The Hormel Institute

University of Minnesota

06 ANNUAL REPORT 07

Progress Through Dedication

A YEAR OF HISTORIC GROWTH 06-07

In an unprecedented move of generosity and philanthropic support, The Hormel Foundation and Hormel Foods Corporation donated over $15 million to The Hormel Institute for a major expansion and renovation. The state-of-the-art cancer research facility, now under construction, is targeted for completion Summer of 2008.

The project broke ground in August of 2006 and will triple the size of the 1960 facility. Twenty state-of-the-art research labs will provide space for new scientists and new technology…tools that will propel The Hormel Institute to even greater scientific research achievements.

We appreciate your support and encouragement as together we take The Hormel Institute to a new era. Together we can celebrate knowing that today's research leads to tomorrow's cures.

— The Hormel Institute, University of Minnesota


LINCOLN
ELECTRIC

Message from the Director
Dr. Zigang Dong

According to a recent report of the World Health Organization of the United Nations, cancer is one of the leading causes of death worldwide. Cancer affects us all – rich and poor, man and woman, young and old. Yet many cancer deaths could be prevented by early detection, treatment and cure.

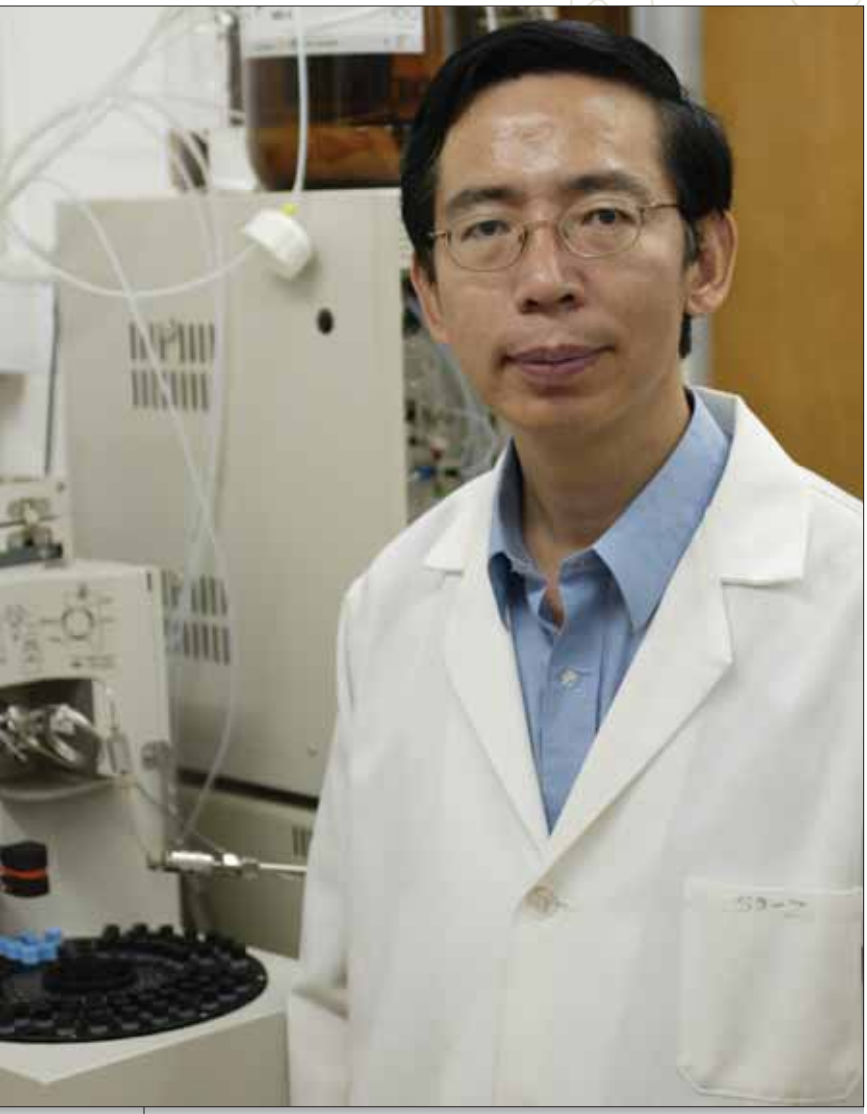
The Hormel Institute is rapidly becoming a recognized leader in the scientific field showing that dietary factors modulate crucial cellular signal transduction pathways in cancer development and prevention. The Institute was one of the first to report the discovery of key molecular targets and mechanisms in tumor promotion. The Hormel Institute is gaining a solid reputation as a leading research institute making major contributions to the identification and characterization of natural chemopreventive agents that are nontoxic but highly effective as anticancer agents.

