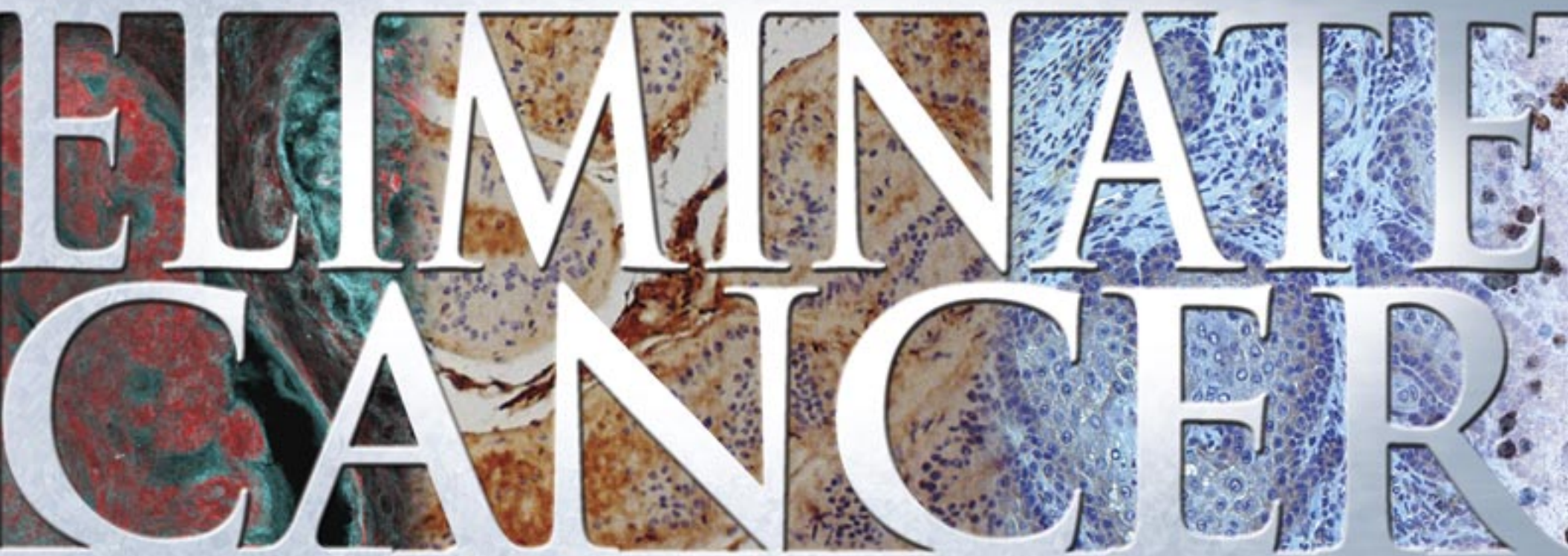


IMPROVE THE HEALTH OF THE WORLD

ELIMINATE CANCER

The title 'ELIMINATE CANCER' is rendered in large, white, serif capital letters. The letters are filled with various microscopic images of cancer cells, showing different cellular structures and colors like blue, brown, and red.

THE HORMEL INSTITUTE

UNIVERSITY OF MINNESOTA

2012 - 2013 ANNUAL REPORT

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Today's **RESEARCH**
Tomorrow's **CURES**

The mission of The Hormel Institute is to conduct research and provide education in the biological sciences with applications in medicine and agriculture. In pursuit of this mission, and as intended by its founders, The Hormel Institute generates fundamental knowledge and disseminates it to the scientific community worldwide. It also serves as a center of technical and educational expertise for the benefit of the Austin community, the surrounding region and the State of Minnesota.



"Most human cancers are preventable, or treatable, if discovered at an early stage."

MESSAGE FROM THE DIRECTOR DR. ZIGANG DONG

Even though the total number of deaths due to cancer in the United States is declining, cancer is still the leading cause of death worldwide. Most human cancers are preventable or treatable if discovered at an early stage. The Hormel Institute is a leading medical research institute making major contributions to the identification and characterization of novel molecular and cellular targets as well as agents for the prevention and therapy of human cancer. During 2013, The Hormel Institute experienced continued success obtaining research funding and producing major research breakthroughs even in a national environment of overall decreased funding for research.

With the support of Senator Dan Sparks and Representative Jeanne Poppe, the State of Minnesota bonding bill, signed by Governor Mark Dayton, included funding of \$13.5 million to the City of Austin Port Authority to lead the construction project for The Hormel Institute's next expansion. The Hormel Foundation, led by Chairman Gary Ray, announced \$23 million in funding to support the project. The construction is currently in the design process, with groundbreaking scheduled for 2014. The new building will be home to the International Center for Research Technology (ICRT) and The Hormel Institute.

The ICRT is a collaborative project with manufacturers of technology, such as IBM Rochester, to develop new technology to accelerate discovery and facilitate the comprehensive study of human diseases by combining analysis of protein structure/function with advanced methods of data management and drug screening. U.S. Representative Tim Walz and U.S. Senators Al Franken and Amy Klobuchar have shown strong support to The Hormel Institute by acquiring funding for the purchase of high-end equipment to establish the ICRT.

Indeed, the year 2012-13 was another great year. We are thankful for the generous support of The Hormel Foundation, Hormel Foods, University of Minnesota, and Mayo Clinic. In particular, I would like to thank Mr. Gary Ray, Mr. Jeff Ettinger, Mr. Richard Knowlton, Mr. Joel Johnson, Ms. Bonnie Rietz, Mr. Jerry Anfinson, and Mr. Steve Rizzi. We thank Drs. Eric Kaler and Brian Herman (University of Minnesota) and Drs. John Noseworthy, Glenn Forbes, Robert Diaiso, and Greg Gores (Mayo Clinic) for their leadership and support. We thank our elected leaders, U.S. Representative Tim Walz, U.S. Senators Al Franken and Amy Klobuchar, Minnesota Governor Mark Dayton, Minnesota State Senator Dan Sparks, and Minnesota State Representative Jeanne Poppe for their continued support.

CELLULAR AND MOLECULAR BIOLOGY

Executive Director/Section Leader

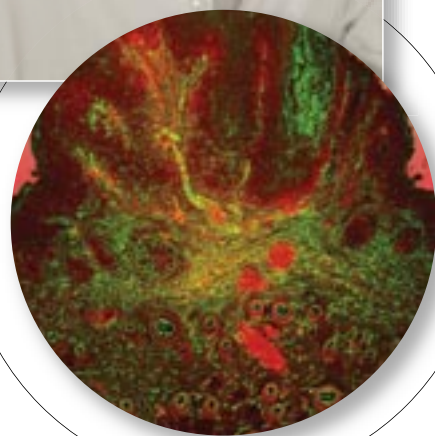
Zigang Dong, M.D., Dr. P.H.

McKnight Presidential Professor in Cancer Prevention

Hormel/Knowlton Professor



Many proteins are overexpressed only in cancer. The epidermal growth factor (green) is highly expressed in skin tumors and is a major chemotherapy target in breast cancer.



Cancer is one of the leading causes of human death worldwide. Throughout history, humankind has won the battle against deadly diseases, including small pox and polio, by defeating them through prevention and treatment. By focusing on the molecular mechanisms explaining how normal cells can undergo neoplastic transformation induced by carcinogens and tumor promoters, we have discovered that key protein kinases, transcriptional factors, and other signaling molecules are critical factors in cancer development and significant targets for cancer prevention and treatment.

Skin cancer is the most common human malignancy in the world and the number one cancer in terms of incidence in the USA. The major etiological factor of human skin cancer is the chronic exposure to UV light from the sun. Numerous oncogenic and/or protective signaling pathways are activated in UV-induced carcinogenesis. We found that the UV-induced signal transduction pathways are mediated primarily through signaling cascades involving the mitogen-activated protein (MAP) kinases, epidermal growth factor receptor (EGFR), CB1/2, transient receptor potential channel vanilloid subfamily 1 (TRPV1), TOPK, ribosomal S6 kinase 2 (RSK2), and mitogen and stress activated protein kinase 1/2 (MSK1/2), which results in the modification of transcription factors, including activator protein-1 (AP-1), nuclear factor-kappaB (NF-kB), signal transducer and activator of transcription (STATs), p53 and nuclear factor of activated T cells (NFAT). We also found that histone phosphorylation is critical to mediate UV or other tumor promoter induced apoptosis and cancer formation.

RSK2 plays an important role in cell proliferation and transformation induced by tumor promoters, such as epidermal growth factor (EGF) mediated through the N-terminal kinase domain of RSK2 in JB6 Cl41 mouse skin epidermal cells in vitro. We examined the effect of knocking down RSK2 expression on EGF-induced anchorage-independent transformation in the premalignant HaCaT human skin keratinocyte cell line and on soft agar colony growth of SK-MEL-28 malignant melanoma (MM) cells. We found that the phosphorylated protein levels of RSK2 were enhanced in cancer tissues compared with normal tissues in a human skin cancer tissue array. RSK2 knockdown inhibited proliferation and anchorage-independent transformation of HaCaT cells and soft agar colony growth of MM cells. Importantly, activated RSK2 protein levels were highly abundant in human skin cancer tissues compared with matched skin normal tissues. Our results demonstrated that RSK2 plays a key role in neoplastic transformation of human skin cells and in skin cancer growth.

The serine-threonine mitogen-activated protein kinase family member T-LAK cell-originated protein kinase (TOPK/PBK) is heavily involved in tumor development and highly overexpressed in many cancers, such as colorectal cancer and skin cancer. Despite the identification of TOPK as a promising novel therapeutic target, no inhibitor of TOPK has yet been reported. We screened 36 drug candidates and identified the novel TOPK inhibitor HI-TOPK-032. HI-TOPK-032 strongly suppressed TOPK kinase activity but had little effect on extracellular signal-regulated kinase 1 (ERK1), c-jun-NH2-kinase 1, or p38 kinase activities. HI-TOPK-032 also

inhibited anchorage-dependent and -independent colon cancer cell growth by reducing ERK-RSK phosphorylation as well as increasing colon cancer cell apoptosis. Administration of HI-TOPK-032 suppressed tumor growth in a colon cancer xenograft model. Our findings show that HI-TOPK-032 is a specific inhibitor of TOPK both in vitro and in vivo that may be developed further as a potential therapeutic against colorectal cancer.

TRAF2 has an important function in mediating the TNF-R signaling pathway toward activation of NF- κ B and JNKs. We have revealed a novel function of TRAF2 in the epidermal growth factor (EGF) signaling pathway. Knockdown of TRAF2 blocked EGF-induced AP-1 activity and anchorage-independent cell transformation. Notably, we showed that EGF induces RSK2 ubiquitination, and knocking down TRAF2 suppresses ubiquitination of RSK2 induced by EGF. We also found that TRAF2 affects RSK2 activity through RSK2 ubiquitination. RSK2 plays a critical



“We have discovered critical factors in cancer development and significant targets for cancer prevention and treatment.”

(Left to right) Front row: Kangdong Liu, Alyssa Langfald, Ke Yao, Tatiana Zykova, Srinivasa Reddy Kanamata Reddy, Ann M. Bode, Zigang Dong, Ziming Dong, Naomi Oi, Eunmiri Roh, Kun Yeong Lee, Hiroyuki Yamamoto, Hyo-Sun Kim, Margarita Malakhova, Do Young Lim.

Back row: Wei Li, Wei-Ya Ma, KiBeom Bae, DongHoon Yu, Haitao Li, Hong-Gyum Kim, Hongxun Wang, Xiaoyu Chang, Yang Fu, Joohyun Ryu, Cheng Juan Zhang, Seung Ho Shin, Ge Yang, Hanyong Chen.

Not pictured: Feng Zhu, Cong Peng, MeeHyun Lee, Yan Li, Xiang Li, Yuqiao Sheng, Soouk Kang, JongEun Kim.

role in AP-1 activity mediated through CREB and c-Fos, which regulates anchorage-independent cell transformation.

Activator protein-1 (AP-1) regulates a wide range of cellular processes, including proliferation, differentiation, and apoptosis. As a transcription factor, AP-1 is commonly found as a heterodimer comprised of c-Jun and c-Fos proteins. However, other heterodimers may also be formed, but their function is not known. A gain-of-function study performed by overexpressing junD and c-fos and a loss-of-function study using morpholino junD demonstrate a critical role for AP-1JunD/c-Fos in hematopoiesis during *Xenopus* embryogenesis. Our findings identify AP-1JunD/c-Fos as a novel hematopoietic transcription factor and the requirement of AP-1JunD/c-Fos in BMP-4-induced hematopoiesis during *Xenopus* hematopoiesis.

Inorganic arsenic is a well-documented human carcinogen associated with cancers of the skin, lung, liver, and bladder. The underlying mechanisms explaining the tumorigenic role of arsenic are not well understood. Exposure to a low dose of arsenic trioxide (As₂O₃) caused transformation of BALB/c 3T3 cells. In addition, in a xenograft mouse model, tumor growth of the arsenic-induced transformed cells was increased dramatically. In arsenic-induced transformed cells, polycomb group (PcG) proteins, including BMI1 and SUZ12, were activated resulting in enhanced histone H3K27 tri-methylation levels. Histone H3K27 tri-methylation returned to normal in BMI1- or SUZ12-knockdown BALB/c 3T3 cells compared with BMI1- or SUZ12-wildtype cells after arsenic exposure. As a consequence, the expression of p16INK4a and p19ARF was recovered in arsenic-treated BMI1- or SUZ12-knockdown cells. Thus, arsenic-induced cell transformation was blocked by inhibition of PcG function. Taken together, these results strongly suggest that the polycomb proteins, BMI1 and SUZ12 are required for cell transformation induced by organic arsenic exposure.

Nutritional or dietary factors have attracted a great deal of interest because of their perceived effective chemopreventive cancer activity. They are perceived as being generally safe and may have the efficacy for preventing or reversing premalignant lesions and reducing second tumor incidence. We have studied the effects of these compounds, such as (-)-epigallocatechin-3-gallate (EGCG), theaflavins, caffeine, myricetin, gingerol, luteolin, and resveratrol.

We have developed in silico computer screening and kinase profiling methods to identify the novel molecular targets of chemopreventing agents and tools to develop novel inhibitors/drugs for these specific cancer targets. For example, in silico computer screening and kinase profiling results suggest that the EGF receptor (EGFR), phosphoinositide 3-kinase (PI3K), and Src are potential targets for taxifolin.

Pull-down assay results showed that EGFR, PI3K, and Src directly interacted with taxifolin in vitro, whereas taxifolin bound to EGFR and PI3K, but not to Src in cells. ATP competition and in vitro kinase assay data revealed that taxifolin interacted with EGFR and PI3K at the ATP-binding pocket and inhibited their kinase activities. Western blot analysis showed that taxifolin suppressed UVB-induced phosphorylation of EGFR and Akt, and subsequently suppressed their signaling pathways in JB6 P+ mouse skin epidermal cells. The effect of taxifolin on UVB-induced signaling pathways and PGE₂ generation was reduced in EGFR knockout murine embryonic fibroblasts (MEF) compared with EGFR wild-type MEFs. Taxifolin also inhibited EGF-induced cell transformation. Importantly, topical treatment of taxifolin to the dorsal skin significantly suppressed tumor incidence, volume, and multiplicity in a solar UV (SUV)-induced skin carcinogenesis mouse model. Further analysis showed that the taxifolin-treated group had a substantial reduction in SUV-induced phosphorylation of EGFR and Akt in mouse skin. These results suggest that taxifolin exerts chemopreventive activity against UV-induced skin carcinogenesis by targeting EGFR and PI3K.

We showed that quercetin-3-methyl ether and norathyriol are novel ERKs inhibitors. Quercetin-3-methyl ether inhibited proliferation of mouse skin epidermal JB6 P+ cells by inducing cell cycle G2-M phase accumulation. It also suppressed 12-O-tetradecanoylphorbol-13-acetate-induced neoplastic cell transformation. Western blot and kinase assay data revealed that quercetin-3-methyl ether inhibited ERKs kinase activity and attenuated phosphorylation of ERKs. Pull-down assays revealed that quercetin-3-methyl ether directly binds with ERKs. Furthermore, a loss-of-function ERK2 mutation inhibited the effectiveness of the quercetin-3-methyl ether.

We also found that norathyriol inhibits ERK1/2 kinase activities and attenuates UVB-induced phosphorylation of the mitogen-activated protein kinase (MAPK) cascades. Direct binding of norathyriol with ERK2 was confirmed by a co-crystal structure. Norathyriol inhibited cell growth in mouse skin epidermal JB6 P+ cells by inducing G2-M phase arrest. Mouse skin tumorigenesis data clearly showed that treatment with norathyriol significantly suppressed solar UV-induced skin carcinogenesis in vivo.

We have studied the novel use of FDA-approved drugs for cancer treatment. For example, ceftriaxone, an FDA-approved third-generation cephalosporin antibiotic, has antimicrobial activity against both gram-positive and gram-negative organisms. Generally, ceftriaxone is used for a variety of infections, such as pneumonia, meningitis, and gonorrhea. Its primary molecular targets are the penicillin-binding proteins. However, other activities of ceftriaxone remain unknown. We reported for the first time that ceftriaxone has antitumor activity. Kinase profiling results

predicted that Aurora B might be a potential “off” target of ceftriaxone. Pull-down assay data confirmed that ceftriaxone could bind with Aurora B cells. Furthermore, ceftriaxone suppressed anchorage-independent cell growth by targeting lung cancer cells. Importantly, in vivo xenograft animal model results showed that ceftriaxone effectively suppressed lung tumor growth by inhibiting Aurora B. These data suggest the anticancer efficacy of ceftriaxone for the treatment of lung cancers through its inhibition of Aurora B.

N-(4-hydroxyphenyl) retinamide (4HPR, fenretinide) is a synthetic retinoid that has been tested in clinical trials as a cancer therapeutic and chemopreventive agent. Until now, no direct cancer-related molecular target has been reported to be involved in the antitumor activities of 4HPR. We found that 4HPR inhibited mammalian target of rapamycin (mTOR) kinase activity by directly binding with mTOR, which suppressed the activities of both the mTORC1 and the mTORC2 complexes. The predicted binding mode of 4HPR with mTOR was based on a homology computer model, which showed that 4HPR could bind in the ATP-binding pocket of the mTOR protein through hydrogen bonds and hydrophobic interactions. In vitro studies also showed that 4HPR attenuated mTOR downstream signaling in a panel of non-small-cell lung cancer cells, resulting in growth inhibition. The expression of mTOR downstream signaling molecules in tumor tissues was also decreased after 4HPR treatment. Our results identified mTOR as a direct antitumor target of 4HPR, providing a valuable rationale for guiding the clinical uses of 4HPR.

Aurora kinases play an important role in chromosome alignment, segregation, and cytokinesis during mitosis. We used a ligand docking method to explore the novel scaffold of potential Aurora B inhibitors. One thousand compounds from our in-house compound library were screened against the Aurora B structure and one compound, designated as HOI-07, was selected for further study. HOI-07 potently inhibited Aurora B kinase activity without obvious inhibition of another 49 kinases, including Aurora A. This compound suppressed Aurora B kinase activity in lung cancer cells, resulting in apoptosis induction, G(2)-M arrest, polyploidy cells, and attenuation of cancer cell anchorage-independent growth. Moreover, knocking down the expression of Aurora B effectively reduced the sensitivity of cancer cells to HOI-07. HOI-07 treatment effectively suppressed the growth of A549 xenografts, without affecting the body weight of mice. The expression of phospho-histone H3, phospho-Aurora B, and Ki-67 also was suppressed in the HOI-07 treated group. Taken together, we identified HOI-07 as a specific Aurora B inhibitor, which deserves further investigation.

In summary, we address fundamental questions concerning the response of animal and/or human cells to carcinogens and tumor promoters, such as UV light,

arsenic, TPA, and growth factors. We have established a series of necessary models and systems, such as the over-agar assay for cell transformation, gene knockout mice, transcription factor/luciferase promoter stably transfected cells and transgenic mice, as well as gene knockdown (siRNA) or dominant negative mutant stably transfected cell lines. These models have been utilized extensively to examine the tumor promoter-induced signal transduction pathways and their role in cell neoplastic transformation. We have systematically studied the signal transduction networks induced by solar UV, UVA, UVB and UVC. Such studies have provided the basis for the carcinogenic process caused by environmental carcinogens and molecular mechanisms for cancer prevention.

Many nutritional/dietary compounds appear to act on multiple tumor promoter-induced carcinogenesis processes and thus can be used for chemopreventing agents. Large-scale animal and molecular biology studies are needed to address the bioavailability, toxicity, molecular target, signal transduction pathways, and side effects of dietary factors. Clinical trials based on clear mechanistic studies also are needed to assess the effectiveness of these dietary factors in the human population. A continuing emphasis on obtaining rigorous research data and critical analysis of those data regarding these and other food factors is vital to determine the molecular basis and long-term effectiveness and safety of these compounds as chemopreventive agents. Articles on our work using the supercomputer and molecular modeling and simulation were published in *Nature Reviews Cancer* and other top-tier journals in the last few years.

