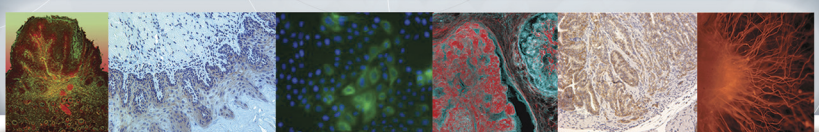
The Hormel Institute

University of Minnesota Mayo Clinic



Improve the Health of the World

2010–2011 Annual Report

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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

I am very pleased to report another successful year for The Hormel Institute. The Hormel Institute continues to appreciate the high production of publications in the world's most prestigious journals and 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 August 2010, The Hormel Institute and Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences hosted the "2nd China-U.S. Forum on Frontiers of Cancer Research" in Guangzhou, China. More than 200 scientists and top officers from both countries attended the meeting and discussed their findings for more effective prevention of human cancer. The attendance by the meeting speakers from the public health field made this another very successful conference.

Another important collaboration is an effort between The Hormel Institute, the U of M Supercomputer 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 complete protein crystallography laboratory including robotics and a diffraction lab. The third step was completed in early 2011 with the purchase and set-up 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. U.S. Congressman Tim Walz has shown 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.

The Hormel Foundation, University of Minnesota, and Mayo Clinic agreed to establish a new research institute, Mayo Clinic Hormel Institute. The faculty, staff, and students at The University of Minnesota Hormel Institute and the newly established Mayo Clinic Hormel Institute will work tightly together to study medical science.

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 and Mr. Gary Ray for their continued interest and support of the Institute, Mr. Joel Johnson, Mr. Jeff Ettinger, and Dr. Phil Minerich for their generous support and Dr. Robert Bruininks and Dr. Tim Mulcahy for their leadership and support. We thank Dr. John Noseworthy, Dr. Hugh Smith, Dr. Glenn Forbes, Dr. Robert Rizza, Dr. Robert Diasio, and Mayo Clinic for their support. We thank our elected leaders, U.S. Representative Tim Walz, U.S. Senator Amy Klobuchar, U.S. Senator Al Franken, 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.

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

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 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, UVB 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, 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-κB), 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 and blocking the receptor with capsaicin (found in hot peppers) causes an even greater increase in skin carcinogenesis. This work was featured on the cover of Cancer Research.

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 typosine kinase, which is associated with the ζ subunit of the

"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) Front row: Tatyana Zykova, Hua Xie, Zigang Dong

Second row: Naomi Oi, Danielle Jondal (Intern), Ann Bode

Third row: Xiang Li, Lindsey Jacobsen (Intern)

Fourth row: Wei-Ya Ma, MyoungOk Kim, MeeHyun Lee, Cong Peng

Fifth row: Jixia Li, Andria Carper, Steven Rizzi (Intern), Dong-Joon Kim

Sixth row: Do Young Lim, Margarita Malakhova, Sung Young Lee, Kun Yeong Lee, Tae-gyu Lim

Seventh row: Hong-Gyum Kim, Dong Hoon Yu, Zunnan Huang

Eighth row: JongEun Kim, Feng Zhu, Hiroyuki Yamamoto

Ninth row: Ke Yao, Mi Sung Kim, Sung Keun Jung

Tenth row: Hanyong Chen, Haitao Li, Hongxun Wang, Alyssa Langfald, Yan Li

Not pictured: Yong Yeon Cho, Srinivasa Reddy Kanamata Reddy, Chul Ho Jeong, Soouk Kang, Tao Yin (Andy) Lou, Shengqing Li, Kang Dong Liu, Janos Nadas, Priya Rathinaswamy, Darya Urusova, Weihong Wen, Eunjin Cho, Young Jin Jeon, TingTing Li, Nu Ry Song, A Ram Shin, JinYoung Suh, Svetlana Ermakova

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 over-expressed 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 also featured as a cover story in Cancer Research. We have determined the structure of RSK2. Such knowledge will help to design new drugs against cancer.

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 combination 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.

We have reported that (-)-epigallocatechin-3-gallate (EGCG) from green tea or theaflavins (TFs) from black tea inhibit tumor promoter induced AP-1, NFκB 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. Our work on structure determination of EGCG/Pin-1 has been recognized by others as "a beautiful example of the use of chemical biology to validate a novel molecular target for cancer prevention."

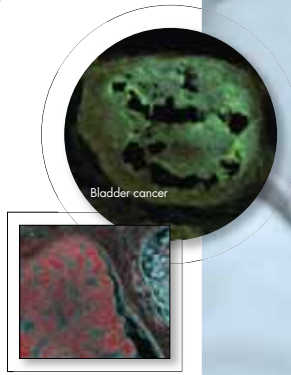
We have teamed with IBM and its Blue Gene group under the leadership of Mike Good and the University of Minnesota Super Computing Institute to use the world's fastest supercomputer to understand complex diseases like cancer and to screen anticancer drugs for cancer prevention and treatment. In collaboration with Dr. Paul Limburg (Mayo Clinic Rochester), we will conduct clinical trials to use cancer preventive agents developed in our Institute. We continue collaborations with Dr. Tim Bowden and Dr. David Alberts at the University of Arizona on skin cancer prevention. 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 and long-term effectiveness and safety of these compounds as chemopreventive agents. Our work on using the supercomputer and molecular modeling and simulation was published as a Nature Reviews Cancer article in March 2011.

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



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 past year has seen a focus on improving our novel instrument for monitoring interfaces over a flowing aqueous phase. This includes the development of a small weighing mechanism for monitoring surface tension and improvements in the design of the microfluidic flow cell.

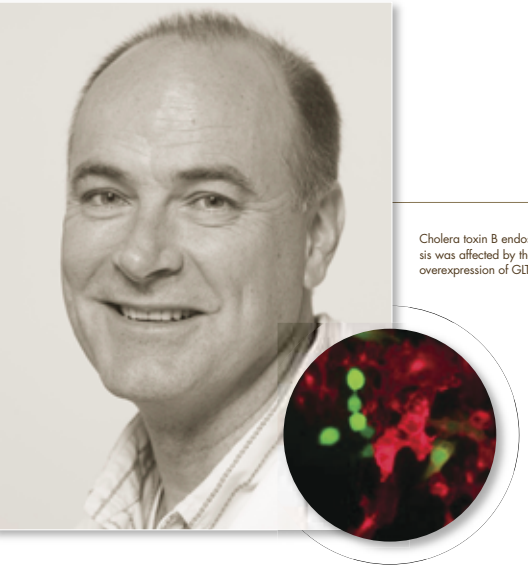
Other Professional Activities
Howard Brockman

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

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

"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."

MEMBRANE BIOCHEMISTRY
Section Leader
Rhoderick E. Brown, Ph.D.
Professor



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

Biomembranes function as barriers that surround cells, but enable selective control for entry of beneficial nutrients and exit of toxic by-products. Biomembranes consist of thin, flexible layers that are only two molecules thick. The molecules that form this double-layer structure are known as lipids. Biomembranes also provide internal partitions within cells that enable formation of 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 furthered under¬standing of why biomembranes so often come under direct attack during cancer and infectious disease.

Our research is focused on a class of membrane lipids known as sphingolipids. Certain sphingo¬lipids, along with cholesterol, serve as key lipid components needed for formation of membrane microdomains, commonly referred to as "rafts." Because rafts appear to function as organizing regions for certain signaling kinases as well as target sites for certain viruses and bacteria, we have focused our efforts on rigorously defining the physical basis for raft micro¬domain functionality. We have developed ways to quantitatively measure the lateral elasticity within model membranes, to accurately assess the physical changes that occur within the membrane "raft environment" when the content and structure of sphingolipids and sterols becomes altered, and to assess sphingolipid lateral distributions. Our research has provided increased under¬standing of the sphingolipid structural features that affect their interactions with other membrane lipids and helped define the physical nature of the membrane environment produced by sphingo¬lipid compositional changes. This new knowledge is especially important for understand¬ing how the raft microdomain environment regulates the membrane translocation of proteins that have "affinity" for sphingolipids.

The processes used by cells to form and maintain sphingolipid-enriched domains are not well understood but could involve specific proteins that can bind and transfer sphingolipids between membrane surfaces. Thus, much of our recent efforts have been directed toward a family of mammalian proteins known as glycolipid transfer proteins (GLTPs) that can specifically bind and transfer glycosphingolipids between membranes.
We have found that GLTP functionality is regulated by lipid composition and packing within membranes. We have gained fundamental insights into lipid structural features that control both the lateral and transmembrane distributions of sphingolipids in membranes using a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR). 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. Our molecular biophysical studies have resulted in the first molecular cloning of human GLTP and related homologs from various mammals, plants, and fungi. We have found that mammalian GLTP transcripts encode very highly conserved amino acid sequences. Genetic engineering approaches have enabled us to produce human GLTP in bacterial expression systems and to purify sufficient quantities to successfully crystallize the proteins, and to solve their conformational structures in glycolipid-free form as well as complexed with different glycolipids, in collaboration with structural biologists at Memorial Sloan Kettering Cancer Center in New York and at CIC bioGUNE in Derio, Spain. 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.