By focusing on cancer, The Hormel Institute has experienced a dramatic increase in external research funding even in the national environment of overall decreased funding for research. Currently, every section of The Institute has at least one R01 grant from the National Institutes of Health (NIH), and all sections have multiple grants from NIH and/or other funding agencies. Two new research sections were added this past year. Dr. D. Joshua Liao (Translational Cancer Research) and Dr. Peter Ruvolo (Signal Transduction and Apoptosis) joined The Hormel Institute in December 2006 and January 2007, respectively.

The Hormel Foundation has provided consistent financial and advisory support to The Hormel Institute over the years since The Institute's creation in 1942. The Foundation has recently recognized the success of The Institute and, along with Hormel Foods Corporation, has provided major funding for the expansion of the existing Institute facilities. The expansion will consist of the construction of a new two-story building that will house 20 research laboratories. In addition, the existing building will be completely renovated to accommodate a new conference center, library, media center and office and research support space. Groundbreaking occurred August 21, 2006 with completion of the entire project scheduled for Summer 2008. The Hormel Foods Corporation and Mayo Clinic Rochester are providing engineering advisory services and other assistance.

All of these accomplishments would not be possible without the generous ongoing support of The Hormel Foundation and Hormel Foods Corporation. In particular, I would like to thank Mr. Richard Knowlton for his continued interest and support of The Institute, Mr. Joel Johnson, Mr. Jeff Ettinger, Mr. Gary Ray, Mr. Jerry Anfinson and Mr. Larry Pfeil for their generous support, and Dr. Tim Mulcahy for his understanding and support. The Hormel Institute is a team project. By working together, we will help to lead our university in realizing the goal of becoming a top research institution worldwide.


Nikon



CELLULAR AND MOLECULAR BIOLOGY

SECTION LEADER
ZIGANG DONG, M.D., DR. P.H.
MCKNIGHT PRESIDENTIAL PROFESSOR IN CANCER PREVENTION
HORMEL/KNOWLTON PROFESSOR,
EXECUTIVE DIRECTOR

Cancer is one of the leading causes of death in today's world. In order to facilitate the development of chemopreventive and chemotherapeutic agents that specifically target molecules important in cancer development, we must know the enemy – we must understand carcinogenesis. The prevailing thought today is that cancer may be prevented or treated by targeting specific cancer genes, signaling proteins and transcription factors.

Cancer is a multistage process, consisting of initiation, promotion and progression stages. Although each stage may be a possible target for chemopreventive agents, because of its extensive length, the promotion stage has the most potential to be reversed. 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.

Another major goal 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. Over the years, we have been working to identify those mechanisms through our work with signal transduction pathways. Signal transduction is the process by which information from a stimulus outside the cell is transmitted from the cell membrane (e.g., through its receptor) into the cell and along an intracellular chain of signaling molecules to stimulate a response. 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.

The expression of genes transcriptionally induced by tumor promoters, such as arsenic, EGF, TPA, or UV, is required to implement the process of tumor promotion. Many transcription factors involved in tumorigenesis are tightly regulated by the mitogen-activated protein (MAP) kinase signaling cascades. The MAP kinase signaling pathways are critical for activator protein-1 (AP-1) activation. AP-1 is known to be involved in cancer development and suppressing its activation can inhibit tumorigenesis. An important group of AP-1 activators are the c-Jun N-terminal kinases 1, 2, and 3.

