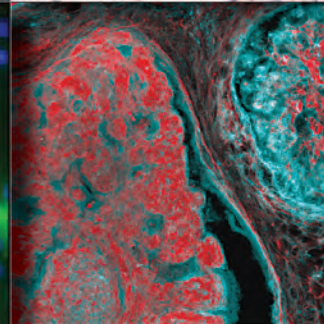
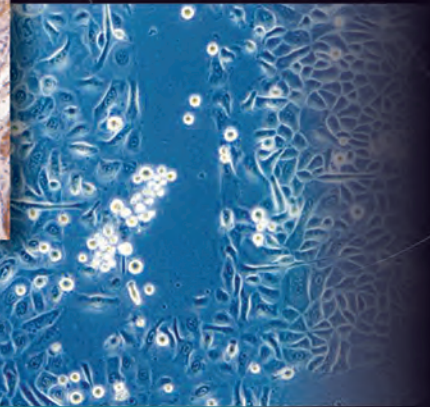
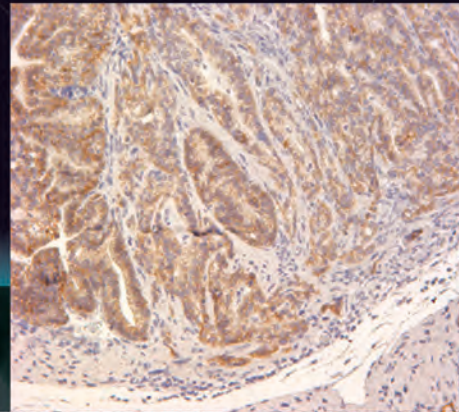


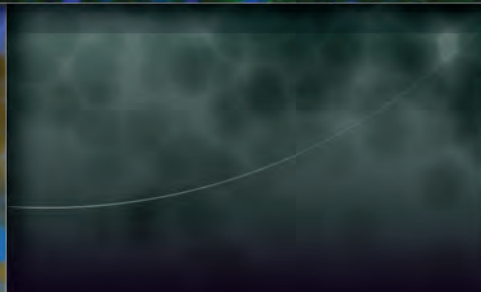
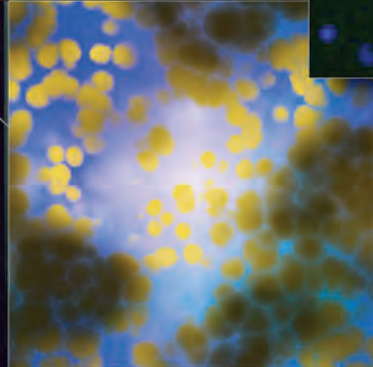
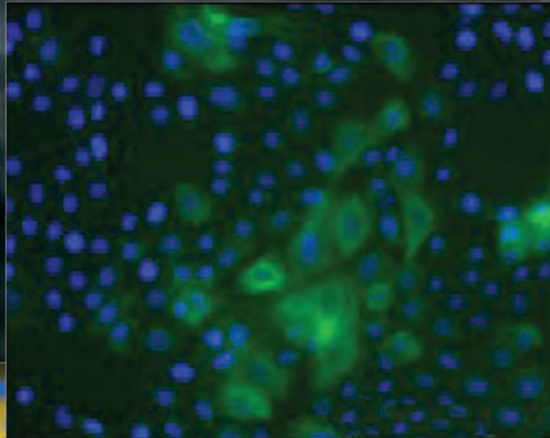
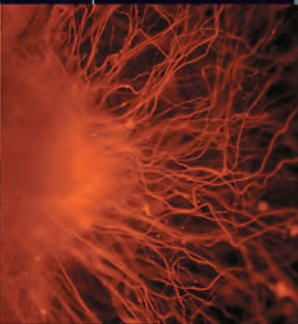
# THE HORMEL INSTITUTE

UNIVERSITY OF MINNESOTA

09-10 ANNUAL REPORT



IMPROVE THE HEALTH OF THE WORLD



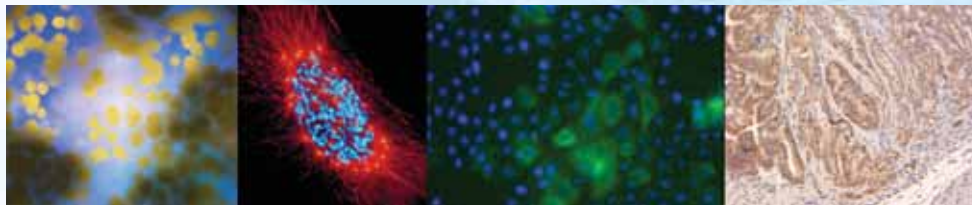


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The mission of The Hormel Institute is to conduct research and provide education in the biological sciences with applications in medicine and agriculture. In pursuit of this mission, and as intended by its founders, The Hormel Institute generates fundamental 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.



MESSAGE FROM THE DIRECTOR  
DR. ZIGANG DONG

In the United States, despite overall decreases in incidence and mortality, cancer continues to devastate the lives of many Americans. Approximately 41% of Americans will be diagnosed with cancer at some point in their lives and about 21% will die from cancer. Cancer is a leading cause of death worldwide. In contrast to the situation in America, deaths from cancer worldwide are projected to continue to rise with an estimated 12 million deaths by 2030. Cancer is one of the major physical, social and economic burdens and public health threats worldwide. The Hormel Institute continues to focus its work on cancer research.

The Hormel Institute was one of the first to report the discovery of key molecular targets and mechanisms of tumor promotion and carcinogenesis. The Hormel Institute continues to enjoy its leadership in the scientific field showing that dietary factors modulate crucial cellular signal transduction pathways in cancer development and prevention. As a leading research institute, The Hormel Institute is making a major contribution to the identification and characterization of natural chemopreventive agents that are highly effective with fewer side effects.

By focusing on cancer, The Hormel Institute has experienced a continual increase in external research funding even in the national environment of overall decreased funding for research.

In October 2009, The Hormel Institute and Central South University of China hosted the "2009 China-U.S. Forum on Frontiers of cancer research: focus on prevention" in Changsha, China. More than 100 scientists and top officers from both countries attended the meeting and discussed their findings for more effective prevention of human cancer. The attendance of experts from the public health field

made the conference very productive.

The University of Minnesota regards The Hormel Institute as one of the research units that will help the University reach its goal of becoming one of the top three public research universities in the world. "The expansion of The Hormel Institute builds on the momentum of the past decade at the University of Minnesota," said Dr. Robert Bruininks, President of the University of Minnesota. "Our state has the second most vibrant biomedical sciences corridor in the country, and the groundbreaking research conducted at The Hormel Institute and in our laboratories statewide will continue to make vital contributions to the treatment and prevention of cancer and other chronic diseases, as well as Minnesota's economy and quality of life."

One of the important collaborations includes an effort between The Hormel Institute, the U of M Supercomputing Institute, and IBM to identify and delineate key protein-protein interactions and protein-small molecule interactions by computer simulation and then to validate the interaction in vivo. In collaboration with IBM, The Hormel Institute became the first research facility (January 2008) in the state of Minnesota to own the world's most powerful supercomputer: the IBM BlueGene/L. The purchase of the BlueGene/L is the first step in establishing an International Center for Research Technology (ICRT) to be housed at The Hormel Institute in Austin, Minnesota, in collaboration with The Development Corporation of Austin (DCA), MN. The second step is also complete with the addition of a protein crystallography laboratory including robotics and a diffraction lab. The third step should be completed in early 2011 with the addition of a mass spectroscopy facility. The ICRT will provide the most cutting edge tools of technology available today to researchers working at biobusinesses, medical centers, colleges and universities in



the southern region and statewide. In particular, the ICRT will work with manufacturers of technology, like IBM Rochester, to develop new technologies to accelerate discovery and facilitate comprehensive study of human disease by combining analyses of protein structure/function with advanced methods of data management and drug screening. The ICRT will also work with smaller biobusinesses in the state and region to provide consultation and services. The net result will be a greater understanding of biological systems for improving the quality of life in Minnesota, the nation, and the world, and a dramatic, positive impact on economic development in Bioscience and Biotechnology for the state of Minnesota. During this last fiscal year, U.S. Congressman Tim Walz visited The Hormel Institute twice and showed very strong support to the Institute by acquiring funding of almost \$2 million toward the purchase of the high-end instrumentation in establishing the ICRT. The Hormel Institute and Mayo Clinic are working to establish an Office of Translational Research onsite at The Hormel Institute. The purpose of this office will be to facilitate movement of basic research findings into the clinic.

All of these accomplishments would not be possible without the generous ongoing support of The Hormel Foundation and Hormel Foods. In particular, I would like to thank Mr. Richard Knowlton for his continued interest and support of the Institute, Mr. Joel Johnson, Mr. Jeff Ettinger, Mr. Gary Ray and Dr. Phil Minerich for their generous support, and Dr. Robert Bruininks and Dr. Tim Mulcahy for their leadership and support. We thank Dr. Hugh Smith, Dr. Glenn Forbes, and Mayo Clinic for their support. We thank our elected leaders, U.S. Representative Tim Walz, U.S. Senator Amy Klobuchar, Minnesota State Senator Dan Sparks, and Minnesota State Representative Jeanne Poppe. The Hormel Institute is a team project. By working together, we will win the war against cancer and achieve the goal of a cancer-free world.

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“By working together, we will win the war against cancer and achieve the goal of a cancer-free world.”

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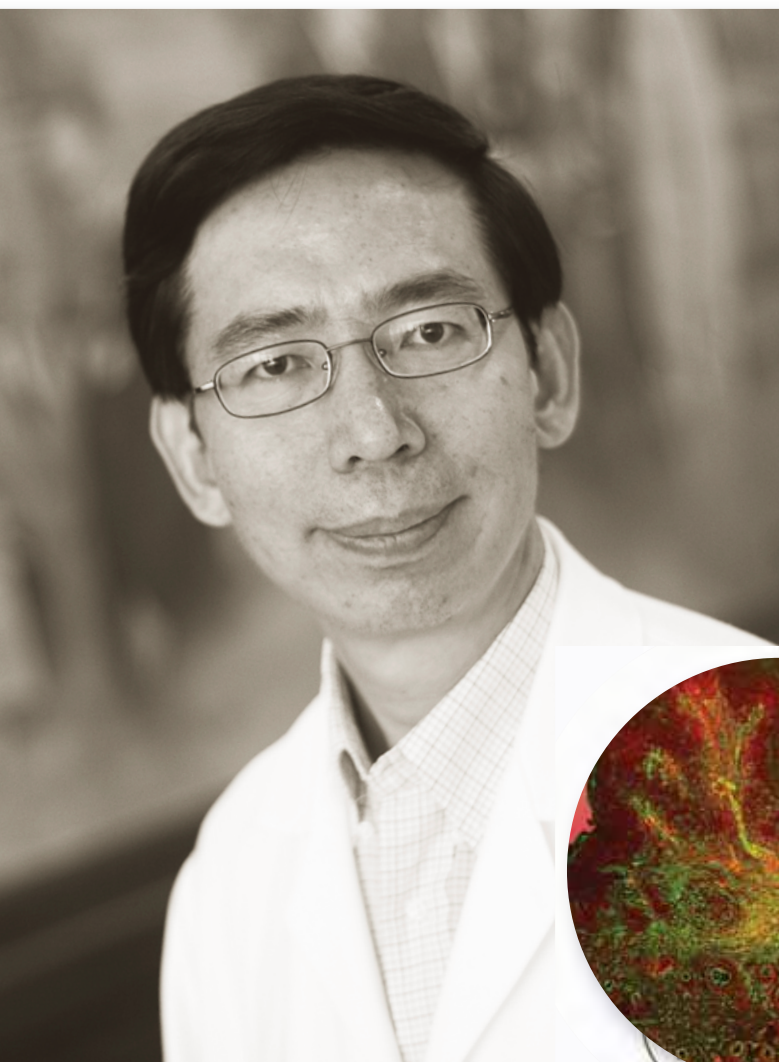
## CELLULAR AND MOLECULAR BIOLOGY

Executive Director/Section Leader

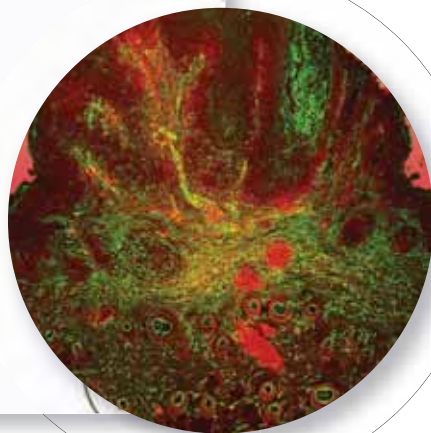
Zigang Dong, M.D., Dr. P.H.

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 death in today's world. The prevailing thought today is that cancer can be prevented or treated by targeting specific cancer genes, signaling proteins and transcription factors. By focusing on the molecular mechanisms explaining how normal cells can undergo neoplastic transformation induced by tumor promoters, we have discovered that several specific transcription factors and protein kinases 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 is the number one cancer in the terms of incidence in the USA. The major etiological factor of human skin cancer is the chronic exposure to UV light from sun. UV irradiation is categorized by wavelength as UVA I (340-400 nm), UVA II (320-340 nm), UVB (280-320 nm), and UVC (180-280 nm). In mouse skin, UV light acts as both an initiator, presumably by causing DNA damage leading to gene mutations, and as a tumor promoter. The mechanisms behind the tumor promoting ability of UV are areas of intense study in our laboratory. 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, cannabinoid receptor 1/2 (CB1/2), epidermal growth factor receptor (EGFR), 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- $\kappa$ B), 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 promotion induced apoptosis and cancer formation.

The transient receptor potential channel vanilloid subfamily 1 (TRPV1) belongs to a diverse family of proteins comprised of non-selective cation channels. The TRPV1 is not only expressed in neuronal tissues, but has also been detected in epidermis, dermal blood vessels, normal human keratinocytes, mast cells, appendage epithelial structures, human cultured fibroblasts, human hair follicles, human lung BEAS-2B cells, and HaCaT cells, but the function of TRPV1 in non-neuronal cells and tissues is unclear. Notably, the absence of TRPV1 in mice results in a striking increase in skin carcinogenesis.





Because of their analogous expression in apparently almost every tissue, JNK1 and JNK2 have most often been considered to have overlapping or redundant functions. However, JNK1 deficient mice develop more UVA-induced papillomas than either JNK wildtype or JNK2 deficient mice supporting a specific role for JNK1 and JNK2 in tumorigenesis.

Another major goal of our section is to identify anticancer agents that have low toxicity with fewer adverse side effects, which may be used alone or in com-

**“Cancer is a deadly disease that can happen in men and women, black and white, rich and poor, people in developed and developing countries.”**

(Left to right) Left bench: Chul Ho Jeong, K. Srinivasa Reddy, Eunjin Cho, Sung Young Lee

Right bench: Tao Yin (Andy) Lau, Zunnan Huang, Hanyong Chen

First row: Alyssa Langfald, Margarita Malakhova, Yong Yeon Cho, Zigang Dong, Ann Bode, Naomi Oi, Nu Ry Song, Kun Yeong Lee, MyoungOk Kim, MeeHyun Lee, Soouk Kang, Tatyana Zykova, Dasha Urusova, Lisa Wester (Intern)

Second row: Sung Keun Jung, Jonathon Wilson (Intern), Dong-Joon Kim, Katie Hoff (Intern), Dong Hoon Yu, Weihong (Wendy) Wen, Hong-Gyum Kim, Xiang Li, Jixia Li, Shengqing Li, Wei-Ya Ma, Priya Rathinaswamy

Last row: Tae-gyu Lim, Jinhwan Choi, Yan Li, Janos Nadas, Cong Peng, Haitao Li

Not pictured: Ke Yao, Feng Zhu, Young-Sam Keum, Sung-Hyun Kim, Honglin Li, Kang Dong Liu, Madhu Mottamal, Angelo Pugliese, Yanming Xu, Ji-Shuai Zhang, Andria Carper

bination with traditional chemotherapeutic agents to prevent or treat cancer. Many dietary factors have potent anticancer activities that work through, as yet, unknown mechanisms. Various dietary factors, including many isolated from green and black tea, potatoes, broccoli, peanuts, ginger root and rice, can have effects on key signaling molecules crucial in cancer development and prevention.



Over the last few years, our laboratory has shown that various specific kinases and their target substrates appear to exhibit a distinctive activity or higher expression in cancer tissues compared to normal tissues; and therefore might be excellent targets for chemopreventive agents. These proteins include vimentin, glucose-regulated protein 78 (GRP78), insulin-like growth factor receptor 1 (IGF-1R), paxillin, T-LAK cell-originated protein kinase (TOPK), c-Jun N-terminal Kinase 2, the zeta chain associated protein of 70 kDa (ZAP-70), cyclin-dependent kinase 3 (Cdk3), CB1/2, C-terminal Src kinase (CSK), the transient receptor potential channel vanilloid subfamily 1 (TRPV1), extracellular signal-regulated kinase 8 (ERK8) and NIMA-related kinase 6 (NEK6).

TOPK is overexpressed in highly proliferating tumors such as leukemias and myelomas, and appears to play a key role in tumorigenesis or metastasis. Cell lines expressing high levels of TOPK are more resistant to arsenite-induced apoptosis than cell lines with low TOPK expression. TOPK is also highly expressed in human colorectal cancer tissues and cell lines and plays an important role in the transformation of colorectal cancer. TOPK promotes transformation in vitro and in vivo and knockdown of TOPK in HCT116 colorectal cancer cells reduces this cell line's tumorigenic properties in vitro and in vivo. TOPK can phosphorylate Prx1 at Ser32 to prevent UVB-induced cell death.

ZAP-70 is a Syk (spleen tyrosine kinase) family tyrosine kinase, which is associated with the  $\zeta$  subunit of the T cell receptor (TCR). The ZAP-70 protein is primarily expressed in T and natural killer (NK) cells and plays an essential role in signaling through the T cell antigen receptor. Notable, ZAP-70 is highly expressing in leukemias.

Cdk3, a member of the cdk family of kinases, plays a critical role in cell cycle regulation and is involved in G0-G1 and G1-S cell cycle transitions. Cdk3 is overexpressed in glioblastoma tissue and various cancer cell lines.

CSK can bind with c-Jun and phosphorylate c-Jun at Y26 and Y170. Phosphorylation of c-Jun by CSK, opposite to JNK1 and ERKs, promoted its degradation and reduces c-Jun stability. By promoting c-Jun degradation, CSK helps to maintain a low steady-state level of c-Jun and inhibits AP-1 activity and cell transformation caused by c-Jun, and thus controls cell proliferation under normal growth conditions. A loss of functional CSK is related to increase carcinogenesis.

We have carefully studied the regulatory mechanism of RSK activity. We found that the N-terminal kinase domain of RSK2 plays a key role in substrate phosphorylation. Our data suggest that RSK2 may be a good target for cancer prevention or treatment. These data were featured as a cover story in *Cancer Research*.

We have also focused on the effects of tea in inhibiting carcinogenesis. We have reported that (-)-epigallocatechin-3-gallate (EGCG) from green tea or theaflavins (TFs) from black tea inhibit tumor promoter induced AP-1, NF $\kappa$ B activation, MAP kinase activation and cell transformation. Searching for the EGCG "receptor" or high affinity proteins that bind to EGCG is the first step in understanding the molecular and biochemical mechanism of the anticancer effects of tea polyphenols. Recently, we identified the intermediate filament protein, vimentin, GRP78, ZAP-70, and insulin-like growth factor receptor 1 (IGF-1R), as novel EGCG-binding proteins. Intermediate filament (IF) proteins, such as vimentin, have an important functional involvement in cell division and proliferation. EGCG has been reported to inhibit cell proliferation of a variety of cell lines and in our work, when vimentin expression was suppressed, cell growth was inhibited.

We have teamed with IBM and its Blue Gene group under the leadership of Mike Good and the University of Minnesota Super Computing Institute to use the world's fastest supercomputer to understand complex diseases like cancer and to screen anticancer drugs for cancer prevention and treatment. In collaboration with Dr. Paul Limburg (Mayo Clinic Rochester), we will conduct clinical trials to use cancer preventive agents developed in our Institute. We have systematically studied and identified key protein kinases that directly phosphorylate p53 and histone proteins.

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 extensively utilized 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.

Nutritional or dietary factors have attracted a great deal of interest because of their perceived ability to act as highly effective chemopreventive agents. They are perceived as being generally safe and may have efficacy as chemopreventive agents by preventing or reversing premalignant lesions and/or reducing second primary tumor incidence. Many of these compounds appear to act on multiple tumor promoter-stimulated cellular pathways. Some of the most interesting and well-documented are resveratrol and components of tea, EGCG, theaflavins and caffeine. Other potentially effective dietary compounds include myricetin, gingerol, and luteolin. 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 are also 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, long-term effectiveness and safety of these compounds as chemopreventive agents.