"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."

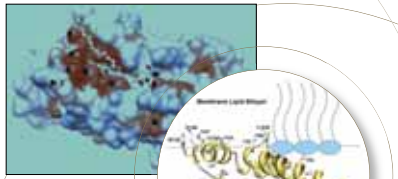
Data reported in PLoS Biology, The Journal of Biological Chemistry, Biophysical Journal, and Biochemistry have led to new insights into how GLTP adapts to accommodate different glycolipids within its liganding site, provided understanding into the functional roles played by intrinsic tryptophan residues in membrane interaction and glycolipid binding, and revealed the structural basis for the narrower glycolipid selectivity displayed by a fungal GLTP ortholog.

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

We anticipate that elucidation of the fundamental structure-function relationships governing GTLP action will facilitate development of the means to pharmacologically modulate GLTP and enhance its potential use as a biotech-

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



Other Professional Activities
Rhoderick E. Brown

Editorial Advisory Boards
Chemistry and Physics of Lipids
Journal of Lipids
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.

Primary interests of the Nutrition and Metabolism section are the effects of body weight and food intake on the development of breast cancer using mouse models. Studies have included effects of genetic and dietary-induced obesity on breast/mammary tumor development particularly with respect to body fat and serum IGF-I, leptin and adiponectin levels. Other studies have assessed the impact of different types of calorie restriction on the prevention of mammary tumors in several different transgenic mice models. Of particular note, we have consistently found that periods of moderately severe calorie restriction followed by refeeding, which we term intermittent calorie restriction results in greater protection than does the same degree of restriction implemented in a chronic fashion. Overall, both interventions result in 20-25% calorie reduction. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the IGF-axis. Based on results of our studies, we have hypothesized that the altered, i.e., reduced adiponectin:leptin ratio associated with obesity, provides a permissive environment for tumor development. In contrast, the reductions of IGF-I and leptin and increased adiponectin:leptin ratio resulting from periods of calorie restriction in the intermittent restriction protocol results in reduced mammary tumor development and decreased mammary tumor incidence in comparison to ad libitum fed mice as well as in the mice that are chronically calorie restricted. These studies are now being expanded by Dr. Michael Grossmann to include the interaction of an omega-3 fatty acid in combination with intermittent calorie restriction on the development of mammary tumors in a project funded by Susan G. Komen for the Cure. This study uses a model of breast cancer 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.

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. 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.

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 chemical 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.

> "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."

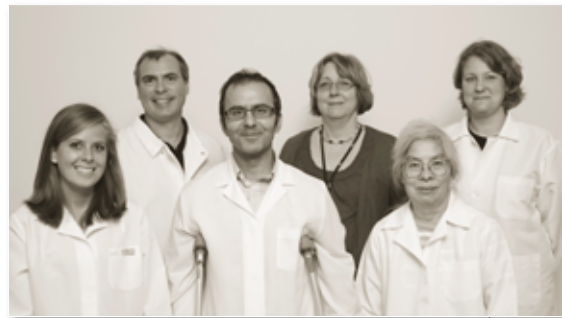
Overall, our findings should be of importance in understanding the impact of body weight on the development of several types of cancer. Further, the protective effect of intermittent calorie restriction which indicates that the manner in which calories are restricted has a significant impact should provide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

Other Professional Activities
Margot P. Cleary

Invited speaker:
Annual AACR meeting Orlando, FL April 2011

Presentations:
AACR Frontiers in Cancer Prevention Meeting Philadelphia November 2010
DOD IMPACT Meeting Orlando FL March 2011
AACR Annual Meeting Orlando FL April 2011

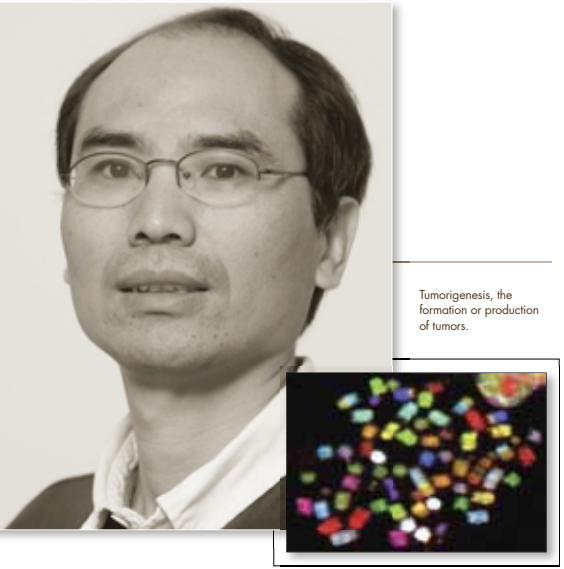
NIH Study Section Meeting May 2011



Left to right: Sarah Ewing (Intern), Michael Grossmann, Soner Dogan, Margot Cleary, Nancy Mizuno, Christine Seppanen
Not pictured: Olga Rogozina

CELL DEATH AND CANCER GENETICS

Section Leader
Yibin Deng, M.D., Ph.D.
Assistant Professor



Tumorigenesis, the formation or production of tumors.

The central role of p53 in suppressing tumor development and mediating cancer therapy 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 eliminate cancer cells remain poorly understood. Our laboratory focuses 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. In the past year, our laboratory has made progresses in the following three major areas:

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

While many studies have focused on the role of apoptosis or/and senescence in p53-mediated tumor suppression and therapeutic responses, the recent findings suggest 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. DRAM (Damage-Regulated Autophagy Modulator) has been recently identified as a direct target of p53 and the DRAM protein mediates p53-induced autophagy and thus may contribute to tumor suppression and cancer therapy. To investigate the physiological contribution of DRAM to p53-mediated tumorigenesis and cancer therapy in vivo, we generated conditional DRAM knockout mice by gene targeting. Our preliminary findings suggest that DRAM potentially functions as a tumor suppressor since deletion of DRAM promotes spontaneous tumor development in mice. Furthermore, disruption of DRAM-mediated autophagy in cancer cells increases resistant to chemotherapy. We are also utilizing the conditional DRAM knock-out mice to breed with p53-mediated apoptosis deficient mice (p53R172Pknock-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 studies strongly support the hypothesis that p53-induced apoptosis, autophagy and senescence cooperate together to effectively inhibit tumor development and mediate therapeutic efficacy of p53 in vivo. We expect that our continue studies utilizing genetic engineered mouse models 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.

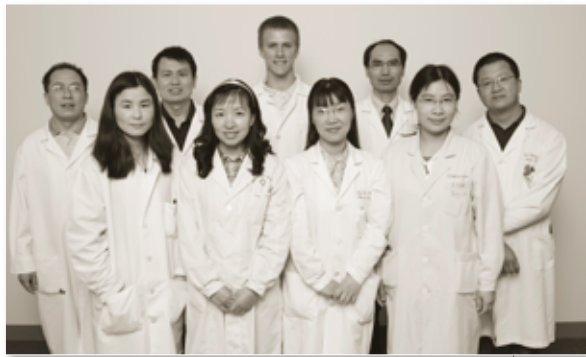
2. Gain-of-function of mutant p53 in telomere dysfunction-induced mammary tumorigenesis

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 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 are utilizing 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 basis of selective killing of cancerous 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 comprehensive combination of genomic and proteomic analyses of cancer, computational modeling of cancer pathways, RNAi-based screening, and functional testing in cell culture and animal models of cancer to identify the 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 the molecular targets in prostate cancer cells contributing to the Warburg effect (cancer cells prefer to metabolize glucose by glycolysis even in the presence of ample oxygen, named as aerobic glycolysis), which leads to tumor growth, progression, and metastasis. Our preliminary studies identify the Achilles's Heel of AKT that hyperactivated AKT can be exploited to selectively target human prostate cancer cells containing high level of AKT activity and loss of p53 through inhibition of glycolysis. We will test our hypothesis in suppressing tumor development using our engineering prostate cancer mouse model. We believe that our proposed studies would provide compelling rationale to design clinical trials in prostate cancer patients using the compounds targeting glycolysis.



Left to right: Jinakang Deng, Yan Cheng, Lei Wang, Liyan Zhao, Kyle Auringer (Intern), Xiaolan Guo, Yibin Deng, Yanmei Zou, Hua Xiong
Not pictured: Tao Lin, Siquan Tang

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. Our work is also relevant to identifying potential targets for chemotherapy agents.