Other Professional Activities

Zigang Dong

- Grant Reviewer, National Institutes of Health
- Editor, Associate Editor or Editing Board Member
 - Cancer Research
 - Cancer Prevention Research
 - Molecular Carcinogenesis
 - Carcinogenesis
 - International Journal of Biological Sciences
 - Food Factors

MEMBRANE BIOCHEMISTRY

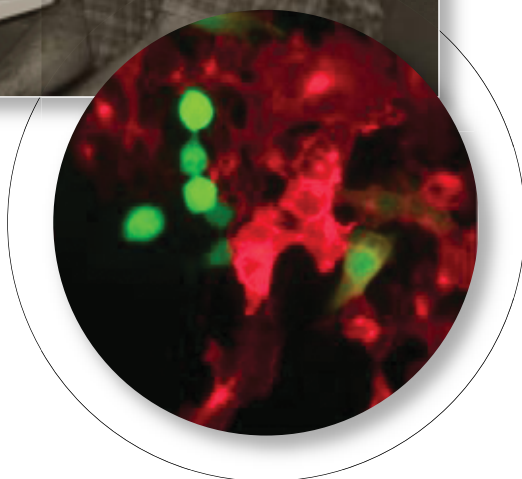
Section Leader

Rhoderick E. Brown, Ph.D.

Professor



Cholera toxin B endocytosis was affected by the overexpression of GLTP.



Cells need barriers to envelope their contents and compartmentalize their functions. The barriers need to be very thin and flexible while also being selective for entry of nutrients and export of toxic by-products. To construct such barriers, cells produce specialized lipids that are polar at one end and nonpolar at the opposite end. Because the polar ends prefer to be in contact with water and the nonpolar ends do not, these special lipids readily form thin, flexible, layers only two molecules thick, (i.e. bilayers) which commonly are known as cell membranes. In addition to surrounding mammalian cells, biomembranes partition cells internally and enable formation of various functionally specialized compartments. Interestingly, there are many more varieties of lipids found in membranes than are needed to form bilayers. Over the past decade or so, it has become clear that some membrane lipids can function as intracellular messenger signals that regulate cell growth, proliferation, and programmed cell death processes, while other membrane lipids appear to cluster together in bilayers to form microdomains able to control the spatial distribution and lateral interactions of certain membrane proteins. The discovery of these new functions for membrane lipids underscores why biomembranes often come under direct attack during cancer and infectious disease.

Our research is focused on a membrane lipid class known as sphingolipids. Along with cholesterol, certain sphingo-lipids serve as key components needed for formation of membrane “raft” microdomains. Rafts appear to function as organizing regions for certain signaling kinases as well as target sites for certain viruses and bacteria. Our earlier efforts focused on rigorously defining the physical basis for raft micro-domain functionality. To do so, we developed ways to quantitatively measure the lateral elasticity within model membranes to accurately assess the physical changes that occur within the membrane “raft environment” when the content and structure of sphingolipids and sterols become altered as well as assess changes in sphingolipid lateral distributions. Our research defined structural features of sphingolipids that regulate their interactions with other membrane lipids and provided insights into the unique physical features in membrane microdomains at the heart of their lateral organizing functionality, which is key for spatially organizing and regulating various proteins that interact with membranes.

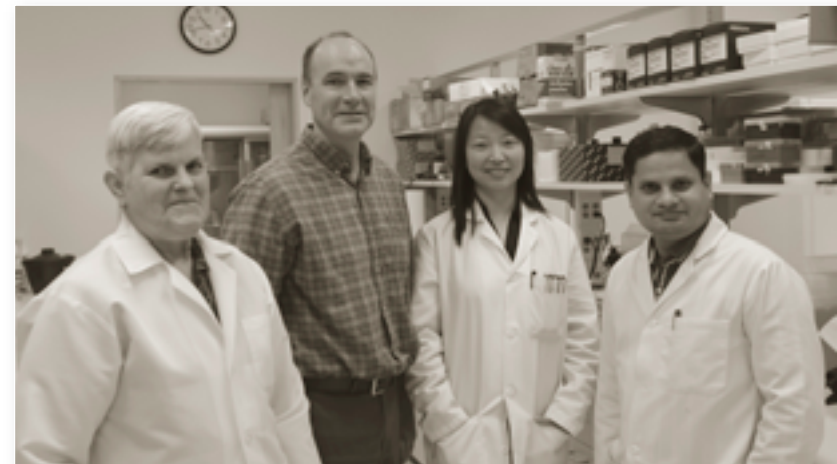
The processes used by cells to form and maintain sphingolipid-enriched microdomains could involve specific proteins able to bind and transfer sphingolipids between membrane surfaces. Accordingly, much recent effort in our lab has been directed toward a protein family known as glycolipid transfer proteins (GLTPs) that can specifically bind and transfer glycosphingolipids between membranes. We have found that GLTP functionality is regulated by lipid composition and packing within membranes. To gain fundamental insights into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we have used a combination of biophysical approaches (fluorescence spec-

troscopy, Langmuir surface balance approaches, calorimetry, NMR). We now are applying this basic knowledge to decipher the functional regulation of GLTP, such as exactly how GLTPs accomplish the intermembrane transfer of glycolipids. Our molecular biological studies have resulted in the first molecular cloning of human GLTP and shown that related homologs exist in mammals, plants, and fungi originating from mRNA transcripts that encode conserved amino acid sequences. Genetic engineering approaches have enabled production of human GLTP and related homologs in bacterial expression systems and purification of sufficient quantities to crystallize the proteins and solve their conformational structures both in glycolipid-free form and complexed with different glycolipids in collaborative studies with structural biologists at Memorial Sloan Kettering Cancer Center in New York and at CIC bioGUNE in Derio, Spain. We discovered that human GLTP forms a novel structural fold among known proteins. As a result, the Protein Data Bank designated human GLTP as the founding member and prototype of the new GLTP superfamily, enabling our findings to be published in *Nature*, *PLoS Biology*, *Structure*, *The Journal of Biological Chemistry*, *Biophysical Journal*, and *Biochemistry*. Our studies have revealed: i) how GLTP adapts to accommodate different glycolipids within its binding site; ii) the functional role played by intrinsic tryptophan residues in membrane interaction and glycolipid binding, and iii) the structural basis for the narrower glycolipid selectivity of a fungal GLTP ortholog.

In very recent investigations also published in *Nature*, we have reported the discovery of a new GLTP structural homolog in human cells that we named ceramide-1-phosphate transfer protein (CPTP). Remarkably, the lipid specificity of CPTP has evolved for binding/transfer of ceramide-1-phosphate rather than glycolipids even though CPTP still forms a GLTP-fold encoded by a completely different gene than GLTP. With collaborating investigators at Virginia Commonwealth University, we have shown that, when human cells become depleted of CPTP, newly synthesized ceramide-1-phosphate accumulates in the Golgi. The over accumulation triggers the action of cytoplasmic phospholipase A2 responsible for generating arachidonic acid that becomes metabolized further into pro-inflammatory eicosanoids.

“The discovery of these new functions for membrane lipids underscores why biomembranes often come under direct attack during cancer and infectious disease.”

We anticipate that elucidation of the fundamental structure-function relationships governing GLTP and CPTP action will facilitate development of the means to pharmacologically modulate GLTP and enhance its potential use as a biotechnological resource, (i.e. nanotool) for targeted manipulation of cellular glycolipid composition. Such strategies could provide new ways to introduce specific sphingolipid antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new therapeutic approaches to treat disease processes involving sphingolipids.



Left to right: Helen Pike, Rick Brown, Xiuhong Zhai, Shrawan Kumar Mishra
Not pictured: Yuan Sun

Our exciting progress to date emphasizes the need for continuing studies into the workings of GLTP, CPTP, and other proteins containing GLTP-like motifs using comprehensive strategies involving biophysical, cell, and molecular biological approaches. Our recent investigations of the gene organization and transcriptional status in humans and other mammals now provide a firm foundation for identification and characterization of inherited diseases involving GLTP and CPTP. Our ongoing efforts benefit from collaborations with researchers at Memorial Sloan Kettering Cancer Center in New York; Virginia Commonwealth University in Richmond, The Russian Academy of Sciences in Moscow; CIC bioGUNE in Derio, Spain; and Mayo Clinic. Our research continues because of financial support received from the National Institute of General Medical Sciences, the National Cancer Institute of NIH and The Hormel Foundation.

NUTRITION AND METABOLISM

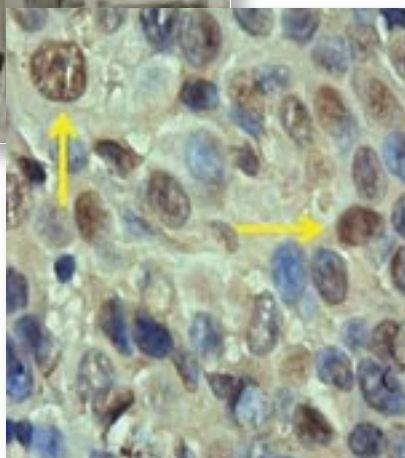
Section Leader

Margot P. Cleary, Ph.D.

Professor



Pictured is an estrogen receptor from a series of images showing the staining of mammary tumors for adipokine (made in fat tissue) growth factors. Brown staining are the proteins of interest.



Primary interests of the Nutrition and Metabolism section are the effects of body weight and food intake on the development of breast cancer using mouse models. Past studies have included effects of genetic and dietary-induced obesity on breast/mammary tumor development, particularly with respect to body fat and serum IGF-I, leptin and adiponectin levels. Other studies have assessed the impact of calorie restriction on the prevention of mammary tumors in several mice models of breast cancer. Of particular interest, we consistently find that periods of moderately severe calorie restriction followed by refeeding, which we term “intermittent calorie restriction,” results in much greater reduction in mammary tumor incidence than the same degree of restriction implemented chronically with both interventions resulting in 20-25% calorie reduction. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the IGF-axis. Based on results of our studies, we have hypothesized that the altered, i.e., reduced adiponectin:leptin ratio, which is characteristic of obesity, provides a permissive environment for tumor development. In contrast, the reductions of IGF-I and leptin and increased adiponectin:leptin ratio resulting from intermittent calorie restriction results in reduced mammary tumor development and decreased mammary tumor incidence in comparison to ad libitum fed mice as well as in the mice that are chronically calorie restricted. These studies have been expanded by Dr. Michael Grossmann to include the interaction of an omega-3 fatty acid in combination with intermittent calorie restriction on the development of mammary tumors in a project funded by Susan G. Komen for the Cure. This study uses a model of breast cancer that previously was found to be only partially responsive to the intermittent calorie restriction protocol. Further, there have been reports that omega-3 fatty acids may have cancer-preventing action but the published results have not been consistent. Initial results indicate that the combination of omega-3 fatty acid and intermittent calorie restriction is more protective than the restricted protocol using omega-6 fatty acid.

Our most recent work focuses on the potential effect of the diabetic treatment drug metformin on mammary tumor development. This study is being conducted in a transgenic mouse model to mimic postmenopausal breast cancer and includes obese as well

as normal weight subjects. The intervention is being started when the mice are middle-aged to reflect what would occur in at-risk women. It has been suggested that metformin's protective effects are similar to those of calorie restriction; therefore we also are directly comparing the effects of metformin to calorie restriction. We also are planning to undertake studies related to the effects of metformin on cancer progression.

Other Professional Activities

Margot P. Cleary

Invited speaker:

United Way, Austin, MN

Hormel Foods, Austin, MN

Purdue University, West Lafayette, IN

International Association for the Study of Obesity/World
Cancer Research Fund, London, UK

Presentations:

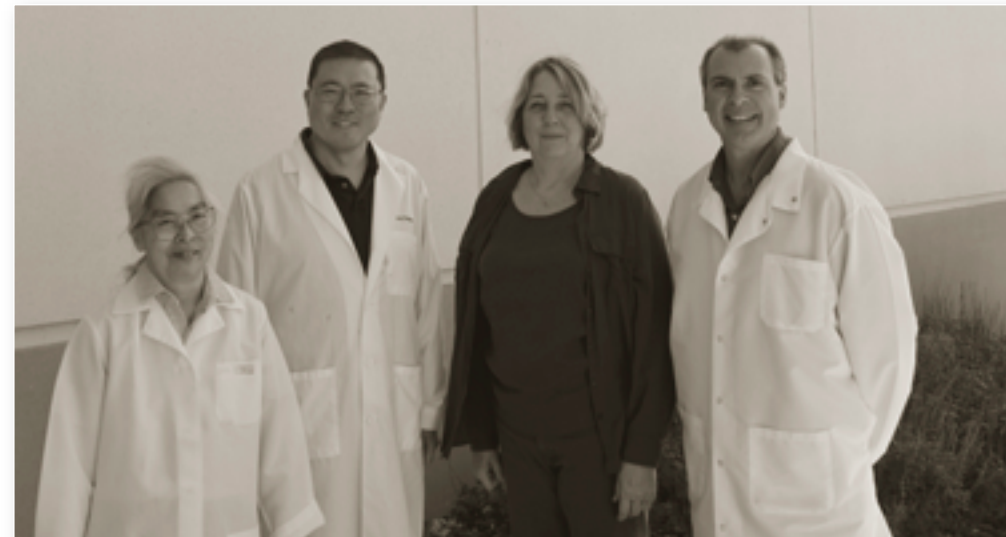
AACR 11th Annual Frontiers in Cancer Prevention Meeting -
Anaheim, CA

61st Annual American Society of Mass Spectrometry -
Minneapolis, MN

Grant Review Committees:

3 NIH Study Section Meetings (January, February, June)

“Our most recent work focuses on the potential effect of the diabetic treatment drug metformin on mammary tumor development.”



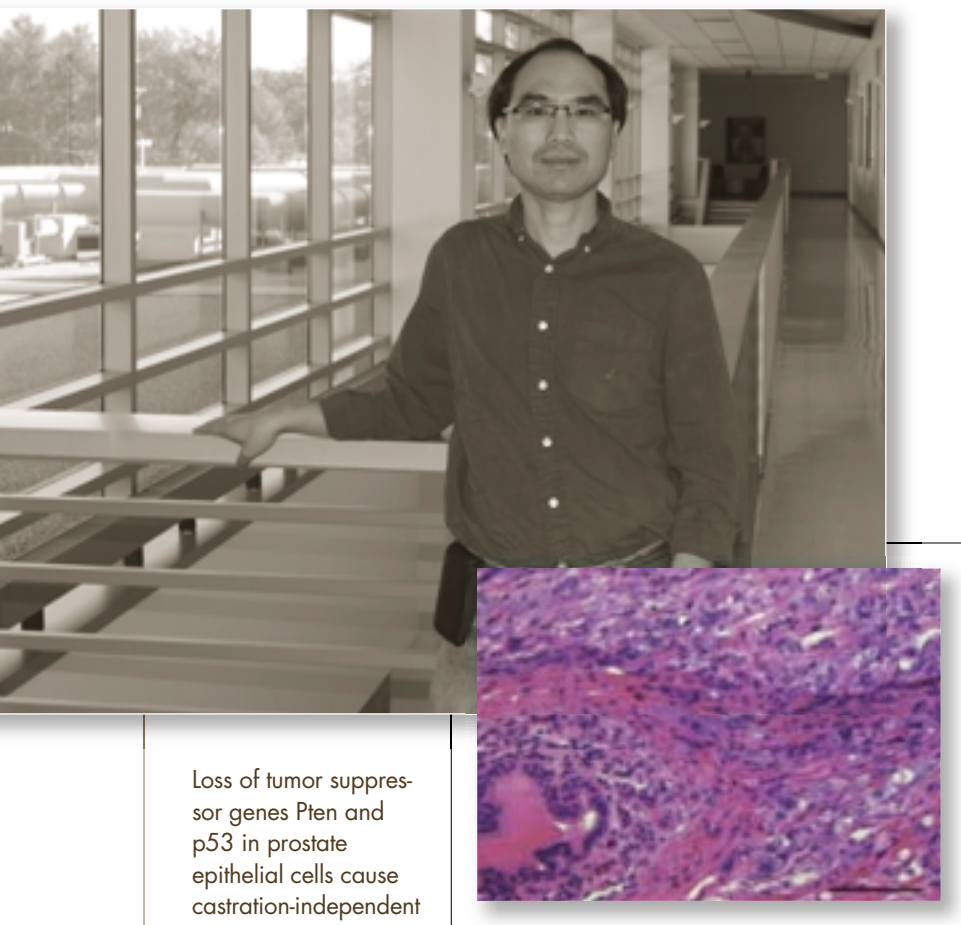
Left to right: Nancy Mizuno, DaQing Yang, Margot Cleary, Michael Grossmann

CELL DEATH AND CANCER GENETICS

Section Leader

Yibin Deng, M.D., Ph.D.

Assistant Professor



Loss of tumor suppressor genes Pten and p53 in prostate epithelial cells cause castration-independent prostate cancer in genetically engineered mouse models.

The TP53 gene encodes a tumor suppressor protein that functions as a stress response and cell cycle checkpoint protein that maintains genomic integrity. The importance of p53 in tumor suppression is highlighted by mutations that perturb p53 function that have been found in more than 50% of human cancers examined. The recent comprehensive sequencing studies sponsored by The Cancer Genome Atlas (TCGA) consortium confirm the high frequency of TP53 mutations in many sequenced human cancers. For example, TCGA studies found that 96% of ovarian cancers, 37% of breast cancers, 54% of colorectal cancers, and 81% of lung squamous cell carcinomas displayed TP53 mutations. However, how wild-type p53 inhibits tumor development and why mutant p53 promotes tumor progression or/and metastasis remains poorly understood.

Our laboratory focuses on understanding the molecular mechanisms by which p53-induced signaling pathways, such as apoptosis, senescence, autophagy, and cell metabolism, contribute to p53-mediated tumor suppressive function. On the other hand, we study whether and how the oncogenic gain-of-function property of mutant p53 promotes malignant progression and tumor metastasis. To translate our bench work to bedside, we also apply genomic and proteomic approaches, bioinformatics, computational modeling, RNAi-based screening, and genetically engineered mouse (GEM) models that recapitulate the key features of human cancers to discover crucial “druggable” targets for cancer patients. Our ultimate goal is to find novel targets, small molecular compounds and drug combinations that selectively and efficiently kill cancer cells harboring “unique” genetic alterations in patients while leaving the normal cells unharmed. In the past year, our laboratory has made progress in the following three major areas:

1. Understanding p53-mediated signaling pathways in tumor suppression in vivo. While many studies have focused on the role of apoptosis and/or senescence in p53-mediated tumor suppression, recent findings suggest that p53 also induces autophagy. Autophagy is an evolutionarily conserved and highly regulated homeostatic process by which cellular proteins, protein aggregates and organelles are removed through a lysosomal degradation pathway. However, the function of p53-mediated autophagy in tumorigenesis remains unknown. DRAM (Damage-Regulated Autophagy Modulator) recently has been identified as a direct target of p53. DRAM mediates p53-induced autophagy and thus may contribute to tumor suppression. To investigate whether DRAM-induced autophagy contributes to p53-mediated tumor suppression in vivo, we generated conditional DRAM knockout mice. Our findings suggest that DRAM potentially functions as a tumor suppressor because deletion of DRAM promotes spontaneous tumor development in mouse models. Currently, we are dissecting the molecular basis by which DRAM deficiency driven tumorigenesis in vivo. We also are exploring our recent findings related to the crosstalk between p53-initiated autophagy and p53-mediated cell metabolism in tumor initiation, progression and metastasis.

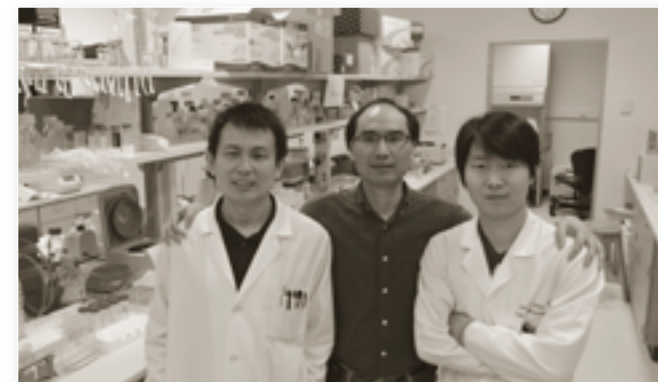
To answer the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing tumor development in vivo, we have generated “triple” mutant mice utilizing the conditional DRAM knockout mice to breed with mice deficient in p53-mediated apoptosis (p53R172P knock-in or PUMA knockout) and senescence-deficient mice (p21 knockout). Our current studies strongly support our hypothesis that p53-induced apoptosis, autophagy and senescence cooperate together to effectively inhibit tumor formation in vivo. We expect that, by utilizing these genetically engineered mouse models, we will be able to identify crucial molecular targets contributing to p53-mediated tumor suppressive function in vivo.

2. Gain-of-function of mutant p53 in telomere uncapping-driven mammary tumorigenesis Human sporadic breast carcinomas are characterized by the presence of complex cytogenetic aberrations. One of the foremost challenges for breast cancer researchers is to develop experimental model systems that identify pathogenetic events driving breast tumor development. Our long-term goal in this project is to establish “chromosomal instability” mouse breast cancer models and discover the “causal” genomic events driving breast tumorigenesis in vivo. One important mechanism that can give rise to the unstable breast cancer genome is the dysfunction of telomeres. Telomeres are nucleoprotein caps that protect chromosomal ends from being recognized as damaged DNA and prevent chromosome end-to-end fusions. Telomeres that no longer can exert end-protective functions are said to be dysfunctional, and these telomeres could arise either from progressive telomere attrition (telomere shortening) or when components of the telomeric DNA binding proteins, termed shelterin complex, are perturbed (telomere uncapping). In human breast carcinomas, chromosomal instability by dysfunctional telomeres is associated with the transition from benign ductal hyperplasia to malignant ductal carcinoma in situ. This strongly supports the notion that telomere dysfunction-induced chromosome instability initiates the development of breast cancers. Our laboratory has been engineering a novel mouse breast cancer model harboring telomere uncapping-induced chromosomal instability without affecting the activity of telomerase. In addition, the mouse model also expresses “hot spot” mutant p53 protein in breast epithelium. We believe that this mouse model will faithfully recapitulate the genetic abnormality commonly observed in human sporadic breast carcinomas. We are establishing and utilizing this novel mouse breast cancer model to identify the key genetic pathways perturbed in chromosomal instability driven mammary tumorigenesis and target these pathways with novel therapeutics that may potentially suppress human breast cancer. In addition, we are using genetic and pharmacological approaches in genetically engineered mouse models to confirm our cell-based studies in vitro and to identify the critical downstream targets contributing to mutant p53 gain-of-function in promoting tumor metastasis in vivo.