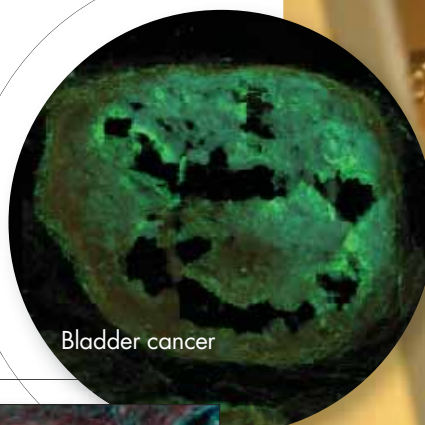
*Other Professional Activities*  
Zigang Dong

Grant Reviewer

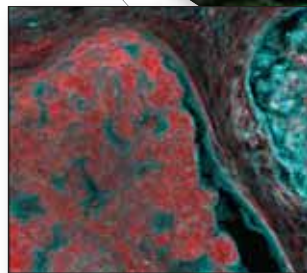
- National Institutes of Health

Editor, Associate Editor or Editing Board Member

- Cancer Research
- Cancer Prevention Research
- Molecular Carcinogenesis
- Carcinogenesis
- International Journal of Biological Sciences
- Food Factors



Bladder cancer



Colon cancer



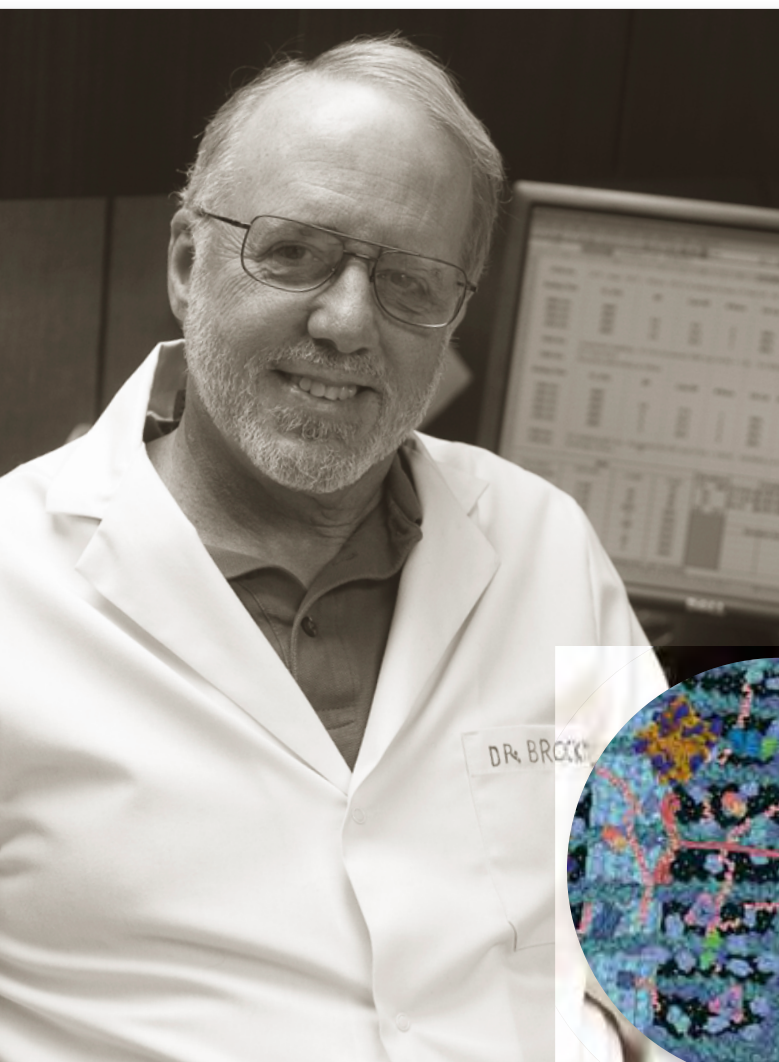


## BIOPHYSICS

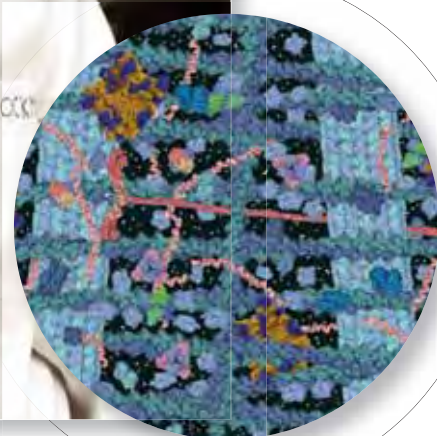
Section Leader

Howard L. Brockman, Ph.D.

Professor



Cytosol is the fluid portion of a cell's cytoplasm exclusive of organelles and membranes.



Our lab's main research interest is elucidation of interfacial structure and regulation of enzyme catalyzed reactions occurring at interfaces: investigation of the interactions of soluble proteins with interfaces, the relation of interfacial structure to catalytic properties of enzymes at interfaces and lipid-mediated signal transduction. We also design instrumentation and methods for surface chemical analysis.

The key component at the heart of the novel microfluidic film balance, on which our work depends, is a flow cell that maintains a constant depth (<150  $\mu\text{m}$ ) of the liquid flowing through a channel that is open on its upper surface to the atmosphere. The interface between the flowing liquid and the air serves as a renewable platform at which lipids or proteins can be immobilized in the interface by self or directed assembly. Relevant examples of such assembly are the formation of an antibody monolayer by adsorption from the aqueous phase and the formation of a lipid monolayer by spreading of lipid onto the surface from a volatile organic solvent. Subsequently, the adsorption of solute, e.g. a protein, to this interface from the aqueous phase can be optically measured.

Previously, we described improvements in this flow cell and associated instrumentation that increased sensitivity and stability and, importantly, insured that solute interaction with the test interface was the only adsorption measured by the system.

In the present year, we have made further improvements in flow cell design and have collaborated with Dr. Rhoderick Brown's group to use this instrument to study the ability of a glycolipid transport protein (GLTP) to recognize interfaces and catalyze the removal of its substrate. Previously, Dr. Brown's group had shown that highly curved surfaces, as exemplified by small unilamellar lipid vesicles, supported higher rates of GLTP-catalyzed glycolipid exchange than did larger, less curved vesicles. Our instrument allowed measurement of the removal of a fluorescent glycolipid analog from a planar, monomolecular matrix of phospholipids for which the phospholipid composition and lateral packing density could be controlled.

We observed that, with a tightly-packed matrix of zwitterionic phospholipid species tested, GLTP in the aqueous phase flowing under the





lipid monolayer was unable to catalyze glycolipid or phospholipid removal as measured by the loss of fluorescent analogs from the planar monolayer. There was also no evidence of binding of GLTP to the monolayer. However, lowering the packing density of the matrix phospholipids facilitated both GLTP adsorption and glycolipid, but not phospholipid, analog removal. Because the monolayers were globally planar at both packing densities, the results suggest that membrane curvature per se was not responsible for the faster rates of glycolipid exchange observed earlier with vesicles of low radius. Instead, the important factor seems to be the spacing between the phospholipid headgroups. Whether the improved glycolipid removal at lower matrix packing density is a result of increased fluctuations of glycolipid toward the aqueous phase, increased access of protein binding to the interface or both, is not clear at this point.

*“In the present year, we have made further improvements in flow cell design and have collaborated with Dr. Brown’s group to use this instrument to study the ability of a glycolipid transport protein (GLTP) to recognize interfaces and catalyze the removal of its substrate.”*

The presence of an acidic phospholipid (5%) in a mostly phosphatidylcholine matrix allowed adsorption of GLTP to tightly packed monolayers and facilitated glycolipid analog removal. This stimulation of the transport half reaction was further enhanced if phosphatidylethanolamine (15%) was also present. These observations are consistent with the biological activity of GLTP occurring at cell membranes exposed to the cytosol which contain both acidic phospholipids and phosphatidylethanolamine.



Left to right: Dmitry Malakhov, Bill Momsen, Howard Brockman, Maureen Momsen, Nancy Mizuno

*Other Professional Activities*  
*Howard Brockman*

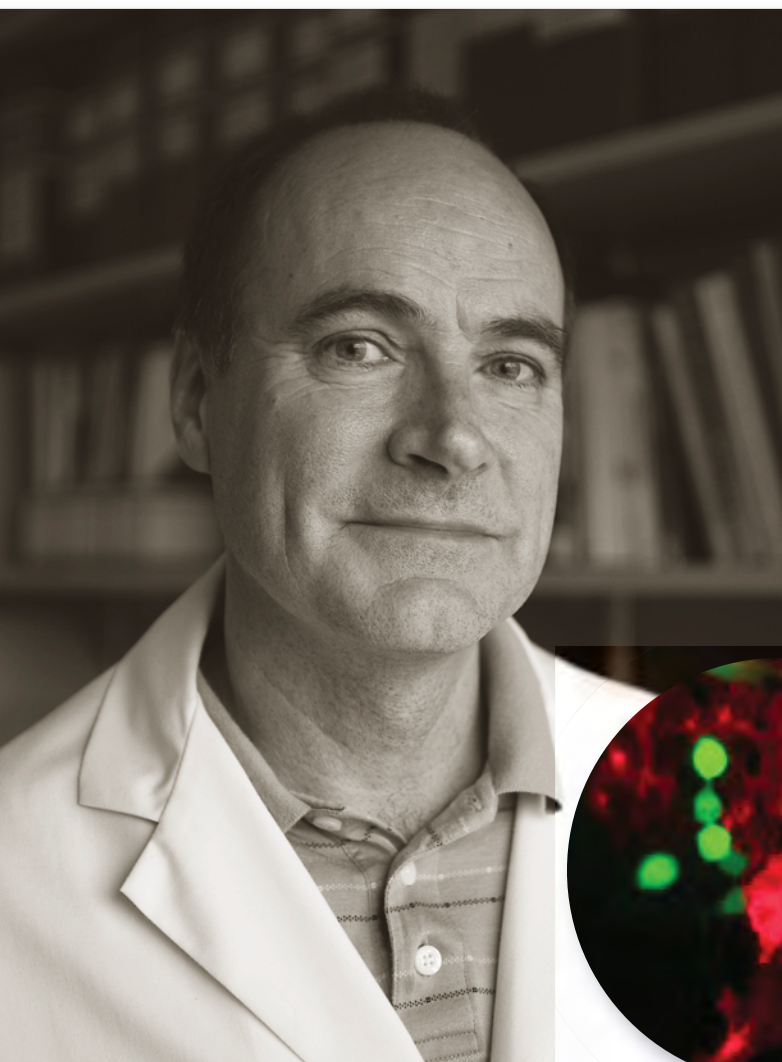
Member:  
NIH Special Emphasis Panel/Scientific Review Group, January, 2010.

## MEMBRANE BIOCHEMISTRY

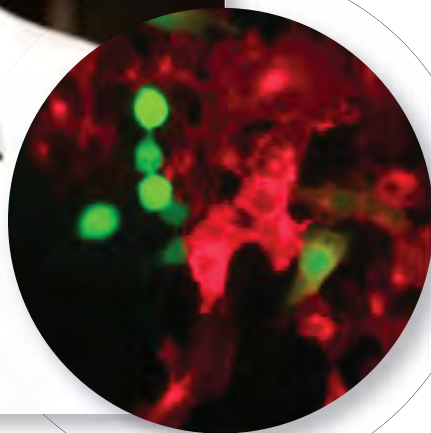
Section Leader

Rhoderick E. Brown, Ph.D.

Professor



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



Biomembranes provide borders around cells and are made up of complex mixtures of lipid molecules. Many of these lipids possess special physiochemical features that enable them to self-assemble into thin and flexible layers that are two molecules thick. The resulting bilayers act as barriers to maintain cell integrity, while enabling beneficial nutrients to enter and toxic by-products to exit in selective fashion. Biomembranes also internally partition the cell into different specialized compartments. Interestingly, there are many more varieties of lipids in membranes than are needed to form the bilayers. Certain kinds of membrane lipids recently have been shown to function as messenger signals within cells, while other membrane lipids appear to cluster together to form microdomains able to control the spatial distribution and lateral interactions of certain kinds of membrane proteins that regulate cell growth, proliferation, and programmed cell death processes. The discovery of these new functions for membrane lipids has energized the field of cell biomembrane research and has helped to further our understanding of how infectious diseases and cancer can alter biomembrane function.

Over the past several years, our lab has provided fundamental insights into how the physical environment within membranes becomes changed when different lipids mix together. These changes can either promote or impede interaction with proteins. We are especially interested in a class of membrane lipids known as sphingolipids. Certain sphingolipids, along with cholesterol, serve as key components needed for formation of membrane microdomains, commonly referred to as “rafts.” Because rafts function as organizing regions for certain signaling kinases as well as target sites for certain viruses and bacteria, special importance has been placed on rigorously defining the physical basis for raft microdomain functionality. We have developed ways to quantitatively measure the lateral elasticity within model membranes and to very accurately assess the physical changes that occur within the membrane “raft environment” when the content and structure of sphingolipids and sterols are altered. Our research has helped to provide an increased understanding of the sphingolipid structural features that affect their interactions with other membrane lipids and define the physical nature of the membrane environment produced by sphingolipid compositional changes. This new knowledge is especially important for understanding how the raft microdomain environment regulates the membrane translocation of pro-



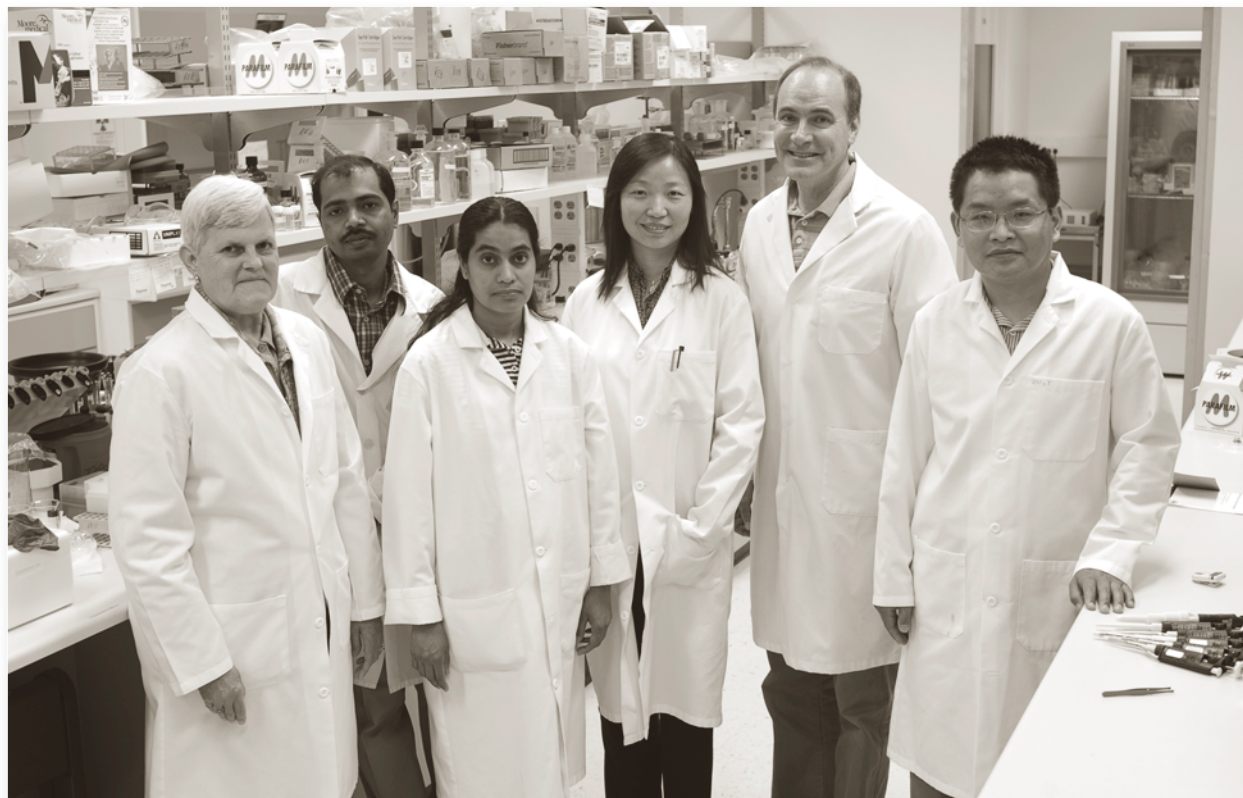
teins that have “affinity” for sphingolipids.

The processes used by cells to form and maintain sphingolipid-enriched domains are not well understood but are likely to involve specific proteins that can bind and transfer sphingolipids between membrane surfaces. Thus, much recent effort has been directed towards a family of mammalian proteins, called glycolipid transfer proteins (GLTPs), that specifically bind and transfer glycosphingolipids between membranes. We have found that GLTP functionality in vitro can be regulated by the composition and packing of lipids within membranes. Use of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR) has enabled us to gain

**“Over the past several years, our lab has provided fundamental insights into how the physical environment within membranes becomes changed when different lipids mix together.”**

fundamental understanding into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids in phospholipid membranes. We are applying this basic knowledge to decipher the functional regulation of GLTP. Exactly how GLTPs accomplish the intermembrane transfer of glycolipids is being actively studied with the long range goal of determining whether GLTPs actively participate in the assembly and maintenance of sphingolipid-enriched rafts within biomembranes. Our molecular biological studies have resulted in the first molecular cloning of human GLTP and related homologs from porcine and bovine brain and mouse skin fibroblasts. We found that mammalian GLTP transcripts encode very highly conserved amino acid sequences. Genetic engineering approaches have enabled us to produce human GLTP using bacterial expression systems and to purify sufficient quantities to successfully crystallize

the protein, and to solve the conformational structure of GLTP in its glycolipid-free form as well as complexed with different glycolipids, in collaboration with structural biologists at Memorial Sloan Kettering Cancer Center in



Left to right: Helen Pike, Ravikanth Kamlekar, Roopa Kenoth, Xiuhong Zhai, Rick Brown, Xianqiong Zou  
Not pictured: Young-Guang Gao

New York. The completely novel structural fold of GLTP has resulted in human GLTP being designated as the founding and prototypical member of the new GLTP superfamily of proteins, enabling publication of our findings in *Nature*. New data reported in *PLoS Biology*, *The Journal of Biological Chemistry*, and *Biophysical Journal* have led to new insights into how GLTP adapts to accommodate different glycolipids within its liganding site, provided understanding into the functional roles played by intrinsic tryptophan residues in membrane interac-



tion and glycolipid binding, and revealed the structural basis for the narrower glycolipid selectivity displayed by a fungal GLTP orthologs.

We expect elucidation of the fundamental structure-function relationships governing GTLP action to 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 GSL antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new therapeutic approaches to treat disease processes involving glycolipids.

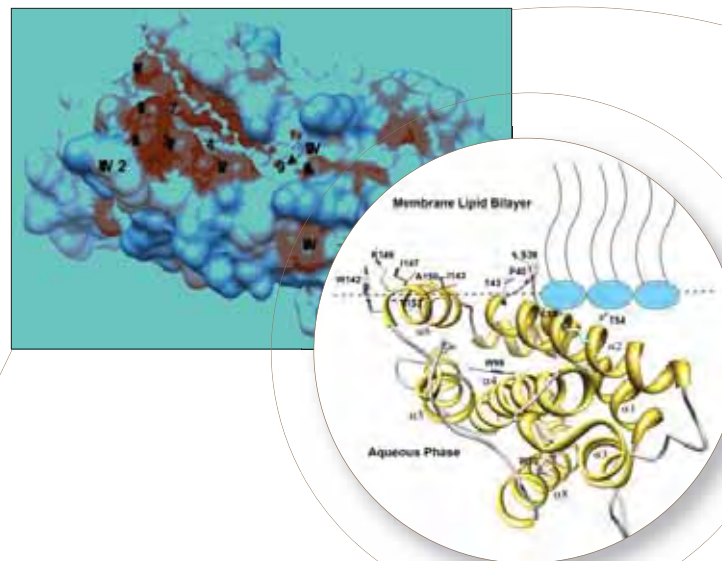
Our progress to date emphasizes the need for continuing investigations into the workings of GLTP, and other proteins containing GLTP-like motifs, using a combination of biophysical, cell, and molecular biological approaches. Our very recent investigations of GLTP gene organization and transcriptional status in humans and other mammals are expected to provide a firm foundation for the future identification and characterization of inherited diseases involving GLTP. Our research efforts are possible because of long-standing support from the National Institute of General Medical Sciences division of NIH and The Hormel Foundation that supports our ongoing efforts as well as collaborations with researchers at the Mayo Clinic, The Russian Academy of Sciences in Moscow, at CIC bioGUNE in Derio, Spain, and at The Mount Sinai Medical Center in New York. Newer shared NIH National Cancer Institute funding supports our collaboration with researchers at Sloan Kettering Memorial Cancer Center in New York City.

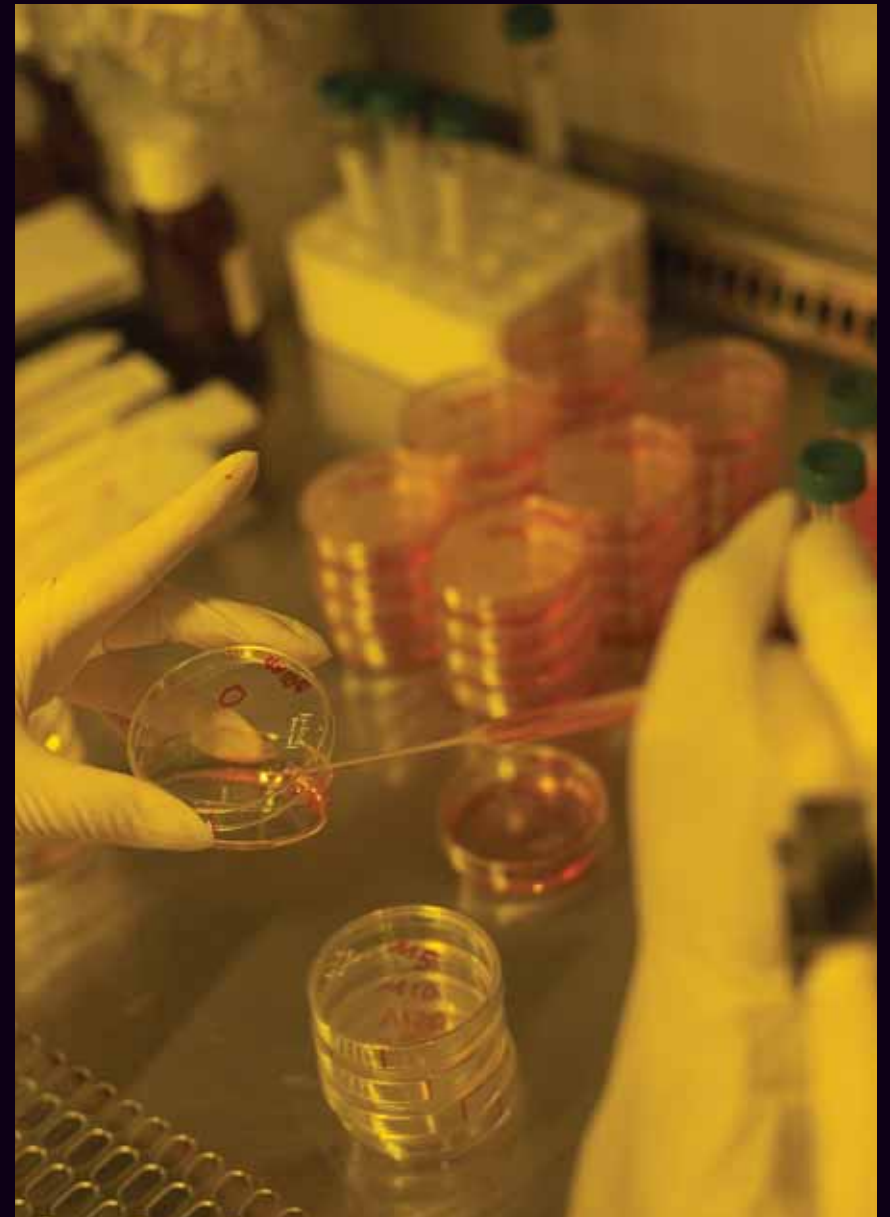
#### *Other Professional Activities*

*Rhoderick E. Brown*

Editorial Advisory Board: Chemistry and Physics of Lipids,  
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Biophysical Society Congressional Liaison Volunteer





## NUTRITION AND METABOLISM

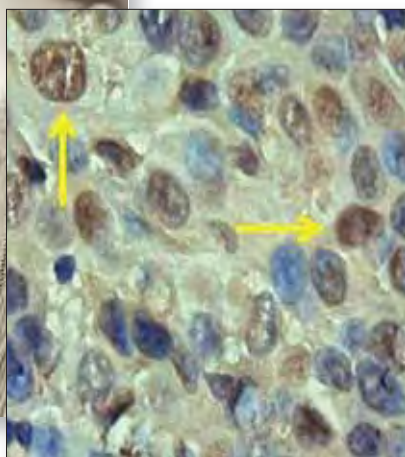
Section Leader

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.