Experimental research results:

1. Coordinating cytokinetic furrow formation with anaphase onset

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

> "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."

2. Centrosome duplication

When CHO cells are arrested in S-phase, they undergo repeated rounds of centrosome duplication without cell cycle progression. While the increase is slow and asynchronous, the number of centrosomes in these cells 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 α/γ-tubulin and centrin 2 – assemble at the nuclear periphery. If the colcemid is washed out, these nuclear-associated centrosomal foci disappear. In their place, multiple centriole-containing centrosomes assemble, which nucleate microtubule asters, and can form functional mitotic spindle poles. The eventual number of centrosomes that assemble following colcemid washout increases with time, even though

Left to right: Hanna Middlebrook (Intern), Edward Hinchcliffe, Kul Karanjeet
Not pictured: Cydney Bagne

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.

3. *Building a bipolar spindle*

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

We 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 α -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 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.

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

We are currently investigating the role of the tektin proteins in establishing the spindle midzone. Tektins were first identified as components of axonemal microtubules, where they are thought to impart structural rigidity and complex periodic spacing to these highly stable microtubules. Our recent results suggest that tektins localize to the overlapping microtubules at the spindle midzone, where they also play an important role in the spindle midzone. This region of the mitotic spindle 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.

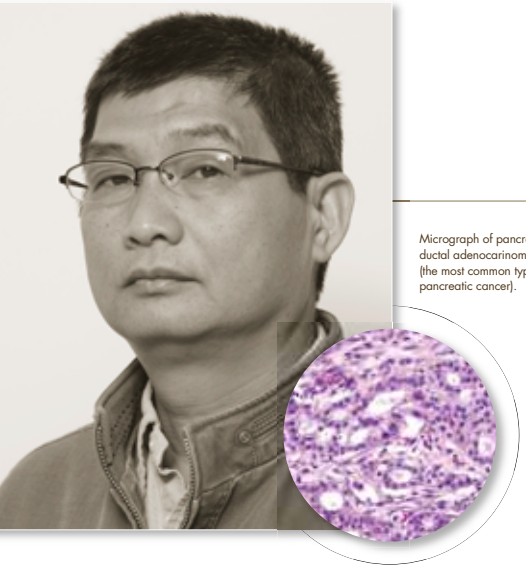
A detailed understanding of the regulation of cell division and cytokinesis will advance our knowledge of the biology of cancer – itself a disease characterized by unregulated cell proliferation. Together, these studies should provide a fertile source of potential targets for future anti-cancer drugs.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

Other Professional Activities
Edward H. Hinchcliffe

Ad hoc reviewer:
- National Science Foundation
- Ohio Cancer Research Foundation
- Wellcome Trust UK
- Deutsche Forschungsgemeinschaft (DFG: German Research Foundation)

TRANSLATIONAL CANCER RESEARCH

Section Leader
D. Joshua Liao, Ph.D.
Associate Professor

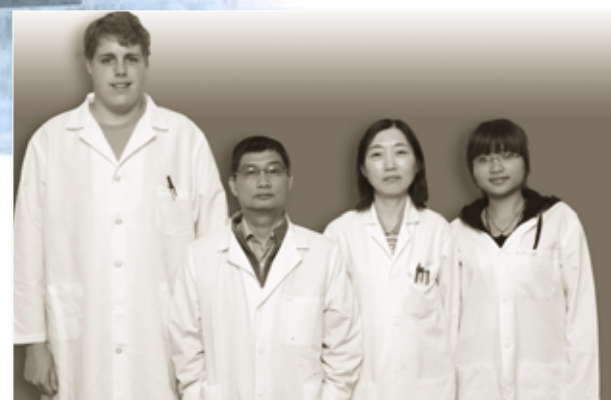


Micrograph of pancreatic ductal adenocarinoma (the most common type of pancreatic cancer).

Since we shifted our research project to a novel area coined by us as "cancer ribonomics" in 2009, in the past year we have been aggressively working on establishing a series of techniques required by this project and have solved several technical hurdles. One large hurdle is how to clone chimeric RNA in which one partner gene is known while the other is completely unknown and cannot be predicted from human or mouse genome, since these chimeric RNAs are new genes occurring at the RNA level, not at the genomic DNA level. We have established a novel strategy called "tailing RNA" to link all RNAs at their tail with a short sequence of multiple guanine (which is one of the four nucleotides that encode genetic information) and an artificial sequence that can be used as primer. With this tail, we can amplify and clone all mRNAs, including those chimeras, into a vector using a technique call the "TOPO cloning," and then sequence all the RNAs. We are currently fine-tuning some technical conditions to optimize this novel strategy of gene cloning, which may have a patent potential. In addition, we have achieved some critical data to formulate a pilot proposal to DOD and received a grant under the IDEA Award mechanism to support our project. The DOD Breast Cancer IDEA Award funds a small percentage of the proposals submitted under this category, proving that our project is highly competent.

In the past year, we also summarized data on a few previous research projects, including some collaborative ones with our partners in China, and published several research papers. We also published two perspective articles that describe our unique thoughts on the mechanisms for cancer formation and progression. These perspective articles were well received by our peers in cancer research, based on the feedback we received from peers worldwide.

"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: Stephen Brockman (Intern), Joshua Liao, Yuan Sun, Yun Zhao
Not pictured: Jian-min Wu, FeiXiang Wu, BingKun Xie

STEM CELLS AND CANCER

Section Leader
Rebecca J. Morris, Ph.D.
Professor

Skin keratinocytes

Research in the Morris laboratory continues to focus on the role of 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 play a previously 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 used the Krt1-15CrePR1;R26R transgenic mouse to determine the contribution of keratin 15 positive cells from the hair follicle to skin tumor development by following the labeled progeny of the keratin 15 expressing cells into papillomas. We have made three novel observations. First, we found that keratin 15 expressing cells contribute to most of the papillomas by 20 weeks of promotion. Second, in contrast to the transient behavior of labeled keratin 15-derived progeny in skin wound healing, keratin 15 progeny persist in papillomas and some malignancies for many months following transient induction of the reporter gene. Third, papillomas have surprising heterogeneity not only in their cellular composition, but also in their expression of the codon 61 signature Ha-ras mutation with approximately 30 percent of keratin 15-derived regions expressing the mutation. Together, these results demonstrate that keratin 15 expressing cells of the hair follicle contribute to cutaneous papillomas with long term persistence and a subset of which express the Ha-ras signature mutation characteristic of initiated cells.

Understanding keratinocyte stem cell regulation is important in understanding the pathogenesis of wound healing and nonmelanoma 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). In this report, 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. 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.

Bone morphogenetic proteins comprise a family of evolutionarily conserved growth factors and morphogens, belonging to the transforming growth factor β super-family. Bmps exert a wide range of morphogenetic activity in different cells. Recently, we reported that Bmp5 is a candidate gene for keratinocyte stem cell regulation in the mouse. We sequenced the Bmp5 gene in various mouse strains and checked the expression of Bmps 2-7 in FACS sorted keratinocytes namely CD34+/α-6 integrin positive cells (a keratinocyte stem cell population), CD34+depleted/α-6 integrin positive keratinocytes, and cancer cells such as squamous cell carcinomas papillomas, and spindle cell tumors. We discovered some novel mutations and deletion among various mouse strains, and variable expression profiles of various Bmps in epidermal stem cells and cancer cells. Our findings support the conclusion that Bmp5 may be a cancer susceptibility gene, and it may have a role during the hair follicle cycling or various phases of cutaneous developmental like Bmp2 and Bmp4.

Our laboratory previously identified the mouse Ksc-2 locus on chromosome-4 associated with an in vitro keratinocyte large colony phenotype. We therefore screened SNPs between D4Mit104 and D4Mit288 in C57BL/6 and BALB/c using a web resource of the Mouse Genome Informatics database. We filtered the SNPs based on their type (synonymous or non-synonymous (ns)) and found 4208 SNPs within the high linkage region, including 2522 nsSNPs within 66 known and 8 predicted genes. We prioritized these genes considering keratinocyte gene expression and potential function. Hence, we chose Toll like receptor 4 for further study. We found a significant enrichment for Tlr4 mRNA in freshly harvested, alpha-6 integrin+/CD34+ hair follicle stem cells, and receptor co-localization with CD34 in the hair follicles. Analysis of Annexin-V revealed that bacterial lipopolysaccharide protected stem cells against apoptosis, and increased Ki-67 expression in cultured keratinocytes. These results suggest further consideration of Tlr4 may be instructive due to its known involvement in innate immunity, and especially in light of recent evidence implicating it directly in LPS-induced proliferation of mesenchymal stem cells as well as indirectly without canonical signaling in expansion of hematopoietic stem cells. Hence it is not surprising that skin has well developed innate immunity. What is surprising is that keratinocyte stem cells have a profile of enhanced expression of many of genes involved in innate immunity, and several of these then reside within the Ksc2 locus.