3. Exploring the molecular targets involved in selective killing of cancer cells Our laboratory has a long-standing interest in understanding genetic pathways that allow for selective killing of cancer cells while leaving normal cells unharmed. Through multidisciplinary collaborations, we are using a comprehensive combination of genomic and proteomic analyses of cancer, computational modeling of cancer pathways, RNAi-based screening, and functional testing in cell culture and animal models of cancer to identify the crucial pathways that are linked to therapeutic selectivity. Recently, we have made progress in our study on prostate cancers. Prostate cancer is the second-leading cause of cancer-related deaths in males after lung cancer and strikes one in six men in the USA. Recent

“Our laboratory has a long-standing interest in understanding genetic pathways that allow for selective targeting of cancer cells while leaving normal cells unharmed.”

advances in whole genome and exome sequencing suggest that co-deletions of tumor suppressors Pten and p53 occurs frequently in lethal human castration-resistant prostate cancer (CRPC). Genetic studies in mouse models support that Pten and p53 co-deletions play a causal role in the development of CRPC in vivo. Thus, finding effective and selective means of killing prostate cancer cells carrying Pten/p53 deficiency is critical to success-



Left to right: Lei Wang, Yibin Deng, Yingjie Zhang
Not pictured: Li Chang, Tao Lin, Fengxia Wu

fully treat CRPC. However, this strategy is limited by the scarcity of identified crucial targets required for Pten/p53 deficiency driven CRPC. We used bioinformatics and genetic approaches to find that hexokinase II (HK2), which catalyzes the first step of glucose, is elevated significantly in human prostate cancer harboring Pten/p53 deletions. Mechanistically, deletion of Pten increases HK2 mRNA translation through activation of AKT-mTOR-4EBP1 axis and loss of p53 enhances HK2 mRNA stability through inhibition of miR-143 biogenesis. Genetic and pharmacological studies demonstrated that HK2-mediated aerobic glycolysis, known as the Warburg effect, is required for tumor growth of human CRPC cells harboring Pten/p53 deficiency in xenografts model. Whereas targeting HK2-initiated glycolysis activates AMPK-dependent autophagy for cell survival, and pharmacologically co-targeting glycolysis with 2-deoxyglucose (2-DG) and autophagy with chloroquine (CQ) selectively induces cancer cell apoptosis to cause near-complete tumor remission in the Pten/p53 deficiency-driven CRPC mouse models. Our findings provide a novel therapeutic strategy for the patients with currently incurable CRPC. Our laboratory also is utilizing multiple genetic approaches to identify targets that can be targeted selectively in human lung and colon cancers.

Our research projects are supported by grants from National Cancer Institute, including K01, R21, and R01 awards.

In addition, three postdoctoral fellows from my laboratory presented their research work at the 2013 American Association for Cancer Research (AACR) Annual Meeting (April 6-10, Washington D.C.).

CELLULAR DYNAMICS

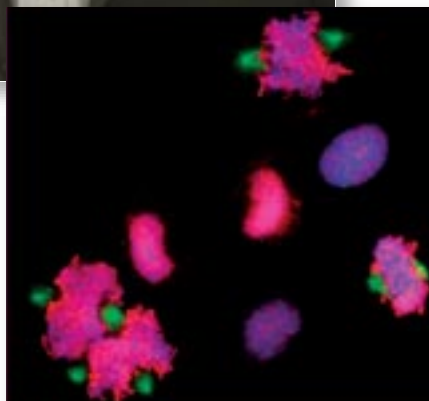
Section Leader

Edward H. Hinchcliffe, Ph.D.

Associate Professor



Ovarian cell with multiple centrosomes, mimicking a pre-cancerous state – microtubules in red, centrosomes in green, chromosomes in blue.



Our section studies the molecular mechanisms that regulate normal cell division and the roles of centrosome reproduction in ensuring the bipolarity of this process. Recently, we have focused on chromosome instability, or the gain/loss of whole chromosomes during mitotic division, which is associated with tumor progression.

Chromosome instability (CIN) is a hallmark of solid tumors and contributes to the genomic heterogeneity of tumor cells. There are multiple mechanisms believed to underlie the generation of CIN, including cell cycle defects, abnormal centrosome duplication and function, premature chromatid disjunction, and centrosome separation errors. However, despite an increasingly mechanistic understanding of how CIN is generated, we know relatively little about how chromosome missegregation becomes transduced into cell transformation and tumorigenesis. At the heart of this issue is the question of how a single missegregated chromosome can trigger the p53/p21 pathway and induce durable cell cycle arrest. Current work focused on DNA damage caused by lagging chromosomes is part of the answer. However, to date, no mechanisms have been identified that monitor chromosome mispositioning – either before or after anaphase – at the single chromosome level.

We have developed a novel method to induce CIN, based on cell chilling/re-warming, that allows us to generate populations of cells with either lagging chromosomes in the furrow or syntelic chromosomes distal to one of the poles. This latter population presumably contains missegregated chromosomes that do not undergo DNA damage, and we will test this. Thus, an innovative feature of our work is to investigate the differences in cellular response to CIN with and without commensurate DNA damage.

The centrosome is an organelle that nucleates and organizes the microtubule cytoskeleton. This, in turn, is used to build the bipolar mitotic spindle, which is responsible for aligning and segregating the duplicated chromosomes during cell division. Centrosomes are thought to play a major role in establishing the bipolarity of the mitotic spindle. To ensure this, the single centrosome normally duplicates exactly once during the cell cycle, yielding a pair of centrosomes that form the two spindle poles. In many cancer cells, the number of centrosomes increases, resulting in a small but significant number of cells with more than two spindle poles and an increase

in the probability of abnormal cell division. Therefore, it is important to understand the molecular mechanisms that drive normal centrosome duplication, and importantly, restrict centrosome duplication to once per cell cycle.

In our lab, we use cultured mammalian cells and cytoplasmic extracts generated from *Xenopus* frogs to examine the basic control mechanisms underlying centrosome duplication, cell division, and cytokinesis. We use advanced imaging techniques, such as live-cell confocal fluorescence microscopy, Fluorescence Recovery After Photobleaching (FRAP), microinjection and microsurgery, to address these fundamental questions in cell biology. Our research has direct relevance to understanding the underlying mechanisms that lead to cancer initiation and progression. Our work also is relevant to identifying potential targets for chemotherapy agents.

Experimental research results

1. Coordinating cytokinetic furrow formation with anaphase onset

The cell division furrow – created by the recruitment of actin filaments and the motor protein myosin II – is formed between the separating sister chromatids at anaphase. This furrow constricts the dividing cell into two daughters. In order to ensure that cytokinesis occurs in the right place and at the right time, the positioning of the cleavage furrow must be coupled to the segregation of the chromosomes. This occurs through signaling via the microtubule network, specifically the dynamic astral microtubules and the stable overlapping midzone microtubules. Both of these classes of microtubules are important for signaling the formation of the cytokinetic furrow and ensuring that the furrow remains restricted to the cell center. We are investigating the regulation of furrow formation using live-cell imaging and single-cell manipulation. We are taking advantage of the fact that microtubules are extremely sensitive to temperature and can be disassembled by cold treatment without causing harm to the cell. When the cells are warmed up, the microtubules re-assemble, and the cell cycle proceeds on its way. Using this system and spinning disk confocal microscopy, we are able to examine the roles of candidate regulatory mechanisms, including Aurora B kinase, Polo-like kinase 1, and the relative contributions of the astral and midzone microtubules. Our goal is to integrate molecular studies with live-cell physiology to understand the mechanisms underlying cell division.

We have found that there is a period following the onset of anaphase where the cell cortex can respond to furrow-inducing signals, and this period is sensitive

to the loss of microtubules and activity of Polo-like kinase 1. However, once cells progress beyond this point, the furrow will form, regardless of whether microtubules persist. Polo-like kinase 1 activity also is not required after this “point of no return,” adding kinase inhibitors after this point does not affect the ability of a furrow to assemble.

2. Centrosome duplication

When CHO cells are arrested in S-phase, they undergo repeated rounds of centrosome duplication without cell cycle progression. While the increase is slow and asynchronous, the number of centrosomes in these cells rises with time. To investigate mechanisms controlling this duplication, we have arrested CHO cells in S-phase for up to 72 hours and inhibited centriole formation by treatment with the microtubule poison

“Our research has direct relevance to understanding the underlying mechanisms that lead to cancer initiation and progression.”

colcemid. We find that in such cells, the pre-existing centrosomes remain and a variable number of centrosomal foci

– containing α / γ -tubulin and centrin 2 – assemble at the nuclear periphery. If the colcemid is washed out, these nuclear-associated centrosomal foci disappear. In their place, multiple centriole-containing centrosomes assemble, which nucleate microtubule asters, and can form functional mitotic spindle poles. The eventual number of centrosomes that assemble following colcemid washout increases with time, even though the number of nuclear-associated centrosomal foci does not increase. Importantly, the number of centrosomes that assemble following colcemid washout corresponds to the number of centrosomes that form during S-phase arrest alone. This suggests that during S-phase, a core centrosome activity repeatedly replicates even if centrioles themselves are prevented from duplicating, and this activity has the capacity to dictate the assembly and copy number of new centrosomes.



Left to right: Kul Karanjeet, Edward Hinchcliffe

3. *Building a bipolar spindle*

Mitosis must be carried out with high fidelity to ensure that each daughter cell receives a complete complement of the genome. Mistakes in the cell division process can have disastrous consequences for the cell, leading to aneuploidy, cellular transformation, and tumorigenesis. The centrosome is known to play a critical structural role in the cell division process – it organizes the microtubule network during interphase and astral microtubules at the spindle poles during mitosis.

We currently are using microsurgery coupled with time-lapse videomicroscopy of living acentrosomal cells to investigate the role of the centrosome in cell cycle regulation. To directly visualize the role of microtubules and regulatory molecules during the acentrosomal cell cycle, we have generated primate kidney cell line (BSC-1 cells) that constitutively express α -tubulin coupled to GFP. We have found that, after several hours, acentrosomal cells reform their microtubule network into an organized array. Interestingly, the acentrosomal microtubule focus can separate into two distinct poles prior to nuclear envelope breakdown. This demonstrates that the splitting of the microtubule network does not require a centrosome, contrary to previously held notions. However, we found that in the absence of a centrosome, the splitting of the microtubule network is inefficient; ~40% of acentrosomal cells enter mitosis with a monopolar spindle. These cells cannot bipolarize, and fail cytokinesis. Thus, there is some aspect of the centrosome that ensures that the microtubule network will split and separate before the onset of mitosis. It could be that acentrosomal microtubule focus is deficient in the recruitment of some key factor(s) necessary to ensure accurate splitting. This factor could be a regulatory activity, a structural activity, or a combination of the two. It also is possible that the acentrosomal microtubule focus lacks sufficient microtubules to interact with the cell cortex. Regardless of the mechanism, our work reveals that centrosomes are absolutely necessary to ensure fidelity during mitotic spindle assembly.

4. *Tektin proteins: key to spindle poles and spindle midbodies*

We currently are investigating the role of the tektin proteins in establishing the spindle midzone. Tektins first were identified as components of axonemal microtubules, where they are thought to impart structural rigidity and complex periodic spacing to these highly stable microtubules. Our recent results suggest that tektins localize to the overlapping microtubules at the spindle midzone, where they also play an important role in the spindle midzone. This region of the mitotic spindle responsible for initiating cytokinesis, and is required for the process to continue. Many key regulators of late mitotic events, along with cytokinesis localize to

the spindle midzone. When tektin 2 (one of three distinct tektins found in vertebrates) is knocked down using shRNAs, the midzone microtubules fail to become compacted and appear to exhibit abnormal plus-end microtubule motility. The result is failure of cytokinesis.

In addition to the tektins, we are exploring the role of two highly conserved proteins called EFHC 1 & 2. These Ca²⁺-binding proteins also are involved in centriole assembly and the formation of midbodies. Importantly, mutations in these proteins lead to abnormal cell division, which is associated with neurological birth defects.

We are interested in uncovering the molecular mechanisms underlying these observations. We currently are examining the motility of several key regulators of midzone function: PRC1 and Kif4, in response to experimental loss of tektin 2 and or EFHC 1&2. We are using live-cell imaging and FRAP analysis to examine the role played by tektins in regulating these important components of the cell division apparatus.

A detailed understanding of the regulation of cell division, cytokinesis and chromosome instability will advance our knowledge of the biology of cancer – itself a disease characterized by unregulated cell proliferation and chromosome missegregation. Our work will provide for a mechanistic understanding of key cell-cycle events that may contribute to cancer progression. Together, these studies also will provide a source of potential targets for future anti-cancer drugs.

Other Professional Activities

Edward H. Hinchcliffe

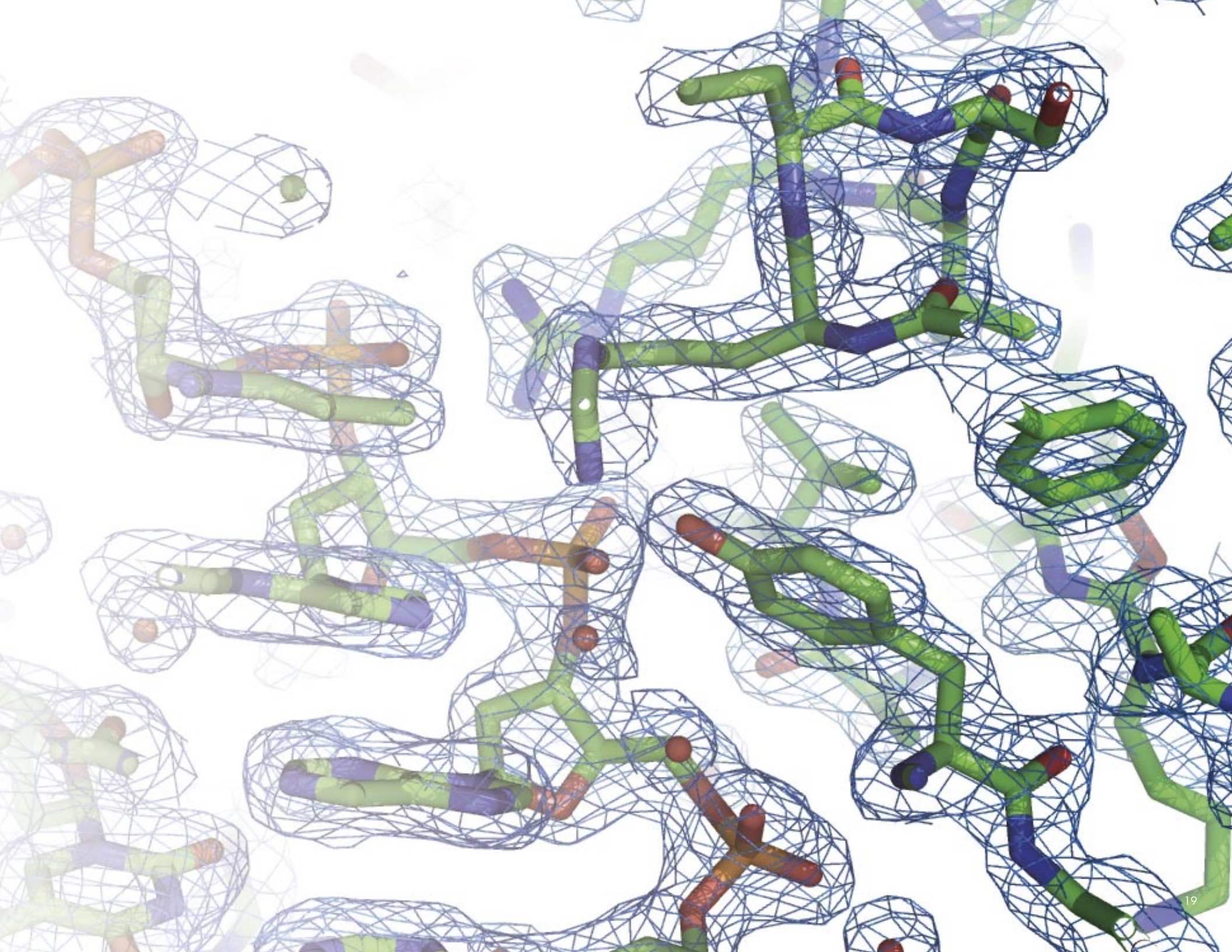
Review panel, National Science Foundation

Ad hoc reviewer:

National Science Foundation

Wellcome Trust UK

Deutsche Forschungsgemeinschaft (DFG: German Research Foundation)

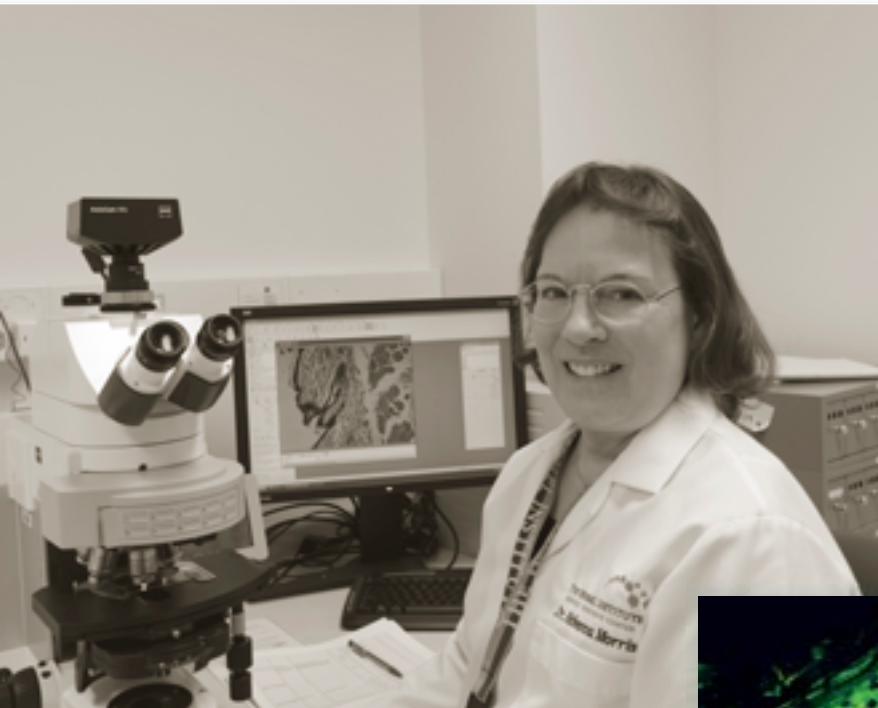


STEM CELLS AND CANCER

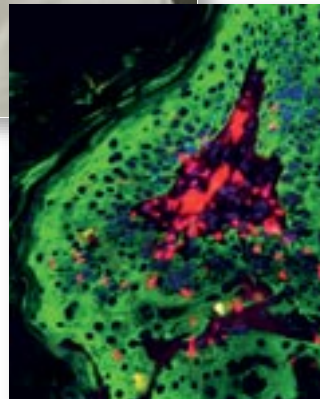
Section Leader

Rebecca J. Morris, Ph.D.

Professor



Skin keratinocytes



Research in the Morris laboratory continues to focus on the role of adult tissue stem cells in the pathogenesis of non-melanoma skin cancer. We have recently demonstrated that certain stem cells in the hair follicles are tumor-initiating cells. This past year, we have first studied the recruitment of bone marrow derived cells to developing skin tumors, and then we have demonstrated in an in vitro migration assay, that primary epidermal keratinocytes are notably attracted to bone marrow cells cultured beneath a collagenous matrix and a filter.

The epidermal layer of the skin is composed largely of cells called keratinocytes. Keratinocytes in the basal layer are organized into subpopulations based on their proliferative nature and include stem cells (relatively rare) and transit amplifying cells (comprise most of the proliferating cells). When a stem cell divides, one daughter usually remains a stem cell while the other daughter gives rise to transit amplifying cells with limited proliferative potential. Upon completion of their divisions, transit amplifying cells undergo an orderly maturation process called terminal differentiation that includes their outward displacement through the suprabasal layers, production of high molecular weight keratins, loss of their nuclei, and formation of an impervious outer structure called the cornified envelope. This process is exceptionally ordered and maintains the normal thickness and cellularity, and the normal functions of the epidermis throughout life. In the past, the Morris laboratory has focused on the stem cells of the hair follicles because they not only serve as a reservoir of epidermal cells, they also possess remarkable regenerative potential and are known to be able to reconstitute a graft, to heal wounds, and even to give rise to non-melanoma skin cancer. This year we have examined the possibility of a dynamic interaction between bone marrow cells and the cutaneous epithelium.