Our lab's primary interests include the effects of body weight on the development of breast cancer using mouse models. Studies include 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. We are also determining if characteristics of the cancer cells are affected by obesity. These studies have been complemented by in vitro experiments. Additional investigations are focused on the effect of caloric restriction on the development of breast/mammary tumors and prostate cancer using mouse models. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the IGF-axis. Recent studies have expanded studies to the effects of obesity on prostate cancer development. We are also investigating the effects of specific long chain fatty acids as chemopreventive agents and the effect of reactive oxygen species in the protective effect of calorie restriction.

The major focus of research in the Nutrition and Metabolism Section has been the interaction of caloric intake, changes in body weight and the development of breast cancer. We have recently expanded our intervention strategies to prostate cancer. One area of investigation has been to assess the effects of caloric restriction, as well as body weight changes and/or weight gain/loss, on tumorigenesis. The focus was initially on serum leptin and IGF-I as mediators of tumor growth with recent expansion to an additional protein, adiponectin. Similar to leptin, adiponectin is synthesized in adipose tissue, however, in contrast to leptin, its synthesis declines with increasing body weight and body fat. Furthermore, recent studies indicate that lower serum adiponectin levels are associated with the development of several malignancies, including breast and prostate cancers. Additionally, in vitro studies show that addition of adiponectin reduces proliferation of both breast and prostate cancer cells and may enhance cell death.

For our mammary tumor studies, both transgenic mice and xenograft mice models are used. We have been comparing the tumor preventing effects of different modes of calorie restriction and have found that intermittent caloric restriction is more protective in the prevention of mammary tumor development than is the same degree of caloric intake imposed by chronic (evenly spaced) restriction. We have completed several longitudinal studies where serum samples were obtained prior to tumor detection in order to identify biomarkers. Some of the results support a role for elevated serum IGF-I lev-



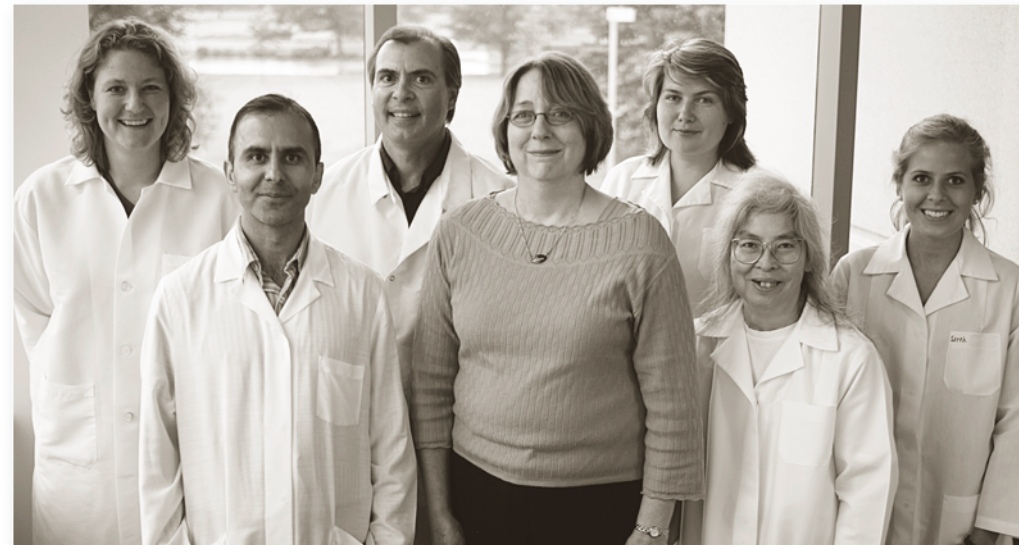
els in the development of mammary tumors. Of particular note, we find that the protective effect of intermittent calorie restriction is associated with reductions in IGF-I and leptin levels and a marked increase in the adiponectin:leptin ratio. We have complementary studies indicating that a high adiponectin:leptin ratio in vitro is associated with decreased breast cancer cell proliferation. This has led us to hypothesize that the individual levels of these factors is not as important as their interrelationship. Presently, we are evaluating the impact of high fat feeding during refeeding to determine how this affects mammary tumor development and/or prevention. Additionally Dr. Christine Seppanen has recently received funding from the American Institute for Cancer Research to analyze tissues to determine if the protective effect of intermittent calorie restriction also involves oxidation reactions. Further, Dr. Michael Grossmann is studying 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 which was previously 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 are very promising with the combination of omega-3 fatty acid and intermittent calorie restriction being more protective than the restricted protocol using omega-6 fatty acid.

*“The major focus of research in the Nutrition and Metabolism Section has been the interaction of caloric intake, changes in body weight and the development of breast cancer.”*

We have also investigated the effects of intermittent restriction intervention in a model for prostate cancer, TRAMP mice. This intervention also protected against prostate cancer development as reflected by a delay in the initial detection of the disease as well as a later age at death. Furthermore, the intermittent restriction appears to be far superior to chronic calorie restriction which had little effect on prevention of prostate cancer in TRAMP mice. We have also assessed the effects of obesity on the development of prostate cancer. Our initial goal was to study the effects of obesity initiated at different ages on the development of prostate cancer using the TRAMP model. However, there were technical difficulties inducing the obesity with the chem-

ical agent we were using. We have now completed a diet-induced obesity study in the TRAMP mice. The results indicate that obesity is associated with more severe disease which is similar to what has been reported for humans.

Overall, our findings should be of importance in understanding the impact of body weight on the development of several types of cancer. Further, the protective effect of intermittent calorie restriction which indicates that the manner in which calories are restricted has a significant impact should provide insights into designing cancer prevention strategies.



Left to right: Christine Seppanen, Soner Dogan, Michael Grossmann, Margot Cleary, Olga Rogozina, Nancy Mizuno, Sarah Ewing (Intern)

#### *Other Professional Activities*

*Margot P. Cleary*

#### *Invited speaker:*

- New York State University at Albany Cancer Center, Albany, NY, November 2009
- Penn State University, State Park, PA, March 2010

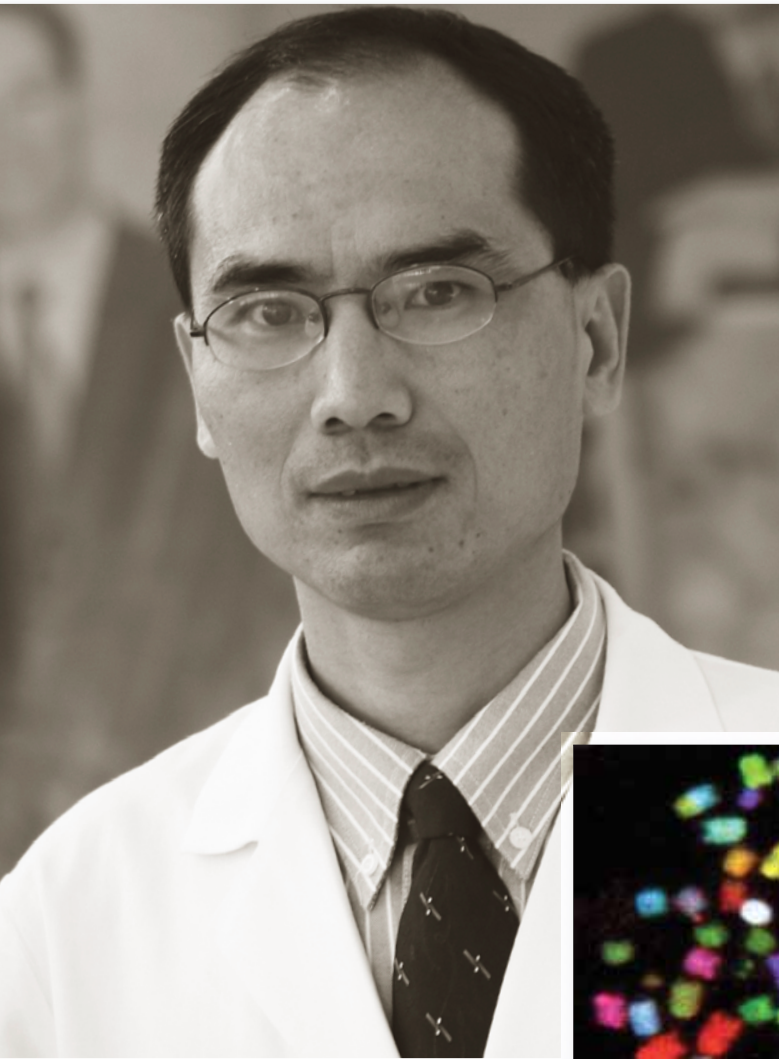
NIH Study Section meetings, October, 2009, February 2010 and June 2010

## CELL DEATH AND CANCER GENETICS

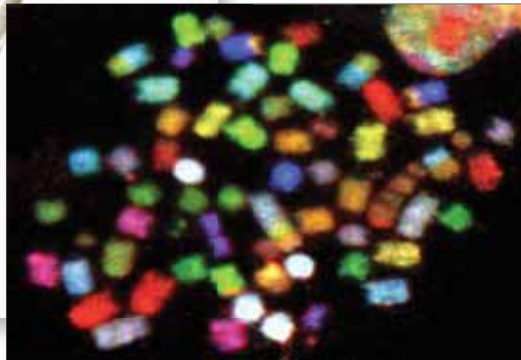
Section Leader

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

Assistant Professor



Tumorigenesis, the formation or production of tumors.



The importance of p53 as a tumor suppressor is underscored by the fact that mutations that perturb p53 function have been found in more than 50% of human cancers. However, the molecular mechanisms by which p53 eliminates cancer cells remains poorly understood. In the past year, our laboratory continues to focus on understanding how wild-type p53 controls apoptosis, senescence, and autophagy in pre-cancerous cells and cancerous cells, and how mutant p53 identified in cancer patients disrupts these processes and impacts tumor initiation, progression, metastasis and cancer therapy in vivo. The research in our laboratory can be divided into three major areas:

### 1. *Understanding p53-mediated tumor suppression and cancer therapy in vivo*

While many studies have focused on the role of apoptosis and/or senescence in p53-mediated tumor suppression and therapeutic responses, recent findings indicate that p53 induces a novel pathway known as autophagy. Autophagy is a cellular self-digestion pathway involved in protein and organelle degradation in the lysosome. A recent new study has identified that DRAM (Damage-Regulated Autophagy Modulator) is a direct target of p53 and the DRAM protein mediates p53-induced autophagy and thus may contribute to tumor suppression and cancer therapy. To study the physiological contribution of DRAM to p53-mediated tumorigenesis and cancer therapy in vivo, we generated conditional DRAM knockout mice by gene targeting.

Our laboratory is using the conditional DRAM knock-out mice to breed with p53-mediated apoptosis deficient mice (p53R172P knock-in or PUMA knockout) and senescence-deficient mice (p21 knockout) to generate the “triple” mutant mice dissecting the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing spontaneous tumor development in vivo. Our current preliminary studies support our hypothesis that p53-induced apoptosis, autophagy and senescence cooperate together to effectively prevent cancer development and mediate therapeutic efficacy of p53 in vivo. We expect that our studies will identify novel molecular targets that could be exploited for cancer prevention and personalizing cancer therapies against more than 50% of human tumors with mutant p53.



## 2. Gain-of-function of mutant p53 in telomere dysfunction-induced mammary tumorigenesis

Human sporadic breast carcinomas are characterized by the presence of complex cytogenetic aberrations. This represents one of the foremost challenges for breast cancer researchers to develop experimental model systems to 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 involved in breast tumorigenesis in vivo. One important mechanism that can give rise to the unstable breast cancer genome is the dysfunction of telomeres, the nucleoprotein caps that protect chromosomal ends from being recognized as damaged DNA and inhibit chromosome end-to-end fusions. Telomeres that can no longer exert end-protective functions are said to be dysfunctional, and these telomeres could arise either from progressive telomere attrition

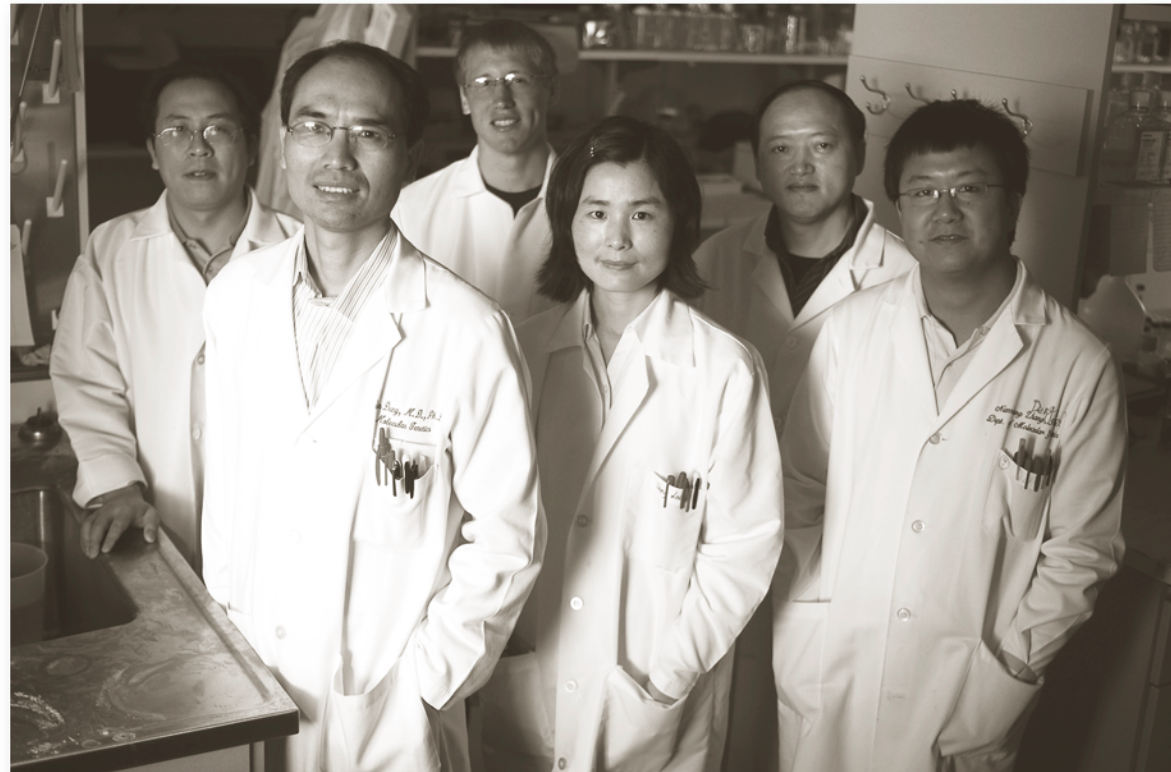
(telomere shortening), or when components of the telomeric DNA binding proteins, termed shelterin complex, are perturbed (telomere uncapping). In human breast carcinomas, the observation that chromosomal instability fueled by dysfunctional telomeres is associated with the transition from

benign ductal hyperplasia to malignant ductal carcinoma in situ (DCIS) 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 bearing telomere uncapping-induced chromosomal instability without disturbance of telomerase and expression of “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 will employ this novel mouse breast cancer model to analyze the key genetic pathways perturbed in chromosomal instability-driven mammary tumorigenesis and target these pathways with novel therapeutics to potentially suppress human breast cancer.

“The importance of p53 as a tumor suppressor is underscored by the fact that mutations that perturb p53 function have been found in more than 50% of human cancers.”

## 3. Exploring the molecular and cellular basis of selective killing of cancer cells

Our laboratory has a long-standing interest in understanding genetic pathways that allow for selectively targeting cancer cells while leaving normal cells untouched. Through multidisciplinary collaborations, we are using a compre-



Left to right: Jiankang Deng, Yibin Deng, Andrew Maiers (Intern), Yan Cheng, Siqian Tang, Hua Xiong

hensive 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 key pathways that are linked to therapeutic selectivity with the long-term goal of identifying new targets to specifically kill cancerous cells and combat acquired drug resistance. Currently, our laboratory has identified several compounds in selectively targeting human colon, breast and prostate cancer cells in vitro. We will test their efficacy in suppressing tumor development using our engineering cancer mouse model.

## CELLULAR DYNAMICS

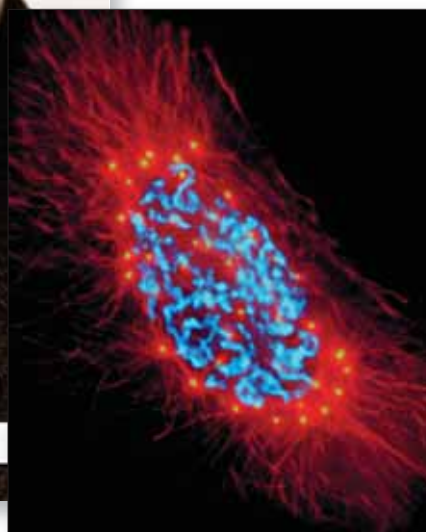
Section Leader

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 is currently funded by an R01 research grant from the National Institutes of General Medicine to study the molecular mechanisms that regulate cell division, and the roles of centrosome reproduction in ensuring the bipolarity of this process.

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.

It is also important to understand how the division of the cell into two (cytokinesis) is coupled with the segregation of the chromosomes during anaphase. This process is mediated by a transient microtubule structure called the spindle midzone. As the sister chromatids disjoin, and segregate to the opposing poles, the overlapping microtubules at the cell center assemble several key signaling complexes. These in turn recruit the cytoskeletal proteins necessary to physically divide the cell into two. We are interested in identifying the mechanisms used to build the spindle midzone, with particular attention to the role of the tektin family of proteins.

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.



### Experimental research results

1. 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 does rise 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 colcemid. We find that in such cells, the pre-existing centrosomes remain, and a variable number of centrosomal foci – containing  $\alpha/\gamma$ -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. 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.

2. 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 ane-

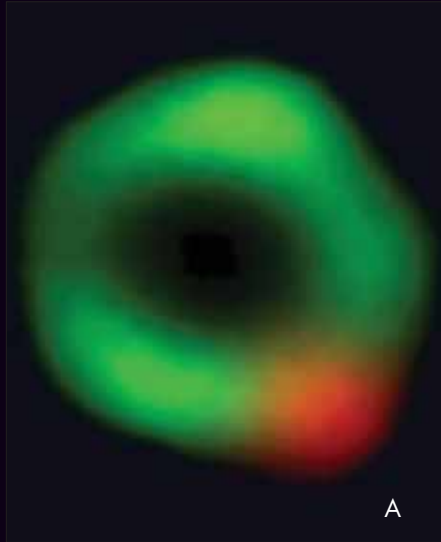
“A detailed understanding of the regulation of cell division will advance our knowledge of the biology of cancer – itself a disease characterized by unregulated cell proliferation. Together, these studies should provide a fertile source of potential targets for future anti-cancer drugs.”

uploidy, 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.

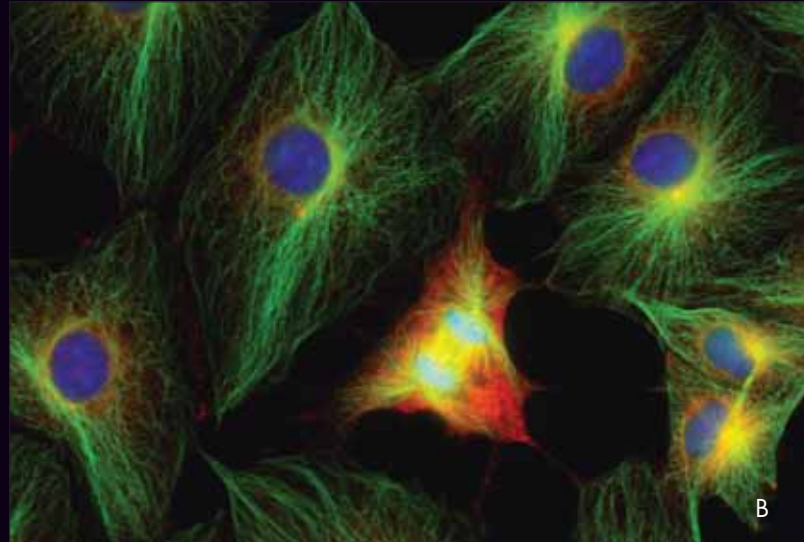


Left to right: Cydney Bagne, Edward Hinchcliffe, Tana Lukes (Intern), Kul Karanjeet

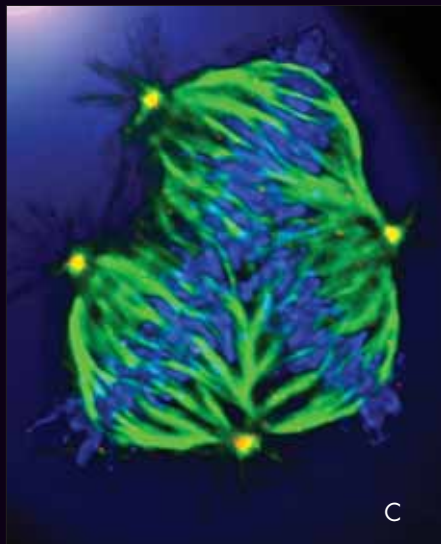
We are currently using microsurgery coupled with time-lapse videomicroscopy of living acentrosomal cells to investigate the role of the centrosome in cell cycle regulation. To directly visualize the role of microtubules, and regulatory molecules during the acentrosomal cell cycle, we have generated primate kidney cell line (BSC-1 cells) that constitutively express  $\alpha$ -tubulin coupled to GFP. We find that after several hours, acentrosomal cells re-form their microtubule network into an organized array. Interestingly, the acentrosomal microtubule focus can separate into two distinct poles prior to nuclear envelope



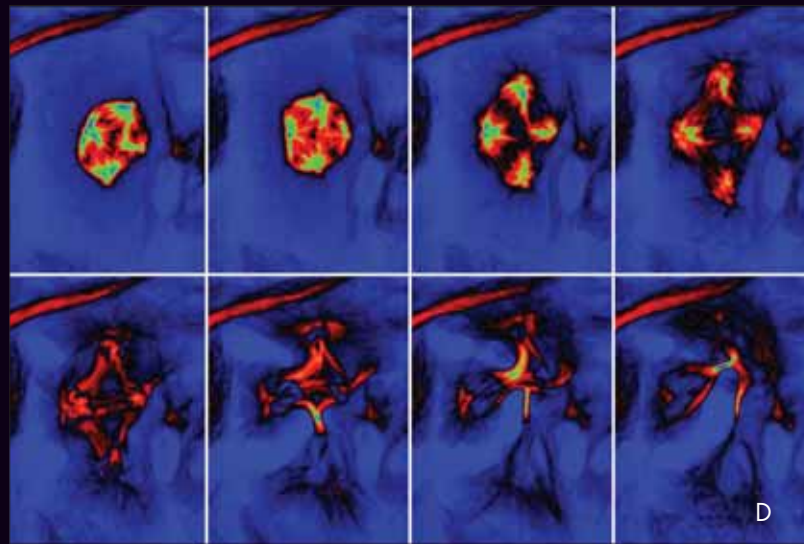
A



B



C



D

A. High-magnification view of a centrosome. Gamma tubulin in green, SAS-6 in red.

B. Low-magnification view of epithelial cells. The center cell is undergoing anaphase. Microtubules in green, dynein in red, chromosomes in blue.