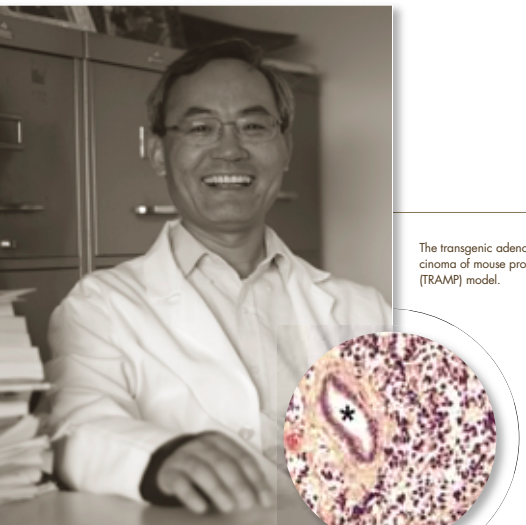
> "In continuing studies, we demonstrate that bone marrow cells may have an unsuspected role in skin tumor development."

Although a stem cell origin for tumors was postulated nearly 200 years ago, a critical role of keratin-15 expressing hair follicle stem cells during skin tumorigenesis has only recently been established. In addition to tissue stem cells, bone marrow cells (BMCs) can play a reparative function in damaged organs and were found to contribute to cancer development as demonstrated in recent gastric cancer study of bone marrow-derived cells (BMDCs) in the presence of Helicobacter felis-induced chronic inflammation. To examine exogenous cellular sources in skin tumor development, we examined BMDCs in papillomas during chemically induced carcinogenesis in mice following gender-mismatched allogeneic bone marrow transplantation. First, we detected proliferating genetically marked, Y-chromosome positive keratin immunoreactive BMDCs in the basal epithelium of the papillomas. Second, an enhanced contribution of bone marrow-derived epithelial cells was observed in ulcer-related skin lesions. Furthermore, keratin expression was induced from a subset of plastic attached BMCs after co-culture with primary keratinocytes separated by a filter and BMP-5 treatment. Therefore, these results demonstrated that a subset of highly plastic BMDCs participate as a new epithelial cell source in chronically damaged skin lesions including papillomas and ulcers.

Left to right: Nyssa Readio, Heuijoon Park, Rebecca Morris, Ashok Singh, Anupama Singh

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.

The Cancer Biology section continued its research which involved understanding the cellular and molecular mechanisms by which selenium compounds and metabolites mediate cancer chemoprevention and treatment as well as identifying and developing novel cancer chemopreventive and therapeutic agents based on Chinese and Oriental medicinal herbs. Highlights of this research included 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 may contribute to their anti-cancer activities. 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.

Pentagalloylglucose studies

Penta-1,2,3,4,6-O-galloyl-beta-d-glucose (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. 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.

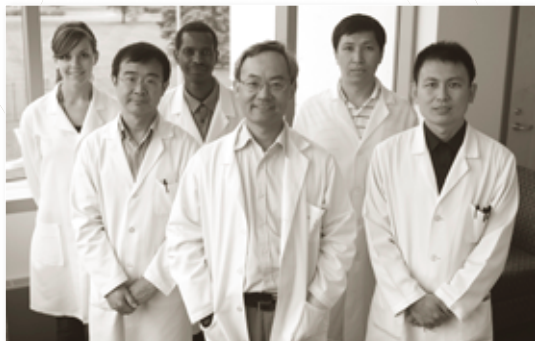
Studies with a novel herbal compound

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. 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. Studies 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 identified to be devoid of COX-inhibitory activity yet displays much more potent tumor cell growth-inhibitory activity in vitro compared with sulindac sulfide. SSA may be a chemopreventive candidate against prostate glandular epithelial carcinogenesis.

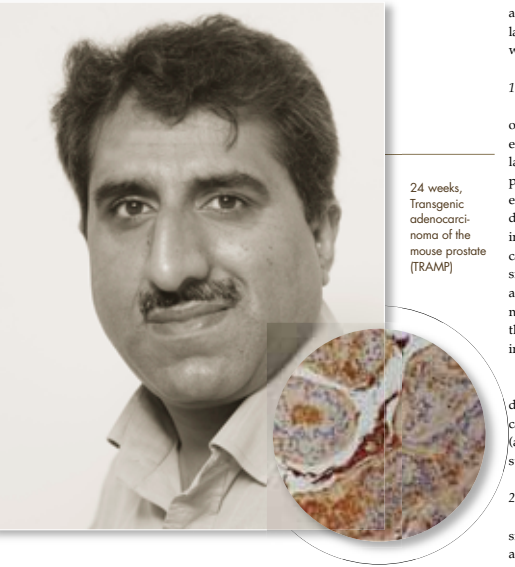
"Our section's long-term goals are to understand the biochemical, cellular and molecular processes crucial for the genesis of cancer and to develop mechanism-based cancer prevention and therapeutic strategies for implementation through supplements, functional and medicinal foods or drug approaches."



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

MOLECULAR CHEMOPREVENTION AND THERAPEUTICS

Section Leader
Mohammad Saleem Bhat, Ph.D.
Assistant Professor



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

The long term goals of this section are the following:

- understanding the biochemical, cellular and molecular processes crucial for the development of prostate and pancreatic cancer.
- identifying potential agents those 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, could 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 bed-side use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer and are known to confer aggressiveness to cancer cells are (1) abolishment of senescence of normal prostate epithelial cells, (2) self-renewability of prostate cancer cells even after chemotherapy and radiation, and (3) 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-renewability of tumor cells is an essential defining property of a pluripotent stem cell–like phenotype of cancer cell which distinguishes it from other cell types. Stem cell–resembling population of cancer cells among the heterogeneous mix of cells constituting a tumor have been reported to be essential for tumor progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells 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) has been reported to be involved in self-renewability, cell cycle regulation, and senescence. Bmi-1 is a transcription repressor and has emerged as an important member of PcG family. We are investigating the role for Bmi-1 protein in prostate cancer development. We hypothesize that Bmi-1 protein could be developed as a diagnostic and prognostic of prostate cancer.

> "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."

3. *Reactivation of Tumor Supperrosr Genes: Testing combinatorial approach of gene*

Early development of cancer is largely dependent upon androgens and simultaneous suppression of tumor suppressor genes predispose the initiated and premalignant prostate epithelial cells to acquire malignant phenotype. Among the phenotypic changes, the premalignant cells acquire increased motility, changes in cytoskeleton, changes in cell adhesion characteristics and increased tendency for clonal expansion. The interaction between SLIT-ligand and its receptor Roundabout (Robo-1) is reported to guide axons during development of the nervous system. During organogenesis, the SLIT–ROBO pathway regulates numerous processes including cell proliferation, migration and adhesion that seem to be important in the development of disparate tissues including those of the reproductive system. SLIT3-ROBO1 signaling has been shown to promote cell adhesion by stimulating the interaction between E-cadherin and beta-catenin at the plasma membrane. Various studies suggest the SLIT/ROBO network acts as a tumor suppressor system in humans. We have started a broad program that is aimed to delineate the mechanism of action (tumor suppressor action) of SLIT/ROBO human cancers. We are investigating whether reactivation of SLIT/ROBO system (in cancer cells within tumors) would stop the growth and proliferation of tumor cells and their dissemination to other body parts . To test our hypothesis, we are adopting novel approaches such as combining gene therapy and chemotherapy. Currently, we are focussing on prostate, pancreatic and skin cancer (melanoma) for this program. We are running this program in colloboration with Division of Translation Studies, Masonic

Left to right: Ashley Holdgrafer (Intern), Shrawan Kumar Mishra, Mohammad Saleem Bhat, Hifzur Siddique, Abigail Thompson (Intern)
Not pictured: Neelofar Jan Bhat, Mohammad Naime

Cancer Center, University of Minnesota. This program has high translational potential for cancer patients.

4. Role of S100A4 in the development of prostate cancer

S100A4, also known as mts1, CAPL, p9Ka, and metastasin, belongs to the S100 super-family of calcium-binding proteins and is located in a 2.05 Mbp segment of the genomic DNA of chromosome 1q21 region where most of the S100 family of gene cluster occurs. S100A4 protein has been reported to be associated with invasion and metastasis of cancer cells and 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 form plays a tumor promoting role in the development of prostate cancer by regulating the function of Nuclear Factor kappa B/Receptor for Advanced Glycation End products molecular circuitry.