During the past decade, others have demonstrated that bone marrow derived epithelial cells are recruited to sites of chronic inflammation; however, the clinical significance has been questioned because the number of recruited bone marrow cells was low. We used allogeneic bone marrow transplantation in the context of the classical multistage model for murine cutaneous carcinogenesis to probe the recruitment of bone marrow derived epithelial cells in skin tumors initiated with the carcinogen, dimethylbenz[a]anthracene (DMBA), and promoted with the phorbol ester, 12-O-tetradecanolyphorbol-13-acetate (TPA). We detected clusters of bone

marrow derived epithelial cells in over 40 percent of papillomas where they occupied 25 percent or more of the lesional area. In dysplastic ulcers, the magnitude of the recruitment was greater. The bone marrow derived epithelial cells clustered in the cutaneous epithelium where they became immunoreactive to epidermal keratins, and proliferated and stratified, thereby contributing comparably in the lesions with the progeny of hair follicle stem cells in engrafted Krt1-15Cre;R26R mice. Moreover, cytokeratins were detected by immunostaining and quantitative real time polymerase chain reaction in plastic adherent bone marrow cells cultured in the presence of filter-separated epidermal keratinocytes. Cytokeratin production was enhanced by bone morphogenetic protein 5. We conclude that large numbers of bone marrow derived epithelial cells are recruited to a subset of cutaneous papillomas and dysplastic ulcers and reflect a previously unrecognized systemic contribution to these lesions. Ultimately, these findings may provide potential targets for treatment of non-melanoma skin cancer.

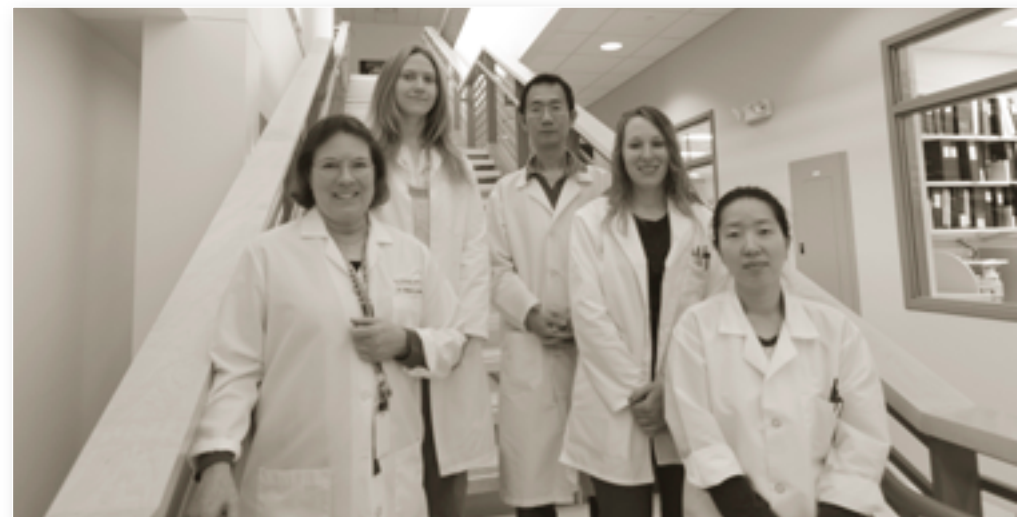
We have also investigated the effects of bone marrow cells in vitro on freshly harvested epidermal keratinocytes. We propose the novel concept that skin egress, entering the circulation, and traveling throughout the body may be a new behavior of epidermal stem cells. We propose that sunburn following exposure to

sunlight has the capacity to make skin stem cells migrate. We are addressing the following question: Do hair follicle stem cells migrate from the skin following sunburn as a consequence of ultraviolet light induced inflammation? Our hypothesis is that sunburn makes the hair follicles stem cells leave the skin and enter the blood circulation, and home to the bone marrow. Although in vivo studies are currently well under way, we designed an in vitro migration assay to investigate the effects of fresh bone marrow cells on migratory behaviors of epidermal keratinocytes. We found that adult epidermal keratinocytes migrate through a collagenous matrix and a filter preferentially towards fresh bone marrow cells. The keratinocytes prefer bone marrow cells

“The skin provides an anatomical barrier to physical, chemical, and biological agents. Hence, it is not surprising that it should have well-developed innate immunity.”

as bait several fold over 3T3 fibroblastic cells, fetal bovine serum, or other keratinocytes. We also found that about 27% of CD49f+/CD34+ hair follicle stem cells have receptors for stromal derived factor 1-alpha, and that keratinocytes migrate towards SDF1-alpha better than controls, but not quite as well as whole bone marrow. This result suggests that SDF1-alpha may be among the cytokines capable of mobilizing the keratinocytes for migration. We are currently examining whether there are other factors produced by bone marrow that could recruit keratinocytes away from the hair follicles.

In summary, research in the Morris laboratory this past year highlights an interaction between cells of the bone marrow and the cutaneous epithelium. Going forward, we will continue to investigate the reciprocal dynamic interactions between bone marrow and the skin in the context of cutaneous carcinogenesis.



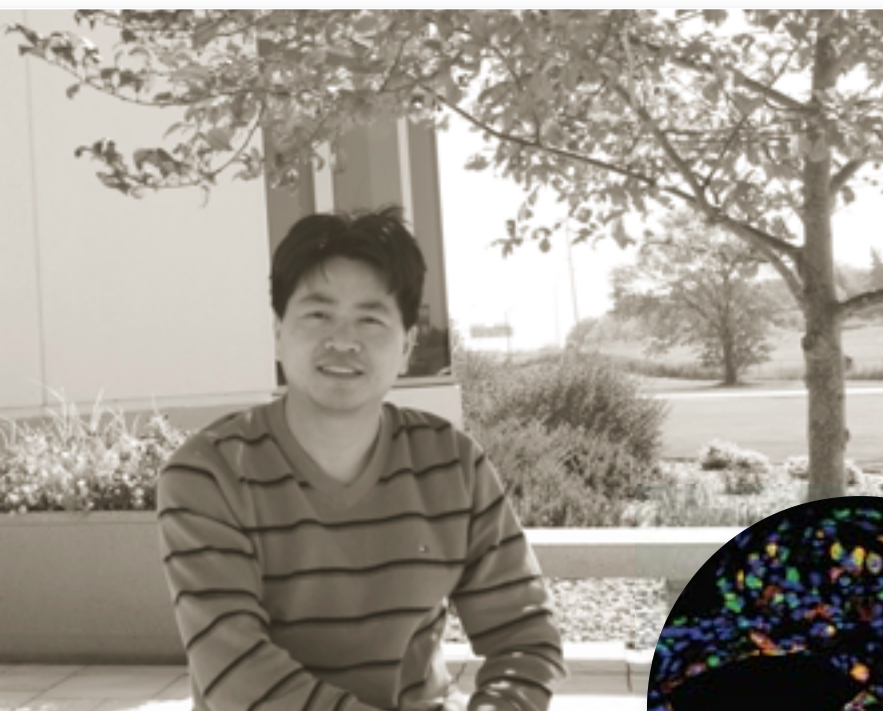
Left to right: Rebecca Morris, Nyssa Readio, Yong Li, Kelly Johnson, Mi Sung Kim

IMMUNOREGULATION OF AUTOIMMUNE DISEASES AND CANCER

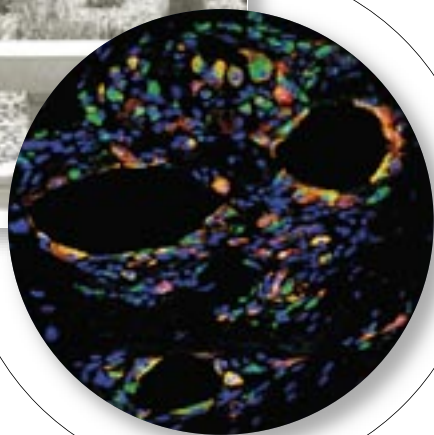
Section Leader

Bing Li, Ph.D.

Assistant Professor



A-FABP (red color) is abundantly expressed in tumor infiltrated macrophages (green color) in breast cancer.



The main focus in this section is to understand the role of fatty acid binding proteins (FABPs) in autoimmune diseases and cancer development. FABPs constitute a family of small, highly homologous intracellular lipid chaperones which have been recognized as central regulators of both metabolic and inflammatory pathways. We have shown that adipose FABP (A-FABP) and epidermal FABP (E-FABP) play important roles in autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) model, a mouse model of human multiple sclerosis (MS), and in different types of cancer, including breast cancer, skin cancer and colon cancer. However, the exact mechanisms underlying these observations remain to be determined. Currently, research in my laboratory strives to understand how FABPs regulate cellular metabolism and intracellular signal transduction pathways in leukocytes, to determine the mechanisms by which FABPs link metabolism and complex diseases, and to identify specific inhibitors of FABPs for potential drug discovery.

For the immunoregulation of autoimmune diseases, we are focusing on the EAE model to dissect how E-FABP regulates leukocyte differentiation and functions and to development of E-FABP inhibitors for treatment of EAE. MS continues to be a serious public health problem without a curative treatment. Although the development of MS is attributed to a combination of genetic and environmental factors, the exact cause of MS is not completely understood. The strategies of MS therapy are to modify the disease course and manage symptoms. Therefore, identification of new targets for prevention and management of MS are urgently needed. This project is to identify E-FABP as a new risk factor for MS and to produce mechanistic insights into modification of EFABP activity for MS management. As lipid chaperones, FABPs can regulate cellular metabolism and function through enabling fatty acid distribution and coordinating their responses. Since fatty acids function both as energy sources and as signaling molecules, FABPs have been identified as central regulators of metabolic and inflammatory pathways. In our previous studies, we have shown that E-FABP deficiency significantly protects mice against the development of EAE, a mouse model of MS. Mechanistically, E-FABP regulates the function of both antigen presenting cells and autoreactive T cell subsets. For example, E-FABP deficient macrophages and dendritic cells are defective in producing proinflammatory cytokines and are inefficient in antigen presentation. EFABP, but not other FABPs, is abundantly expressed in a type of T lymphocytes, which can drive pathogenic T cell differentiation to MS. Furthermore, we have demonstrated that E-FABP can counter-regulate regulatory T cell differentiation through

regulation of lipid-mediated pathway. E-FABP-deficient T cells show enhanced PPAR γ expression and reduced expression of ROR γ t and ROR α . Currently, we have identified several promising small molecules that can ameliorate the symptoms of EAE through modulating EFABP/PPAR pathways. Thus, E-FABP offers a new target for MS pathogenesis and targeting E-FABP may represent a novel strategy for MS and other inflammatory diseases.

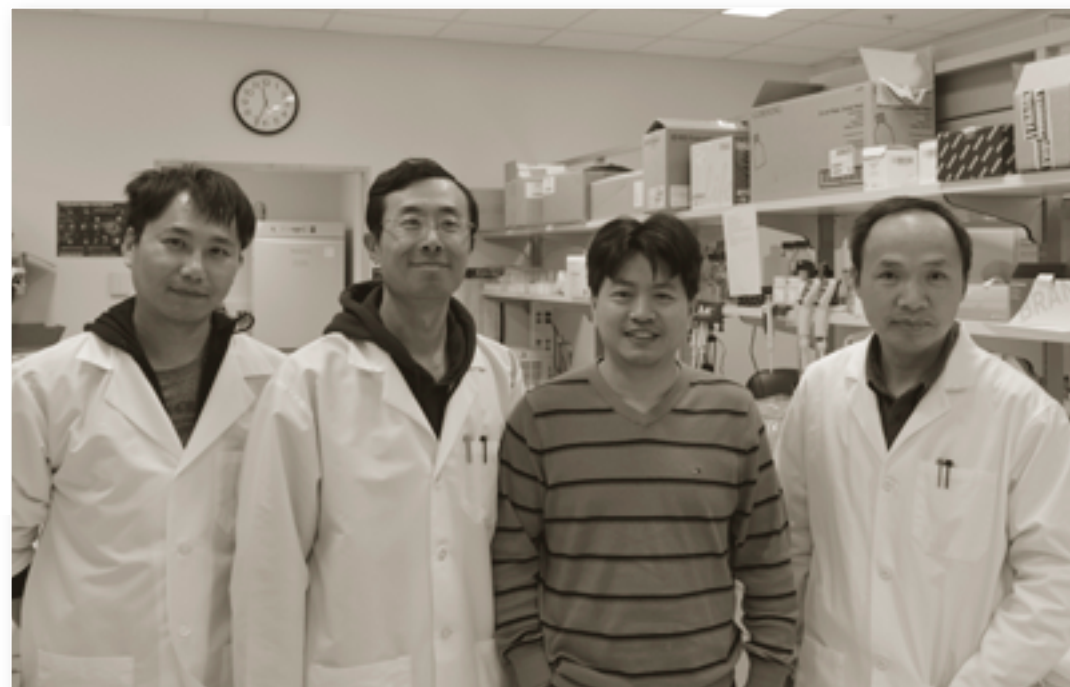
For the immunoregulation of cancer development, we are focusing on mouse models of breast cancer. Each year, breast cancer kills nearly half-a-million women, of whom about 90% die from distant metastases. Therefore, uncovering new mechanisms of breast cancer development and identifying anti-metastatic agents represent critically important foci for prevention and/or treatment of breast cancer. In addition to such underlying risk factors as genetic background, family and reproductive history and aging per se, epidemiologi-

cal studies have identified that obesity is associated with poor prognosis and increased mortality in women with breast cancer. Given the rising rates of obesity in the United States and worldwide, there is an urgent need to identify biological mediator(s) which

can link obesity, immunosurveillance and breast cancer development. The goal of this research project is to identify new mediators and to produce mechanistic insights into the biology of their action in mediating breast cancer progression and metastasis. Carcinogenesis is a multistep complex process that depends on the crosstalk between cancer cell intrinsic factors and extrinsic immunosurveillance effects. Obesity has been established as a risk factor for cancer incidence and cancer mortality. It is likely that obesity may contribute to cancer development either through promotion of cancer cell intrinsic transformation or through subversion of the extrinsic host immune system. Our preliminary studies have demonstrated that crosstalk of tumor cells and tumor infiltrating macrophages can significantly stimulate the cytoplasmic expression of A-FABP in macrophages, which switches the phenotype of macrophages to pro-tumor development. Strikingly, a strain of mice that lacks A-FABP has been found to be protected from breast cancer development. While FABPs are traditionally recognized as cytoplasmic lipid chaperones enabling lipid distribution and coordinating their responses

“Carcinogenesis is a multistep complex process that depends on the crosstalk between cancer cell intrinsic factors and extrinsic immunosurveillance effects.”

inside cells, we have found that obesity can significantly upregulate A-FABP expression in both macrophages and adipocytes. More importantly, tumor associated adipocytes can secrete a large amount of A-FABP into circulation in response to exposure to tumors, which may serve as a plasma biomarker for cancer early diagnosis. Therefore, our studies suggest that A-FABP exerts its effects through both local (cytoplasmic) and systemic (circulating) actions. A-FABP may promote carcinogenesis and tumor development by targeting both cancer cells and immune cells and offers a new therapeutic target for cancer treatment. In this manner, A-FABP may represent a new link between obesity and cancer.



Left to right: Enyu Rao, Qiang Li, Bing Li, Yuwen Zhang
Not pictured: Xiao-ning Gao

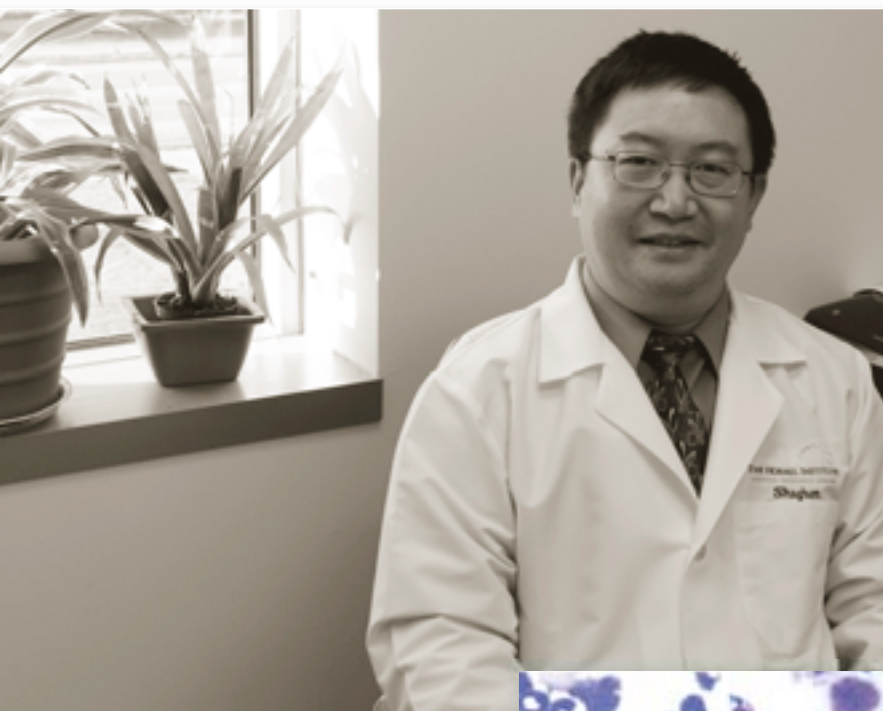
In summary, our studies have revealed that FABPs play essential roles in regulating cellular metabolism and immune functions. While A-FABP is more critical in regulating functions of macrophages and adipocytes in tumor development, E-FABP exhibits a unique role in T cell differentiation in inflammatory autoimmune diseases. These results will have significant implications in their potential applications.

CANCER EPIGENETICS & EXPERIMENTAL THERAPEUTICS

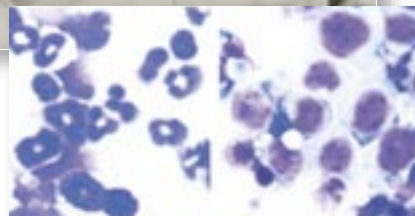
Section Leader

Shujun Liu, Ph.D.

Assistant Professor



Giemsa-stained bone marrow cells from leukemia-bearing lean (left) and obese (right) mice.



Primary interests of our research section are the following:

- to understand the molecular mechanisms and the roles of aberrant epigenetics and protein kinase activities in cancer pathogenesis
- to translate the discoveries from bench to bedside by means of characterizing novel therapeutic reagents
- to develop innovative vehicles to efficiently and specifically deliver the drugs to the disease sites.

In our laboratory, studies have included the cause of DNA hypermethylation and abnormal protein kinase activity, the mechanistic link between obesity and cancer, the identification of new therapeutic reagents, the dissection of molecular basis underlying the anti-cancer actions of bioactive compounds, and the development of innovative nanoparticulates for drug delivery.

The molecular rules underlying aberrant epigenetics

DNA methylation occurs at the 5-position of cytosine in a CpG dinucleotide context and is a major epigenetic mechanism regulating chromosomal stability and gene expression. DNA methylation is under control of DNA methyltransferases (DNMTs), including DNMT1, DNMT3a and DNMT3b. In cancers, DNMTs are highly expressed and the tumor suppressor genes (TSGs) are frequently silenced by promoter hypermethylation. However, the molecular processes behind abnormal DNMT expression remain largely unknown. We have demonstrated that the Sp1/miR29 feedback loop critically regulates the expression of DNMTs. Ten-eleven translocation (TET) protein family also significantly modulates the DNA methylation program through controlling DNMT gene transcription. Pharmacological modulation of Sp1/miR29 network by siRNA or/and small molecules changes DNA methylation status leading to the reexpression of TSGs and the inhibition of leukemia growth. Since Sp1 and miR29b target DNA methylation at multiple levels, we demonstrated that the combination of Sp1 inhibitors (siRNA or bortezomib) with synthetic miR29b synergistically suppresses their downstream signaling cascades. Furthermore, miRNA target prediction indicates that TET1 is a putative target of miR29b. Hence, we reasoned that miR29b could monitor DNA methylation through TET1 abrogation. In addition, we demonstrated the critical role of miR101 in controlling DNMT3a expression, thereby the DNA methylation program. All these observations point out the complexity of DNA methylation machinery, which may explain, at least in part, why current epigenetic therapies in cancers are unsatisfactory.

The molecular mechanisms controlling the transcription of protein kinases

It is well known that abnormal kinase activities are essential in cancer initiation and metastasis, but the main focuses currently are to pharmacologically inhibit kinase activities without the consideration of kinase overamplification. We and others have demonstrated that kinase gene overexpression is involved in the development, progression and drug resistance of cancer and in survival in some

patient subpopulations. However, how protein kinases are transcriptionally regulated remains largely undefined. We previously reported that receptor tyrosine kinases (i.e., KIT and FLT3) are regulated by Sp1/miR29 network. Given the critical roles of Sp1/miR29 in DNMT gene regulation, we proposed that aberrant DNMT function may control the hyperactive kinase pathway. Indeed, our studies showed that DNMT upregulation increases KIT expression leading to KIT specific and global kinase over-function. These findings identify the regulatory and functional interactions between kinases and DNA methyltransferases, and suggest that misregulated KIT signaling and DNA hypermethylation cooperatively contribute to cancerous lesions.

Mechanistic links between obesity and leukemia

Obesity is a “disease” with abnormal body fat accumulation. The World Health Organization estimates that approximately one quarter of the population worldwide is obese. Emerging data indicate that obesity is a major risk factor for human malignancies. It can increase the occurrence of cancerous lesions and decrease the benefit of therapy. However, the molecular mechanisms underlying these phenomena are poorly understood. We observed that higher BMI (body mass index) associates with shorter overall survival in leukemia patients. When leukemia cells were transplanted into obese or lean mice, we found that, compared to the lean counterparts, obese mice display exacerbated leukemic disease, thus experimentally demonstrating the contribution of obesity to leukemogenesis in mice. The future directions are to delineate the mechanistic pathways controlling the obesity-associated leukemogenesis.