C. Multipolar mitotic spindle. Microtubules in green, centrosomes in red, chromosomes in blue.

D. Frames from time-lapse video microscopy, showing a tetrapolar mitotic spindle undergoing anaphase. The green GFP-microtubules have been pseudo-colored to highlight intensities.



breakdown. This demonstrates that the splitting of the microtubule network does not require a centrosome, contrary to previously held notions. However, we find 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 is also 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 in order to ensure fidelity during mitotic spindle assembly.

3. We are currently investigating the role of the tektin proteins in establishing the spindle midzone. Tektins were first identified as components of axonal 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 is 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. We are interested in uncovering the molecular mechanisms underlying this observation. We are currently examining the motility of several key regulators of midzone function: PRC1 and Kif4, in response to experimental loss of tektin 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 will advance our knowledge of the biology of cancer – itself a disease characterized by unregu-

lated cell proliferation. Together, these studies should provide a fertile source of potential targets for future anti-cancer drugs.

#### *Other Professional Activities*

*Edward H. Hinchcliffe*

#### Review panel member:

National Science Foundation

#### Ad hoc reviewer:

National Science Foundation

Ohio Cancer Research Foundation

Wellcome Trust UK

Deutsche Forschungsgemeinschaft (DFG: German Research Foundation)

#### Invited Editor:

*Seminars in Cell and Developmental Biology*

#### Instructor:

Analytical and Quantitative Light Microscopy course, Marine Biological Laboratory, Woods Hole, MA

#### Invited seminar speaker:

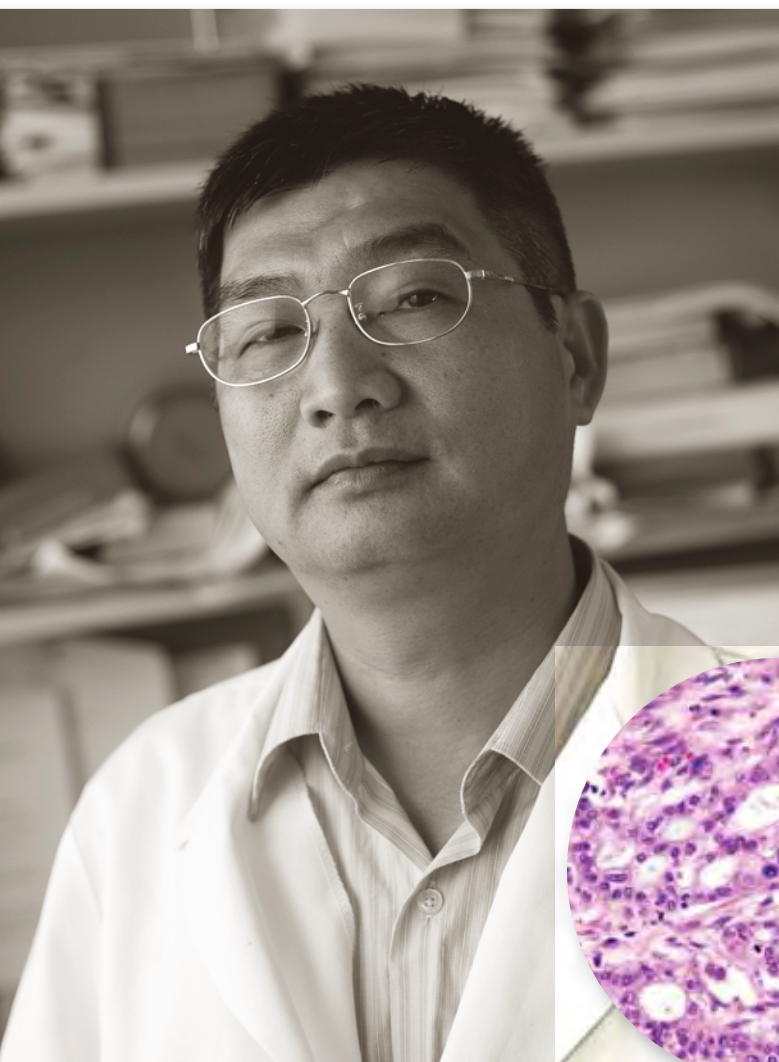
University at Albany, Cancer Research Center, Albany, NY

## TRANSLATIONAL CANCER RESEARCH

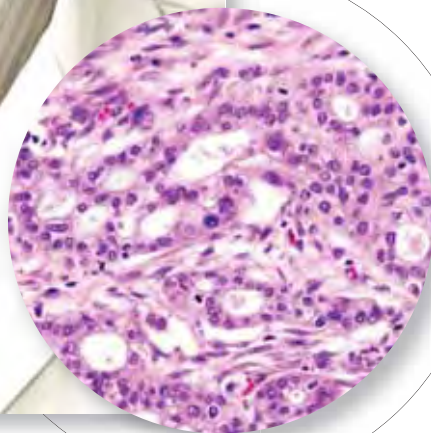
Section Leader

D. Joshua Liao, Ph.D.

Associate Professor



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



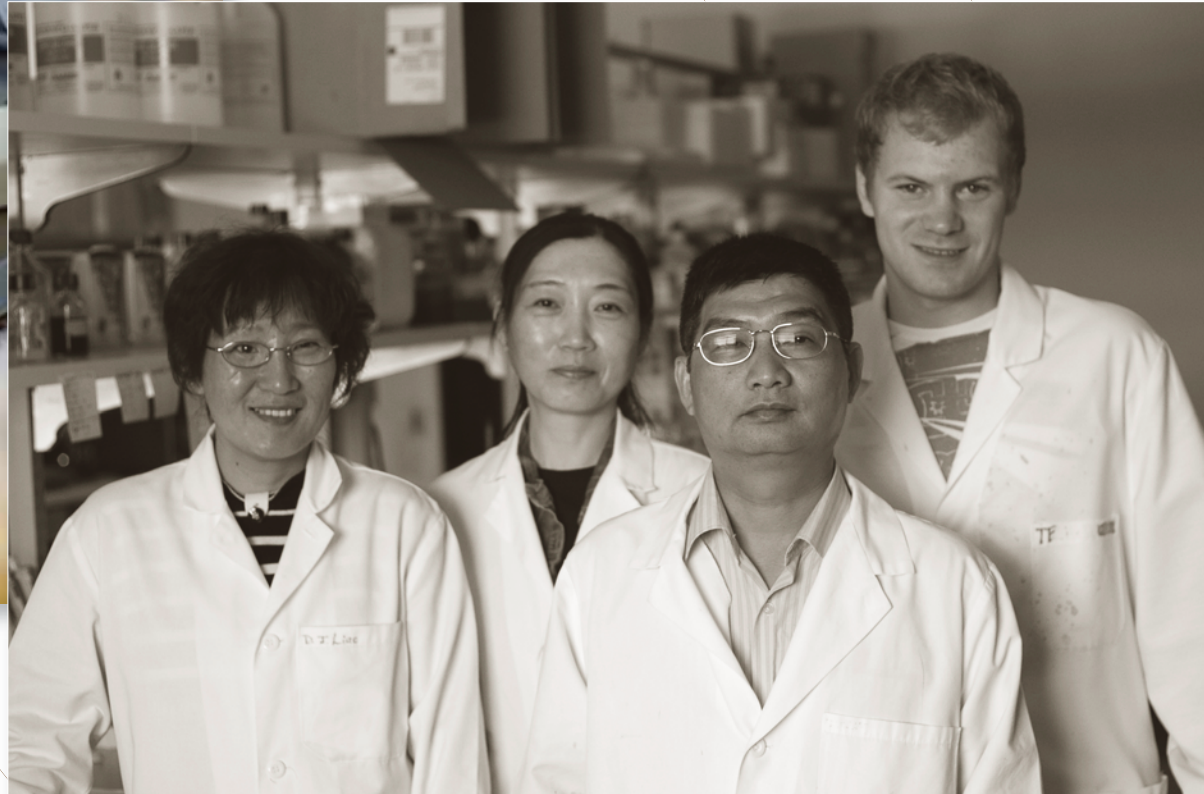
We shifted our research focus to a novel project of how ribonomic changes (i.e. changes in RNA processing) affect formation of breast and pancreatic cancers and progression of these cancers to metastatic or chemoresistant status. While genomic alterations (i.e. changes in DNA) in cancer cells have been studied for over a century, alterations in RNA processing, collectively coined herein as ribonomics, have just been studied recently in cancer cells. Unlike cis-splicing that occurs within a pre-mRNA and is most studied, trans-splicing takes place between two different pre-mRNAs that can be transcribed from different chromosomes, resulting in a chimeric RNA. The ENCODE, an international collaborative research project on RNA, shows that 65% of the genes tested are involved in formation of chimeric RNA via trans-splicing, which changes the definition of a “gene” in the post-ENCODE era. Our laboratory currently focuses on how aberrant expression of c-myc and cyclin D1 affects alternative cis-splicing and trans-splicing of certain oncogenes and tumor suppressor genes, and how these splicing processes influence progression of breast and pancreatic cancer cells to metastatic or chemoresistant status. Moreover, we also study how c-myc and cyclin D1 regulate expression of certain microRNA to influence formation of breast and pancreatic cancers, because different patterns of alternative splicing generate different microRNAs. By manipulating c-myc or cyclin D1 regulated splicing processes, we hope to develop some novel strategies or agents for gene-targeting molecular chemotherapy of advanced breast and pancreatic cancers.

Another of our projects is to develop chemical compounds that inhibit or degrade cyclin D1 and c-Myc oncoproteins. Our previous studies show that although c-Myc can cause cancer formation, c-Myc overexpressing cancers are actually more sensitive to certain chemotherapeutic agents. On the contrary, overexpression of cyclin D1 imposes chemoresistance on cancer cells. Co-expression of c-myc and cyclin D1 renders breast and pancreatic cancer cells aggressiveness. Targeting both cyclin D1 and c-myc should be more efficient in chemotherapy. We have recently developed some chemical cyclin D1-cdk4 inhibitors and c-Myc inhibitors and will test whether combined treatment of these two types of chemicals result in a better treatment efficacy.





“By manipulating c-myc or cyclin D1 regulated splicing processes, we hope to develop some novel strategies or agents for gene-targeting molecular chemotherapy of advanced breast and pancreatic cancers.”



Left to right: Jian-Min Wu, Yuan Sun, Joshua Liao, Matt Lindell (Intern)  
Not pictured: Min Yang

## STEM CELLS AND CANCER

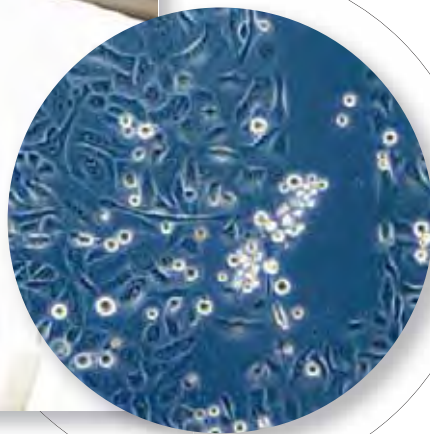
Section Leader

Rebecca J. Morris, Ph.D.

Professor



Skin keratinocytes



Research in our laboratory continues to focus on the role of stem cells in the pathogenesis of non-melanoma skin cancer. We have demonstrated that certain stem cells in the hair follicles are skin tumor initiating cells. We have also demonstrated that mice bearing a mutation in a candidate stem cell regulatory gene have in vitro and in vivo skin stem cell phenotypes as well as an increased susceptibility to skin cancer. In continuing studies, we demonstrate that bone marrow cells may have an unsuspected role in skin tumor development.

The multistage model of non-melanoma skin carcinogenesis has contributed significantly to our understanding of epithelial cancer in general. We developed the Krt1-15CrePR1;R26R transgenic mice to determine the contribution of hair follicle bulge stem cells to skin tumor development by following the labeled progeny of the keratin 15 expressing cells from the hair follicle bulge. We present three novel observations. First, in contrast to the widely held view that squamous papillomas originate in the epidermis, we found that hair follicle bulge stem cells contribute to virtually 100 percent of the papillomas by 20 weeks of promotion. Second, in contrast to the transient behavior of labeled bulge derived progeny in skin wound healing, keratin-15 derived cells persist in papillomas and some malignancies for many months following transient induction of the reporter gene. Third, papillomas have surprising heterogeneity in their expression of the codon 61 signature Ha-ras mutation with approximately 30% of bulge-derived regions expressing the mutation. Together, these results demonstrate that keratin-15 expressing cells of the hair follicle bulge contribute directly to cutaneous papillomas with long term persistence and a subset of which express the Ha-ras signature mutation characteristic of initiated cells.

Keratinocyte stem cells have an unquestioned role in maintaining the normal structure and function of the epidermis and hair follicles and are thought to be important players in inherited and acquired skin disease. Hence, identification of genes regulating their number and proliferative potential is a critical problem in cutaneous biology. Understanding keratinocyte stem cell regulation is important in understanding the pathogenesis of wound healing and non-melanoma skin cancer. We previously used a sensitive and quantitative assay for in vitro keratinocyte colony formation and mapped the keratinocyte stem cell-locus (Ksc1)

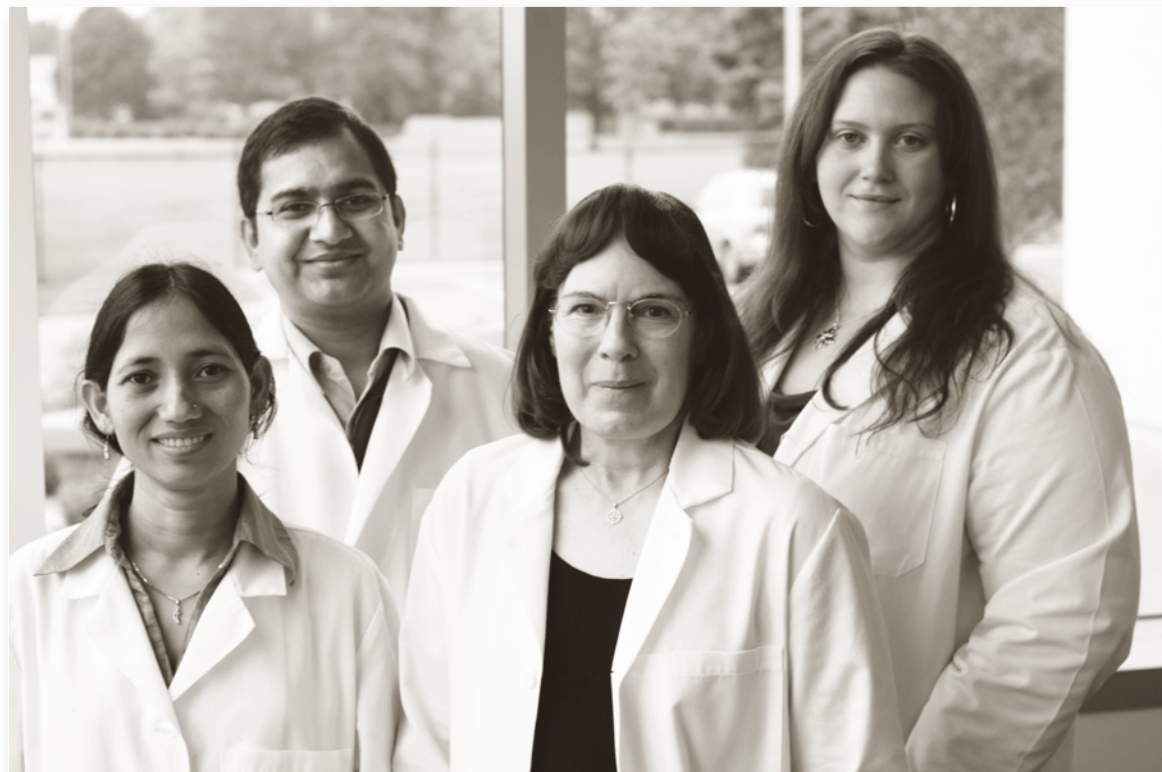


on mouse chromosome 9. Examination of the candidate genes in this locus disclosed a sequence variant in the gene for bone morphogenetic protein 5 (Bmp5). We used a naturally occurring mouse with a null mutation in this gene to probe stem cell properties in mouse epidermis. We found that the mutant keratinocytes had a significant reduction in the size and number of clonogenic keratinocytes. The mutant mice had a 50% reduction in the number of label-retaining cells when compared with their littermates, but showed a significant increase in the number of pulse-labeled cells. Addition of exogenous Bmp5 protein increased the number and size of keratinocyte colonies in the mutant as well as their wild-type littermates. Surprisingly, the mutant mice showed at least a two-fold increase in skin tumor susceptibility over their littermates. We conclude that a naturally occurring mutation in Bmp5 affects keratinocyte stem cell proliferation and skin tumor susceptibility and is a candidate stem cell regulatory gene in the Ksc1 locus.

Continuing research is in progress to determine the role of bone marrow derived cells in skin cancer development. Although such cancers are widely believed to originate from the transformation of epidermal or hair follicle stem cells, the recent demonstration that gastric cancer can be derived from bone marrow cells has challenged this dogma. We have used both in vitro and in vivo models to address this problem. We first determined that bone marrow adherent cells can be cultivated for several weeks in culture but fail to produce keratins. However, if the bone marrow cells are cultivated in the presence of skin keratinocytes, even if they are separated by a filter, some of the bone marrow cells will become keratin immunoreactive. This finding indicates that the bone marrow adherent cells do not need to fuse with the skin keratinocytes in order to begin to produce keratins. We have also demonstrated that bone marrow cells can infiltrate the epidermal layer of the skin in a gender mis-matched model of bone marrow transplantation. In this model, clusters of bone marrow derived cells identified by green fluorescent

**“In continuing studies, we demonstrate that bone marrow cells may have an unsuspected role in skin tumor development.”**

protein and a Y-chromosome are found in skin tumors as well as at sites of chronic skin damage, and in many cases immunoreact with skin keratin antibodies. These findings suggest that bone marrow derived cells may play a role in skin cancer. Further studies are in progress to determine this role.



Left to right: Anupama Singh, Ashok Singh, Rebecca Morris, Nyssa Readio  
Not pictured: Meepa Lokuge

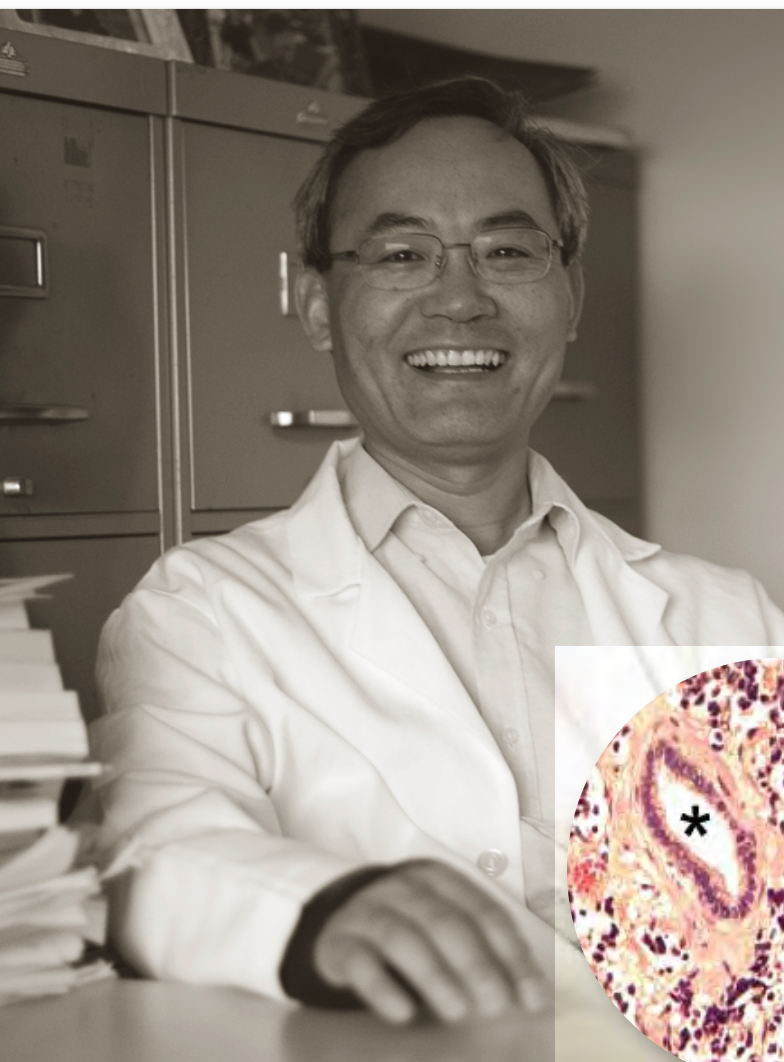
In summary, research in our laboratory continues to highlight the role of skin stem cells in the pathogenesis of non-melanoma tumor development, and hints at a possible role for bone marrow derived cells. Going forward, we will continue to investigate the regulation of skin stem cells in cancer and the role of hair follicle stem cells and bone marrow derived cells as tumor initiating cells and as tumor propagating cells.

## CANCER BIOLOGY

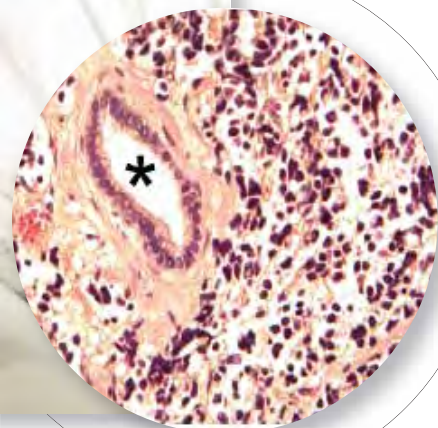
Section Leader

Junxuan (Johnny) Lü, Ph.D.

Professor



The transgenic adenocarcinoma of mouse prostate (TRAMP) model.



Our section's long-term goals are to understand the biochemical, cellular and molecular processes crucial for the genesis of cancer and to develop mechanism-based cancer prevention and therapeutic strategies for implementation through supplements, functional and medicinal foods or drug approaches. Our research program has continued to focus on the following areas:

- Sustaining our research excellence in understanding the cellular and molecular mechanisms by which selenium compounds and metabolites mediate cancer chemoprevention and treatment.
- Identifying and developing novel cancer chemopreventive and therapeutic agents based on Chinese and Oriental medicinal herbs.

Highlights of our research include studies on *in vitro* and *in vivo* Selenium, Pentagalloylglucose, a novel herbal compound, and a novel sulindac derivative.