5. Transition of androgen-depedent 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 or castration-resistant type of disease. We are testing whether isoforms or splice variants of androgen receptor play a role in the castration-resistance of prostate cancer.

6. 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, and mangoes, as well as in herbs such as aloe vera. Our laboratory has shown that Lupeol application on skin prevents cancer development in animal models. Further, we have shown that Lupeol treatment inhibits the growth of prostate, pancreatic, and skin tumors (of human origin) using relevant mouse models. These studies have generated interest in studying Lupeol for other cancer types.

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

Functional food is any healthy food claimed to have a health-promoting or disease-preventing property beyond the basic function of supplying nutrients. Functional chocolate consumption has been associated with improvements in delayed oxidation of low-density lipoprotein cholesterol and lowered blood pressure in humans. Cocoa-based chocolate consumption has been associated with short-term improvements in delayed oxidation of low-density lipoprotein cholesterol, improved endothelial function, lowered blood pressure, and improved platelet function. Epicatechin is the major component of cocoa powder. We have employed a technique (celled ACTICOA) that provides the cocoa polyphenol powder highly rich in epicatechin content. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of premalignant prostate and pancreatic cells while sparing normal cells via modulation of NFκB signaling pathway. We are testing cocoa polyphenol in animal models evaluating its preventive as well as therapeutic value against cancer. For our studies, we have collaborated with Barry Calibaut (Belgium), one of the leading companies in the world producing functional foods including functional chocolates. We are seeking funds for support of this research study. Our current research programs are sponsored by federal agencies including 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 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, 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 efforts 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.

> "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. "

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. The past year, we have published related work (Park et al, 2010) and other related work will get published soon. Apparently, FANCD2 is closely involved with the molecular players that 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: Fred Dudimah, Panneer Selvam, Peiwen Fei, Guangzhi Dong
Not pictured: Sinto Sebastian Chirackal, Suvamoy Datta, Hwan Ki Park

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.

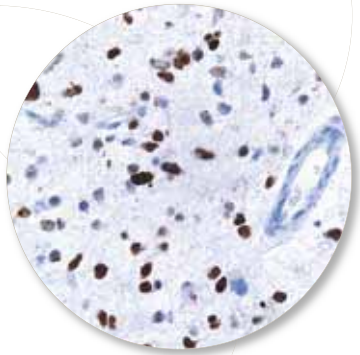
B. P53 Signaling Pathway

Investigating the mechanisms underlying function of p53 initiated by hypoxia, which is encountered mostly by tumor cells.

Previous studies involved searching for p53 target genes that can be upregulated by wt p53 under normoxia (Panneerselvam, et al, 2011) 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.



CANCER BIOMARKERS AND DRUG RESISTANCE

Section Leader

Ann M. Bode, Ph.D.

Professor

Immunohistological Staining of Cox2 in Squamous Cell Carcinoma

Our laboratory is funded by two different National Institutes of Health contracts. The purpose of the studies on the contract entitled "Measurement of Specific Signal Transduction Endpoints To Identify Potential Biomarkers And Mechanisms of Action of Specific Preventive Agents: Lapatinib, Targretin, IGF-1R Inhibitor, Polyphenon E, Naproxen and NO Naproxen" is to identify and measure specific cellular signal transduction endpoints with the purpose of identifying potential biomarkers and mechanisms of action of the specific agents listed in the title.

This work assignment was initially divided into 3 portions that included preliminary studies, studies with mammary tumors and normal mammary glands, and effects of chemopreventive agents in in vivo mammary and bladder models. The primary purpose of this work is to determine whether specific signal transduction molecules can serve as reliable endpoint biomarkers for clinical trials as well as providing insight into the mechanism(s) by which selected anticancer agents modulate their preventive effects. The work eventually expanded to include human bladder cancer and human mammary cancer cell culture models. The development and identification of reliable biomarkers will allow us to 1) assess the efficacy of potential chemopreventive or therapeutic agents for clinical trials; 2) identify patients who will respond to specific drug treatments; and 3) determine the mechanisms of action of specific agents or mixtures of agents (e.g., food mixtures). These are major objectives in the field of chemoprevention and cancer therapeutics. To identify biomarkers, we use a variety of techniques, including immunohistochemisty, Western blot analysis, protein array analysis, and cell culture.

The second contract is entitled "Use of Cell Culture in Testing Efficacy of Potential Chemopreventive Agents and Determining Biomarker Changes Related to Efficacy of These Agents: Ki Ras Related Agents, AMP Kinase Activators; PARP Inhibitors." In this contract, we work with a variety of investigators across the U.S.

The use of cell culture to investigate the relative efficacy of various members of a class of inhibitors for efficacy as well as to identify specific biomarkers that may reflect mechanistic changes relevant to chemoprevention appears quite obvious. There are alterations that can be observed in cell culture both in terms of biomarker changes that may prove useful in supporting the more expensive in vivo studies that may follow. Although this approach may prove applicable to the widest range of agents or classes of agents, we examine agents from 4 classes of agents. Agents are examined in various cell lines which are relevant to the specific class of agents.

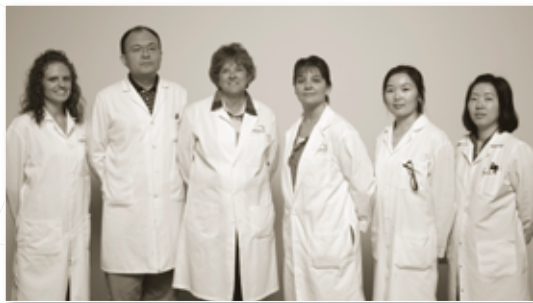
This work assignment is comprised of 3 projects:

Project 1. The use of Ki Ras mutant and Ki Ras wildtype cell lines to define the sensitivity to RAL inhibitors prior to in vivo studies. A variety of RAL inhibitors, which are related to Ki Ras activation are tested in cell lines with or without Ki ras mutations to determine relative sensitivity as well as examine its effects on downstream proteins including Akt, MAPKs. Based on these studies these agents are tested in an in vivo model, which either develops or fails to develop Ki Ras mutations.

Cancer Biomarkers and Drug Resistance – a new research section added in 2011.

Project 2. The use of colon cell lines with altered expression of specific biomarkers (Cox-2, Cyclin D1) to use as a positive control in determining RT-PCR primers, which can be used in formalin fixed materials.

Project 3. The use of Neu expressing or ER positive breast cancer cell lines to test the effect of RXR inhibitors, targretin and UAB, on migration and invasion along with other characteristics of cancer.

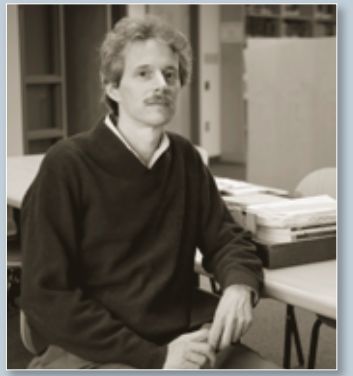


Left to right: Alyssa Langfald, Hongxun Wang, Ann Bode, Andria Carper, Jixia Li, Mi Sung Kim

Left to right: Michelle Jacobson, Teri Johnson, Ellen Kroc, Angela Zago, Melissa Fortsch
Not pictured: Andria Hansen, Leonda Lerud, Jennifer Mittelsted

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.



LIBRARIAN
Andy Lucas

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

INSTRUMENT CORE FACILITY
Todd Schuster
Senior Lab Technician

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

OFFICE
Supervisor
Associate Director
Ann M. Bode, Ph.D.

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

Office Staff
Betsy Mentel, Executive Office and Administrative Specialist
Tonya Poorman, Principal Office and Administrative Specialist
Becky Smit, Principal Accounts Specialist

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

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

PUBLIC RELATIONS AND DEVELOPMENT
Gail Dennison

World-wide recognition and support of The Hormel Institute's cutting-edge cancer research continued to grow throughout 2010-11, through the collective efforts of the Institute, our leaders and our partners. We remain deeply thankful for those who support the vision of the Institute's continued growth and development as well as 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
- Minnesota State Representative Rich Murray
- 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
- 5th District Eagles Cancer Telethon
- Karl R. Potach Foundation
- Lyle Area Cancer
- AgStar
- 4-H Mower County
- Austin Bruins
- Deryl Arnold Memorial Golf Tournament
- Dave "Tolly" Tollefson Memorial Golf Tournament
- Fishing for a Cure
- Mower County USBC Association's "Bowl for the Cure"
- Timothy Muellner Memorial Golf Tournament
- VFW Ladies Auxiliary
- Strides for a Cure
- Volunteers

Partnerships & Collaborations

Courtesy of Austin Daily Herald

U.S. Sen. Al Franken speaks with The Hormel Institute's Associate Director Dr. Ann M. Bode on April 27, 2011, during the senator's first visit to the Institute. Leaders from the City of Austin, Hormel Foods Corp. and The Hormel Foundation helped welcome Franken to the Institute.