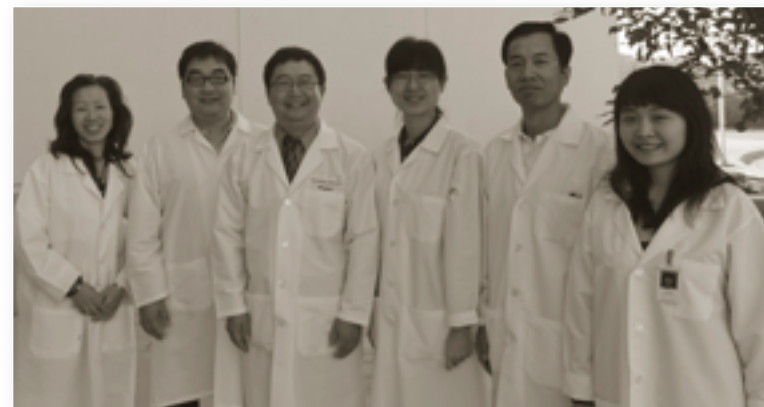
Molecular mechanisms of anti-cancer actions of bioactive compounds

Due to the essential roles of aberrant DNA methylation in cancers, DNA hypomethylating agents (i.e., 5-Azacytidine and 5-aza-2'-deoxycytidine) have been in clinical use for decades. While some positive response has been achieved, the majority of leukemia patients relapse and eventually die of their disease, arguing for the new type of DNMT inhibitors with different structure and distinct mechanisms. Because of the anti-cancer activity and lower toxicity to normal cells, numerous plant extracts have been tested in vitro and in vivo with huge therapeutic potentials. We have demonstrated that certain types of bioactive compounds [i.e., thymoquinone (TQ), echinomycin or emetine] suppress the expression of DNMT1, DNMT3a and DNMT3b resulting in global DNA hypomethylation and the re-expression of TSGs through promoter hypomethylation. Functionally, these compounds suppress cancer cell proliferation in vitro and metastatic growth in vivo. While the underlying molecular mechanisms remain elusive, these compounds may hold promise in human cancer therapy.

Developing multifunctional drug and gene delivery nanoparticles for cancer therapy

The current chemotherapeutic drugs (i.e., small molecules, siRNA or miRs), although they display promising anti-cancer activity, suffer from a variety of drawbacks when administered particularly in vivo, including rapid clearance, lack of tissue selectivity, high affinity to plasma proteins and poor cellular uptake. We have developed new liposomal formulations and synthesized nanoparticles to efficiently deliver the aforementioned drugs. We have successfully delivered bortezomib, miR29 and Sp1 siRNA by nanoparticles in vitro and in vivo. As a consequence of efficient delivery, we observed that liposomal bortezomib has a decrease of clearance and thereby an increase of drug exposure to leukemia cells existing in blood, compared to those of free bortezomib in mice. Due to this change, liposomal bortezomib induced a long-term disease free remission in 80% of DKI AML mice and 100% of LGL leukemia IL-15 Tg mice. We also evidenced the synergistic effects of combined liposomal bortezomib with nano-miR29b on leukemia cell

“Epigenome and kinome cooperatively, but not independently, determine the cancer cell's fate.”



Left to right: JiuXia Pang, Fei Yan, Shujun Liu, Xiao-ning Gao, Shengcai Wei, Na Shen

growth in mice. Recently, we synthesized HDL/AuNP nanoparticle and successfully delivered small molecule compounds into leukemia cells. These results revealed that nano-drug delivery displays huge potential to improve therapeutic efficacy while reducing its side effects, including decreased drug toxicity, altered pharmacokinetics, improved drug solubility and more specific target binding.

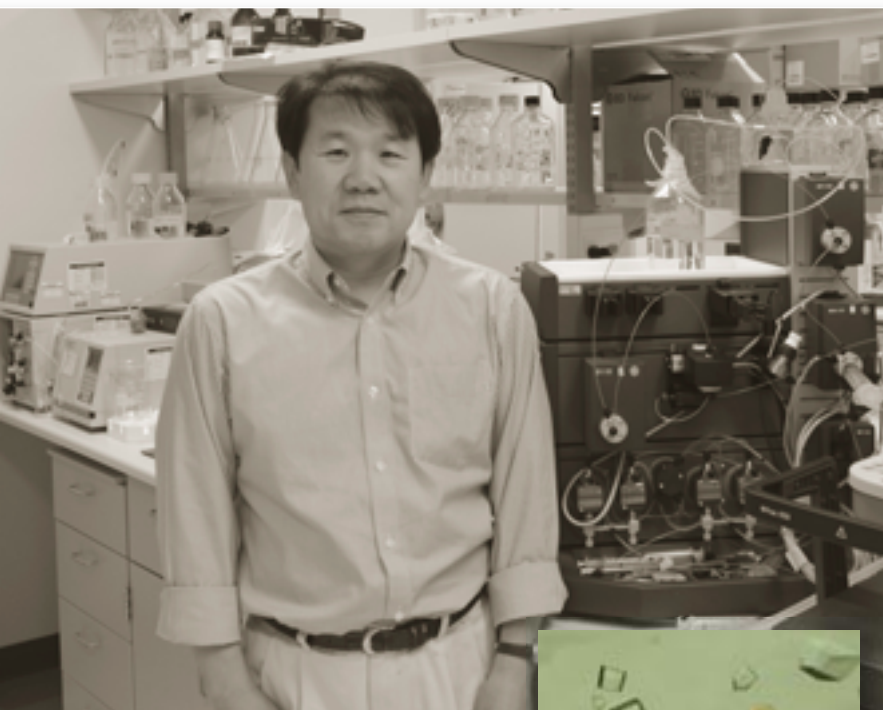
Overall, our discoveries offer new insights into the molecular biology of cancer, advance our understanding of nanoscience with efficient delivery vehicle for miRs and small molecule compounds, and foster the translation of nanotechnology solutions to biomedical applications thereby improving the management of cancerous lesions.

STRUCTURAL BIOLOGY

Section Leader

Young-In Chi, Ph.D.

Assistant Professor



Crystal specimens of a protein/DNA complex used for structure determination by X-rays.



Structural biology is a branch of biomedical science concerned with molecular structures of biological macromolecules, such as proteins and nucleic acids. With their biological functions tightly coupled to their molecular structures, elucidating atomic details of their structures – either alone or in complex with their functional binding partners – is crucial to understanding the molecular mechanisms underlying their physiological functions. Biomolecules are too small to see even with the most-advanced electron microscope. Special techniques have to be employed to do this, and we particularly harness X-ray crystallography as a main experimental tool to elucidate three-dimensional structures. This technique involves various disciplines of modern biomedical research, such as molecular biology, protein chemistry, biophysics, and various computations. We also perform diverse functional studies to complement our structural studies.

The structural information with accurate atom positions can be very useful. It not only allows the understanding of how biological molecules function, but also provides the opportunity to modulate their functions by a means of rational drug design and therapeutic intervention. For example, if we know the atomic details of molecular interactions, such as enzyme-substrate or protein-ligand interactions, then we can design small compounds that either can block or enhance the interactions of the two molecules. Well-known examples of structure-based drug design are protease inhibitors of HIV for the treatment of AIDS and a kinase inhibitor (Gleevec) for the treatment for chronic myeloid leukemia.

Currently, our research is focused on elucidating the atomic details of key molecular interactions involved in various human diseases, such as diabetes and cancer. In particular, we are focusing on transcriptional regulators involved in diabetes and protein functional modulators involved in tumor progression and metastasis. We apply structural biology to gain a better understanding of their normal function and dysfunction in the disease state and an opportunity to discover or design functional modulators.

HNF1 α (Hepatocyte Nuclear Factor1 α) and HNF4 α are the master regulators of pancreatic β -cell development and function, and their mutations are the most common monogenic causes of diabetes. Because transcription factors orchestrate the manufacturing of proteins that make up living tissues and regulate all of the body's functions, any genetic defects in them can lead to serious illnesses, such as developmental defects, metabolic disorders, and malignant tumors. Over the years, we have determined the crystal structures of the functional complexes made by HNF1 α and HNF4 α . These structures provided valuable information on the molecular basis of target gene recognition, ligand-mediated activation, and functional disruption by disease-causing mutations. However, these structures provided only partial answers as to how their full transcriptional activities arise, and how these proteins are involved in additional protein-protein interactions and physiological functions. Moreover, critical structural information is

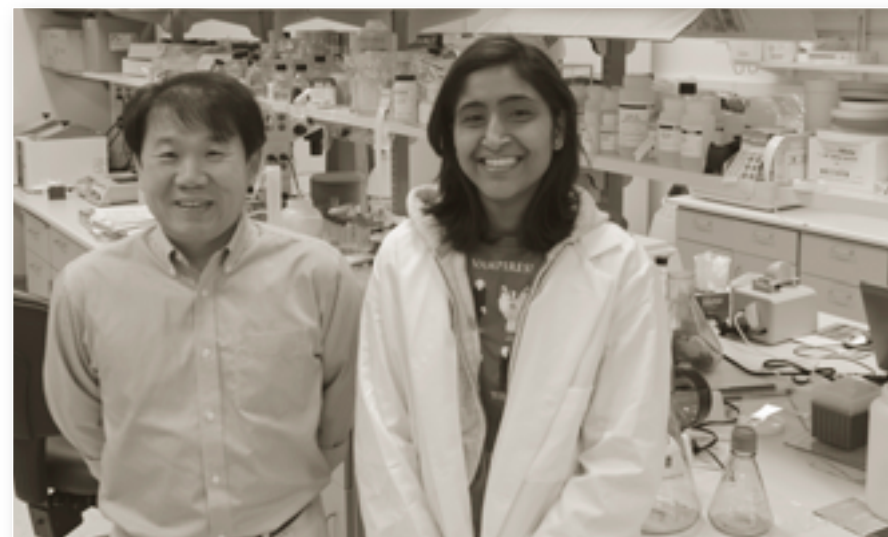
largely lacking on how the molecular interactions occur during the multi-complex formation and how they are disrupted by MODY mutations. Therefore, we set out to identify unknown functional binding partners of HNF1 α and HNF4 α in β -cells, and study the physiological implications of these interactions, especially on insulin secretion that is impaired in MODY patients, and perform structural studies of the complexes and functional characterization of MODY mutations. We generated significant preliminary data last year and published a few papers on some of the earlier findings, including functional interactions between HNF4 α and the mediator component of the main transcriptional machinery (MED25). Currently, we are in the process of following up with additional findings on the putative binding partners and their physiological implications. These findings will advance the current understanding of the transcription regulatory network in β -cells and provide a new avenue for diabetes treatment/prevention strategies by discovering novel and more effective target sites for designing and further improving partial agonists selectively against them.

Dub3 is a ubiquitin hydrolase (de-ubiquitinase) and key protein that relays extrinsic signals to regulate epithelial-mesenchymal transition (EMT) and metastasis in breast cancer, which can serve as a druggable target for treating triple negative/basal-like breast cancers. To gain the ground work for structure-based rational drug design against this protein, we set out to determine the crystal structure determination of the Dub3 catalytic domain alone and/or its complex ubiquitin, its substrate. We made sufficient progress last year and are in the process of improving the crystals and finishing up the structure determination. Upon completion of the structures, we will conduct a computer-aided docking analysis of chemical library compounds to discover/design specific inhibitors of Dub3 to improve the prognosis of these hard-to-treat breast cancers. Candidate compounds will be purchased and tested in vitro and in vivo for their ability to suppress the de-ubiquitinase activity of Dub3. These findings will validate the effectiveness of Dub3 target strategy and possibly open new doors for therapeutic intervention.

Additional projects in the lab include autophagy-related proteins and functional RNA molecules with therapeutic potential. Research in our laboratory will continue to this end, and target molecules will be expanded to include more cancer-related proteins. Crystal structure determination, functional studies, and drug discovery will con-

“Currently, our research is focused on elucidating the atomic details of key molecular interactions involved in various human diseases, such as diabetes and cancer.”

tinue. Successful outcomes of these projects will provide a critical basis for human physiology, dysfunction in the disease state, and a better strategy for therapeutic intervention. The institutional support has been playing a vital role, and I look forward to continuing our efforts by working with our Institute’s section leaders and the colleagues around the University of Minnesota community and Mayo Clinic.



Left to right: Young-In Chi, Puja Singh
Not pictured: James Endrizzi, Eun Hee Han

Other Professional Activities

Young-In Chi

Invited speaker:

University of Kentucky, International Conference of RNA Nanotechnology and Therapeutics

University of Minnesota, Rochester, BICB program

Ad-hoc Journal Article Review:

Nucleic Acid Research

European Journal of Medical Genetics

Acta Crystallographica section D

MOLECULAR CHEMOPREVENTION AND THERAPEUTICS

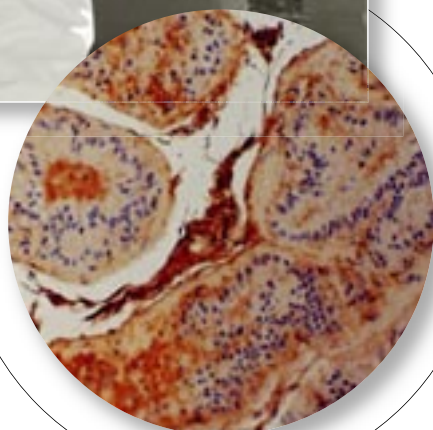
Section Leader

Mohammad Saleem Bhat, Ph.D.

Assistant Professor



24 weeks, Transgenic adenocarcinoma of the mouse prostate (TRAMP)



The long-term goals of this section are the following:

1. Understanding the biochemical, cellular and molecular processes crucial for the development of hormone-related (prostate and breast cancer) and lethal (pancreatic & colon cancer) cancers.
2. Identifying potential agents that could be used to treat and prevent cancer in humans.
3. Identifying novel tissue, serum and urine-based diagnostic and predictive biomarkers for prostate and breast cancer.
4. Understanding the causes of disparity in prostate and breast cancer diagnosis and outcome of therapy in African Americans.

The major focus of our laboratory is in the area of translational research. The following programs are underway in our laboratory:

Research Projects Underway

1. Investigation of mechanisms of chemoresistance in prostate cancer patients

Prostate cancer is the most common visceral cancer diagnosed in men; it is the second-leading cause of cancer-related deaths in males in the United States and the Western world. The lack of effective therapies for advanced prostate cancer reflects, to a large extent, the paucity of knowledge about the molecular pathways involved in prostate cancer development. After undergoing chemotherapy and radiotherapy, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of new predictive biomarkers will be important for improving clinical management, leading to improved survival of patients with prostate cancer. Such molecular targets, especially those that are indicative of proliferation, invasiveness of the disease and survival of cancerous cells (even after chemotherapy) also will be excellent candidate targets for staging the disease and establishing effectiveness of therapeutic and chemopreventive intervention of prostate cancer. We investigate the molecular mechanism that causes the failure of chemotherapy and radiotherapy in cancer patients. We have identified several molecules (genes and gene products) responsible for the development and recurrence of aggressive forms of cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb group gene and stem cell factor), cFLIP (a caspase-8 inhibitor) and matriptase (a serine protease). The main objective of these studies is to take the bench-side research to the bed-side use in clinics.

2. Role of cancer stem cells in prostate cancer development and outcome of therapy

The critical pathological processes that occur during the development and progression of human prostate cancer and are known to confer aggressiveness to cancer cells are (1) abolishment of senescence of normal prostate epithelial cells, (2) self-renewability

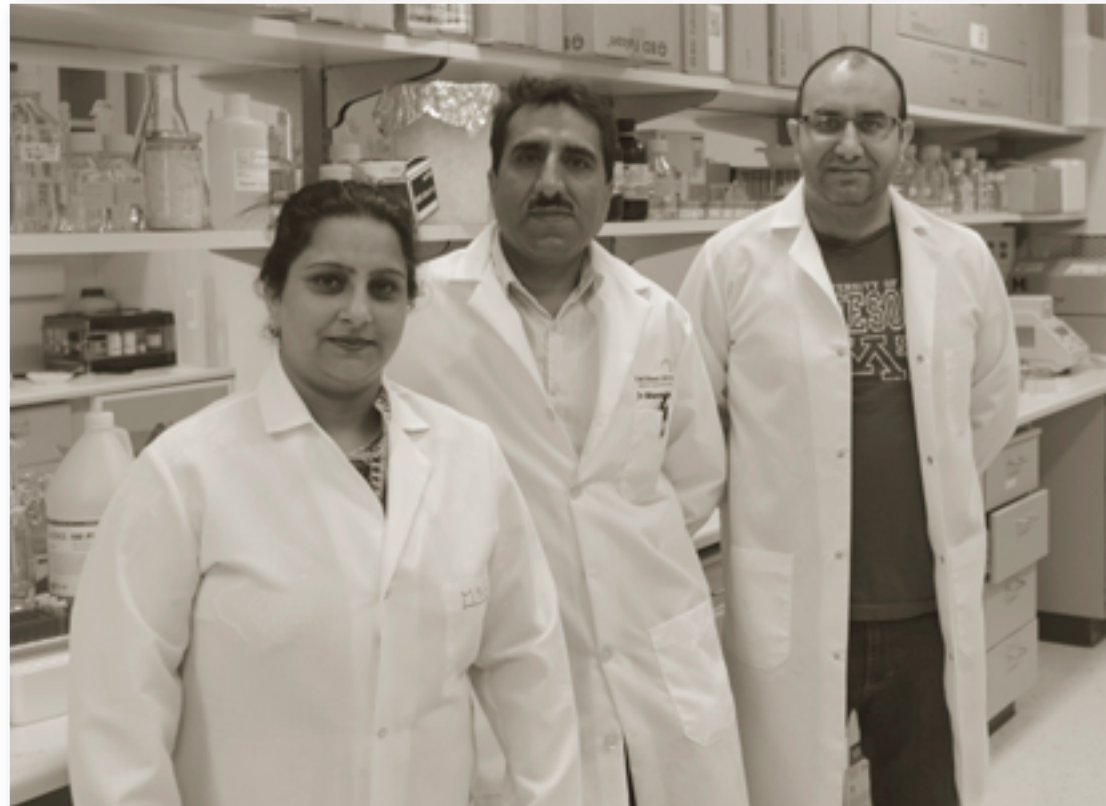
of prostate cancer cells even after chemotherapy and radiation, and (3) dys-regulated cell cycle resulting in unchecked proliferation of cancer cells. Cellular senescence is physiologically important because it is a potent tumor suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumor cells is an essential defining property of a pluripotent stem cell-like phenotype of cancer cell, which distinguishes it from other cell types. Stem cell-resembling population of cancer cells among the heterogeneous mix of cells constituting a tumor have been reported to be essential for tumor progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells that do not respond to chemotherapy or radiotherapy possess the traits of stem cells, thus regenerating themselves even after chemo or radiotherapy treatment. Polycomb group (PcG) family of proteins (which form multi-meric gene-repressing complexes) has been reported to be involved in self-renewability, cell cycle regulation, and senescence. BMI-1 is a transcription repressor and has emerged as an important member of PcG family. We are investigating the role for Bmi-1 protein in prostate cancer development. We hypothesize that BMI-1 protein could be developed as a diagnostic and prognostic of prostate cancer.

3. Reactivation of tumor-suppressor genes

Early development of cancer is largely dependent upon androgens and simultaneous suppression of tumor-suppressor genes predispose the initiated and premalignant prostate epithelial cells to acquire malignant phenotype. Among the phenotypic changes, the premalignant cells acquire increased motility, changes in cytoskeleton, changes in cell adhesion characteristics, and increased tendency for clonal expansion. The interaction between SLIT-ligand and its receptor Roundabout (Robo-1) is reported to guide axons during development of the nervous system. During organogenesis, the SLIT-ROBO path-

“Our laboratory is engaged in identifying novel molecules (genes and proteins) which could be used as biomarkers for the diagnosis and staging of disease as well as act as molecular targets for therapeutic agents for treating cancer.”

way regulates numerous processes, including cell proliferation, migration, and adhesion, that seem to be important in the development of disparate tissues, including those of the reproductive system. SLIT-ROBO1 signaling has been shown to promote cell adhesion by stimulating the interaction between E-cadherin and beta-catenin at the plasma membrane. Various studies suggest the SLIT/ROBO network acts as a tumor suppressor system in humans. We have started a broad program that is aimed to delineate the mechanism of action



Left to right: Neelofar Jan Bhat, Mohammad Saleem Bhat, Aejaz Sultan Parray
Not pictured: Hifzur Siddique

(tumor suppressor action) of ROBO in human cancers. We are investigating whether reactivation of the ROBO system (in cancer cells within tumors) would stop the proliferation and dissemination of tumor cells to other body organs. To test our hypothesis, we are adopting novel approaches, such as combining gene therapy and chemotherapy. Currently, our focus is to test our hypothesis in prostate, pancreatic and skin cancer (melanoma). We are running this

program in collaboration with the Division of Translation Studies, Masonic Cancer Center, University of Minnesota. This program has high translational potential for cancer patients.