### *In vitro and in vivo Selenium studies*

The induction of G(1) cell cycle arrest and apoptosis by second-generation selenium compounds (e.g., methylselenol precursors such as methylseleninic acid, MSeA) may contribute to their anti-cancer activities. We have documented previously induction of G(1) arrest and apoptosis by MSeA in association with upregulation of cyclin-dependent kinase inhibitor (CDKI) proteins P21Cip1 and/or P27Kip1 in DU145 prostate cancer cells. However, whether these CDKIs play a critical mediator role in G(1) arrest and apoptosis by MSeA has not been addressed. In the present work, we show exposure of p53-mutant DU145 cells to sub-apoptotic concentrations of MSeA induced p21cip1 mRNA (3 h) and protein (6 h) much faster than p27kip1 mRNA (12 h) and protein (12 h). Knocking down of P21 by siRNA completely abolished G(1) arrest induction by MSeA in DU145 cells, yet si-p27 RNA had no attenuation effect on the G(1) arrest. Depletion of P21Cip1 alone or both P21Cip1 and P27Kip1 increased MSeA-induced caspase-mediated apoptosis. Immunoprecipitation detected increased binding of P21Cip1 to CDK2 and CDK6 in MSeA-exposed DU145 cells. In DU145 xenografts from mice acutely treated with MSeA p.o., the induction of p21Cip1 was observed at 72 h of daily exposure. In p53-wild type LNCaP PCa cells and p53-null PC-3 PCa cells, MSeA modestly and transiently upregulated P21Cip1 protein level, subsiding to basal level by 24 h, without affecting P27Kip1 abundance in the same duration. Si-p21 RNA knockdown in these cells have only a partial effect to reverse G(1) arrest induction by MSeA. Together, our data support persistent, p53-independent, P21Cip1



induction as a critical mediator of MSeA-induced G(1) arrest in DU145 PCa cells, however, P21Cip1 induction and G(1) arrest were not necessary for, and may antagonize, caspase-mediated apoptosis.

Because the Selenium (Se) and Vitamin E Cancer Prevention Trial (SELECT) failed to show the efficacy of selenomethionine for prostate cancer prevention, there is a critical need to identify safe and efficacious Se forms for future trials. We have recently shown significant preventive benefit of methylseleninic acid (MSeA) and Se-methylselenocysteine (MSeC) in the transgenic adenocarcinoma mouse prostate (TRAMP) model by oral administration. The present work applied iTRAQ proteomic approach to profile protein changes of the TRAMP prostate and to characterize their modulation by MSeA and

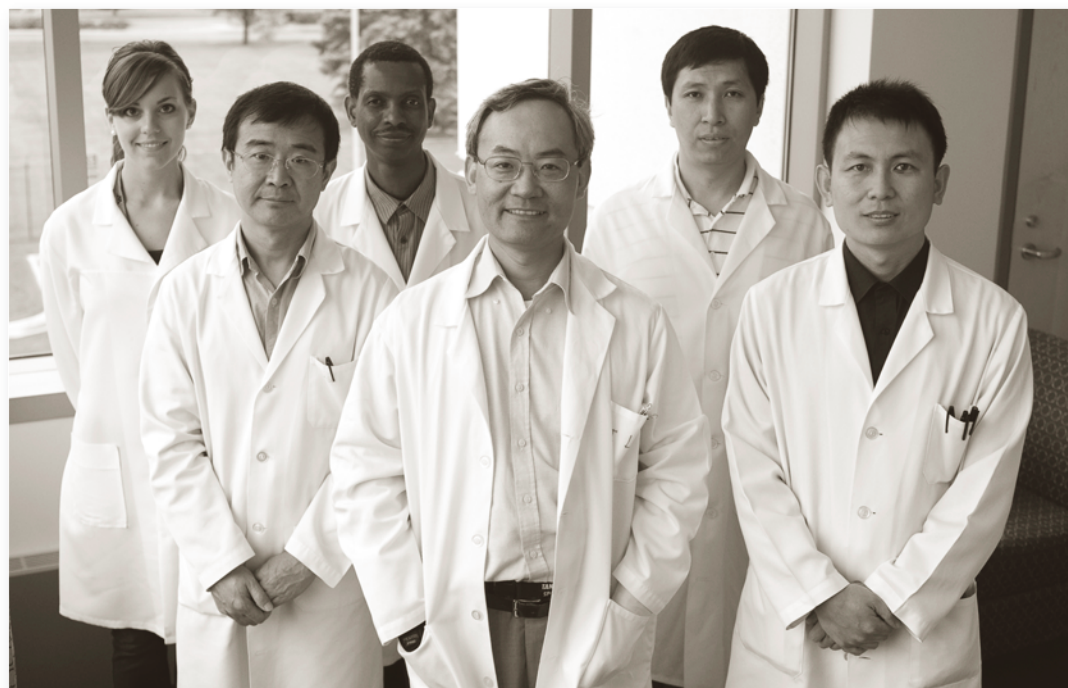
MSeC to identify their potential molecular targets. Dorsolateral prostates from wild-type mice at 18 weeks of age and TRAMP mice treated with water (control), MSeA, or MSeC (3 mg Se/kg) from 8 to 18 weeks of age were pooled (9-10 mice per group) and subjected to protein extraction, followed by protein denaturation, reduction, and alkyla-

tion. After tryptic digestion, the peptides were labeled with iTRAQ reagents, mixed together, and analyzed by two-dimensional liquid chromatography/tandem mass spectrometry. Of 342 proteins identified with >95% confidence, the expression of 75 proteins was significantly different between TRAMP and wild-type mice. MSeA mainly affected proteins related to prostate functional differentiation, androgen receptor signaling, protein (mis)folding, and endoplasmic reticulum-stress responses, whereas MSeC affected proteins involved in phase II detoxification or cytoprotection, and in stromal cells. Although MSeA and MSeC are presumed precursors of methylselenol and were equally effective against the TRAMP model, their distinct affected protein profiles suggest biological differences in their molecular targets out-

**“Our section’s long-term goals are to understand the biochemical, cellular and molecular processes crucial for the genesis of cancer and to develop mechanism-based cancer prevention and therapeutic strategies for implementation through supplements, functional and medicinal foods or drug approaches.”**

weigh similarities.

This research suggests that the efficacious methylselenium compounds are more than just methylselenol precursors and should be developed individually as potential candidate second-generation selenium agents for future translational investigation.



Left to right: Maggie Craven (Intern), Yubo Chai, Katai Nkhata, Johnny Lu, Yong Zhang, Lei Wang  
Not pictured: Cheng Jiang, Jinhui Zhang, Hwan Hyun Kim, Li Li, Ahmad Shaik, Emily Kain Quealy

#### *Pentagalloylglucose studies*

We authored a comprehensive expert review of the different reported activities of 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucose (PGG). PGG is a polyphenolic compound highly enriched in a number of medicinal herbals. Several in vitro and a handful of in vivo studies have shown that PGG exhibits multiple biological activities which implicate a great potential for PGG in the therapy and prevention of several major diseases including cancer and diabetes. Chemically and functionally, PGG

appears to be distinct from its constituent gallic acid or tea polyphenols. For anti-cancer activity, three published *in vivo* preclinical cancer model studies with PGG support promising efficacy to selectively inhibit malignancy without host toxicity. Potential mechanisms include anti-angiogenesis; anti-proliferative actions through inhibition of DNA replicative synthesis, S-phase arrest, and G(1) arrest; induction of apoptosis; anti-inflammation; and anti-oxidation. Putative molecular targets include p53, Stat3, Cox-2, VEGFR1, AP-1, SP-1, Nrf-2, and MMP-9. For anti-diabetic activity, PGG and analogues appear to improve glucose uptake. However, very little is known about the absorption, pharmacokinetics, and metabolism of PGG, or its toxicity profile. The lack of a large quantity of highly pure PGG has been a bottleneck limiting *in vivo* validation of cancer preventive and therapeutic efficacies in clinically relevant models.

Penta-1,2,3,4,6-O-galloyl-beta-d-glucose (PGG) suppresses the *in vivo* growth of human DU145 and PC-3 prostate cancer xenografts in nude mice, suggesting potential utility as a prostate cancer chemotherapeutic or chemopreventive agent. Our earlier work implicates caspase-mediated apoptosis in DU145 and LNCaP prostate cancer cells as one mechanism for the anticancer activity. We show here that, in the more aggressive PC-3 prostate cancer cell line, PGG induced programmed cell deaths lacking the typical caspase-mediated apoptotic morphology and biochemical changes. In contrast, PGG induced patent features of autophagy, including formation of autophagosomes and lipid modification of light chain 3 after 48 hours of PGG exposure. The "autophagic" responses were also observed in the murine TRAMP-C2 cells. Caspase inhibition exacerbated PGG-induced overall death. As for molecular changes, we observed a rapid inhibition of the phosphorylation of mammalian target of rapamycin-downstream targets S6K and 4EBP1 by PGG in PC-3 and TRAMP-C2 cells but not that of mammalian target of rapamycin itself, along with increased AKT phosphorylation. Whereas the inhibition of phosphatidylinositol 3-kinase increased PGG-induced apoptosis and autophagy, experiments with pharmacologic inducer or inhibitor of autophagy or by knocking down autophagy mediator Beclin-1 showed that autophagy provided survival signaling that suppressed caspase-mediated apoptosis. Knocking down of death receptor-interacting protein 1 kinase increased overall death without changing light chain 3-II or caspase activation, thus not supporting death receptor-interacting protein 1-necroptosis for PGG-induction of autophagy or



other programmed cell death. Furthermore, PGG-treated PC-3 cells lost clonogenic ability. The induction by PGG of caspase-independent programmed cell death in aggressive prostate cancer cell lines supports testing its merit as a potential drug candidate for therapy of caspase-resistant recurrent prostate cancer.

#### *Studies with a novel herbal compound*

Farnesiferol C (FC) is one of the major compounds isolated from *Ferula assafoetida*, an Asian herbal spice used for cancer treatment as a folk remedy. Here, we examined the hypothesis that novel antiangiogenic activities of FC contribute to anticancer efficacy. In human umbilical vein endothelial cells (HUVEC), exposure to the 10 to 40  $\mu\text{mol/L}$  concentration range of FC inhibited vascular endothelial growth factor (VEGF)-induced cell proliferation, migration, invasion, tube formation, and the expression of matrix metalloproteinase-2. In addition, FC inhibited the angiogenic sprouting of VEGF-treated rat aorta in an *ex vivo* model. Furthermore, FC inhibited

the *in vivo* growth of mouse Lewis lung cancer allograft model by 60% ( $P < 0.001$ ) at a daily *i.p.* dosage of 1 mg/kg body weight without any negative effect on the weight of the host

mice. Immunohistochemistry staining showed decreased microvessel density (CD34) and proliferative index (Ki-67) without affecting the apoptotic (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling) index. Mechanistically, FC decreased the binding of VEGF to VEGFR1/Flt-1, but not to VEGFR2/KDR/Flk-1. In terms of early signaling, FC exerted a rapid inhibitory action (examined within 10 minutes) on VEGF-induced autophosphorylation of VEGFR1 without affecting that of VEGFR2. Nevertheless, FC decreased the phosphorylation of most of the kinases downstream of VEGFR2: focal adhesion kinase, Src, extracellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase, and c-jun-NH(2)-kinase without affecting AKT. Computer simulation suggests that FC may inhibit Src or focal adhesion kinase protein activities directly through its docking to their ATP-binding sites. Taken together, the multitargeting actions of FC, particularly VEGFR1 inhibition, may make it a novel drug candidate to complement current VEGF/VEGFR2-targeting antiangiogenic modalities for cancer.



### *Studies with a novel sulindac derivative*

Nonsteroidal anti-inflammatory drugs including sulindac are well documented to be highly effective for cancer chemoprevention. However, their cyclooxygenase (COX)-inhibitory activities cause severe gastrointestinal, renal, and cardiovascular toxicities, limiting their chronic use. Recent studies suggest that COX-independent mechanisms may be responsible for the chemopreventive benefits of nonsteroidal anti-inflammatory drugs and support the potential for the development of a novel generation of sulindac derivatives lacking COX inhibition for cancer chemoprevention. A prototypic sulindac derivative with a N,N-dimethylammonium substitution called sulindac sulfide amide (SSA) was recently identified to be devoid of COX-inhibitory activity yet displays much more potent tumor cell growth-inhibitory activity in vitro compared with sulindac sulfide. In this study, we investigated the androgen receptor (AR) signaling pathway as a potential target for its COX-independent anti-neoplastic mechanism and evaluated its chemopreventive efficacy against prostate carcinogenesis using the transgenic adenocarcinoma of mouse prostate model. The results showed that SSA significantly suppressed the growth of human and mouse prostate cancer cells expressing AR in strong association with G(1) arrest, and decreased AR level and AR-dependent transactivation. Dietary SSA consumption dramatically attenuated prostatic growth and suppressed AR-dependent glandular epithelial lesion progression through repressing cell proliferation in the transgenic adenocarcinoma of mouse prostate mice, whereas it did not significantly affect neuroendocrine carcinoma growth. Overall, the results suggest that SSA may be a chemopreventive candidate against prostate glandular epithelial carcinogenesis.

### *Collaborations*

- Sung-Hoon Kim, Kyunghee University, Korea, to identify and develop novel agents for prostate cancer prevention based on Oriental medicine
- Margot Cleary, Section of Nutrition and Metabolism, on selenium as a preventive agent for prostate cancer with the TRAMP model
- Chengguo Xing, U of M Department of Medicinal Chemistry, for synthesis of decursin-derivatives and isolation of penta galloyl glucose from tannic acid
- Gary Piazza, Southern Research Institute, Birmingham, AL, on the prostate cancer chemoprevention by novel sulindac derivatives devoid of COX-2 inhibitor activity

### *Other Professional Activities*

*Junxuan (Johnny) Lü*

#### *Invited speaker:*

- “Prostate Cancer Chemoprevention by Selenium and Oriental Herbal Compounds”, Rutgers University School of Pharmacy, NJ
- “Prostate Cancer Chemoprevention by Second Generation Selenium”, University of California, Davis, Sacramento, CA
- “Prostate Cancer Chemoprevention by Selenium and Herbal Compounds”, Penn State Medical School Department of Biochemistry and Molecular Biology, Hershey, PA
- “Cancer Chemoprevention by Selenium and Herbal Compounds”, Purdue University Department of Foods and Nutrition, West Lafayette, IN
- “Anti-cancer Activities of Penta-1,2,3,4,6-O-galloyl-beta Glucose”, University of Minnesota Department of Food Science and Nutrition
- “Penta-1,2,3,4,6-O-galloyl-beta Glucose for Cancer Chemoprevention and Treatment”, ChonBuk National University School of Dentistry, JeonJu, South Korea
- “Penta-1,2,3,4,6-O-galloyl-beta Glucose for Cancer Chemoprevention and Treatment”, Seoul National University College of Pharmacy, Seoul, South Korea
- “Penta-1,2,3,4,6-O-galloyl-beta Glucose for Cancer Chemoprevention and Treatment”, China National Conference of Cancer Molecular Pathology, Fourth Military Medical University, Xi’An, China
- “Oriental Herbal Compounds for Prostate Cancer Chemoprevention and Treatment”, 2009 Asia-Pacific Conference of Tumor Biology, Xi’An, China
- “Penta-1,2,3,4,6-O-galloyl-beta Glucose for Cancer Chemoprevention and Treatment”, College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, China
- “Cancer Prevention by Selenium”, KyungHee University, Seoul, South Korea
- Plenary Presentation “Penta-1,2,3,4,6-O-galloyl-beta Glucose for Cancer Chemoprevention, an Update”, KyungHee University CPMDRC International Symposium, Seoul, South Korea

#### *Grant Reviewer:*

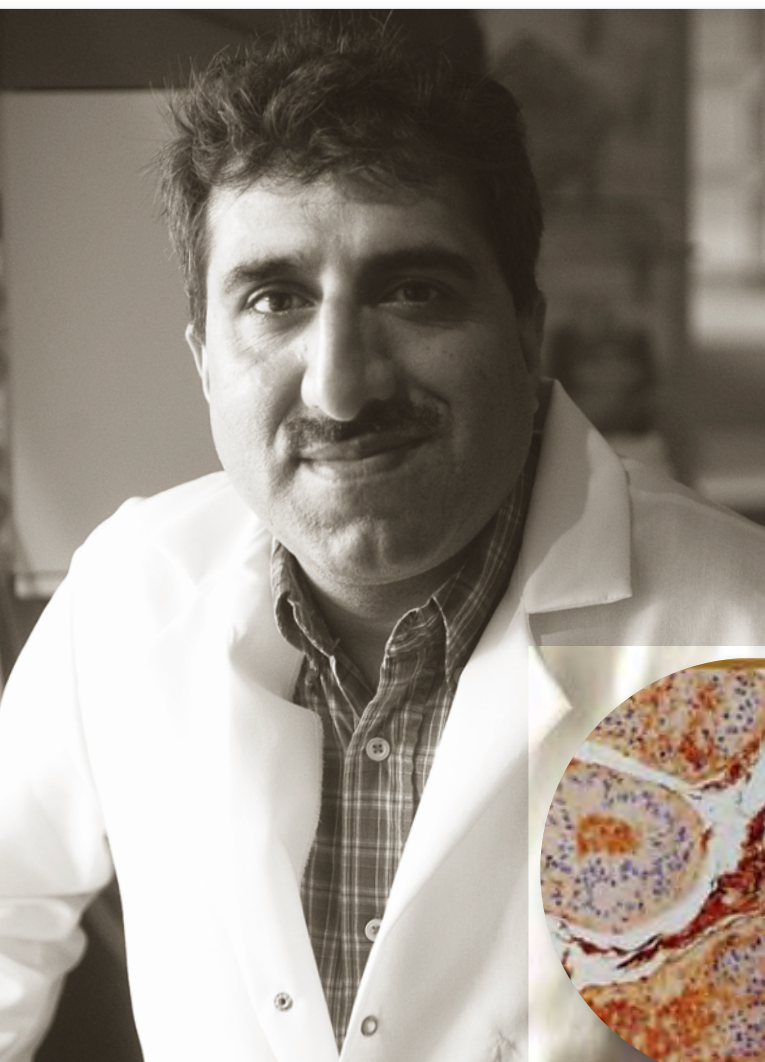
- NIH Special Emphasis Panel ZRG1 OTC-N (02)
- NIH “Dietary Supplement Research Centers: Botanicals (P50)”
- NIH Special Emphasis Panel ZRG1 OTC-B(02)M (Chairperson)
- NIH Cancer Biomarkers Study section

## MOLECULAR CHEMOPREVENTION AND THERAPEUTICS

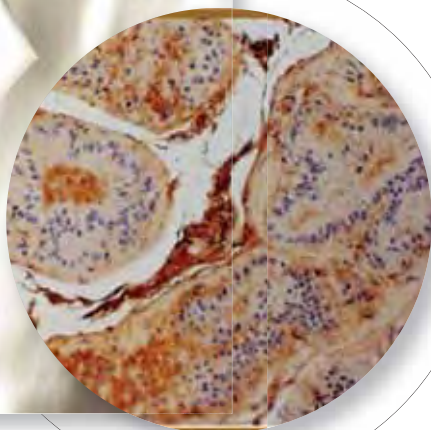
Section Leader

Mohammad Saleem Bhat, Ph.D.

Assistant Professor



24 weeks,  
Transgenic  
adenocarci-  
noma of the  
mouse prostate  
(TRAMP)



Molecular Chemoprevention and Therapeutics is a new research section as of February 2010. The long term goals of this section are the following:

- Understanding the biochemical, cellular and molecular processes crucial for the development of prostate and pancreatic cancer.
- Identifying potential agents that could be used to treat and prevent cancer in humans.

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

### *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) will also 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 casapse-8 inhibitor) and matriptase (a serine protease). The main objective of these studies is to take the bench-side research to the bedside 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) dysregulated 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-renewa-



bility 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 which 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 multimeric gene-repressing complexes) have 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. 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 has been reported to be 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, provide evidence that S100A4 protein, both in its intracellular and extracellular state, plays a tumor promoting role in the development of prostate

*“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.”*

cancer by regulating the function of Nuclear Factor kappa B/Receptor for Advanced Glycation End products molecular circuitry.

### 4. Transition of androgen-dependent prostate cancer to androgen-independent phenotype

Androgen-independent prostate cancer type is a highly aggressive cancer type and interestingly, androgen receptor (which generally responds to androgen) remains active and functional in such disease type. We are studying the mechanism through which androgen receptor becomes functional in prostate cancer patients exhibiting androgen-independent type of disease.



Left to right: Rhiannon Bauman (Intern), Hifzur Siddique, Mohammad Saleem Bhat  
Not pictured: Neelofar Jan Bhat

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

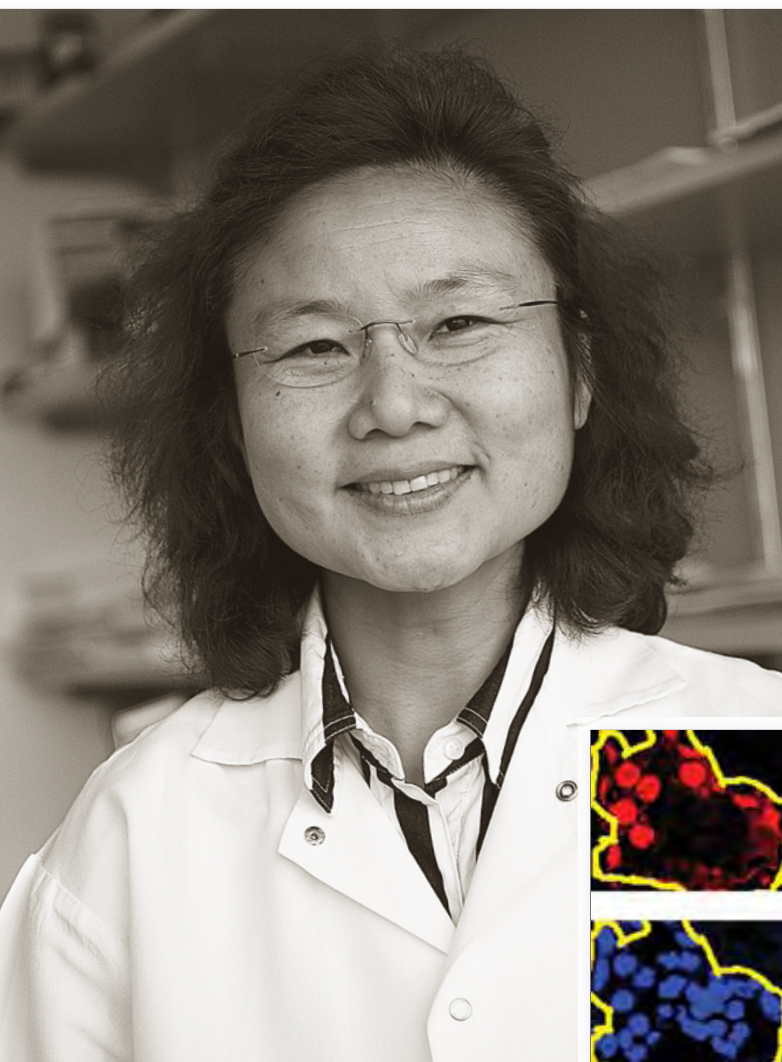
Another major goal of our laboratory is to identify novel and non-toxic agents that could be developed as chemopreventive and chemotherapeutics agents for either inhibiting cancer development or treating cancer in humans. We have identified a non-toxic compound called “Lupeol” exhibiting a potential 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, 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. Our research programs are sponsored by several federal agencies (in the form of research grants) which include National Institutes of Health and the American Institute of Cancer Research.