Courtesy of Austin Daily Herald

U.S. Rep. Tim Walz views The Hormel Institute's X-ray crystallography laboratory during a visit on Aug. 11, 2010, that included him receiving a "Hero of Cancer Research" award from the Institute for his work in securing nearly $2 million in federal technology grants for The Hormel Institute since 2006.

Dr. Zigang Dong, Executive Director of The Hormel Institute, speaks Sept. 11, 2010, with Dave Thompson and Gary Ziegler of the Lyle Area Cancer group during an event at the Institute to show appreciation to the annual Eagles Cancer Telethon and its supporters.

Two mothers and a grandmother of three Austin Bruins players embrace following a ceremonial puck drop Feb. 5, 2011, during the first "Paint the Rink Pink" hockey game to raise money and awareness for The Hormel Institute's breast cancer research. With pink ice and pink jerseys, the event raised more than $22,000 for breast cancer research at the Institute.

Dr. Kurt Potach speaks in August 2010 during the 13th annual Karl Potach Memorial Golf Tournament, an Austin event in memory of his son Karl, who died at age 4 from a type of cancer called Wilms' tumor. Proceeds from the Karl Tourney help fund research exclusively on Wilms' tumor at The Hormel Institute.

Left to right: Craig Jones, Mike Conway, Tim Lastine, Theresa Tucker
Not pictured: Rose Srock, Ryan Wiersma, Gary Bush

RESEARCH SUPPORT SERVICES (RSS)
Supervisor: Craig Jones

IIt has been another exciting year for RSS. The Blue Gene supercomputing project is continuing to be an exciting part of the group's duties. The Blue Gene has a computational speed of approximately 4.7 TFlops (Trillion Floating point operations per second) enabling researchers to screen 2.1 million drug compounds for cancer protein interactions in a few weeks. These kinds of calculations were just not possible even a few years ago. But the most exciting news is the anticipated arrival of a new Linux cluster supercomputer. The system is going to operate many times faster than the Blue Gene and be a standard Linux system allowing quick software porting and implementation. It is currently out on an RFP and scheduled to be installed later in 2011. This spring we added the Triple TOF Mass Spectrometer to complement the X-Ray Crystallography and Supercomputing core facilities.

We continue to provide instrument maintenance as well as computer, graphics, telecommunication, network, and Internet support for The Hormel Institute. Maintenance includes a wide variety of scientific instruments, from complex to simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our work load. As always, the security needs of the network keep us busy. You know what they say in the IT world, "The only constant is change" and that is very evident in network security.

Serving as the building coordinator of the beautiful new facility is a great job. The Institute has now settled into the facility and is functioning as it was intended. We have set up laboratories for the new research section leaders and with only minor changes are making the building even more scientist friendly to facilitate the research.

Left to right: Brandon Hoium, Duane Graff, Mark Severtson, Randy Johnson
Not pictured: Norman Johnson

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: Danielle Jondal, Hanna Middlebrook, Sarah Ewing
Second row: Abigail Thompson, Ashley Holdgrafer, Lindsey Jacobsen
Third row: Kyle Auringer, Stephen Brockman, Steven Rizzi

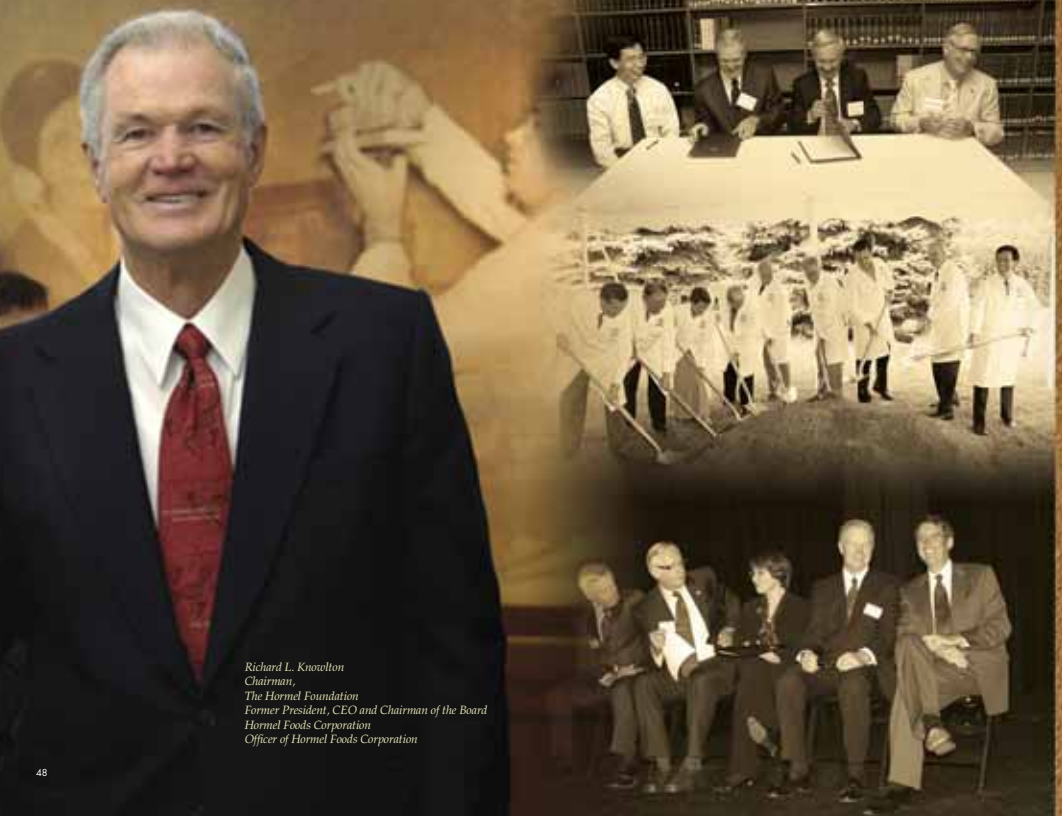
PARTNERSHIPS FOR SUCCESS

Improving the world has been The Hormel Foundation's top priority since its inception 70 years ago by Hormel Foods Corporation founder George A. Hormel and his son Jay C. Hormel.

This continues to be accomplished through scientific research at The Hormel Institute. Started by Jay Hormel in 1942 and gifted to the University of Minnesota, The Hormel Foundation provides significant, annual support to the Institute for its world-renowned cancer research.

The Hormel Institute is deeply grateful for unwavering support from The Hormel Foundation – support that accelerates discoveries in our aggressive fight against cancer.

THE HORMEL FOUNDATION



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 and the science within is the most important project in The Hormel Foundation's history."

Richard L. Knowlton, long-time chairman of The Hormel Foundation and former CEO of Hormel Foods Corporation, has helped The Hormel Institute grow substantially while it has achieved ongoing, world-renowned success with cutting-edge cancer research.

Working with Dr. Zigang Dong, Executive Director of The Hormel Institute, Knowlton has provided strong leadership, vision, friendship and unwavering support. An Austin, Minn., native, Knowlton oversaw the Institute's 2006-2008 expansion project led by The Hormel Foundation that tripled its size and doubled employment.

With his retirement in December 2011 after more than 30 years on The Hormel Foundation s Board of Directors, The Hormel Institute's faculty and staff express their deep gratitude for the many ways Knowlton has supported the Institute and the goal to improve the health of the world.

Richard L. Knowlton

The Hormel Institute Publications

July 1, 2010 — June 30, 2011

H.I. No. 1771
Convergence of Rad6/Rad18 and fanconi anemia tumor suppressor pathways upon DNA damage.
Park WH, Wang H, Zhang J, Datta S, and Fei P. PloS One, Oct 13;5(10) (2010).

H.I. No. 1772
A novel sulindac derivative lacking COX-inhibitory activities suppresses carcinogenesis in the transgenic adenocarcinoma of mouse prostate model.
Zhang Y, Zhang J, Wang L, Quealy E, Gary BD, Reynolds RC, Piazza GA, and Lü J. Cancer Prev Res. Jul; 3(7):885-95 (2010).

H.I. No. 1782
Proteomic profiling of potential molecular targets of methyl-selenium compounds in the transgenic adenocarcinoma of mouse prostate model.
Zhang J, Wang L, Anderson L, Witthuhn B, Xu Y, and Lü J. Cancer Prev Res (Phila Pa). Aug; 3(8):994-1006 (2010).