4. Role of S100A4 in the development of prostate cancer

S100A4, also known as mts1, CAPL, p9Ka, and metastasin, belongs to the S100 super-family of calcium-binding proteins and is located in a 2.05 Mbp segment of the genomic DNA of chromosome 1q21 region, where most of the S100 family of gene cluster occurs. S100A4 protein has been reported to be associated with invasion and metastasis of cancer cells and frequently over expressed in metastatic tumors, normal cells with uninhibited movement, such as macrophages, transformed cells and in various cancer types, such as breast, ovary, thyroid, lung, esophageal squamous cell carcinoma, gastric, colon, and prostate. Earlier, we reported that S100A4 is overexpressed during progression of prostate cancer in humans and in TRAMP mouse, an autochthonous transgenic model that develops prostate cancer in a manner similar to human disease. Recently, we showed that S100A4 regulates the events leading to proliferation and invasion of prostate cancer cells. We showed that S100A4 guides the invasive phenomenon of prostate cancer cells by regulating transcription and function of matrix metalloproteinase (MMP-9) in prostate cancer cells. S100A4 is notably known for its role in metastasis. By creating a transgenic mouse model of prostate cancer lacking S100A4, we, for the first time, provided evidence that S100A4 protein, both in its intracellular and extracellular form, plays a tumor-promoting role in the development of prostate cancer by regulating the function of Nuclear Factor kappa B/Receptor for Advanced Glycation End products molecular circuitry.

5. Transition of androgen-dependent prostate cancer to androgen-independent phenotype

Aberrant Androgen receptor (AR) expression and activation promoted by mutations, and binding partner misregulation, is presented in several clinical manifestations, including androgen insensitivity syndrome, acne vulgaris, androgenetic alopecia, benign prostate hyperplasia (BPH), and different types of cancers in humans. AR has been found to be a principal driver of initiation and progression of prostate cancer. The initial stage of prostate cancer is dependent on androgen, and can be managed by a series of therapies that are antagonist to AR or suppress AR signaling. However, the success of these therapies is temporary and after a short remission period, tumors reappear as androgen-independent or commonly known as castration-resistant prostate cancer (CRPC).

It is noteworthy that FDA-approved agents (androgen receptor signaling inhibitors), such as Bicalutamide, that are widely used in clinics to treat cancer, show dismal results in men with advanced prostatic malignancy. Recently, it has been observed that overexpression of AR is the most common event associated with CRPC. AR (which generally responds to androgen) remains active and functional in CRPC disease. We are studying the mechanism; through which AR becomes functional in prostate cancer patients exhibiting CRPC disease. Emergence of CRPC phenotype depends on different mechanism such as activation of receptor tyrosine kinase, uncontrolled cell growth, genomic mutation of AR that allows response to nonspecific AR-ligands. We are testing whether isoforms or splice variants of androgen receptor play a role in the CRPC disease. It has been reported that AR splice variants activate genes involved in the metabolism of androgens and provide a survival advantage for cells in a low-androgen environment. Our laboratory has identified the mechanism through which AR-variants induce their pro-growth activity in tumor cells. Notably, we have identified an agent that inhibits the activity of AR-variants in CRPC cells. The validation of this mechanism-based agent in animal models is expected to provide an excellent alternative or adjuvant modality for the treatment of advanced prostate cancer, particularly of CRPC phenotype.

6. Investigating the causes of racial disparity in prostate cancer

According to American Cancer Society, the higher overall cancer death rate among African American men is due largely to higher mortality rates from prostate, lung, and colorectal cancers. Although the overall racial disparity in cancer death rates has decreased, the death rate for all cancers combined continues to be 32% higher in African American men than in Caucasian men. African American men with prostate cancer have worse disease, with a higher incidence, are younger in age with more advanced disease at diagnosis, as well as a worse prognosis, compared to Caucasian men. In addition to socioeconomic factors and lifestyle differences, molecular alterations have been reported to contribute to this discrepancy. Recent developments in genetics, proteomics, and genomics, among other molecular biotechnologies, are anticipated to greatly aid the advancement of translational research on prostate cancer racial disparity and hopefully will culminate in the discovery of novel mechanisms of disease, in addition to prognostic markers and novel therapeutic approaches. The research project running in our section is aimed to investigate the molecular mechanisms that cause the failure of therapy of cancer in African Ameri-

can men. Though widely used in clinics, the PSA has been reported to be insufficient as a reliable biomarker for prognosis of prostate cancer in African American men. The larger aim is to identify novel biomarkers that could be used for prostate cancer prognosis in Caucasians as well as in African American men. We recently showed that BMI1, a stem cell protein, could be developed such a sensitive and reliable blood biomarker for prostate cancer disease in Caucasian as well as African American men.

7. Lupeol, a dietary triterpene: testing its efficacy for the prevention and treatment of prostate, pancreatic and colon cancer

Another major goal of our laboratory is to identify novel and non-toxic agents that could be developed as chemopreventive and chemotherapeutics agents for either inhibiting cancer development or treating cancer in humans. We have identified a non-toxic compound called “lupeol” exhibiting a potential to be developed as a chemopreventive and chemotherapeutic agent against cancer. Lupeol, a fruit and vegetable based triterpene, is found in olives, grapes, cucumbers, berries, and mangoes, as well as in herbs, such as aloe vera. Our laboratory has shown that lupeol application on skin prevents cancer development in animal models. Further, we have shown that lupeol treatment inhibits the growth of prostate, pancreatic, and skin tumors (of human origin) using relevant mouse models. These studies have generated interest in studying lupeol for other cancer types. We recently observed that lupeol has the potential of improving chemotherapy in colon cancer. Our pharmacokinetic studies have shown that lupeol is bioavailable in relevant mouse models after consumption (as oral administration).

8. Testing cocoa polyphenol (dark chocolate)-based functional foods in the prevention and treatment of cancer

Functional food is any healthy food claimed to have a health-promoting or disease-preventing property beyond the basic function of supplying nutrients. Functional chocolate consumption has been associated with improvements in delayed oxidation of low-density lipoprotein cholesterol and lowered blood pressure in humans. Cocoa-based chocolate consumption has been associated with short-term improvements in delayed oxidation of low-density lipoprotein cholesterol, improved endothelial function, lowered blood pressure, and improved platelet function. Epicatechin is the major component of cocoa powder. We have employed a technique (called ACTICOA) that provides the cocoa polyphenol powder highly rich in epicatechin content. Our studies show that

epicatechin rich cocoa polyphenol selectively inhibits growth of premalignant prostate and pancreatic cells while sparing normal cells via modulation of NFκB signaling pathway. We are testing cocoa polyphenol in animal models evaluating its preventive as well as therapeutic value against cancer. For our studies, we have collaborated with Barry Calibaut (Belgium), one of the leading companies in the world producing functional foods including functional chocolates. We are seeking funds for support of this research study.

Our Research Partner Institutions

Our section has joined hands with internationally renowned research institutions and investigators in its quest to defeat the lethal disease of cancer in humans. Studies are underway in partnership with the following research institutions:

1. *Institute for Cancer Biology, Danish Cancer Society, Copenhagen, Denmark*
2. *Research Center for Advanced Science and Technology, University of Tokyo, Japan*
3. *Mayo Clinic, Rochester, MN, USA*
4. *Roswell Park Cancer Institute, Buffalo, NY, USA*
5. *Center for Prostate Disease Research, Uniformed Services University of the Health Sciences, Bethesda, MD, USA*
6. *Albert Einstein College of Medicine, Bronx, NY, USA*
7. *University of Illinois-Chicago, IL, USA*
8. *Clark-Atlanta University, Atlanta, GA, USA*

CANCER BIOMARKERS AND DRUG RESISTANCE

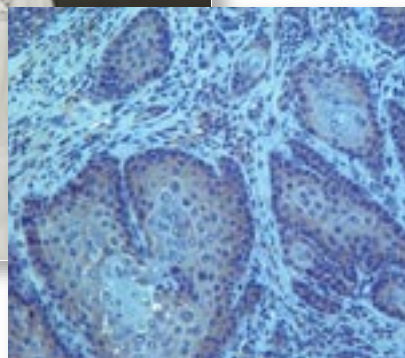
Section Leader

Ann M. Bode, Ph.D.

Professor



Immunohistological staining of Cox2 in squamous cell carcinoma

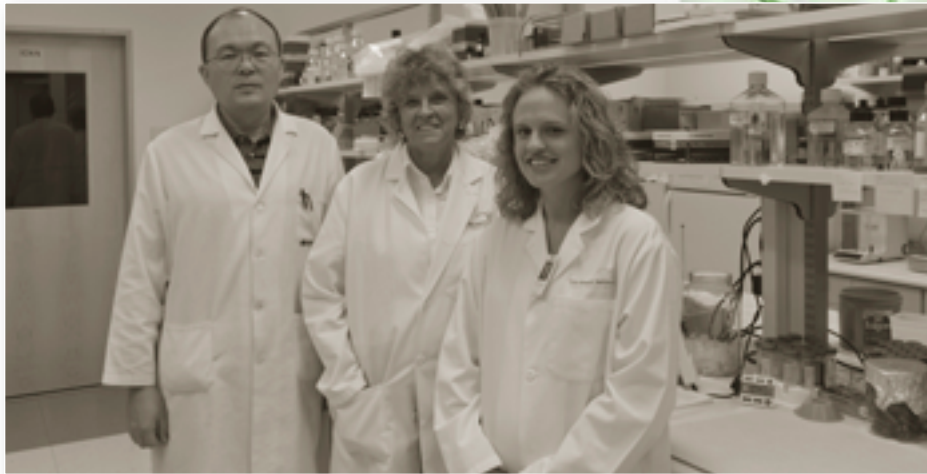


Our laboratory is funded by a National Institutes of Health (NIH) contract and Pediatric Pharmaceuticals. The purpose of the NIH studies is to identify and measure specific cellular signal transduction endpoints with the purpose of identifying potential biomarkers and mechanisms of action of the various anticancer agents. The work funded by Pediatric Pharmaceuticals focuses on the anti-skin cancer effects of ginger compounds.

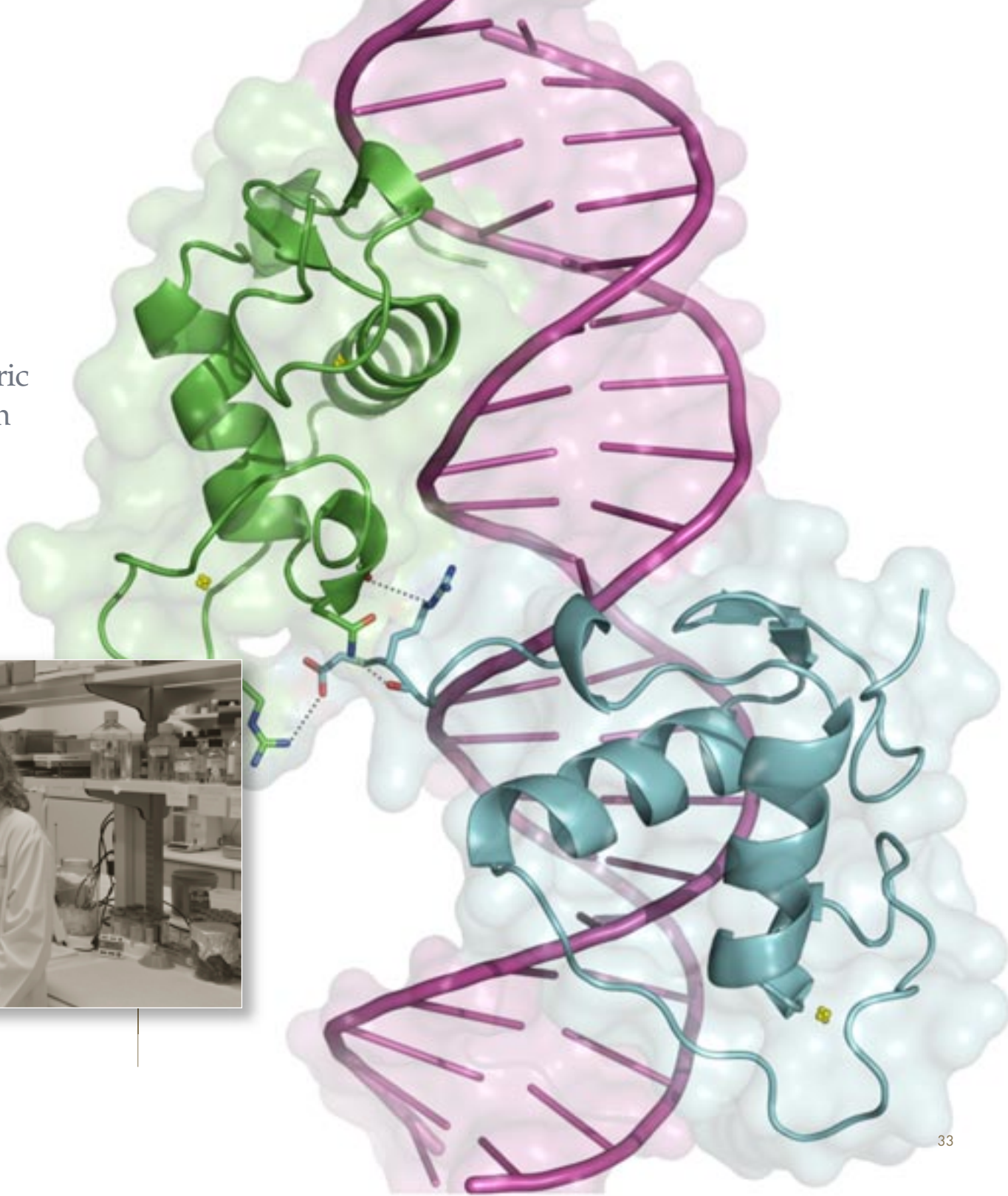
The NIH funded work focuses on studies with mammary tumors and normal mammary glands, and effects of chemopreventive agents in in vivo mammary models. The primary purpose of this work is to determine whether specific signal transduction molecules can serve as reliable endpoint biomarkers for clinical trials as well as provide insight into the mechanism(s) by which selected anticancer agents modulate their preventive effects. The development and identification of reliable biomarkers will allow us to 1) assess the efficacy of potential chemopreventive or therapeutic agents for clinical trials; 2) identify patients who will respond to specific drug treatments; and 3) determine the mechanisms of action of specific agents or mixtures of agents (e.g., food mixtures). These are major objectives in the field of chemoprevention and cancer therapeutics. To identify biomarkers, we use a variety of techniques, including immunohistochemistry, Western blot analysis, protein array analysis, and cell culture. The use of Neu expressing or ER positive breast cancer cell lines to test the effect of RXR inhibitors, targeetin and UAB, on migration and invasion along with other characteristics of cancer is being investigated.

Our work funded by Pediatric Pharmaceuticals has focused on developing a ginger-based formulation to treat and/or prevent solar UV-induced skin cancer.

“Our work funded by Pediatric Pharmaceuticals has focused on developing a ginger-based formulation to treat and/or prevent solar UV-induced skin cancer. ”



Left to right: Hongxun Wang, Ann M. Bode, Alyssa Langfald
Not pictured: Mi Sung Kim

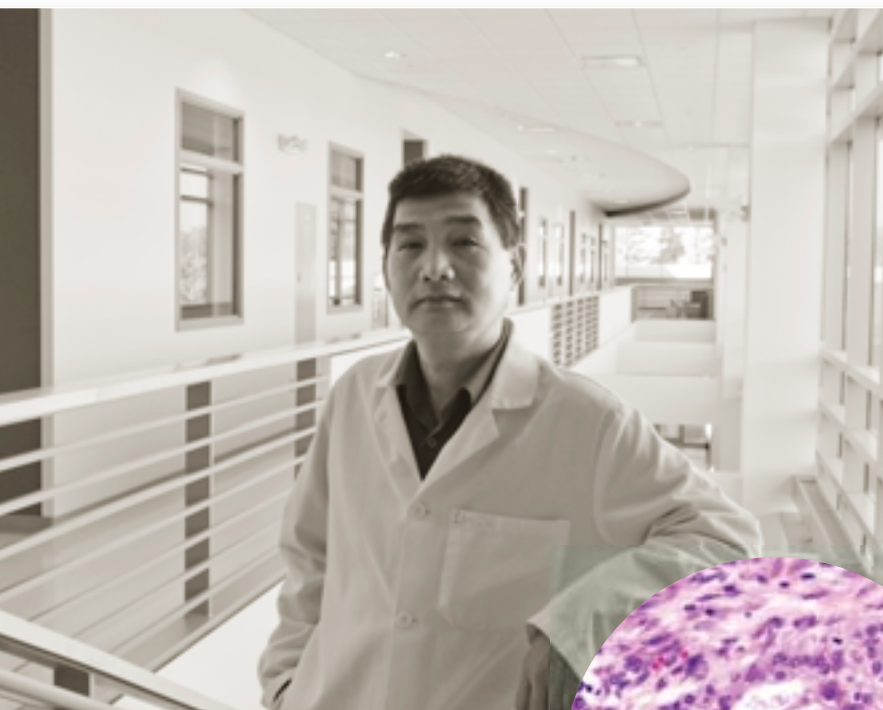


TRANSLATIONAL CANCER RESEARCH

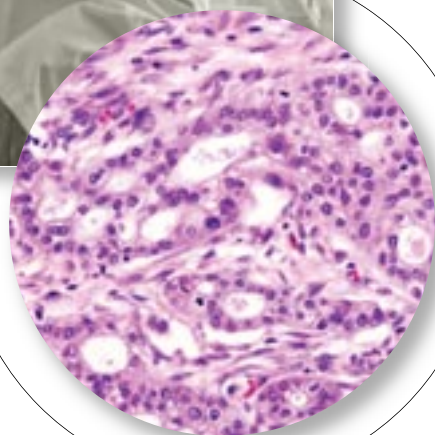
Section Leader

D. Joshua Liao, M.D., Ph.D.

Associate Professor



Micrograph of pancreatic ductal adenocarcinoma (the most common type of pancreatic cancer).

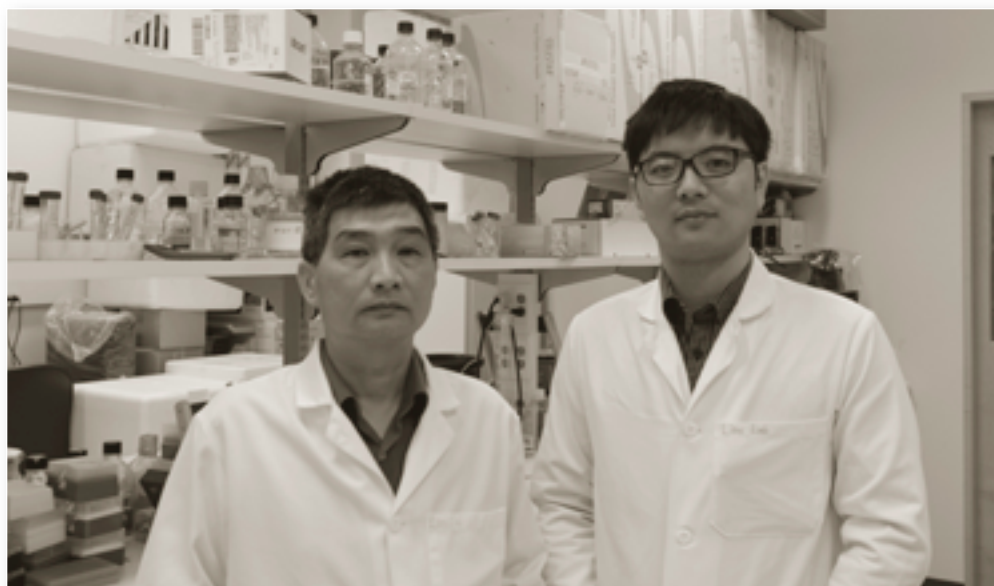


In the past year, with funding provided by the DOD Breast Cancer Idea Award, we established and published several methods that solve bottleneck difficulties for cloning fusion RNA and antisense-accompanied RNA. During the establishment of these novel techniques, we further confirmed and provided explanations for our conclusion stated in last year's report that the majority of chimeric RNAs in various databases, especially those containing a short homologous sequence shared by the two partners, are technical artifacts. In addition, we performed bioinformatic analyses of expression sequence tags (EST) in various databases and identified, for the first time, trimeric and tetrameric RNAs, (i.e. RNA molecules containing three or four different genes' sequences). We also have found that many chimeric or trimeric RNAs encompass mitochondrial (mt) sequence, i.e. are fusions between mtRNA and nuclear RNA (nRNA). In some mtRNA-nRNA fusions, as well as in some ESTs that are derived only from mtRNA, the mt-sequences are cis- or trans-spliced products. Actually, we have cloned a new cis-spliced mtRNA, coined as 16SrRNA-s. Hence, mtDNA may not always be intron-less as previously thought. Fusion of three or more RNAs to one, fusion of nRNA to mtRNA, and cis- or trans-splicing of mtRNA should all enlarge the cellular RNA repertoire, in turn, enlarging the cellular functions. Therefore, our identification of these novel classes of fusion RNAs and spliced mtRNAs in human cells should significantly advance our understanding of biology and medicine.