UV irradiation is categorized by wavelength as UVA I (340-400 nm), UVA II (320-340 nm), UVB (280-320) nm), and UVC (180-280 nm). In mouse skin, UV light acts as both an initiator, presumably by causing DNA damage leading to gene mutations, and as a tumor promoter. The mechanisms behind the tumor promoting ability of UV are areas of intense study in our laboratory. Numerous

Front Row: Merlene Stiles, Margarita Malakhova, Andria Leyden, Darya Urusova, Myoung Ok Kim, Duo Zheng

Middle Row: Tatyana Zykova, Ji-Shuai Zhang, Feng Zhu, Zheng-Yuan Su, Hong-Gyum Kim, Sang-Muk Oh, Cong Peng, Tao Yin Lau

Back Row: Ke Yoo, Wei-Ya Ma, Ann Bode, Zigang Dong, Yong Yeon Cho, Sung Young Lee, Jung-Hyun Shim

oncogenic and/or protective signaling pathways are activated in UV-induced carcinogenesis. Very little is known about UV-induced phosphorylation of histones, proteins that are very important in the packaging of DNA. However, recent data suggests that MAP kinases have a distinct and key role in mediating that process. Histone H3 is a basic component of the transcriptional machinery and a structural protein of the nucleosome. Phosphorylation of histone H3 probably has an important role in immediate early gene expression, chromatin remodeling, and chromosome condensation during mitosis. UVB irradiation was shown to markedly induce phosphorylation of histone H3 at serine 28 in JB6 Cl41 cells and the phosphorylation was mediated in varying degrees by ERKs, p38 kinase and JNKs.

We found that the UV-induced signal transduction pathways are mediated primarily through signaling cascades involving the MAP kinases, resulting in the modification of transcription factors, including AP-1, nuclear factor kappaB (NF-kappaB), 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.

In addition to the study of UV as a carcinogen and tumor promoter, this laboratory has focused on the elucidation of mechanisms to explain the paradox of arsenic. Arsenic's enigmatic effects make the elucidation of the exact mechanisms of its cancer-causing effects difficult to discern. Arsenic cannot be precisely classified as a carcinogen because it has not been shown conclusively to be an initiating or a promoting agent of carcinogenesis in animals. Furthermore, in contrast to classic tumor promoting agents, its effects are not reversible. We showed that exposure of JB6 Cl41 cells to arsenite induced cell transformation and phosphorylation and activation of ERKS and JNKs. Of particular interest was the finding

that arsenite-induced ERKs activation and cell transformation were blocked in cells expressing the dominant negative ERK2. In contrast, overexpression of a dominant negative JNK1 inhibited arsenite-induced JNK activation but increased arsenite-induced cell transformation. These results demonstrate that activation of ERKs, but not JNKs, by arsenite is required for arsenite's effects on cell transformation. The results of these two studies support the hypothesis that the induction of ERKs by arsenic may promote arsenic's carcinogenic effects, whereas induction of JNKs by arsenic may enhance its apoptotic activity and therefore its anticarcinogenic effects.

Further investigations indicated that MSK1, a downstream kinase of p38 and ERK MAP kinases directly monitors UVB-induced phosphorylation of histone H3 at serine 28. We recently found that Fyn, a member of the Src kinase family, is also involved in the UVB-induced phosphorylation of histone H3 at serine 10. Very little is known about the role of histone H3 phosphorylation in malignant transformation and cancer development. We examined the function of H3 phosphorylation in cell transformation in vivo. Introduction of small interfering (si) RNA-H3 into JB6 cells resulted in decreased epidermal growth factor (EGF)-induced cell transformation. In contrast, wild-type histone H3 (H3 WT)-overexpressing cells markedly stimulated EGF-induced cell transformation, whereas the H3 mutant S10A cells suppressed transformation. When H3 WT was overexpressed, EGF induction of *c-fos* and *c-jun* promoter activity was significantly increased compared with control cells but not in the H3 mutant S10A or S28A cells. In addition, AP-1 activity in H3 WT-overexpressing cells was markedly up-regulated by EGF in contrast to the H3 mutant S10A or S28A cells. These results indicated that the phosphorylation of histone H3 at Ser(10) is an essential regulatory mechanism for EGF-induced neoplastic cell transformation.

We have also focused on the effects of tea in inhibiting carcinogenesis. We have reported that (-)-epigallocatechin-3-gallate (EGCG) from green tea or theaflavins (TFs) from black tea inhibit tumor promoter induced AP-1, NF-kappaB activation, MAP kinase activation and cell transformation. We also showed an inhibitory effect of TFs and EGCG on UVB-induced STAT1 (Ser727), ERKs, JNKs, PDK1 and p90RSK2 phosphorylation. We have shown that EGCG or theaflavins block arsenite-induced apoptosis of JB6 cells. 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 and insulin-like growth factor receptor 1 (IGF-1R), as novel EGCG-binding proteins. Intermediate filament (IF) proteins, such as vimentin, have an important functional involvement in cell division and proliferation. EGCG has been reported to inhibit cell proliferation of a variety of cell lines and in our work, when vimentin expression was suppressed, cell growth was inhibited.