H.I. No. 1783
Penta-O-gallolyl-beta-D-glucose induces G1 arrest and DNA replicative S-phase arrest independently of cyclin-dependent kinase inhibitor 1A, cyclin-dependent kinase inhibitor 1B and P53 in human breast cancer cells and is orally active against triple negative xenograft growth.
Chai Y, Lee HJ, Shaik A, Nkhata K, Xing C, Zhang J, Jeong SJ, Kim SH, and Lü J. Breast Cancer Res. Sep1;12(5):R67 (2010).

H.I. No. 1784
Anti-cancer gallotannin penta-O-galloyl-beta-d-glucose is a nanomolar inhibitor of select mammalian DNA polymerases
Mizushina Y, Zhang J, Pugliese A, Kim SH, and Lü J. Biochem Pharmacol. Oct 15;80(8):1125-32 (2010).

H.I. No. 1785
Preparation of penta-O-galloyl-β-D-glucose from tannic acid and plasma pharmacokinetic analyses by liquid-liquid extraction and reverse-phase HPLC.
Li L, Shaik A, Zhang J, Nhkata K, Wang L, Zhang Y, Xing C, Kim S-H, and Lü J. Journal of Pharmaceutical and Biomedical Analysis. Feb 20;54(3):545-50 (2011).

H.I. No. 1786
Galbanic acid isolated from ferula assafoetida exerts in vivo anti-tumor activity in association with anti-angiogenesis and anti-proliferation.
Kim KH, Lee HJ, Jeong SJ, Lee HJ, Lee EO, Kim HS, Zhang Y, Ryu SY, Lee MH, Lü J, and Kim SH. Pharm Res. Mar;28(3):597-609 (2011).

H.I. No. 1787
Obesity and breast cancer: status of leptin and adiponectin in pathological processes.
Grossmann, ME, Ray A, Nkhata K, Malakov D, Rogozina O, Dogan S, and Cleary MP. Cancer Metastasis Reviews 29:641-653 (2010).

H.I. No. 1788
Effects of intermittent and chronic calorie restriction on mammalian target of rapamycin (mTOR) and IGF-I signaling pathway in mammalian fat pad tissues and mammary tumors.
Dogan S, Johannsen AC, Grande JP, and Cleary MP. Nutrition and Cancer 63:389-401 (2011).

H.I. No. 1789
Effect of chronic and intermittent calorie restriction on serum adiponectin and leptin and mammary tumorigenesis.
Rogozina O, Bonorden M, Seppanen C, Grande JP, and Cleary MP. Cancer Prevention Research 4:568-581 (2011).

H.I. No. 1790
Amphiastral mitotic spindle assembly in vertebrate cells lacking centrosomes.
Hornick JE, Mader CC, Tribble EK, Bagne CC, Vaughan KT, Shaw SL, and Hinchcliffe EH. Current Biology 21:598-605 (2011).

H.I. No. 1791
Polo-like kinase1 is required for recruitment of dynein to kinetochores during mitosis.
Bader JR, Kasuboski J, Winding M, Zhang C, Vaughan PS, Hinchcliffe EH, and Vaughan KT. Journal of Biological Chemistry 286:20769-20777 (2011).

H.I. No. 1792
The complete mitochondrial genome and phylogenetic analysis of Debao pony (Equus caballus).
Jiang Q, Wei Y, Huang Y, Jiang H, Guo Y, Lan G, and Liao DJ. Mol. Biol. Report 38: 593-599 (2011).

H.I. No. 1793
Reviewing once more the c-myc and Ras collaboration: converging at the cyclin D1-CDK4 complex and challenging basic concepts of cancer biology.
Wang C, Lisanti MP, and Liao DJ. Cell Cycle 10 (1): 57-67 (2011).

H.I. No. 1794
Effects of an indolocarbazole-derived cdk4 inhibitor on breast cancer cells.
Sun Y, Li YX, Wu HJ, Wu SH, Wang YA, Luo DZ, and Liao DJ. J Cancer 2:36-51 (2011).

H.I. No. 1795
c-Myc induction of programmed cell death may contribute to carcinogenesis: a perspective inspired by several concepts of chemical carcinogenesis.
Wang C, Tai Y, Lisanti MP, and Liao DJ. Cancer Biol. Therapy 11(7): 615-626 (2011).

H.I. No. 1796
The yin and yang of bone morphogenetic proteins in cancer.
Singh A and Morris RJ. Cytokine and Growth Factor Revs. 21: 299-313 (2010).

H.I. No. 1797
Bone morphogenetic protein 5 regulates the number of keratinocyte stem cells in the skin of mice.
Kamsamaksin T and Morris RJ. J. Invest. Dermatol. 131: 580-585 (2011).

H.I. No. 1798
Glucosinolate enhancement in cabbage induced by sasmonic acid application.
Bode A and Schuster T. Hortscience 45(8):1188–1191 (2010).

H.I. No. 1799
Update on cancer prevention research in the United States and China: the 2009 China—U.S. forum on frontiers of cancer research.
Bode AM, Cao Y, and Dong Z. Cancer Prev Res (Phila) 3, 1630-1637 (2010).

H.I. No. 1800
The two faces of capsaicin.
Bode AM and Dong Z. Cancer Res 71, 2809-2814 (2011).

H.I. No. 1801
Pathologic progression of mammary carcinomas in a C3(1)/SV40 T/t-antigen transgenic rat model of human triple-negative and Her2-positive breast cancer.
Hoenerhoff MJ, Shibata MA, Bode AM, and Green JE. Transgenic Res. 20, 247-259 (2011).

H.I. No. 1802
Cocarcinogenic effect of capsaicin involves activation of EGFR signaling but not TRPV1.
Hwang MK, Bode AM, Byun S, Song NR, Lee HJ, Lee KW, and Dong Z. Cancer Res. Sep 1;70(17):6859-69 (2010).

H.I. No. 1803
Role of NEK6 in tumor promoter-induced transformation in JB6 C141 mouse skin epidermal cells.
Jeon YJ, Lee KY, Cho YY, Pugliese A, Kim HG, Jeong CH, Bode AM, and Dong Z. J Biol Chem. Sep 3;285(36):28126-33 (2010).

H.I. No. 1804
Phosphorylation of sox2 cooperates in reprogramming to pluripotent stem cells.
Jeong CH, Cho YY, Kim MO, Kim SH, Cho EJ, Lee SY, Jeon YJ, Lee KY, Yao K, Keum YS, Bode AM, and Dong Z. Stem Cells. Dec;28(12):2141-50 (2010).

H.I. No. 1805
Coffee phenolic phytochemicals suppress colon cancer metastasis by targeting MEK and TOPK.
Kang NJ, Lee KW, Kim BH, Bode AM, Lee HJ, Heo YS, Boardman L, Limburg P, Lee HJ, and Dong Z. Carcinogenesis Jun;32(6):921-8 (2011).

H.I. No. 1806
sorhamnetin Suppresses Skin Cancer through Direct Inhibition of MEK1 and PI3-K.
Kim JE, Lee DE, Lee KW, Son JE, Seo SK, Li J, Jung SK, Heo YS, Mottamal M, Bode AM, Dong Z, and Lee HJ. Cancer Prev Res (Phila). Apr;4(4):582-91 (2011).

H.I. No. 1807
7,3',4'-Trihydroxyisoflavone, a metabolite of the soy isoflavone daidzein, suppresses ultraviolet B-induced skin cancer by targeting Cot and MKK4.
Lee DE, Lee KW, Byun S, Jung SK, Song N, Lim SH, Heo YS, Kim JE, Kang NJ, Kim BY, Bowden GT, Bode AM, Lee HJ, and Dong Z. J Biol Chem. Apr 22;286(16):14246-56 (2011).

H.I. No. 1808
6,7,4'-trihydroxyisoflavone inhibits HCT-116 human colon cancer cell proliferation by targeting CDK1 and CDK2.
Lee DE, Lee KW, Jung SK, Lee EJ, Hwang JA, Lim TG, Kim BY, Bode AM, Lee HJ, and Dong Z. Carcinogenesis Apr;32(4):629-35 (2011).

H.I. No. 1809
Kaempferol inhibits UVB-induced COX-2 expression by suppressing Src kinase activity.
Lee KM, Lee KW, Jung SK, Lee EJ, Heo YS, Bode AM, Lubet RA, Lee HJ, and Dong Z. Biochem Pharmacol. Dec 15;80(12):2042-9 (2010).

H.I. No. 1810
Molecular targets of phytochemicals for cancer prevention.
Lee KW, Bode AM, and Dong Z. Nat Rev Cancer. Review Mar;11(3):211-8 (2011).

H.I. No. 1811
Histone XH2AX is required for Xenopus anterior neural development: critical role of threonine 16 phosphorylation.
Lee SY, Lau AT, Jeong CH, Shim JH, Kim HG, Kim J, Bode AM, and Dong Z. J Biol Chem. Sep 17;285(38):29525-34 (2010).