## TUMOR SUPPRESSORS AND CANCER SUSCEPTIBILITY SYNDROMES

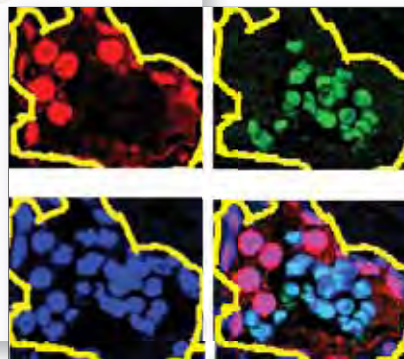
Section Leader

Peiwen Fei, M.D., Ph.D.

Assistant Professor



Tumor suppressor  
signaling in human  
tumor tissues.



Our research interests focus on how tumor suppressors function and what we can learn from cancer susceptibility syndromes. Specifically, we are studying two tumor suppressor signaling pathways, p53 and Fanconi Anemia (FA) signaling pathways, and their implications in tumor suppression and cancer treatment. Our section, which is new to The Hormel Institute as of March, 2010, is funded by an R01 research grant from the National Cancer Institute to study roles of FA signaling pathway in the development of human cancers.

### *A. FA signaling pathway*

Using FA as a unique genetic model system to dissect the FA protein signaling pathway, we determine how FA proteins mediate tumor suppression, and investigate the potential of targeting the FA-BRCA pathway as a therapeutic approach in the treatment of cancer

#### *A1. FA signaling pathway and human cancer*

Our effort began with the discovery that FAVL, a novel variant of FA protein L (FANCL). The extremely high incidence of cancer formation in FA patients prompted us to join with others to investigate how the FA-BRCA pathway is involved in the development of non-FA human tumors. Considering that somatic alterations may alter the FA-BRCA pathway, we started to examine the functional status of the FA-BRCA pathway in 10 randomly selected human tumor cell lines. Interestingly, we found that in a particular lung cancer cell line, Calu-6, activation of Fanconi Anemia Protein D2 (FANCD2) upon MMC treatment was compromised, and furthermore, that this impairment of the FA-BRCA pathway was a result of reduced levels of FANCL (Zhang et al, 2006). We identified this variant of FANCL, named FAVL, and discovered that expression of FAVL is elevated in Calu-6 cells, and 7 more lung cancer cell lines, which lack a functional FA-BRCA pathway to some extent. Whereas it is expressed at lower levels in A549 lung cancer cells, 7 other lung tumor cell lines, and two normal lung cell lines, which harbor an intact FA-BRCA pathway. Moreover, FAVL is also elevated in more than half of 90 cancer tissues samples tested compared with corresponding normal tissues. Importantly, we have determined that overexpression of FAVL compromises FANCD2 activation and confers substantial growth advantages for host cells both in vitro (colony formation in soft agar) and in vivo (xenograft tumor formation). Together, these results suggest that FAVL can promote tumor formation by targeting the FA-BRCA tumor



suppressor pathway (Zhang et al, 2010). Therefore, we have engaged in thoroughly investigating the molecular and mechanistic functions of FAVL as a trigger for altered transduction of the FA-BRCA pathway, thus leading to genomic instability.

#### *A2. The regulation and function of Fanconi Anemia Protein D2 (FANCD2)*

Nearly 95% of Fanconi Anemia (FA) cases result from an improper regulation and expression of FANCD2. The severe bone marrow failure and an extremely high cancer incidence displayed by FA strongly support that FANCD2 plays crucial roles in protection from FA as well as human cancer. However, it is poorly understood how FANCD2 functions.

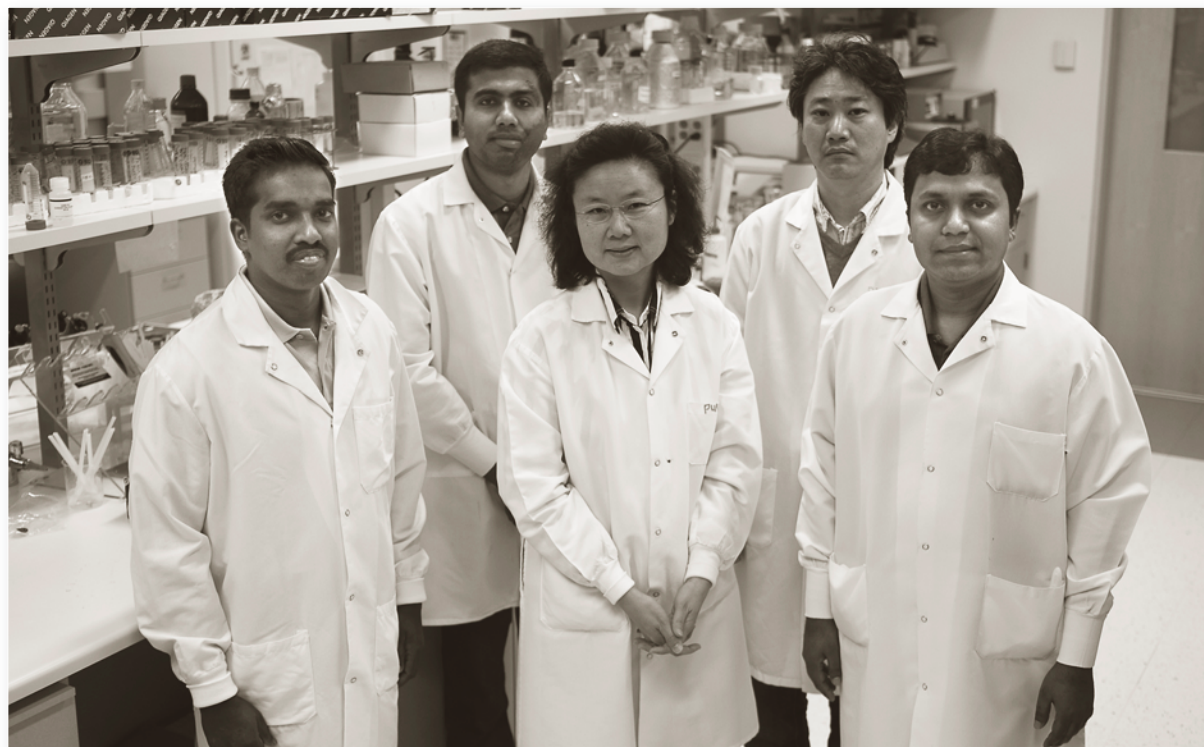
FANCD2 has been proposed to have roles in multiple types of DNA damage repair, including postreplication repair, but its precise function has not been addressed within the framework of specific repair mechanisms. The exception is homologous recombination, but these results

have been considered controversial. Among all repair mechanisms, human postreplication repair has been explored the least. It is generally known as a DNA damage response pathway initiated from stalled replication forks, which helps maintain genome stability. Within this pathway, the monoubiquitinated PCNA, known to be regulated by human homologues of yeast rad6 (HHR6), works in concert with lesion bypass polymerases to process an error-prone or error-free repair. However, the functional mechanisms underlying this repair process in humans are unclear.

We have found that FANCD2 is not only regulated by HHR6 (Zhao et al, 2008) but is also capable of cooperating with a lesion bypass polymerase eta and, possibly, PCNA. Apparently, FANCD2 is closely involved with the molecular players that

**“The expected results of our studies will provide mechanistic insights into the selection pressure that occurs under hypoxia, especially the early-stage function of p53 tumor suppressor protein, and will certainly aid in developing additional tools for fighting against human cancer.”**

have important roles in postreplication repair. Therefore, as suggested, FANCD2 does have roles in postreplication repair, although its roles in other repair mechanisms are unclear and need to be determined. We thus investigate how FANCD2 is involved in the HHR6 signaling to maintain genome stability.



Left to right: Panneer Selvam, Sinto Sebastian Chirackal, Peiwen Fei, Hwan Ki Park, Suvamoy Datta

Our studies are expected to not only provide insights into FANCD2 function but to also advance the understanding of molecular controls over human postreplication repair. Moreover, insights obtained from these studies could lead to the development and availability of additional tools for fighting against both FA as well as human cancer.

#### *B. P53 Signaling Pathway*

Investigating the mechanisms underlying function of p53 initiated by hypoxia,

which is encountered mostly by tumor cells.

Solid tumors are poorly oxygenated compared with normal tissues and possess regions of hypoxia. Antiproliferative effect induced by hypoxia is one of the mechanisms by which stressed cells can be destroyed. In response to hypoxia, activated hypoxia inducible factor 1 (HIF-1) activates genes involved in angiogenesis, anaerobic metabolism, and iron homeostasis which all contribute to adaptive survival. On the other hand, activated HIF-1 also activates proapoptotic members of the Bcl-2 family, including Bnip3L, which induces cell death and plays an essential role in cardiac cell death during hypoxia. Under severe hypoxia, p53 protein probably is stabilized through HIF-1-dependent, and -independent mechanisms. Tumor cells expressing wt p53 are targeted for elimination through its anti-proliferative function under hypoxic conditions. However, hypoxia induces p53 to mutate. The less oxygen, the more mutations in the p53 gene, so cancer cells are not killed; instead, they proliferate. Thus, p53 is a key regulator of proliferation or survival under hypoxia during tumor evolution or progression.

Previous studies involved searching for p53 target genes that can be upregulated by wt p53 under normoxia and hypoxia to elucidate how p53 exerts its tumor suppressor function under hypoxia (Fei et al, 2004). We found that Bnip3L is a proapoptotic transcriptional target of p53. Its knockdown promotes tumorigenicity substantially in mouse tumor xenograft models. Therefore, Bnip3L appears to be the first identified, likely representing a mediator of p53-dependent apoptosis under hypoxia and providing a novel mechanism by which p53 acts as a tumor suppressor *in vivo*.

To continue the study on tumor suppressor activity of p53 initiated by hypoxia, an approach similar to that mentioned above was used. Two novel authentic targets of p53 were found, which can be upregulated by wt p53 under normoxia and hypoxia. These targets are known to be involved in the metabolism of RNA and DNA respectively, representing another novel mechanism by which p53 acts as an *in vivo* tumor suppressor.

The expected results of our studies will provide mechanistic insights into the selection pressure that occurs under hypoxia, especially the early-stage function of p53 tumor suppressor protein, and will certainly aid in developing additional tools for fighting against human cancer.





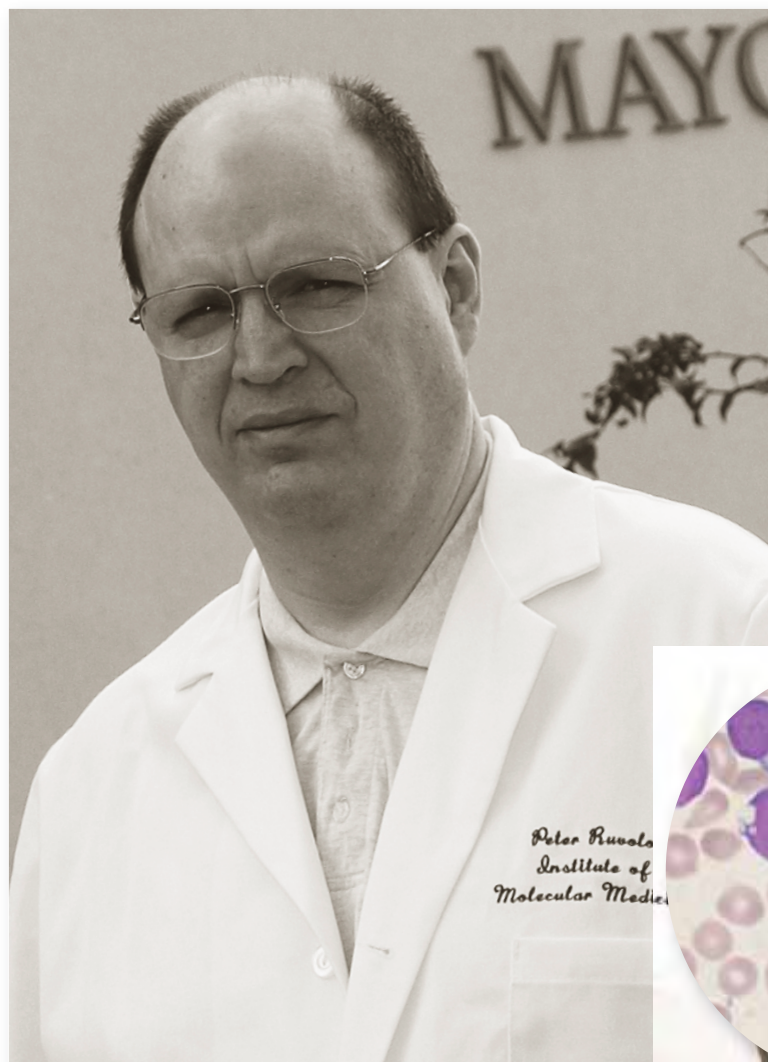
## SIGNAL TRANSDUCTION AND APOPTOSIS

Section Leader

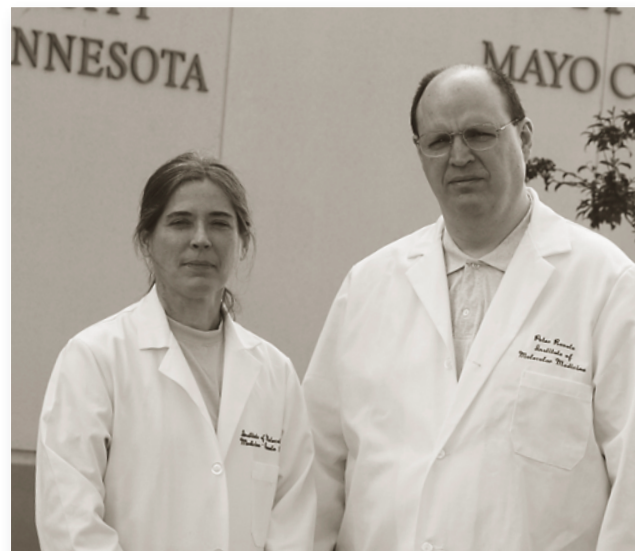
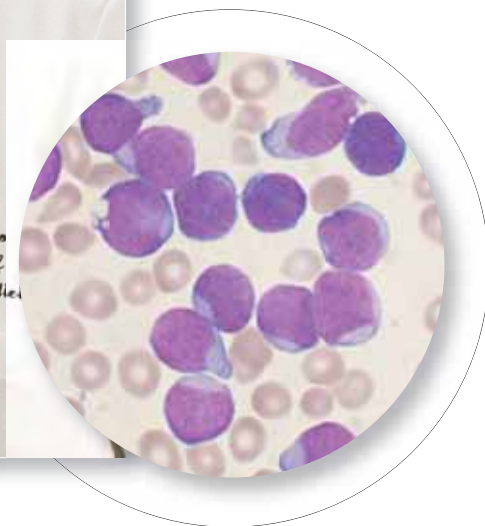
Peter Ruvolo, Ph.D.

Assistant Professor

The Signal Transduction and Apoptosis section continued its research which involved identifying the various cell signaling pathways that regulate cell death and ultimately influence tumor development and drug resistance in cancers such as leukemia and lung cancer. Although acute lymphoblastic leukemia (ALL) is the most common malignancy among children and boasts cure rates ~ 80%, 20% of these children continue to relapse each year making relapsed ALL the 5th most common cancer in pediatrics and the second most common cause of death due to a disease. Novel agents and/or improved therapies are therefore greatly needed for this population of children. Recently, it was found that the dsRNA dependent Protein Kinase (PKR) is basally active in ALL cell lines. This finding is unexpected as PKR was believed to be activated only during stress. In the B-precursor ALL cell line REH, PKR was found to activate the pro-survival kinase AKT. On the other hand, PKR is necessary for drug-induced cell death in REH cells. These findings suggest that PKR may promote cell survival in ALL cells as well as be essential for cell death in response to therapy. Initial data has indicated that PKR is indeed active in ALL blast cells from patients and thus PKR may prove to be a target for treating ALL.



Stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia.



Vivian Ruvolo and Peter Ruvolo



#### 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 11 research sections for their many ongoing research projects. Each of the Institute's cancer research departments is dedicated to preventing or controlling cancer.

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"The outstanding research achievement of The Hormel Institute reflects the collaborative efforts of many. Our team represents unparalleled leaders, world-class faculty and staff and globally recognized medical research partners. By working together, we are improving the health of the world."

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— Dr. Zigang Dong, Executive Director



Left to right: Michelle Jacobson, Jennifer Mittelsted, Ellen Kroc, Teri Johnson, Andria Hansen  
Not pictured: Audrey Colligan, Melissa Fortsch



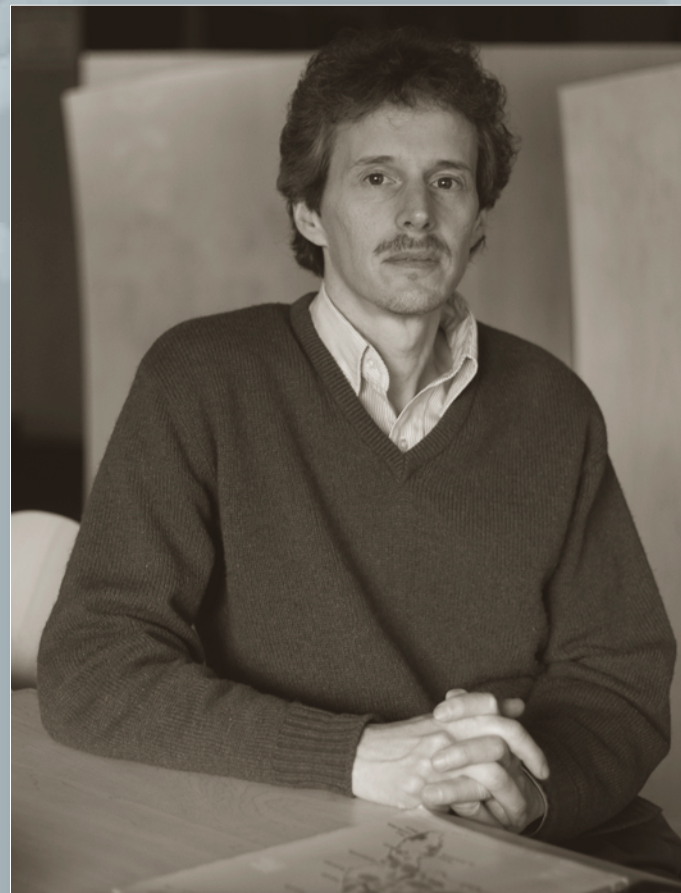


LIBRARIAN  
Andy Lucas

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.

Todd Schuster  
Senior Lab Technician

Schuster operates, maintains and instructs scientists about the shared instruments used at The Hormel Institute for cancer research including FACs cell sorter, FACs calibur flow cytometer, real time PCR, and confocal and fluorescent microscopes.





PUBLIC RELATIONS AND DEVELOPMENT  
Gail Dennison

World-wide recognition and support of The Hormel Institute's cutting edge cancer research continued to grow throughout 2009-10, through the collective efforts of the Institute, our leaders and our partners. We remain thankful for those who support the vision of the Institute's continued growth and development, and its impact worldwide on scientific progress, its impact on humanity through life-enhancing discoveries and its impact locally through adding economic strength and social vibrancy to our community:

- The Hormel Foundation
- Hormel Foods Corporation
- Mayo Clinic - Rochester
- U.S. Representative Tim Walz



- U.S. Senators Amy Klobuchar and Al Franken
- Minnesota State Senator Dan Sparks
- Minnesota State Representative Jeanne Poppe
- Minnesota State Representative Robin Brown
- Austin Area Chamber of Commerce
- Austin Area Foundation
- Austin Convention & Visitors Bureau
- BioBusiness Alliance of Minnesota
- City of Austin
- Development Corporation of Austin
- GRAUC – Greater Rochester Advocates of Universities and Colleges
- IBM Rochester
- LifeScience Alley
- Mower County
- University of Minnesota-Rochester
- Riverland Community College
- Southern Minnesota Initiative Foundation
- Volunteers (led by Gretchen Ramlo)



## 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.

### *Office Staff*

Betsy Mentel, Executive Office and Administrative Specialist

Tonya Poorman, Principal Office and Administrative Specialist

Becky Smit, Principal Accounts Specialist



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Left to right: Betsy Mentel, Dr. Ann M. Bode, Becky Smit, Tonya Poorman





(Left to right) Front row: Rose Srock, Craig Jones  
Second row: Ryan Wiersma, Mike Conway  
Third row: Theresa Tucker, Gary Bush, Tim Lastine

RESEARCH SUPPORT SERVICES (RSS)  
DISTANCE OUTREACH AND EDUCATION (DOE)  
Supervisor: Craig Jones

It has been another exciting year for RSS. The Blue Gene supercomputing project is continuing and has been expanded to include two 3D modeling systems located in the large conference room and the seminar room. These systems use polarized light with inexpensive glasses facilitating detailed visualization for larger groups. We have also added a couple more general purpose molecular modeling workstations. Of course, we continue to provide instrument maintenance, 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 work load.

Our DOE program, in cooperation with The Southern Minnesota Internet Group (SMIG), is making technology available to many rural citizens throughout a large area of Southern Minnesota. The DOE program is configured to be entirely self-sustaining, which gives us the growth potential and flexibility required to provide community-based education and technical support now and in the future. SMIG is a non-profit Minnesota corporation with expressed goals consistent with The Hormel Institute. It is governed by a board of directors selected from the community. The board ensures that our DOE program remains true to the community and its mission. This year, in a cooperative effort between SMIG and the Austin Utilities, Austin has a city-wide wireless system. Our efforts with many of the local school districts, non-public schools, small libraries, and non-profit organizations have improved network technology and Internet availability for public use. We are also helping area organizations with promotion and visibility by assisting with web development and web space.

Serving as the building coordinator of the beautiful new facility has been great. We have set up laboratories for the new research section leaders and remodeled a space in the Annex basement for an X-ray diffraction system. As we settle into our new facility, we continue to increase the overall efficiency of its use.





Left to right: Duane Graff, Norman Johnson, Mark Severtson, Randy Johnson  
Not pictured: Ronald Skjeveland, Donald Bennett, Tommy Wobschall

## 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 tradesman 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 selected undergraduate students work in the Summer Undergraduate Research Experience (SURE) Program with The Hormel Institute scientists. The students work on research projects to expand their knowledge of basic research and to 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.