We continue to enjoy our productive collaborations with Drs. C.S. Yang and Allan Conney at Rutgers University, and Drs. Tim Bowden and David Alberts at the University of Arizona on tea research and skin cancer prevention, respectively. More recently, we have worked with Dr. Yuan-Ping Pang at Mayo Clinic to use high-performance computers, modern chemical synthesis and cancer biology to block JNK and develop anti-cancer drugs. Further, 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 computer to understand complex diseases like cancer; and to screen anti-cancer 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.

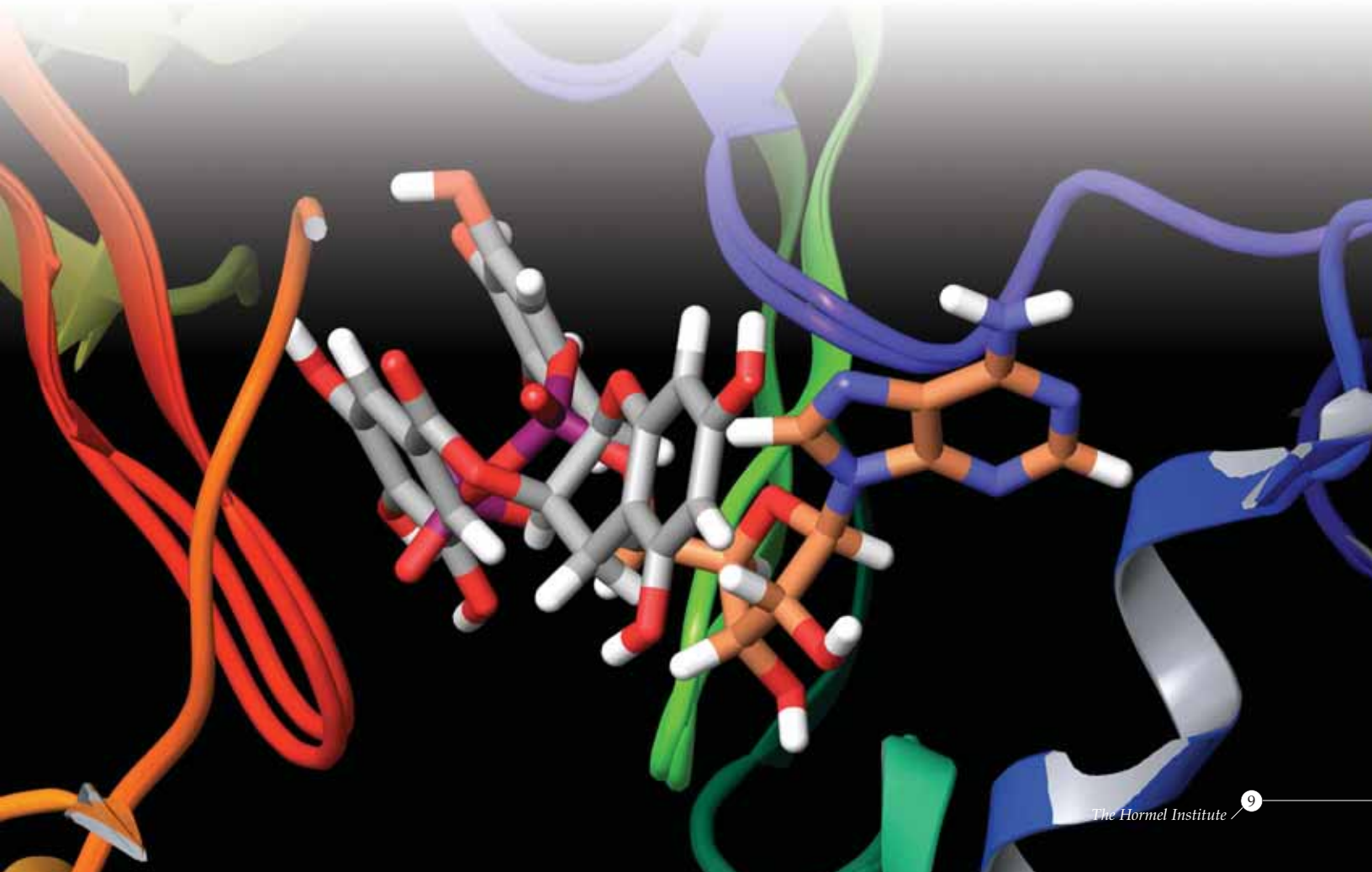
In summary, we address fundamental questions concerning the response of animal and/or human cells to carcinogens and tumor promoters such as UV light, arsenic, TPA and growth factors. We have established a series of necessary models or systems, such as the over-agar assay for cell transformation, gene 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 UVA, UVB and UVC. We have described the critical roles of MAP kinases

