarkers for breast and prostate cancer progression and to unravel the molecular mechanisms of tumorigenesis and metastasis. Aurora A substrates' that are highly associated with survival could supplement standard staging information in primary biopsy samples. The mechanism by which Aurora A functions in tumorigenesis and metastasis should reveal potential drug targets. Since Aurora A is an essential kinase, selective targeting of AA's oncogenic effectors is expected to show less toxicity. Results from these studies also have the potential to facilitate the development of combination therapies using both Aurora A and substrate-targeted drugs.

Also see p. 123.

CYNTHIA STAUFFACHER

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/EXPERTISE: Dr. Stauffacher's laboratory is investigating the molecular modifications and their signaling consequences in the oncogene pair, HCPTP (human low molecular weight protein phosphatase) and EphA2 (ephrin A2) tyrosine kinase receptor. EphA2 receptor has been implicated in the metastatic transformation in a wide range of human cancers, with the phosphorylation state, controlled by HCPTP, a strong determinant of the transformed state of the cell. Using biophysical techniques ranging from mass spectroscopy to NMR and X-ray crystallography, team members 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.

Also see p. 128.

ANDY TAO

THERAPEUTIC OUTCOME: Developing discovery of biomarkers for drug targeting and imaging. Particular interests are breast and live carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Dr. Tao is developing proteomic technologies to identify intracellular drug targets and novel therapeutic and imaging reagents based on dendrimers.
His team also is developing a set of techniques and reagents for the analyses of protein modifications using mass spectrometry, in particular phosphorylation, prenylation, and degradation.

BIOMARKER DISCOVERY: Tao's lab is pursuing proteomic approaches to identify protein biomarkers in serum/plasma as potential biomarkers.

Also see p. 132.

ELIZABETH TAPAROWSKY

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/EXPERTISE: The goal of Dr. Taparowsky's research is to establish how regulation of the AP-1 transcription factor, through natural or artificial means, may be applied to controlling human disease. Her 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 where the pro-inflammatory response is impaired and/or the immune system is unable to fight routine infection.

The team's 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.

Also see p. 133.

DAVID THOMPSON

THERAPEUTIC OUTCOME: Research efforts in the Thompson group address problems in (1) high-throughput screening for membrane-associated methyl transferases, (2) bioresponsive polymer and nanoparticle carriers of nucleic acid therapeutics, and (3) microfabricated particles for drug and gene delivery to glioblastoma and bladder tumor tissue.

DEVELOPMENTAL STAGE: Early to Intermediate

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

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

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

Also see p. 135.

ALEXANDER WEI

THERAPEUTIC OUTCOME: Developing nanoprobes that can be coupled with drug action or drug delivery. Particular interests are breast and colorectal carcinomas.

DEVELOPMENTAL STAGE: Early

RESEARCH INTEREST/EXPERTISE: Dr. Wei is developing non-invasive (in vitro and small-animal in vivo) assays to measure changes in the biomechanical properties of cells and tissues in the tumor microenvironment, using multifunctional nanoprobes. Changes in cellular and tissue biomechanics may be prognostic of tumor cell proliferation, extrasavation, and the onset of metastasis, and serve as a metric for early-stage tumor progression. The nanoprobes also can be triggered to release localized thermal or acoustic responses that can be coupled with drug action or drug delivery.

Sulfated oligosaccharides with specific variations in sulfate patterns are being synthesized and presented as microarrays, for the screening of heparin-binding proteins and other potential serum biomarkers.

Also see p. 140.

MARY WIRTH

THERAPEUTIC OUTCOME: Dr. Wirth's lab is using nanoparticles for a wide range of tools used for biomarker discovery and medical tests.

DEVELOPMENTAL STAGE: Early to Intermediate

RESEARCH INTEREST/EXPERTISE: Wirth's team is speeding up proteomic separations for biomarker discovery by a factor of 10 by using nanotechnology for new materials used for chromatography and electrophoresis, coupled to mass spectrometry.

Also see p. 142.

LIST OF INVESTIGATORS BY CANCER RESEARCH AREA

BIOMARKER DISCOVERY
Cooks, R. Graham
Craig, Bruce
Doerge, Rebecca
Geahlen, Robert
Irudayaraj, Joseph
Knapp, Deborah
Regnier, Fred
Tao, Andy
Teegarden, Dorothy
Waters, David
Yih, Yuehwern

CANCER CELL BIOLOGY
Aguilar, Rubin Claudio
Andrisani, Ourania
Briggs, Scott
Camarillo, Ignacio
Chang, Henry
Charbonneau, Harry
Cheng, Ji-Xin
Fekete, Donna
Fleet, James
Freeman, Jennifer
Geahlen, Robert
Gelvin, Stanton
Hall, Mark
Harrison, Marietta
Hazbun, Tony
Hrycyna , Christine
Hu, Chang-Deng
Irudayaraj, Joseph
Jiang, Qing
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Kirshner, Julia
Konieczny, Stephen
Kuang, Shihuan
Leary, James
Lelièvre, Sophie
Liu, Xiaoqi
Lossie, Amy
Low, Philip
Mendrysa, Susan
Miller, Margaret
Mittal, Suresh
Mohammed, Sulma
Packer, Rebecca
Peer, Wendy
Post, Carol
Ramos-Vara, Jose
Ratliff, Timothy
Robinson, J. Paul
Rundell, Ann
Shah, Kavita
Stauffacher, Cynthia
Stein, Arnold
Tao, Andy
Taparowsky, Elizabeth
Teegarden, Dorothy
Tran, Elizabeth

CHEMICAL & STRUCTURAL BIOLOGY
Bolin, Jeffrey
Chen, Jue
Chmielewski, Jean
Cramer, William
Friedman, Alan
Golden, Barbara
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Parker, Laurie
Post, Carol
Rossman, Michael
Sanders, David
Savinov, Sergey
Shah, Kavita
Simpson, Garth
Stauffacher, Cynthia
Tao, Andy
Thompson, David
Tran, Elizabeth
Wirth, Mary

DRUG DELIVERY & CANCER DIAGNOSTICS
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Cooks, R. Graham
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Ivanisevic, Albena
Kim, Young
Leary, James
Liu, Shuang
Low, Philip
Nolte, David
Packer, Rebecca
Park, Kinam
Regnier, Fred
Robinson, J. Paul
Savran, Cagri
Thompson, David
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DRUG DESIGN & DISCOVERY
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Cooks, R. Graham
Cushman, Mark
Davisson, V. Jo
Ghosh, Arun
Gibbs, Richard
Hazbun, Tony
Hrycyna, Christine
Knapp, Deborah
Lipton, Mark
Low, Philip
McMillin, David
Miller, Margaret
Mittal, Suresh
Park, Kinam
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Snyder, Paul
Waters, David

CANCER PREVENTION
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Burgess , Jay
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Moore, George
Morgan, Susan
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Smith, Al
Story, Jon
Teegarden, Dorothy
Troped, Philip
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SYSTEMS ENGINEERING, MODELING, & PHYSICS
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Morgan, John
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Ramachandran, PV
Raman, Arvind
Ramkrishna, Doraiswami
Regnier, Fred
Reifenberger, Ronald
Rickus, Jenna
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Sundararajan, Raji
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Yih, Yuehwern
Zhang, Dabao
Zhang, Jian
Zhang, Min

DRUG DESIGN & DELIVERY
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Knapp, Deborah
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Mittal, Suresh
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DETECTION TECHNOLOGY
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Liu, Shuang
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Wirth, Mary

TARGET DEVELOPMENT FOR DRUG DISCOVERY
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