(Left to right) Front row: Lisa Wester, Matt Lindell, Katie Hoff  
Second row: Kari Peterson, Rhiannon Bauman, Andrew Maiers  
Third row: Jessica Neumann, Sarah Ewing  
Fourth row: Johnathan Wilson, Tana Lukes, Maggie Craven

# ICRT

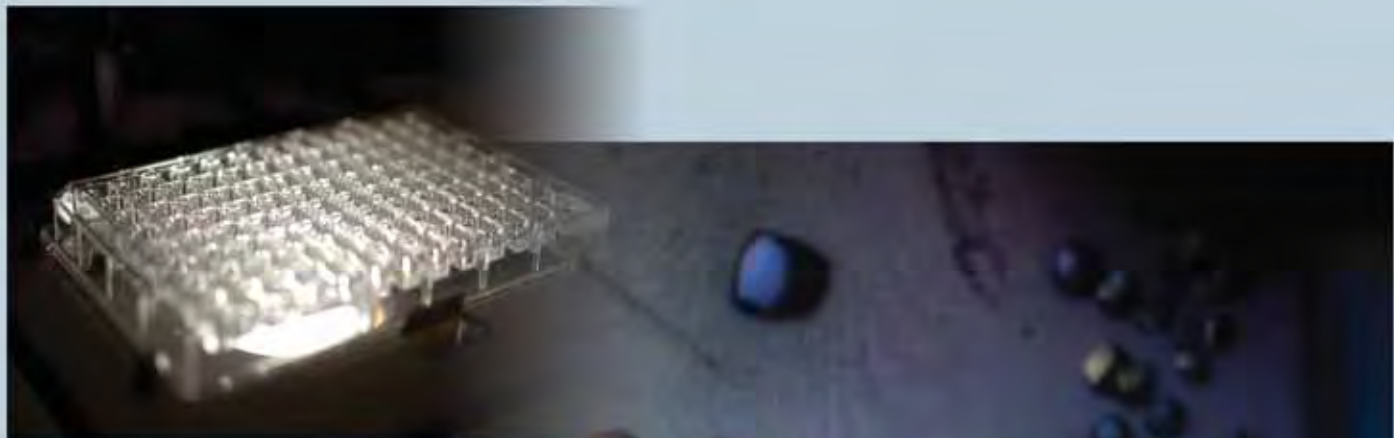
International Center of Research Technology

The Hormel Institute Expansion Project provided space to develop the International Center of Research Technology (ICRT) housed in the new medical research center building.

The ICRT houses the world's most advanced technologies, including IBM's Blue Gene/L supercomputer, used to accelerate cancer research discoveries. In the quest to develop non-toxic, chemo-preventive cancer prevention and control drugs, the Blue Gene/L offers high performance computing technology so The Hormel Institute can achieve groundbreaking discoveries in a timeframe previously not possible.

Instruments and technologies provided within the ICRT at The Hormel Institute include:

- Protein Crystallography Lab
- Confocal Microscope
- Cell Sorter
- 3-D Imaging Equipment
- Blue Gene/L supercomputer



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accelerate cancer  
research discoveries

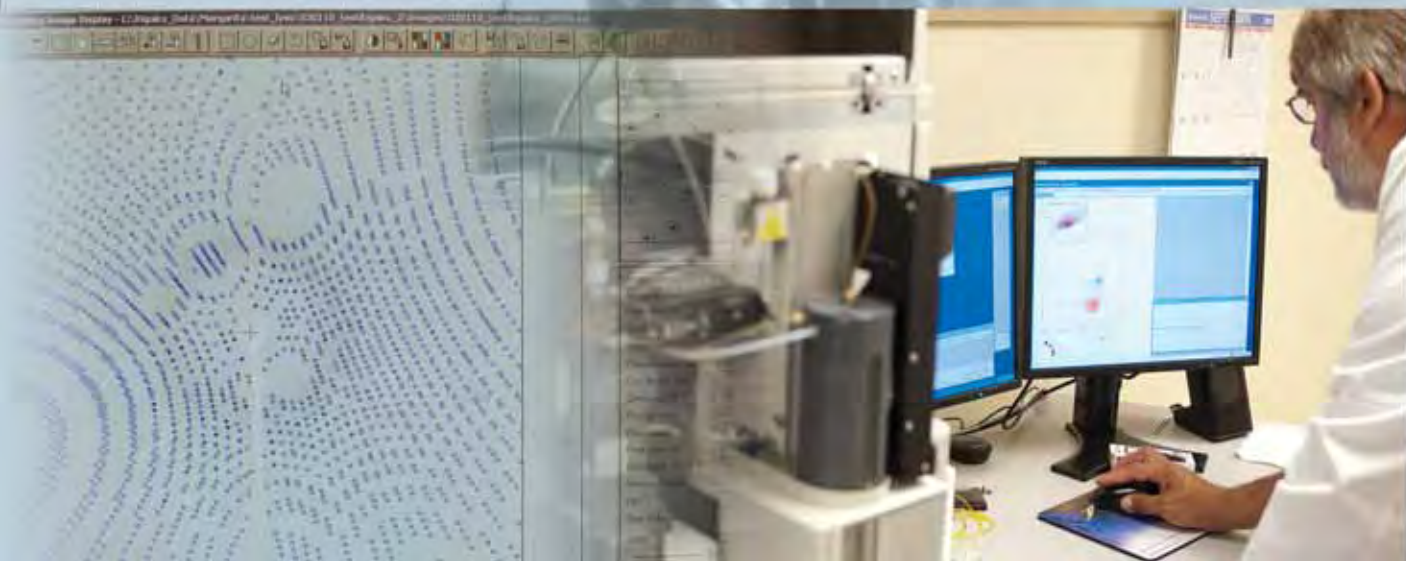
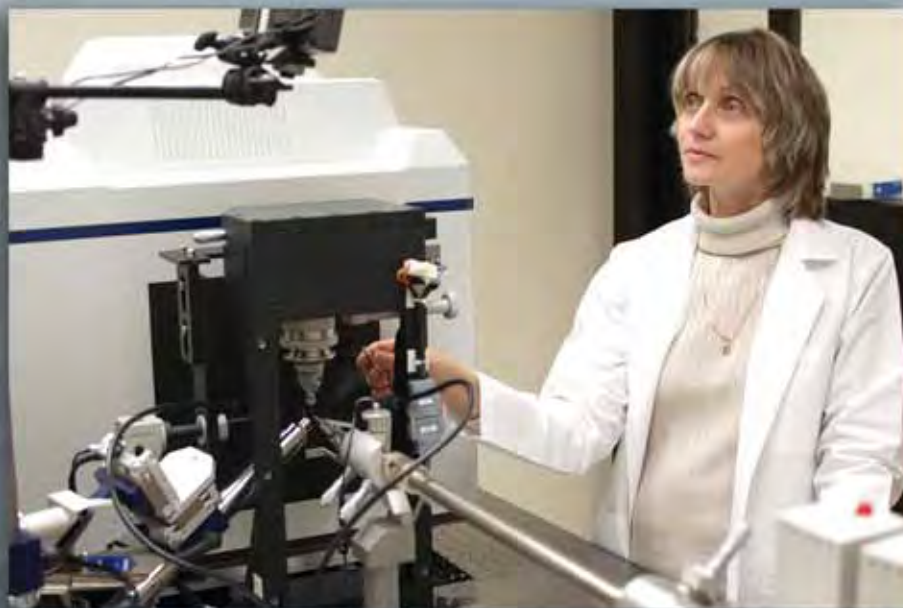
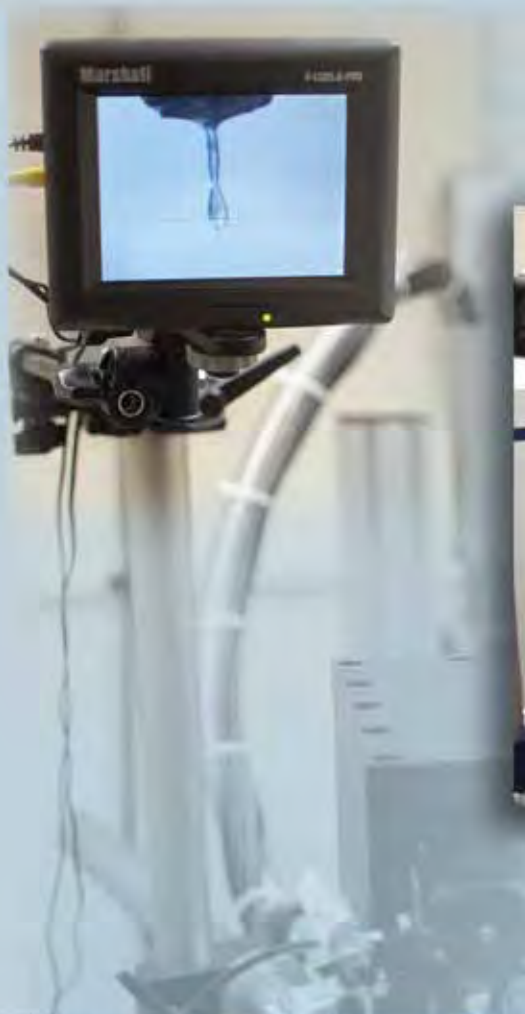
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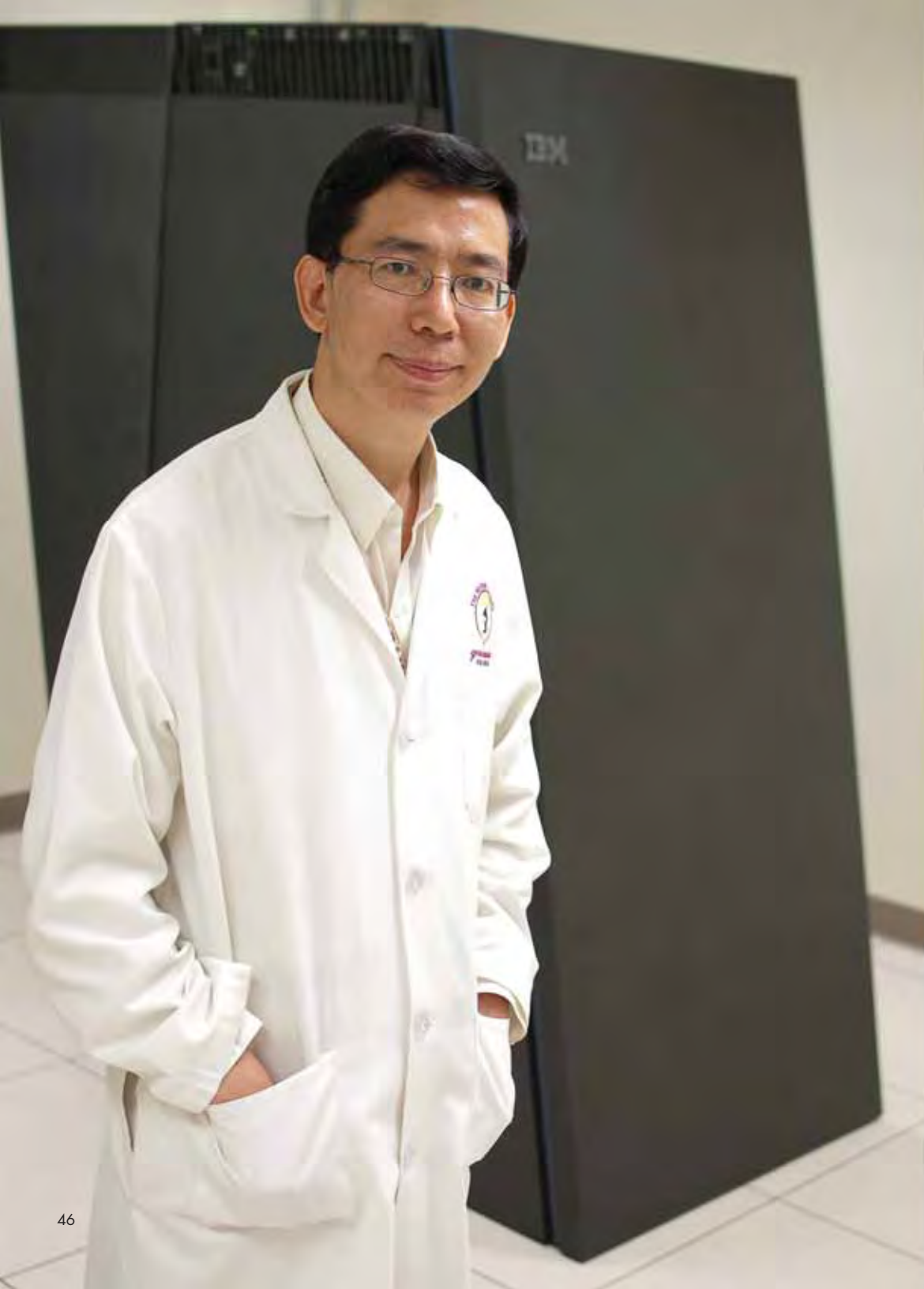




## Protein Crystallography Lab

With recent developments The Hormel Institute has acquired several substantial pieces of cutting edge technologies, including the robotics required for protein crystallography (left) and a complete defraction system (right) to view and solve protein crystal structures. In addition, the Institute acquired technology to allow sorting of individual cell populations (below).





"The Hormel Institute is indebted to our leaders for providing these vital instruments and technologies so research can advance rapidly. Special recognition must be given to our elected leaders –U.S. Representative Tim Walz and U.S. Senator Amy Klobuchar – for the nearly \$2 million in appropriations secured for the advancement of the International Center of Research Technology."

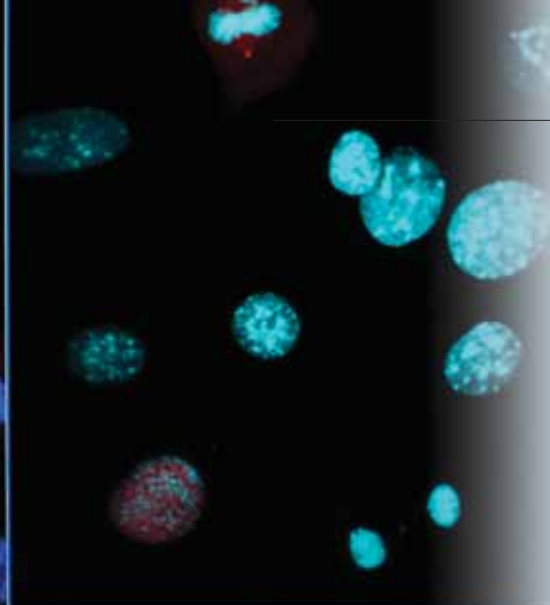
— Dr. Zigang Dong, Executive Director

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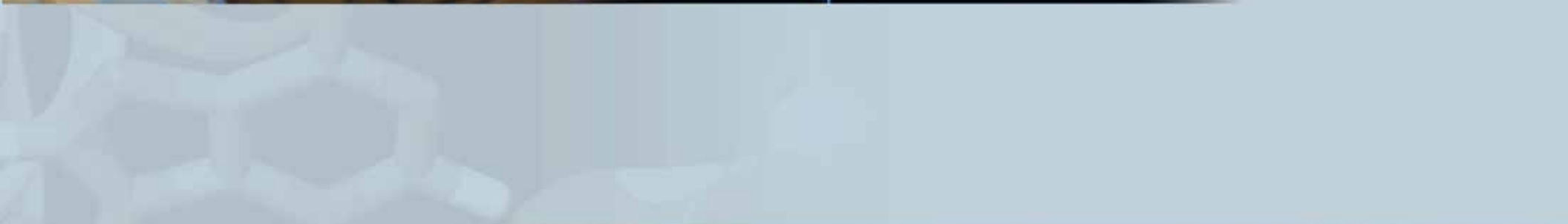
Bioinformatics and  
computational biology  
... using technology to  
advance science.

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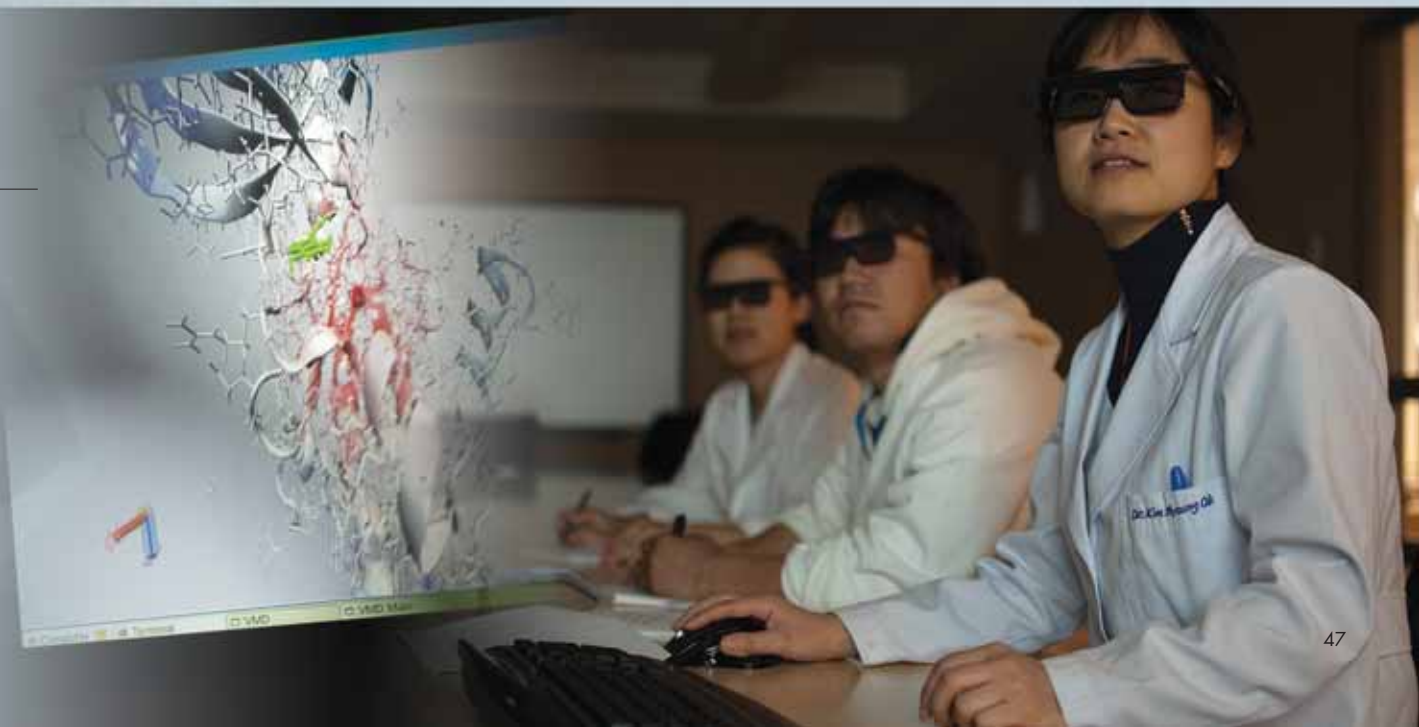




The confocal microscope allows researchers to acquire 3-D images of cells and tissues to facilitate study.



In the field of drug discovery, proteins comprise the most popular targets for small molecules. The specificity of a small molecule for a protein can be attributed to the interactions between them. At the atomic level, the visualization of these interactions in 3-D provides our scientists the necessary molecular information to create better drugs that can target proteins of interest specifically and selectively.





We are proud to join our Hormel Institute staff, led by Dr. Zigang Dong, in announcing new research plans to support our already strong commitment to medical science accompanied by ultra-modern advances.

Our new science addition will provide in-depth reach and capacity for Mayo Clinic where we will enlarge our plans for major medical research.

This thrust will support further science while adding new edges to our work already underway with the University of Minnesota. Exciting challenges and tremendous commitment for medical science!

*Richard L. Knowlton  
Chairman,  
The Hormel Foundation  
Former President, CEO and Chairman of the Board  
Hormel Foods Corporation  
Officer of Hormel Foods Corporation*



"The Hormel Institute is a successful collaboration of many groups – Hormel Foods, Mayo Clinic, the University of Minnesota, the City of Austin and also the federal support that comes from NIH – the National Institutes of Health. In Minnesota, we believe in science and technology. The accomplishments of The Hormel Institute are significant for our state and will help us grow in the important bioscience industry."

*Senator Amy Klobuchar  
U.S. Senate  
Minnesota*

"Mayo Clinic is proud of its historic partnership with The Hormel Foundation and its support and participation in the activities of The Hormel Institute. Mayo is committed to strengthening and building these relationships and is enthusiastic about the opportunities in the future. Our ongoing pledge to the Institute expresses Mayo Clinic's dedication to our partnership."

*Glenn Forbes, M.D.  
Medical Director  
Former Chief Executive Officer  
Mayo Clinic Rochester*







"The Hormel Institute has established a clear reputation as a world-class research facility that creates widespread impacts at the local, state, national, and global levels. The groundbreaking discoveries made by Hormel researchers are a source of great pride for the University of Minnesota."

*R. Timothy Mulcahy, Ph.D.  
Vice President for Research  
University of Minnesota*

"We are proud to be a partner supporting the important cancer research work of The Hormel Institute. Their collaborations with University of Minnesota and Mayo Clinic as well as research institutions around the world bring new and important jobs to rural Minnesota that compete with no others – and their work in cancer research is aimed for the public good. This is exactly the type of project that I will tirelessly advocate for in Congress because it makes sense both from a moral and a fiscal perspective."