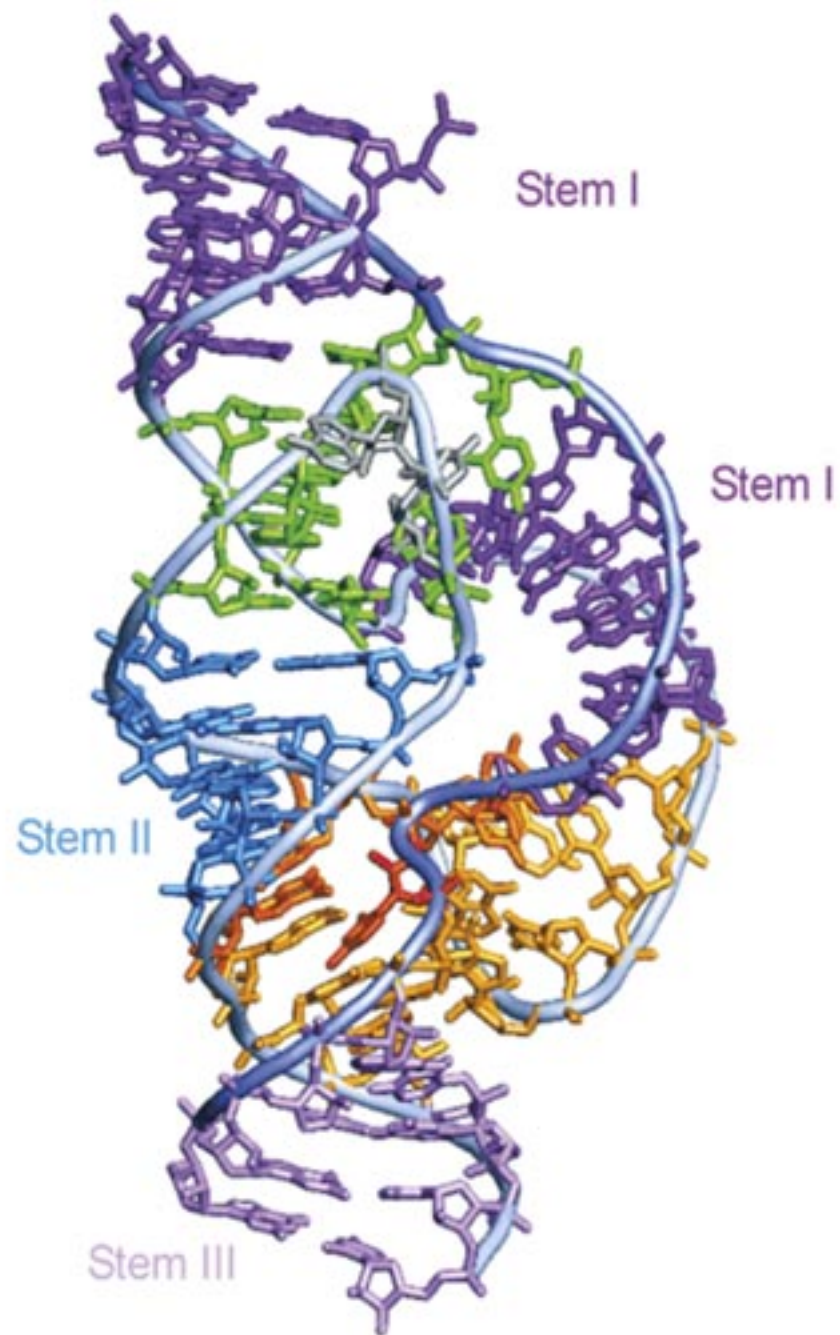
In another project on RSK4 gene, we found for the first time that RSK4 can be transcribed from different initiation sites, and that the pre-mRNAs undergo different alternative splicing. Through these two mechanisms, the RSK4 produces different mRNA variants. We further showed that the protein isoforms encoded by these mRNAs have different functions in tumor biology, which partly solves a long-term puzzle of whether RSK4 is a tumor suppressor gene or an oncogene. While the wild type protein may be tumor suppressive, some of its isoforms in some cell types may be oncogenic.

In the past year, we have published six research articles and coauthored with other labs on three additional publications.

“The methods we established allow us to verify the true existence of the reported RNA chimeras and to clone their full-length sequence.”



Left to right: Joshua Liao, Yongchang Ouyang
Not pictured: Cheng Fu Yuan, Longyu Jin





RESEARCH SUPPORT GROUP

Supervisor
Ellen Kroc

The Hormel Institute's Research Support Group (RSG), supervised by Ellen Kroc, provides vital operational support within the Institute's 12 research sections for their many ongoing research projects. Each of the Institute's cancer research departments is dedicated to preventing or controlling cancer.



Left to right: Ellen Kroc, Michelle Jacobson, Melissa Fortsch, Teri Johnson
Not pictured: Emily Nagle, Scott Pacholl, Andria Hansen, Sherri King, Ambrosia Goodall, Natalie Wilson



Left to right: Lindsey Meyer, Andy Lucas

LIBRARIAN Andy Lucas

The Library serves as the information resource center for The Hormel Institute. It provides print and online materials to support faculty and staff research as well as special projects. The collection consists of approximately 10,250 volumes of bound journals and 2,900 volumes of books and serials. The subjects covered include chemistry, biology, biophysics, medicine, and electronics. Researchers also have access to the services and resources of the University of Minnesota Twin Cities Libraries, the 16th largest in North America by collection size. Books are delivered through the MINITEX delivery service and are available for pickup in The Hormel Institute Library. Articles that are not available in electronic form are obtained through interlibrary loan.

INSTRUMENT CORE FACILITY

Todd Schuster

Senior Lab Technician

Schuster operates, maintains and instructs scientists about the shared instruments used at The Hormel Institute for cancer research. Shared instruments and equipment include: Becton Dickinson FACS Aria II cell sorter, FACSCalibur flow cytometer, ABSCIEX 5600 Triple TOF mass spectrometer and Eksigent NanoLC nano HPLC system, Rigaku X-Ray diffraction system for protein crystallography, confocal and fluorescent microscopes, real time PCR, spectrophotometers, tissue processor and microtome, cryostat, and high speed and ultracentrifuges.



OFFICE

Supervisor

Associate Director

Ann M. Bode, Ph.D.

Our office staff continues to provide excellent editorial and clerical support to the research sections and serves as liaison with the University's central administration departments. Each year, staff members travel to the Twin Cities campus to participate in refresher training and various workshops relevant to their duties.



Left to right: Jessica Thatch, Betsy Mentel, Dr. Ann M. Bode
Not pictured: Tonya Poorman, Becky Smit



Left to right: Kelsey Stough, Gail Dennison, Gretchen Ramlo, Tim Ruzek

PUBLIC RELATIONS AND DEVELOPMENT Gail Dennison, CFRE

Our guiding principle is The Hormel Institute's quest to improve the health of the world. Our focused team of expert researchers aim daily to discover the mechanisms of cancer – what will prevent it and what are healthier paths to controlling it.

In 2012-2013, more individuals and organizations stepped forward to support the groundbreaking cancer research of The Hormel Institute than ever before. The visionary support of The Hormel Foundation, led by Chairman Gary Ray, places The Hormel Institute on a path where the future is truly limitless for what can only be called TRANSFORMATIVE CHANGE.

In short, the following collaborators KNOW and UNDERSTAND the unique story of The Hormel Institute....that in our joined quest for a healthier tomorrow, research must be funded today.

Thank you, from the faculty and staff of The Hormel Institute to our front-line team – and please....join us:

The Hormel Foundation
Hormel Foods Corporation
Mayo Clinic Health System
Minnesota Governor Mark Dayton
U.S. Senator Amy Klobuchar
U.S. Senator Al Franken
U.S. Representative Tim Walz
State Senator Dan Sparks
State Senator David Senjem
State Representative Jeanne Poppe
State Representative Rich Murray
Mayor of Austin - Tom Stiehm
Mayor of Rochester – Ardell Brede
Minnesota Department of Employment & Economic Development
Austin Area Chamber of Commerce
Austin Area Foundation
Austin Convention & Visitors Bureau
BioBusiness Alliance of Minnesota
City of Austin – Austin Port Authority
GRAUC – Greater Rochester Advocates of Universities and Colleges
IBM Rochester
University of Minnesota – Rochester

Mower County
Riverland Community College
Austin Public Schools
Southern Minnesota Initiative Foundation
Karl R. Potach Foundation
Austin Bruins "Paint the Rink Pink"
Austin community's "Paint the Town Pink"
5th District Eagles Cancer Telethon
Lyle Area Cancer
AgStar – Fund for Rural America
The Hormel Institute Mentor Group
Deryl Arnold Memorial Golf Tournament
Dave "Tolly" Tollefson Memorial Golf Tournament
Fishing for a Cure
Mower County USBC Association's "Bowl for a Cure"
VFW Ladies Auxiliary
4-H Mower County
Volunteers
Estate of Carol L. Landgraf
Austin High School Youth Leadership Club "Strides for a Cure"

Sharing The Hormel Institute's Vision of
Today's **RESEARCH**
Tomorrow's **CURES**

PAINT THE TOWN PINK



SUPPORT & COLLABORATION





SIGNIFICANT CONTRIBUTIONS

DR. RALPH T. HOLMAN

1918 - 2012

Former Executive Director at The Hormel Institute
1981 Inductee to National Academy of Sciences
Named Omega 3, Omega 6 Fatty Acids



Left to right: Mike Conway, Tim Lastine, Theresa Tucker, Craig Jones

RESEARCH SUPPORT SERVICES (RSS)

Supervisor: Craig Jones

It has been another exciting year for RSS. The Linux cluster CAL42 (Computational Analysis of Life-sciences 42) has been calculating away simulating protein molecules. We have updated our network servers to virtual servers. Separating server functions to allow for a lot more flexibility by dedicating each virtual server to fewer applications, thereby reducing incompatibilities between applications and power consumption. We will be doing more server upgrades for the expansion next year.

Research Support Services continues to provide instrument maintenance as well as computer, graphics, telecommunication, network, and Internet support for The

Hormel Institute. Maintenance includes a wide variety of scientific instruments, from complex to simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our workload. As always, the security needs of the network keep us busy.

Being the building coordinator of the beautiful Hormel Institute is going to get exciting now that the Institute is moving ahead with a \$27 million expansion project supported by The Hormel Foundation, Austin Port Authority and the State of Minnesota. We will have a lot of planning to do. Not only the building, but also we will need to expand the network infrastructure to make sure it can handle the increased load. There will be 15 new laboratories to set up and all the new instrumentation that goes with them. Next year is looking to be a great year for the Institute.



Left to right: Brandon Hoium, Randy Johnson,
Duane Graff, Mark Severtson

BUILDING OPERATIONS AND MAINTENANCE

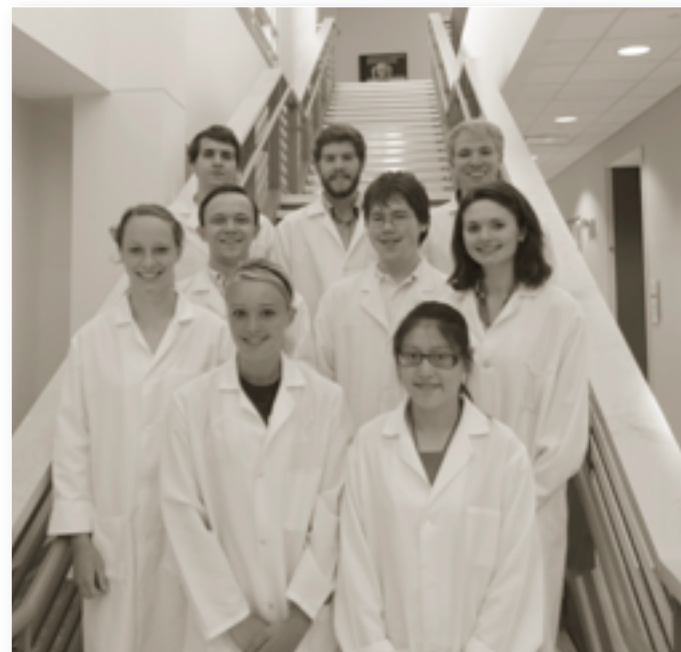
Supervisor: Mark Severtson

The maintenance support unit's main goal is to provide all personnel with a comfortable and safe working environment. Regular inspection and maintenance of all buildings and equipment is performed to assure continuous, efficient operation and comfort. All safety equipment is routinely checked to assure proper operation in the event of an emergency. This unit also is responsible for the receiving, recording and delivering of all incoming supplies and equipment delivered to The Institute. Also occasional minor laboratory and office rearrangement is done to maximize efficient use of space.

This unit has regular contact with University building and safety officials to be certain that various building alterations, repairs and functions are completed according to required code and safety regulations. Local professional tradesmen are also contacted for minor repairs or alterations necessary to keep operations running safely, smoothly and efficiently within the facility. The Building Operations and Maintenance department is very proud of our new addition and remodeled facility. We will all strive to keep it looking and operating with the upmost of efficiency.

S.U.R.E. (SUMMER UNDERGRADUATE RESEARCH EXPERIENCE)

Each year, undergraduate students are selected to work in the Summer Undergraduate Research Experience (SURE) program with The Hormel Institute scientists. Students work on research projects to expand their knowledge of basic research and learn about equipment and techniques that are not generally available in undergraduate academic programs. Each year, students are selected based on their high level of academic achievement as well as their plans to pursue careers in science-related fields.



First row: Megan Tapp, Zijie Xia
Second row: Anna Lampe, John Harringa, Alan Rice, Nicole Shatek
Third row: Logan Worke, Zach Fadness, Lucas Zellmer



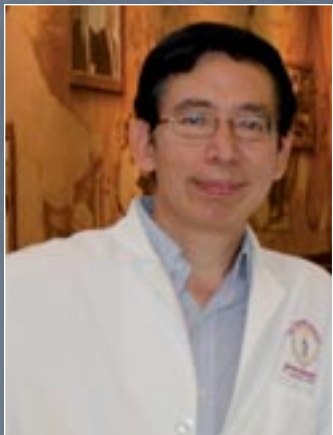
STATE OF MINNESOTA BECOMES PARTNER IN INSTITUTE'S GROWTH

The Hormel Foundation's gift of \$23 million does the following:

- Matches the State of Minnesota's bonding bill to enable Austin/The Hormel Institute to receive \$13.5 million from the state.
- Expands our new state-of-the-art cancer center and DOUBLES its size.
- Adds up to 120 new scientific research and support jobs to the Austin community.
- Provides a stronger path to commercialization opportunities for Austin and southern Minnesota.

Just to share the significance of this gift, consider:

- It is the largest gift by a foundation to a charitable organization, to the University of Minnesota.
- For ROI (Return on Investment) in supporting cancer research, The Hormel Institute for its size:
 - Has more published papers than any other cancer research organization in Minnesota.
 - Has more grant funding than any other cancer research organization in Minnesota.
 - Has the LOWEST COST of conducting cancer research than any other cancer research organization in Minnesota.
- Allows every donated dollar to go 100% directly toward funding cancer research at The Hormel Institute due to The Hormel Foundation covering administrative costs.



Dr. Zigang Dong
Executive Director of The Hormel Institute

"Our cancer research holds tremendous potential to improve cancer prevention and control protocols; that research can move forward and now grow because of The Hormel Foundation's important and critical support."



Gary Ray
Chair of The Hormel Foundation

"This is the kind of investment that Jay Hormel envisioned when he created the Foundation. The Institute is engaged in world-class, cutting-edge research into cancer prevention and treatment that benefits all of us."

THE HORMEL INSTITUTE PUBLICATIONS

JULY 1, 2012 — JUNE 30, 2013

H.I. No. 1875

Quercetin-3-methyl ether inhibits lapatinib-sensitive and -resistant breast cancer cell growth by inducing G(2)/M arrest and apoptosis. Li J, Zhu F, Lubet RA, De Luca A, Grubbs C, Ericson ME, D'Alessio A, Normanno N, Dong Z, Bode AM. *Mol Carcinog.* Feb;52(2):134-43 (2011).

H.I. No. 1876

The role of heterodimeric AP-1 protein comprised of JunD and c-Fos proteins in hematopoiesis. Lee SY, Yoon J, Lee MH, Jung SK, Kim DJ, Bode AM, Kim J, Dong Z. *J Biol Chem.* Sep 7;287(37):31342-8 (2012).

H.I. No. 1877

Aloe-emodin suppresses prostate cancer by targeting the mTOR complex 2. Liu K, Park C, Li S, Lee KW, Liu H, He L, Soung NK, Ahn JS, Bode AM, Dong Z, Kim BY, Dong Z. *Carcinogenesis* Jul;33(7):1406-11 (2012).

H.I. No. 1878

Taxifolin suppresses UV-induced skin carcinogenesis by targeting EGFR and PI3K. Oi N, Chen H, Ok Kim M, Lubet RA, Bode AM, Dong Z. *Cancer Prev Res (Phila).* Sep;5(9):1103-14 (2012).

H.I. No. 1879

Tumor necrosis factor receptor-associated factor family protein 2 is a key mediator of the epidermal growth factor-induced ribosomal S6 kinase 2/cAMP-responsive element-binding protein/Fos protein signaling pathway. Peng C, Zhu F, Wen W, Yao K, Li S, Zykova T, Liu K, Li X, Ma WY, Bode AM, Dong Z. *J Biol Chem.* Jul 27;287(31):25881-92 (2012).

H.I. No. 1880

Identification of mammalian target of rapamycin as a direct target of fenretinide both in vitro and in vivo. Xie H, Zhu F, Huang Z, Lee MH, Kim DJ, Li X, Lim do Y, Jung SK, Kang S, Li H, Reddy K,

Wang L, Ma W, Lubet RA, Bode AM, Dong Z. *Carcinogenesis* Sep;33(9):1814-21 (2012).

H.I. No. 1881

Regulatory mechanisms and clinical perspectives of miRNA in tumor radiosensitivity. Zhao L, Bode AM, Cao Y, Dong Z. *Carcinogenesis* Nov;33(11):2220-7 (2012). Review.

H.I. No. 1882

Polycomb (PcG) proteins, BMI1 and SUZ12, regulate arsenic-induced cell transformation. Kim HG, Kim DJ, Li S, Lee KY, Li X, Bode AM, Dong Z. *J Biol Chem.* Sep 14;287(38):31920-8 (2012).

H.I. No. 1883

Splicing of mouse p53 pre-mRNA does not always follow the "first come, first served" principle and may be influenced by cisplatin treatment and serum starvation. Yang M, Wu J, Wu SH, Bi AD, Liao DJ. *Mol Biol Rep.* Sep;39(9):9247-56 (2012).

H.I. No. 1884

Mitochondrial DNA polymorphisms are associated with the longevity in the Guangxi Bama population of China. Yang X, Wang X, Yao H, Deng J, Jiang Q, Guo Y, Lan G, Liao DJ, Jiang H. *Mol Biol Rep.* Sep;39(9):9123-31 (2012).

H.I. No. 1885

Pseudogenes as weaknesses of ACTB (Actb) and GAPDH (Gapdh) used as reference genes in reverse transcription and polymerase chain reactions. Sun Y, Li Y, Luo D, and Liao DJ. *Plos One* 7(8):e41659 (2012).

H.I. No. 1886

Basic anatomy and tumor biology of the RPS6KA6 gene that encodes the p90 ribosomal S6 kinase-4. Sun Y, Cao SS, Yang M, Wu SH, Wang Z, Lin XK, Song XR, and Liao DJ. *Oncogene* 32 (14): 1794-810 (2013).

H.I. No. 1887

Cyclin D1 protein plays different roles in modulating chemoresponse in MCF7 and MDA-MB231 cells. Sun Y, Luo D-Z, and Liao DJ. *J. Carcinogenesis*, DOI: 2012;11:12. doi: 10.4103/1477-3163.100401 (2012).

H.I. No. 1888

Switch of FANCL, a key FA-BRCA component, between tumor suppressor and promoter by alternative splicing. Yuan CF, Xu NZ, and Liao DJ. *Cell Cycle* 11(18): 3-4 (2012). Invited commentary.

H.I. No. 1889

Keratin 15 expressing stem cells from the hair follicles contribute to papilloma development in the mouse. Li S, Park H, Trempus CS, Gordon D, Liu Y, Cotsarelis G, and Morris RJ. *Mol. Carcinog.* 2012 Mar 16. Doi: 10.1002/mc21896, Epub ahead of print.

H.I. No. 1890

Keratinocyte stem cells and the targets for nonmelanoma skin cancer. Singh A, Park H, Kangsamaksin T, Singh A, Readio N, Morris RJ. *Photochem Photobiol.* Sep-Oct;88(5):1099-110 (2012).

H.I. No. 1891

Epicatechin-rich cocoa polyphenol inhibits kras-activated pancreatic ductal carcinoma cell growth in vitro and in a mouse model. Siddique HR, Liao DJ, Mishra SK, Schuster T, Wang L, Matter B, Campbell PM, Villalta P, Nanda S, Deng Y, Saleem M. *International Journal of Cancer* Oct 1;131(7):1720-31 (2012).

H.I. No. 1892

Interaction with Snv39H1 is critical for snail-mediated E-cadherin repression in breast cancer. Dong C, Wu Y, Wang Y, Wang C, Kang T, Rychahou PG, Chi Y-I, Evers BM, and Zhou BP. *Oncogene* 32: 1351-62 (2013).

H.I. No. 1893

MED25 is a Mediator component of HNF4-driven transcription leading to insulin secretion in pancreatic beta-cells. Han EH, Rha GB, and Chi Y-I. *PLoS One* 7: e44007 (2012).

H.I. No. 1894

Growth and progression of TRAMP prostate tumors in relationship to diet and obesity. Bonorden M, Grossmann M, Ewing S, Rogozina O, Ray A, Nkhata K, Liao DJ, Grande J and Cleary M. *Prostate Cancer* ID 543970 (2012). Epub 2012 Dec 4.

H.I. No. 1895

Combination of intermittent calorie restriction and eicosapentaenoic acid for inhibition of mammary tumors. Mizuno N, Rogozina O, Seppanen C, Liao DJ, Cleary M, Grossmann M. *Cancer Prev. Res. (Phila).* Jun;6(6):540-7 (2013).

H.I. No. 1896

New methods as alternative or corrective measures for the pitfalls and artifacts of reverse transcription and polymerase chain reactions (RT-PCR) in cloning chimeric or antisense-accompanied RNA. Yuan CF, Liu YM, Yang M, and Liao DJ. *RNA Biology.* Apr 16;10(6) (2013).