H.I. No. 1812
TRPV1-antagonist AMG9810 promotes mouse skin tumorigenesis through EGFR/Akt signaling.
Li S, Bode AM, Zhu F, Liu K, Zhang J, Kim MO, Reddy K, Zykova T, Ma WY, Carper AL, Langfald AK, and Dong Z. Carcinogenesis May;32(5):779-85 (2011).

H.I. No. 1813
P21-activated protein kinase (PAK2)-mediated c-Jun phosphorylation at 5 threonine sites promotes cell transformation.
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MST1 promotes apoptosis through phosphorylation of histone H2AX.
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Structural determination and tryptophan fluorescence of heterokaryon incompatibility C2 protein (HET-C2), a fungal glycolipid transfer protein (GLTP), provide novel insights into glycolipid specificity and membrane interaction by the GLTP fold.
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Human glycolipid transfer protein (GLTP) modulates cell shape.
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Health benefits of lupeol: a review of preclinical studies.
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H.I. No. 1829
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The Hormel Institute Seminars

July 1, 2010 — June 30, 2011

Hyong Joo Lee, Ph.D.
Seoul National University
July 21, 2010
"Biomodulation with food components for human health"

Richard Eckert, Ph.D.
University of Maryland School of Medicine
August 30, 2010
"Making sense of skin - regulating keratinocyte differentiation and survival"

James E. Trosko, Ph.D.
Michigan State University Center for Integrative Toxicology
September 3, 2010
"Epigenetic chemical effects on stem cells and cell-cell communication: their roles in the cause and prevention of human carcinogenesis, including in the Barker's Hypothesis"

David J. Odde, Ph.D.
University of Minnesota
November 19, 2010
"Kinetics of microtubule assembly"

Hye-Kyung Na, Ph.D.
Sungshin Women's University
February 4, 2011
"Role of 15-deoxy-delta 12,14-prostaglandin J2 in human breast carcinogenesis"

Yong Q. Chen, Ph.D.
Comprehensive Cancer Center of Wake Forest University
March 30, 2011
"Lipid metabolism in prostate cancer"

Azeddine Atfi, Ph.D.
Harvard School of Dental Medicine
April 8, 2011
"Mechanisms underlying inactivation of the TGF-b tumor suppressor network by the homeodomain protein TGIF"

Young-In Chi, Ph.D.
University of Kentucky
April 12, 2011
"Molecular mechanism of HNF4alpha: a diabetes gene product"

Sumitra Deb, Ph.D.
Virginia Commonwealth University
April 14, 2011
"P53 gain of function mutations and cancer"

Bing-Hua Jiang, Ph.D.
Thomas Jefferson University
April 15, 2011
"Signaling crosstalk of cancer cells and endothelial cells in regulating tumor growth and angiogenesis"

Shujun Liu Ph.D.
The Ohio State University
April 19, 2011
"Molecular pathogenesis of acute myeloid leukemia: implications for new therapeutic strategies"

Michael Fannon, Ph.D.
University of Kentucky
May 12, 2011
"Bioavailability in health and disease"

Leyuan Liu, Ph.D.
Texas A&M Health Science Center
May 17, 2011
"Roles of C19ORF5 in regulation of autophagy and suppression of hepatocarcinomas"

Donald J. Tindall, Ph.D.
Mayo Clinic College of Medicine
May 18, 2011
"Mechanisms of androgen receptor action in prostate cancer progression"

Gennady M. Verkhivker, Ph.D.
University of California San Diego
May 19, 2011
"Translational bioinformatics and computational systems biology in cancer research: from understanding genetic and molecular signatures of human disease to targeting biological pathways and personalized medicine"

Jing Yang, Ph.D.
The Ohio State University College of Medicine and Public Health
May 24, 2011
"Diverse functions of B56 epsilon - a regulatory subunit of PP2A"

Bing Li, Ph.D.
University of Louisville
May 26, 2011
"Regulation of T cell differentiation by epidermal fatty acid binding protein"

Mohammad Athar, Ph.D.
The University of Alabama at Birmingham
June 1, 2011
"Pathogenesis of basal cell carcinoma: genetic susceptibility determinants"

Powel H. Brown, M.D., Ph.D.
The University of Texas
M.D. Anderson Cancer Center
June 9, 2011
"Advances in the prevention of ER-negative breast cancer: molecularly targeted preventive therapy"

Income from Grants and Contracts

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Anticarcinogenic Mechanisms of Tea Constituents (Z. Dong)	*187,169*
*Mechanisms of Chemopreventive Effect of Resveratrol (Z. Dong) **	
Inhibition of Carcinogenesis by Tea and Tea Constituents (Z. Dong)	*114,902*
Molecular Basis of Glycosphingolipid Binding Specificity (R. Brown)	*57,451*
Methyl Selenium for Prostate Cancer Chemoprevention (J. Lü)	*95,000*
Prostate Cancer Chemoprevention by Penta-galloyl-glucose (J. Lü)	*100,000*
The Role of Bone Marrow Derived Cells in Skin Cancer (R. Morris)	*138,63*
Study on Ultraviolet Signal Transduction-ARRA (Z. Dong)	*177,385*
Telomere Dysfunction, p53 and Tumorigenesis (Y. Deng)	*159,325*
Telomere Dysfunction, p53 and Tumorigenesis-ARRA (Y. Deng)	*35,395*
Measurements of Specific Signal Transduction Endpoints (A. Bode)	*126,674*
Proposed Study Employing Computer Simulations and Screening (Z. Dong)	*233,104*
Roles of the Fanconi Anemia Pathway in Bladder Tumorigenesis (P. Fei)	*291,246*
Delaying the Hormone Refractory Prostate Cancer by a Dietary Triterpene Lupeol-ARRA (M.S. Bhat)	*83,377*
Prevention of PTEN Deletion Driven Prostate Cancer by Selenium (Y. Deng and J. Lü)	*54,889*
Use of Cell Culture in Testing Efficacy of Potential Chemopreventative Agents and Determining Biomarker Changes Related to Efficacy of These Agents: Ki Ras Related Agents, AMP Kinase Activators; PARP Inhibitors (A. Bode)	*26,185*
Use of Computer Simulations to Examine Potential Chemopreventive Agents for Potential Targets and Off Target Proteins (Z. Dong)	*4,753*

National Heart, Lung, and Blood Institute

Regulation of Peripheral Protein-Membrane Interactions by Lipid Second Messengers (H. Brockman)	*259,509*

National Institute of Environmental Health Sciences

The Role of Histone Phosphorylation in Arsenic -induced Cell Transformation and Cancer (Z. Dong)	*225,000*

National Institute of General Medical Sciences

*Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown) **	
Mechanisms of Centrosome Reproduction in Animal Cells (E. Hinchcliffe)	*132,002*

National Institute of Arthritis and Musculoskeletal and Skin Diseases

The Regulation of Keratinocyte Stem Cells (R. Morris)	*360,511*

National Center For Complementary and Alternative Medicine

An Oriental Herbal CAM Modality for Prostate Cancer Chemoprevention (J. Lü)	*97,876*

DEPARTMENT OF DEFENSE – U.S. ARMY

The Role of Polycomp Group Gene Bmi-1 in the Development of Prostate Cancer (M.S. Bhat)	*37,517*
*Role of Obesity in Prostate Cancer Development (M. Cleary) **	
RNA Chimeras as a Gene Signature of Breast Cancer (D.J. Liao)	*14,999*

AMERICAN INSTITUTE FOR CANCER RESEARCH

*Dietary Obesity and Prostate Cancer Development in TRAMP Mice (M. Cleary) **	
Calorie Restriction, Lipid Peroxidation, and Mammary Tumors (C. Seppanen)	*34,981*
Targeting cFLIP by Lupeol, a Dietary Triterpene, for Chemoprevention of Pancreatic Cancer (M.S. Bhat)	*64,275*

PEDIATRIC PHARMACEUTICALS

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

SEOUL NATIONAL UNIVERSITY (KOREA)

Biogreen 21 Project (Z. Dong)	*50,402*

SUSAN G. KOMEN FOR THE CURE

Calorie Restriction and Eicosapentaenoic Acid (M. Grossmann)	*120,504*

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care and Other Facilities Equipment Project (Z. Dong)	*497,313*

Other Resources

The Hormel Foundation	*2,301,856*
University of Minnesota	*447,951*
Indirect Cost Return	*1,513,978*
Eagles Cancer Telethon	*130,000*
Mayo Clinic Collaborative Donation	*1,000,000*
Other	*649,469*
Total	**9,823,63**

** Full award amount stated in previous report*

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