*Representative Tim Walz  
U.S. House of Representatives  
First Congressional District*





# THE HORMEL INSTITUTE PUBLICATIONS

JULY 1, 2009 — JUNE 30, 2010

- H.I. No. 1688  
*Resveratrol directly targets COX-2 to inhibit carcinogenesis*  
Zykova T, Zhu F, Zhai X, Ma WY, Ermakova SP, Lee KW, Bode AM, Dong Z  
Mol Carcinog. Oct;47(10):797-805 (2008)
- H.I. No. 1689  
*Mammary tumor development from T47-D human breast cancer cells in obese ovariectomized mice with and without estradiol supplements*  
Nkhata K, Ray A, Dogan S, Grande JP, Cleary MP  
Breast Cancer Res. Treat. 114:71-83 (2009)
- H.I. No. 1690  
*Intermittent calorie restriction delays prostate tumor detection and increases survival time in TRAMP mice*  
Bonorden M, Rogozina O, Kluczy C, Grossmann ME, Grambsch PL, Grande JP, Perkins S, Lokshin A, and Cleary MP  
Nutrition and Cancer 61: 265-275 (2009)
- H.I. No. 1691  
*Superior in vivo inhibitory efficacy of methylseleninic acid against human prostate cancer over selenomethionine or selenite*  
Li GX, Lee HJ, Wang Z, Hu H, Liao JD, Watts JC, Combs GF Jr, Lü J  
Carcinogenesis 29(5):1005-12 (2008)
- H.I. No. 1693  
*Modulation of cell signal transduction by tea and ginger*  
Bode A, Dong Z  
In: Z. Dong, L. Packer, E. Cadenas, Y-J. Surh (eds.), Dietary Modulation of Cell Signaling Pathways, Chapter 2, pp. 45-74, Boca Raton, Florida: CRC Press. (2008)
- H.I. No. 1694  
*Cocoa procyanidins suppress transformation by inhibiting mitogen-activated protein kinase kinase*  
Kang NJ, Lee KW, Lee DE, Rogozin EA, Bode AM, Lee HJ, Dong Z  
J Biol Chem. Jul 25;283(30):20664-73 (2008)
- H.I. No. 1696  
*Human glycolipid transfer protein (GLTP) genes: organization, transcriptional status and evolution*  
Zou X, Chung T, Malakhova M, Pike H, Brown RE  
BMC Genomics 9, 72 (2008)
- H.I. No. 1699  
*p21 activated kinase 5 activates Raf-1 and targets it to mitochondria*  
Wu X, Carr HS, Dan I, Ruvolo PP, Frost JA  
J Cell Biochem.;105:167-175 (2009)
- H.I. No. 1700  
*Cyclin-dependent kinase 3-mediated activating transcription factor 1 phosphorylation enhances cell transformation*  
Zheng D, Cho YY, Lau AT, Zhang J, Ma WY, Bode AM, Dong Z.  
Cancer Res.; 68(18):7650-60 (2008)
- H.I. No. 1701  
*Balance of adiponectin and leptin modulates breast cancer cell growth*  
Grossman ME, Ray A, Dogan S, Mizuno NK, Cleary MP  
Cell Research 18:1-3 (2008)
- H.I. No. 1702  
*Penta-1,2,3,4,6-O-Gallaoyl-B-D-Glucose Induces p53 and Inhibits STAT3 in Prostate Cancer cells in vitro and suppresses prostate xenograft tumor growth in vivo*  
Hu H, Lee HJ, Jiang C, Zhang J, Wang L, Zhao Y, Xiang Q, Lee E-O, Kim S-H, Lü J  
Molecular Cancer Therapeutics Nov 7;(11): 3654 (2008)
- H.I. No. 1703  
*Delphinidin attenuates neoplastic cell transformation by directly inhibiting Raf/MEK/ERK activities*  
Kang NJ, Lee KW, Kwon JY, Heo Y-S, Rogozin EA, Bode AM, Lee HJ, Dong Z  
Cancer Prev Res (Phila Pa) 1(7):522-31 (2008)
- H.I. No. 1704  
*(-)-Epigallocatechin gallate regulates CD3-mediated T cell receptor signaling in leukemia through the inhibition of ZAP-70 kinase*  
Shim J-H, Choi HS, Pugliese A, Choi BY, Bode AM, Dong Z  
J Biol Chem. 283(42):28370-9 (2008)
- H.I. No. 1705  
*PKR regulates B56alpha -mediated BCL2 phosphatase activity in acute lymphoblastic leukemia derived REH cells*  
Ruvolo VR, Kurinna SM, Karanjeet KB, Schuster TF, Martelli AM, McCubrey JA, Ruvolo PP  
J Biol Chem. 283(51):35474-85 (2008)
- H.I. No. 1706  
*Ceramide promotes apoptosis in chronic myelogenous leukemia-derived K562 cells by a mechanism involving caspase-8 and JNK*  
Nica AF, Tsao CC, Watt JC, Jiffar T, Kurinna S, Jurasz P, Konopleva M, Andreeff M, Radomski MW, Ruvolo PP  
Cell Cycle 7: 3362 – 3370 (2008)
- H.I. No. 1707  
*Synthetic triterpenoids have cytotoxicity in pediatric acute lymphoblastic leukemia cell lines but cytotoxicity is independent of induced ceramide increase in MOLT-4 cells*  
Kong G, Wang D, Wang H, Wu J, Bielawski J, Konopleva M, Andreeff M, Ruvolo PP, Maurer BJ  
Leukemia 22: 1258-62 (2008)
- H.I. No. 1708  
*Side chain oxygenated cholesterol regulates cellular cholesterol homeostasis through direct sterol-membrane interactions*  
Gale SE, Westover EJ, Dudley N, Krishnan K, Merlin S, Scherrer DE, Han X, Zhai X, Brockman HL, Brown RE, Covey DF, Schaffer JE, Schlesinger P, Ory DS  
J Biol Chem. 284(3):1755-64 (2009)
- H.I. No. 1709  
*Mitochondria-cytochrome C-caspase-9 cascade mediates isorhamnetin-induced apoptosis*  
Lee HJ, Lee HJ, Lee EO, Ko SG, Bae HS, Kim CH, Ahn KS, Lu J, Kim SH  
Cancer Lett. 270(2):342-53 (2008)
- H.I. No. 1710  
*Myricetin suppresses UVB-induced skin cancer by targeting Fyn*  
Jung SK, Lee KW, Byun S, Kang NJ, Lim SH, Heo YS, Bode AM, Bowden GT, Lee HJ, Dong Z  
Cancer Res. 68(14):6021-9 (2008)
- H.I. No. 1711  
*Anti-invasive and antimetastatic activities of ribosomal protein S6 kinase 4 in breast cancer cells*  
Thakur A, Sun Y, Bollig A, Wu J, Biliran H, Banerjee S, Sarkar FH, Liao DJ  
Clin Cancer Res. 14(14):4427-36 (2008)
- H.I. No. 1712  
*(-)-Epigallocatechin gallate regulates CD3-mediated T cell receptor signaling in leukemia through the inhibition of ZAP-70 kinase*  
Shim JH, Choi HS, Pugliese A, Lee SY, Chae JI, Choi BY, Bode AM, Dong Z  
J Biol Chem. 283(42):28370-9 (2008)
- H.I. No. 1713  
*Protein phosphatase-2A is a target of epigallocatechin-3-gallate and modulates p53-Bak apoptotic pathway*  
Qin J, Chen HG, Yan Q, Deng M, Liu J, Doerge S, Ma W, Dong Z, Li DW  
Cancer Res. 68(11):4150-62 (2008)  
Erratum in: Cancer Res. 2008 Aug 15;68(16):6859
- H.I. No. 1714  
*Cyclin-dependent kinase-3-mediated c-Jun phosphorylation at Ser63 and Ser73 enhances cell transformation*  
Cho YY, Tang F, Yao K, Lu C, Zhu F, Zheng D, Pugliese A, Bode AM, Dong Z  
Cancer Res. 69(1):272-81(2009)
- H.I. No. 1715  
*Quinoline derivative KB3-1 potentiates paclitaxel induced cytotoxicity and cycle arrest via multidrug resistance reversal in MES-SA/DX5 cancer cells*  
Koo JS, Choi WC, Rhee YH, Lee HJ, Lee EO, Ahn KS, Bae HS, Ahn KS, Kang JM, Choi SU, Kim MO, Lu J, Kim SH  
Life Sci. 83(21-22):700-8 (2008)
- H.I. No. 1716  
*Human GLTP and mutant forms of ACD11 suppress cell death in the Arabidopsis acd11 mutant*  
Petersen NH, McKinney LV, Pike H, Hofius D, Zakaria A, Brodersen P, Petersen M, Brown RE, Mundy J  
FEBS J. 275(17):4378-88 (2008)
- H.I. No. 1717  
*Stabilization of quercetin paradoxically reduces its proapoptotic effect on UVB-irradiated human keratinocytes*  
Olson ER, Melton T, Dong Z, Bowden GT  
Cancer Prev Res (Phila Pa). Oct;1(5):362-8 (2008)
- H.I. No. 1718  
*Phase diagrams of lipid mixtures relevant to the study of membrane rafts*  
Goñi FM, Alonso A, Bagatolli LA, Brown RE, Marsh D, Prieto M, Thewalt JL  
Biochim Biophys Acta. Nov-Dec;1781(11-12):665-84 (2008)



- H.I. No. 1719  
*Chemopreventive effect of kava on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone plus benzo[a]pyrene-induced lung tumorigenesis in A/J mice*  
Johnson TE, Kassie F, O'Sullivan MG, Negia M, Hanson TE, Upadhyaya P, Ruvolo PP, Hecht SS, Xing C  
Cancer Prev Res (Phila Pa). Nov;1(6):430-8 (2008)
- H.I. No. 1720  
*The resveratrol analogue 3,5,3',4',5'-pentahydroxy-trans-stilbene inhibits cell transformation via MEK*  
Lee KW, Kang NJ, Rogozin EA, Oh SM, Heo YS, Pugliese A, Bode AM, Lee HJ, Dong Z  
Int J Cancer. 123(11):2487-96 (2008)
- H.I. No. 1721  
*Caffeic acid, a phenolic phytochemical in coffee, directly inhibits Fyn kinase activity and UVB-induced COX-2 expression*  
Kang NJ, Lee KW, Shin BJ, Jung SK, Hwang MK, Bode AM, Heo YS, Lee HJ, Dong Z  
Carcinogenesis. Feb;30(2):321-30 (2009)
- H.I. No. 1722  
*Epstein-Barr virus latent membrane protein 1 mediates serine 25 phosphorylation and nuclear entry of annexin A2 via PI-PLC- PKCalpha/PKCbeta pathway*  
Luo W, Yan G, Li L, Wang Z, Liu H, Zhou S, Liu S, Tang M, Yi W, Dong Z, Cao Y  
Mol Carcinog. Dec;47(12):934-46 (2008)
- H.I. No. 1723  
*In vivo anti-cancer activity of Korean Angelica gigas and its major pyranocoumarin decursin*  
Lee HJ, Lee HJ, Lee EO, Lee JH, Lee KS, Kim KH, Kim SH, Lü J  
Am J Chin Med.;37(1):127-42 (2009)
- H.I. No. 1724  
*Transient receptor potential type vanilloid 1 suppresses skin carcinogenesis*  
Bode AM, Cho YY, Zheng D, Zhu F, Ericson ME, Ma WY, Yao K, Dong Z  
Cancer Res. 69(3):905-13 (2009)
- H.I. No. 1725  
*The prolyl isomerase Pin1 interacts with a ribosomal protein S6 kinase to enhance insulin-induced AP-1 activity and cellular transformation*  
Lee NY, Choi HK, Shim JH, Kang KW, Dong Z, Choi HS  
Carcinogenesis. Apr;30(4):671-81 (2009)
- H.I. No. 1726  
*c-Jun N-terminal kinase 1 phosphorylates Myt1 to prevent UVA-induced skin cancer*  
Choi HS, Bode AM, Shim JH, Lee SY, Dong Z  
Mol Cell Biol. Apr;29(8):2168-80 (2009)
- H.I. No. 1727  
*Cross-sectional analysis of intermittent versus chronic caloric restriction in the TRAMP mouse*  
Bonorden MJ, Rogozina OP, Kluczny CM, Grossmann ME, Grande JP, Lokshin A, Cleary MP  
Prostate. 69(3):317-26 (2009)
- H.I. No. 1728  
*Signal transduction molecules as targets for cancer prevention*  
Bode AM, Dong Z  
Sci Signal. 2(59):mr2 (2009)
- H.I. No. 1729  
*Penta-O-galloyl-beta-D-glucose induces S-and G(1)-cell cycle arrests in prostate cancer cells targeting DNA replication and cyclin D1*  
Hu H, Zhang J, Lee HJ, Kim SH, Lü J  
Carcinogenesis. May;30(5):818-23 (2009)
- H.I. No. 1730  
*Glycolipid acquisition by human glycolipid transfer protein dramatically alters intrinsic tryptophan fluorescence: insights into glycolipid binding affinity*  
Zhai X, Malakhova ML, Pike HM, Benson LM, Bergen HR 3rd, Sugar IP, Malinin L, Patel DJ, Brown RE  
J Biol Chem. 284(20):13620-8 (2009)
- H.I. No. 1731  
*In vivo molecular mediators of cancer growth suppression and apoptosis by selenium in mammary and prostate models: lack of involvement of gadd genes*  
Jiang W, Jiang C, Pei H, Wang L, Zhang J, Hu H, Lü J  
Mol Cancer Ther. Mar;8(3):682-91 (2009)
- H.I. No. 1732  
*Cyclooxygenase-2/prostaglandin E2 pathway mediates icaride II induced apoptosis in human PC-3 prostate cancer cells*  
Lee KS, Lee HJ, Ahn KS, Kim SH, Nam D, Kim DK, Choi DY, Ahn KS, Lu J, Kim SH  
Cancer Lett. 280(1):93-100 (2009)
- H.I. No. 1733  
*Minireview: Obesity and breast cancer: the estrogen connection*  
Cleary MP, Grossmann ME  
Endocrinology. Jun;150(6):2537-42 (2009)
- H.I. No. 1734  
*Methyl-selenium compounds inhibit prostate carcinogenesis in the transgenic adenocarcinoma of mouse prostate model with survival benefit*  
Wang L, Bonorden MJ, Li GX, Lee HJ, Hu H, Zhang Y, Liao JD, Cleary MP, Lü J  
Cancer Prev Res (Phila Pa). May; 2(5):484-95 (2009)
- H.I. No. 1735  
*Methyl-selenium compounds inhibit prostate carcinogenesis in the transgenic adenocarcinoma of mouse prostate model with survival benefit*  
Wang L, Bonorden MJ, Li GX, Lee HJ, Hu H, Zhang Y, Liao JD, Cleary MP, Lü J  
Cancer Prev Res (Phila Pa). May;2(5):484-95 (2009)
- H.I. No. 1736  
*A regulatory mechanism for RSK2 NH(2)-terminal kinase activity*  
Cho YY, Yao K, Pugliese A, Malakhova ML, Bode AM, Dong Z  
Cancer Res. 69(10):4398-406 (2009)
- H.I. No. 1737  
*Cyclin-dependent kinase 3-mediated activating transcription factor 1 phosphorylation enhances cell transformation*  
Zheng D, Cho YY, Lau AT, Zhang J, Ma WY, Bode AM, Dong Z  
Cancer Res. 68(18):7650-60 (2008)
- H.I. No. 1738  
*Anti-androgen receptor signaling and prostate cancer inhibitory effects of sucrose- and benzophenone-compounds*  
Wang Z, Lee HJ, Wang L, Jiang C, Baek NI, Kim SH, Lü J  
Pharm Res. May;26(5):1140-8 (2009)
- H.I. No. 1739  
*Superior in vivo inhibitory efficacy of methylseleninic acid against human prostate cancer over selenomethionine or selenite*  
Li GX, Lee HJ, Wang Z, Hu H, Liao JD, Watts JC, Combs GF Jr, Lü J  
Carcinogenesis. May;29(5):1005-12 (2009)
- H.I. No. 1740  
*Identification of the cyclin D1b mRNA variant in mouse*  
Wu J, Wu SH, Bollig A, Thakur A, Liao DJ  
Mol Biol Rep. May;36(5):953-7 (2009)
- H.I. No. 1741  
*Genome based cell population heterogeneity promotes tumorigenicity: the evolutionary mechanism of cancer*  
Ye CJ, Stevens JB, Liu G, Bremer SW, Jaiswal AS, Ye KJ, Lin MF, Lawrenson L, Lancaster WD, Kurkinen M, Liao JD, Gairola CG, Shekhar MP, Narayan S, Miller FR, Heng HH  
J Cell Physiol. May;219(2):288-300 (2009)
- H.I. No. 1742  
*Effects of Adiponectin and leptin co-treatment on human breast cancer cell growth*  
Nkhata KJ, Ray A, Schuster TF, Grossmann ME, Cleary MP  
Oncol Rep. Jun; 21(6):1611-9 (2009)
- H.I. No. 1744  
*Y-box binding protein-1 serine 102 is a downstream target of p90 ribosomal S6 kinase in basal-like breast cancer cells*  
Stratford AL, Fry CJ, Desilets C, Davies AH, Cho YY, Li Y, Dong Z, Berquin IM, Roux PP, Dunn SE  
Breast Cancer Res. 10(6):R99 (2008)
- H.I. No. 1745  
*Cancer prevention research - then and now*  
Bode AM, Dong Z  
Nature Reviews Cancer 9, 508-516 (2009)
- H.I. No. 1746  
*Effects of gefitinib (Iressa) on mammary cancers: preventive studies with varied dosages, combinations with vorozole or targretin, and biomarker changes*  
Lubet RA, Szabo E, Christov K, Bode AM, Ericson ME, Steele VE, Juliana MM, Grubbs, CJ  
Mol Cancer Ther, 7, 972-9 (2008)
- H.I. No. 1748  
*Epigallocatechin 3-gallate and green tea catechins: United they work, divided they fail*  
Bode AM, Dong Z  
Cancer Prev Res (Phila Pa), 2, 514-7 (2009)



# THE HORMEL INSTITUTE SEMINARS

JULY 1, 2009 — JUNE 30, 2010

H.I. No. 1743

*7,3',4'-trihydroxyisoflavone inhibits epidermal growth factor-induced proliferation and transformation of JB6 P+ mouse epidermal cells by suppressing cyclin-dependent kinases and phosphatidylinositol 3-kinase.*  
Lee DE, Lee KW, Song NR, Seo SK, Heo YS, Kang NJ, Bode AM, Lee HJ, Dong Z. J Biol Chem. 285(28):21458-66 (2010).

H.I. No. 1747

*A selective small-molecule inhibitor of c-Jun N-terminal kinase 1.*  
Yao K, Cho YY, Bode AM, Vummenthala A, Park JG, Liu K, Pang YP, Dong Z. FEBS Lett. 583(13):2208-12 (2009).

H.I. No. 1749

*[6]-Gingerol suppresses colon cancer growth by targeting leukotriene A4 hydrolase.*  
Jeong CH, Bode AM, Pugliese A, Cho YY, Kim HG, Shim JH, Jeon YJ, Li H, Jiang H, Dong Z. Cancer Res. 69(13):5584-5591 (2009).

H.I. No. 1750

*The crystal structure of the active form of the C-terminal kinase domain of mitogen- and stress-activated protein kinase 1.*  
Malakhova M, D'Angelo I, Kim HG, Kurinov I, Bode AM, Dong Z. J Mol Biol. 399(1):41-52 (2010).

H.I. No. 1751

*Characterization of the lateral distribution of fluorescent lipid in binary-constituent lipid monolayers by principal component analysis.*  
Sugár IP, Zhài X, Boldyrev IA, Molotkovsky J, Brockman HL, Brown RE. Int J Biomed Imaging. 2010:125850.

H.I. No. 1752

*Structural diversity of the active N-terminal kinase domain of p90 ribosomal S6 kinase 2.*  
Malakhova M, Kurinov I, Liu K, Zheng D, D'Angelo I, Shim JH, Steinman V, Bode AM, Dong Z. PLoS One. 4(11):e8044 (2009).

H.I. No. 1753

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## INCOME FROM GRANTS AND CONTRACTS

### National Institutes of Health

#### National Cancer Institute

<i>Anticarcinogenic Mechanisms of Tea Constituents (Z. Dong)</i>	187,169
<i>Study on Ultraviolet-induced Signal Transduction (Z. Dong)*</i>	
<i>Intermittent Food Restriction Prevents Mammary Tumors (M. Cleary)*</i>	
<i>Selenium and Prostate Cancer Apoptosis Pathways (J. Lü)*</i>	
<i>Mechanisms of Chemopreventive Effect of Resveratrol (Z. Dong)</i>	156,055
<i>Inhibition of Carcinogenesis by Tea and Tea Constituents (Z. Dong)</i>	114,902
<i>Molecular Basis of Glycosphingolipid Binding Specificity (R. Brown)</i>	71,000
<i>c-Myc, Growth Factor and Breast Cancer (D.J. Liao)*</i>	
<i>Methyl Selenium for Prostate Cancer Chemoprevention (J. Lü)</i>	190,000
<i>Therapy of AML (P. Ruvoilo)</i>	6,757
<i>Prostate Cancer Chemoprevention by Penta-galloyl-glucose (J. Lü)</i>	200,000
<i>The Role of Bone Marrow Derived Cells in Skin Cancer (R. Morris)</i>	35,116
<i>Study on Ultraviolet Signal Transduction-ARRA (Z. Dong)</i>	141,688
<i>Telomere Dysfunction, p53 and Tumorigenesis (Y. Deng)</i>	117,900
<i>Telomere Dysfunction, p53 and Tumorigenesis-ARRA (Y. Deng)</i>	45,221
<i>Measurements of Specific Signal Transduction Endpoints (A. Bode)</i>	103,398
<i>Proposed Study Employing Computer Simulations and Screen (Z. Dong)</i>	94,764
<i>Roles of the Fanconi Anemia Pathway in Bladder Tumorigenesis (P. Fei)</i>	25,812
<i>Delaying the Hormone Refractory Prostate Cancer by a Dietary Triterpene Lupeol (M.S. Bhat)</i>	8,651

#### National Heart, Lung, and Blood Institute

<i>Regulation of Peripheral Protein-Membrane Interactions by Lipid Second Messengers (H. Brockman)</i>	259,509
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#### 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>	237,895
<i>Mechanisms of Centrosome Reproduction in Animal Cells (E. Hinchcliffe)</i>	153,374

#### National Institute of Arthritis and Musculoskeletal and Skin Diseases

<i>The Regulation of Keratinocyte Stem Cells (R. Morris)</i>	286,691
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#### Department of Defense - U.S. Army

<i>The Role of Polycomb Group Gene Bmi-1 in the Development of Prostate Cancer (M.S. Bhat)</i>	5,057
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#### American Institute for Cancer Research

<i>Dietary Obesity and Prostate Cancer Development in TRAMP Mice (M. Cleary)*</i>	
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<i>Calorie Restriction, Lipid Peroxidation, and Mammary Tumors (C. Seppanen)</i>	13,141
<i>Targeting cFLIP by Lupeol, a Dietary Triterpene, for Chemoprevention of Pancreatic Cancer (M.S. Bhat)</i>	20,550

#### Breast Cancer Research Foundation

<i>Body Weight Change, Leptin/Adiponectin and Breast Cancer (M. Cleary)*</i>	
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#### Kyunghee University (Seoul, Korea)

<i>Identification of Novel Anti-androgen Compounds from Oriental Herbal Extracts (J. Lü)</i>	2,500
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#### Minnesota Medical Foundation

<i>Pyranocoumarin Compounds for Breast Cancer Prevention and Treatment (J. Lü)*</i>	
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#### Pardee Foundation

<i>Roles of the mir-17 and mir-221 Clusters of MicroRNAs in Breast Cancer (D.J. Liao)*</i>	
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#### Pediatric Pharmaceuticals

<i>Ginger as an Anti-cancer Agent (A. Bode)*</i>	
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#### Seoul National University (Korea)

<i>Biogreen 21 Project (Z. Dong)</i>	14,444
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#### Susan G. Komen for the Cure

<i>Calorie Restriction and Eicosapentaenoic Acid (M. Grossmann)</i>	125,324
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#### University of Minnesota Rochester

<i>Virtual Screening for Designing Selective ERK Inhibitors (A. Bode)</i>	16,667
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#### U.S. Department of Health and Human Services

<i>Health Care and Other Facilities Equipment Project (Z. Dong)</i>	319,770
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#### Other Resources

<i>The Hormel Foundation</i>	2,158,005
<i>University of Minnesota</i>	447,951
<i>Indirect Cost Return</i>	1,455,777
<i>Eagles Cancer Telethon</i>	135,000
<i>Mayo Clinic Collaborative Donation</i>	1,000,000
<i>Other</i>	942,172

<b>Total</b>	<b>9,317,260</b>
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\* Full award amount stated in previous report.



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