H.I. No. 1897

The S100A4 oncoprotein promotes prostate tumorigenesis in a transgenic mouse model regulating NF B through the RAGE receptor. Siddique H, Adhami V, Parray A, Johnson J, Siddique I, Sheikhan M, Murtaza I, Ambartsumian N, Konety B, Mukhtar H, Saleem M. *Genes & Cancer* June 6, 2013, doi: 10.1177/1947601913492420. [Epub ahead of print]

H.I. No. 1898

BMI1, stem cell factor acting as novel serum-biomarker for Caucasian and African-American prostate cancer. Siddique H, Parray A, Zhong W, Kames R, Bergstrahl E, Koochekpour S, Rhim J, Konety B, Saleem M. *PLoS One* 8(1):e52993 (2013).

H.I. No. 1899

BMI1 polycomb group protein acts as a master switch for growth and death of tumor cells: regulates TCF4-transcriptional factor-induced BCL2 signaling. Siddique H, Parray A, Tarapore RS, Wang L, Mukhtar H, Kames RJ, Deng Y, Konety BR, Saleem M. *PLoS One.* May 6;8(5):e60664 (2013).

H.I. No. 1900

Androgen receptor in human health: a potential therapeutic target. Siddique HR, Nanda S, Parray A, Saleem M. *Curr Drug Targets* Dec;13(14):1907-16 (2012).

H.I. No. 1901

Castration-resistant prostate cancer: potential targets and therapies. Parray A, Siddique H, Nanda S, Konety B, Saleem M. *Biologics* 6:267-76 (2012).

H.I. No. 1902

The glycolipid transfer protein (GLTP) domain of phosphoinositol 4-phosphate adaptor protein-2 (FAPP2): structure drives preference for simple neutral glycosphingolipids. Kamlekar R, Simanshu D, Gao Y, Kenoth R, Pike H, Prendergast F, Malinina L, Molotkovsky J, Venyaminov S, Patel D, Brown R. *Biochim. Biophys. Acta* 1831, 417-427 (2013).

H.I. No. 1903

Structural insights into lipid-dependent reversible dimerization of human GLTP. Samyagina V, Ochoa-Lizarralde B, Popov A, Cabo-Bilbao A, Goni-de-Cerio F, Molotkovsky J, Patel D, Brown R, Malinina L. *Acta Cryst.* D69, 603-616 (2013).

H.I. No. 1904

GLTP-fold interaction with planar phosphatidylcholine surfaces is synergistically stimulated by phosphatidic acid and phosphatidylethanolamine. Zhai X, Momsen W, Malakhov D, Boldyrev I, Momsen M, Molotkovsky J, Brockman H, Brown R. *J. Lipid Res.* 54, 1103-1113 (2013).

H.I. No. 1905

An expedient synthesis of fluorescent labeled ceramide-1-phosphate analogues. Boldyrev I, Brown R, Molotkovsky J. *Russ. J. Bioorganic Chem.* 39, 539-542 (2013).

H.I. No. 1906

Nonvesicular trafficking by ceramide-1-phosphate transfer protein regulates eicosanoids. Simanshu D, Kamlekar R, Wijesinghe D, Zou X, Zhai X, Mishra S, Molotkovsky J, Malinina L, Hinchcliffe

- E, Chalfant C, Brown R, Patel D. *Nature* 500, 463-467 (2013).
- H.I. No. 1907
Specification of hepatopancreas progenitors in zebrafish by hnf1ba and wnt2bb. Lancman J, Zvenigorodsky N, Gates K, Zhang D, Solomon K, Humphrey R, Kuo T, Setiawan L, Verkade H, Chi Y-I, Jhala U, Wright C, Stainier D, Dong Z. *Stem Cells and Regeneration Development* 140, 1669-1679 (2013).
- H.I. No. 1908
Crystal structure of 3WJ core revealing divalent ion-promoted thermostability and assembly of the Phi29 hexameric motor pRNA. Zhang H, Endrizzi J, Yi S, Haque F, Sauter C, Shylakhtenko L, Lyubchenko Y, Guo P, and Chi Y-I. *RNA* 19:1226-1237 (2013).
- H.I. No. 1909
The balance between leptin and adiponectin in the control of carcinogenesis- focus on mammary tumorigenesis. Grossmann M and Cleary M. *Biochimie* 94:2164-2171 (2012).
- H.I. No. 1910
The protective effect of intermittent calorie restriction on mammary tumorigenesis is not compromised by consumption of a high fat diet during refeeding. Rogozina O, Nkhata K, Nagle E, Grande J and Cleary M. *Breast Cancer Res Treat.* 138:395-406 (2013).
- H.I. No. 1911
65,000 shades of grey: use of digital image files in light microscopy. Shaw S and Hinchcliffe E. *Methods in Cell Biology* 114:317-36 (2013).
- H.I. No. 1912
Post-processing for statistical image analysis in light microscopy. Cardullo R and Hinchcliffe E. *Methods in Cell Biology* 114:285-315 (2013).
- H.I. No. 1913
Aberrant overexpression of IL-15 initiates large granular lymphocyte leukemia through chromosomal instability and DNA hypermethylation.
- Mishra A, Liu S, Sams G, Curphey D, Santhanam R, Rush L, Schaefer D, Falkenberg L, Sullivan L, Jarosnyk L, Yang X, Fisk H, Wu L, Hickey C, Chandler J, Wu Y, Heerema N, Chan K, Perotti D, Zhang J, Porcu P, Racke F, Garzon R, Lee R, Marcucci G, Caligiuri M. *Cancer Cell* Nov 13;22(5):645-55 (2012).
- H.I. No. 1914
Reactivation of RASSF1A in breast cancer cells by curcumin. Du L, Xie Z, Wu L, Chiu M, Lin J, Chan K, Liu S, Liu Z. *Nutr Cancer* 64(8):1228-35 (2012).
- H.I. No. 1915
Epigenetics advancing personalized nanomedicine in cancer therapy. Liu S. *Adv Drug Deliv Rev.* Oct;64(13):1532-43 (2012).
- H.I. No. 1916
Curcumin down-regulates DNA methyltransferase 1 and plays an anti-leukemic role in acute myeloid leukemia. Yu J, Peng Y, Wu L, Xie Z, Deng Y, Hughes T, He S, Mo X, Chiu M, Wang Q, He X, Liu S, Grever M, Chan K, Liu Z. *PLoS One* 8(2):e55934 (2013).
- H.I. No. 1917
Studies on the origins of non-melanoma skin cancer in mice. Singh A, Park H, and Morris RJ. *Photochem. Photobiol.* 88:1099-1110 (2012). Invited peer-reviewed article.
- H.I. No. 1918
Innate immunity and the mobilization of keratinocyte stem cells: have the old players entered a new game? Singh A and Morris R. *Exp. Dermatol.* 21:660-664 (2012).
- H.I. No. 1919
CDK2 and mTOR are direct molecular targets of isoangustone A in the suppression of human prostate cancer cell growth. Lee E, Son J, Byun S, Lee S, Kim Y, Liu K, Kim J, Lim S, Park J, Dong Z, Lee KW, Lee HJ. *Toxicol Appl Pharmacol.* May 22;272(1):12-20 (2013).
- H.I. No. 1920
Discovery of the novel mTOR inhibitor and its antitumor activities in vitro and in vivo. Xie H, Lee MH, Zhu F, Reddy K, Huang Z, Kim DJ, Li Y, Peng C, Lim do Y, Kang S, Jung SK, Li X, Li H, Ma W, Lubet R, Ding J, Bode AM, Dong Z. *Mol Cancer Ther.* Jun;12(6):950-8 (2013).
- H.I. No. 1921
Tyrosylprotein sulfotransferase-1 and tyrosine sulfation of chemokine receptor 4 are induced by Epstein-Barr virus encoded latent membrane protein 1 and associated with the metastatic potential of human nasopharyngeal carcinoma. Xu J, Deng X, Tang M, Li L, Xiao L, Yang L, Zhong J, Bode AM, Dong Z, Tao Y, Cao Y. *PLoS One* 8(3):e56114 (2013).
- H.I. No. 1922
Signal transduction and molecular targets of selected flavonoids. Bode AM, Dong Z. *Antioxid Redox Signal.* Jul 10;19(2):163-80 (2013).
- H.I. No. 1923
Autophagy and cellular senescence mediated by Sox2 suppress malignancy of cancer cells. Cho YY, Kim DJ, Lee HS, Jeong CH, Cho EJ, Kim MO, Byun S, Lee KY, Yao K, Carper A, Langfald A, Bode AM, Dong Z. *PLoS One* 8(2):e57172 (2013).
- H.I. No. 1924
Direct targeting of MEK1/2 and RSK2 by silybin induces cell-cycle arrest and inhibits melanoma cell growth. Lee MH, Huang Z, Kim DJ, Kim SH, Kim MO, Lee SY, Xie H, Park SJ, Kim JY, Kundu JK, Bode AM, Surh YJ, Dong Z. *Cancer Prev Res (Phila).* May;6(5):455-65 (2013).
- H.I. No. 1925
Tumor suppressor p16(INK4a) inhibits cancer cell growth by downregulating eEF1A2 through a direct interaction. Lee MH, Choi BY, Cho YY, Lee SY, Huang Z, Kundu JK, Kim MO, Kim DJ, Bode AM, Surh YJ, Dong Z. *J Cell Sci.* Apr 15;126(Pt 8):1744-52 (2013).
- H.I. No. 1926
Sunlight UV-induced skin cancer relies upon activation of the p38alpha signaling pathway. Liu K, Yu D, Cho YY, Bode AM, Ma W, Yao K, Li S, Li J, Bowden GT, Dong Z, Dong Z. *Cancer Res.* Apr 1;73(7):2181-8 (2013).
- H.I. No. 1927
ClnQ-03, a novel allosteric MEK inhibitor, suppresses cancer growth in vitro and in vivo. Kim DJ, Lee MH, Reddy K, Li Y, Lim do Y, Xie H, Lee SY, Yeom YI, Bode AM, Dong Z. *Carcinogenesis* May;34(5):1134-43 (2013).
- H.I. No. 1928
Oligomycin A enhances apoptotic effect of TRAIL through CHOP-mediated death receptor 5 expression. He L, Jang JH, Choi HG, Lee SM, Nan MH, Jeong SJ, Dong Z, Kwon YT, Lee KS, Lee KW, Chung JK, Ahn JS, Kim BY. *Mol Carcinog.* Feb;52(2):85-93 (2013).
- H.I. No. 1929
20-O-beta-d-glucopyranosyl-20(S)-protopanaxadiol, a metabolite of ginseng, inhibits colon cancer growth by targeting TRPC channel-mediated calcium influx. Hwang JA, Hwang MK, Jang Y, Lee EJ, Kim JE, Oh MH, Shin DJ, Lim S, Ji Go, Oh U, Bode AM, Dong Z, Lee KW, Lee HJ. *J Nutr Biochem.* Jun;24(6):1096-104 (2013).
- H.I. No. 1930
Association between PIN1 promoter polymorphisms and risk of nasopharyngeal carcinoma. Lu Y, Huang GL, Pu XX, He YX, Li BB, Liu XY, Dong Z, He Z. *Mol Biol Rep.* May;40(5):3777-82 (2013).
- H.I. No. 1931
(-)-Epigallocatechin-3-gallate inhibition of Epstein-Barr virus spontaneous lytic infection involves ERK1/2 and PI3-K/Akt signaling in EBV-positive cells. Liu S, Li H, Chen L, Yang L, Li L, Tao Y, Li W, Li Z, Liu H, Tang M, Bode AM, Dong Z, Cao Y. *Carcinogenesis* Mar;34(3):627-37 (2013).
- H.I. No. 1932
Src kinase is a direct target of apigenin against UVB-induced skin inflammation. Byun S, Park J, Lee E, Lim S, Yu JG, Lee SJ, Chen H, Dong Z, Lee KW, Lee HJ. *Carcinogenesis* Feb;34(2):397-405 (2013).
- H.I. No. 1933
Structural and functional analysis of the natural JNK1 inhibitor quercetin.
- Baek S, Kang NJ, Popowicz GM, Arciniega M, Jung SK, Byun S, Song NR, Heo YS, Kim BY, Lee HJ, Holak TA, Augustin M, Bode AM, Huber R, Dong Z, Lee KW. *J Mol Biol.* Jan 23;425(2):411-23 (2013).
- H.I. No. 1934
Identification of an Aurora kinase inhibitor specific for the Aurora B isoform. Xie H, Lee MH, Zhu F, Reddy K, Peng C, Li Y, Lim do Y, Kim DJ, Li X, Kang S, Li H, Ma W, Lubet RA, Ding J, Bode AM, Dong Z. *Cancer Res.* Jan 15;73(2):716-24 (2013).
- H.I. No. 1935
Ceftriaxone, an FDA-approved cephalosporin antibiotic, suppresses lung cancer growth by targeting Aurora B. Li X, Li H, Li S, Zhu F, Kim DJ, Xie H, Li Y, Nadas J, Oi N, Zykova TA, Yu DH, Lee MH, Kim MO, Wang L, Ma W, Lubet RA, Bode AM, Dong Z, Dong Z. *Carcinogenesis* Dec;33(12):2548-57 (2012).
- H.I. No. 1936
RSK2 as a key regulator in human skin cancer. Cho YY, Lee MH, Lee CJ, Yao K, Lee HS, Bode AM, Dong Z. *Carcinogenesis* Dec;33(12):2529-37 (2012).
- H.I. No. 1937
Effect of intermittent dosing regimens of erlotinib on methylnitrosourea-induced mammary carcinogenesis. Lubet RA, Szabo E, Iwata KK, Gill SC, Tucker C, Bode AM, Steele VE, Juliana MM, Nicastro HL, Grubbs CJ. *Cancer Prevention Research* May;6(5):448-54 (2013).
- H.I. No. 1938
UVB-induced COX-2 expression requires histone H3 phosphorylation at Ser10 and Ser28. Keum YS, Kim HG, Bode AM, Surh YJ, Dong Z. *Oncogene* Jan 24;32(4):444-52 (2013).

THE HORMEL INSTITUTE SEMINARS

JULY 1, 2012 — JUNE 30, 2013

Priyabrata Mukherjee, Ph.D.

Mayo Clinic

August 8th, 2012

"Self-Therapeutic Nanoparticle: An Emerging Concept in Nanomedicine"

Hosted by: Dr. Zigang Dong and Dr. Ann Bode

Shafiq A. Khan, Ph.D. Mayo Clinic

School of Biology, Georgia Institute of Technology

August 13th, 2012

"TGF β signaling during different stages of prostate cancer"

Hosted by: Dr. Mohammad Saleem Bhat

Kun Ling, Ph.D. Mayo Clinic

Mayo Clinic

August 15th, 2012

"Role of PtdIn4,5P2 Signaling in Cancer Progression"

Hosted by: Dr. Zigang Dong and Dr. Ann Bode

Liang Wang, M.D., Ph.D.

University of North Dakota

August 16th, 2012

Medical College of Wisconsin

"Genetic Markers of Human Cancers for Risk Assessment, Early Detection and Outcome Prediction"

Hosted by: Dr. Zigang Dong and Dr. Ann Bode

Ningling Kang, Ph.D.

Mayo Clinic

August 16th, 2012

"Regulation of the Prometastatic Liver Microenvironment by Stellate Cell Cytoskeleton Regulatory Proteins"

Hosted by: Dr. Zigang Dong and Dr. Ann Bode

Laura Hansen, Ph.D.

Creighton University School of Medicine

August 31st, 2012

"ADAM12 and HER2 in squamous cell carcinoma"

Hosted by: Dr. Zigang Dong

David M. Owens, Ph.D.

"Regulation of Merkel cell homeostasis in the adult skin"

Columbia University Medical Center

September 4th, 2012

Hosted by: Dr. Zigang Dong and Dr. Rebecca Morris



INCOME FROM GRANTS AND CONTRACTS

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

<i>Anticarcinogenic Mechanisms of Tea Constituents (Z. Dong)</i>	\$187,169
<i>Chemoprevention of Skin Cancer (Z. Dong)</i>	\$70,828
<i>Prevention of PTEN Deletion Driven Prostate Cancer by Selenium (Y. Deng)*</i>	
<i>Prevention of Mammary Tumors by Metformin in Comparison to Calorie Restriction (M. Cleary)</i>	\$207,500
<i>Gain of Function Mutant p53 Telomere Uncapping-Driven Breast Tumorigenesis (Y. Deng)</i>	\$207,500
<i>Bioactive Compound Modulation of Epigenetic Regulator Sp1/NFkB/miR Network in AML (S. Liu)</i>	\$27,116
<i>Targeting Aberrant Epigenetics by Nanomedicine (S. Liu)</i>	\$242,511
<i>Molecular Mechanisms and Targets of Soy Compounds in Colon Cancer (Z. Dong)</i>	\$61,152
<i>Developing New Ornithine Decarboxylase Inhibitors to Prevent Skin Cancer (Z. Dong)</i>	\$103,750

National Institute of Environmental Health Sciences

<i>The Role of Histone Phosphorylation in Arsenic-induced Cell Transformation and Cancer (Z. Dong)</i>	\$225,000
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National Institute of General Medical Sciences

<i>Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown)</i>	\$250,000
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National Institute of Arthritis and Musculoskeletal and Skin Diseases

<i>Identification of a Keratinocyte Stem Cell Regulatory Gene (R. Morris)</i>	\$227,079
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American Cancer Society

<i>Translational Regulation of p53 Induction in Response to Cellular Stress (D. Yang)</i>	\$17,500
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National Multiple Sclerosis Society

<i>Regulation of T Cell Subset Differentiation by Epidermal Fatty Acid by E-FABP (B. Li)</i>	\$126,906
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American Diabetes Association

<i>Structural and Functional Studies of HNF 1alpha and HNF 4alpha (Y. Chi)</i>	\$142,500
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Department of Defense – U.S. Army

<i>RNA Chimeras as a Gene Signature of Breast Cancer (D.J. Liao)</i>	\$265,467
<i>A Novel Mechanism for the Pathogenesis of Non-melanoma Skin Cancer (Morris)</i>	\$200,000

AgStar Fund for Rural America

<i>AgStar Research Project (A. Bode)</i>	\$10,000
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Clark Atlanta University

<i>Interaction of Transcriptional Activators and Factors (Bhat)</i>	\$7,900
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University of Alabama at Birmingham

<i>Preclinical in vitro and in vivo Agent Development Assays (Bode)</i>	\$27,049
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United Soybean Board (Z. Dong)

\$15,000

Pediatric Pharmaceuticals

*Ginger as an Anti-cancer Agent (A. Bode) **

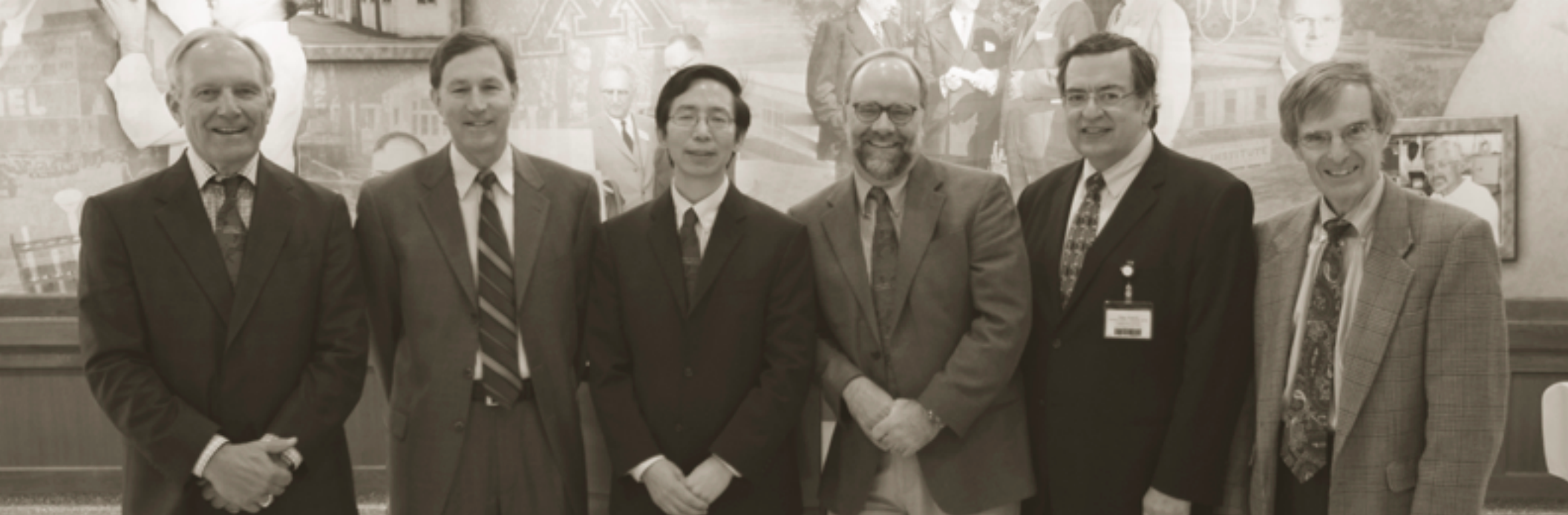
Other Resources

<i>The Hormel Foundation</i>	\$3,983,592
<i>University of Minnesota</i>	\$447,563
<i>Indirect Cost Return</i>	\$1,177,436
<i>Eagles Cancer Telethon</i>	\$165,000
<i>Mayo Clinic Collaborative Donation</i>	\$1,000,000
<i>Other Resources</i>	\$489,257

Total

\$9,854,775

* Full award amount stated in previous report



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