at all three unique wavelengths of UV-induced signal transduction pathways. We have demonstrated the distinctive role of JNK1 and JNK2 in cancer development and have discovered several novel kinases for p53, histone H3, and histone H2AX. Such studies have provided the basis for the carcinogenic process caused by environmental carcinogens and molecular mechanisms for cancer prevention.

Further, we have identified key molecular targets for screening novel natural anticancer drugs with fewer side effects. 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 inositol hexaphosphate, PEITC, ginger and CAPE. 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. 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.

Other Professional Activities
Zigang Dong

Grant Reviewer, National Institutes of Health
Manuscript Review Editor, *Molecular Carcinogenesis, Carcinogenesis, Journal of Biochemistry and Molecular Biology*



BIOPHYSICS

SECTION LEADER
HOWARD L. BROCKMAN, JR., PH.D.
PROFESSOR

Our laboratory is interested in how lipid species composition and packing in membranes regulates the translocation, i.e. adsorption, of proteins to an interface, like the surface of a lipoprotein or one leaflet of a plasma membrane. This interest is prompted by the importance of such interactions in a wide range of cellular and extracellular processes in both normal and disease states. Our prior studies indicated that for a water-soluble protein to interact with a membrane, other than by specific protein-protein interactions or charge-driven binding to anionic lipids, the protein must encounter an area of membrane of a minimal size that is free of obstacles to its hydrophobic residues interacting favorably with the apolar region of the membrane. Examples of obstacles are phospholipid head groups and membrane-resident proteins. We have identified two types of obstacle-free area to which a protein can potentially adsorb. One is simply the water-occupied space between phospholipid head groups, the so-called "free area" in models for lipid diffusion in the membrane plane. We have successfully described protein adsorption mediated by such area with a statistical model that describes the distribution of free area by a Poission distribution. A second type of area that supports protein adsorption is the area occupied by discrete lipid molecules, like diacylglycerols, that do not have the normal head group associated with phospholipids. Diacylglycerols are generated locally in membranes from typical membrane phospholipids during cell stimulation and in lipoproteins by the action of lipases. Protein adsorption to diacylglycerol-occupied area has been successfully described by a binomial distribution. Because both types of area can be present simultaneously in a membrane we have just published a more comprehensive protein adsorption model that includes both types of areas and improves other aspects of the earlier work. This will be further tested with the improved data we expect to obtain when the anticipated NIH funding for our project is received.

Instrument Applications

A new miniaturized flow cell we recently described provides an air-buffer interface to which surface-active molecules can be added to create a test platform for measuring the interaction of solute molecules in an aqueous flow stream with molecules present in the interface. The interface can be formed using self- or directed assembly. Two features help distinguish this technology from similar measurements conducted at solid surfaces. The first is the ability to exercise control over the composition and packing density of receptor molecules in the interface and the second is the ability to completely regenerate the interface after it becomes

Bill Momsen, Howard Brockman, Maureen Momsen
Not shown: Khanh Hoang

unusable due to fouling. These features suggest to us that our technology may find use in screening applications and for long-term monitoring of effluent streams. An example of screening is the interaction of drug candidates with specific membrane surfaces to predict absorbability. Examples of monitoring would be to assess the levels of allergens in food processing streams, toxic substances in industrial waste streams and the presence of toxins/biowarfare agents in water or air. For proof of concept experiments in monitoring, we have studied antigen-antibody interactions between an antibody in a monolayer and an antigen in the solution flowing underneath. With this assay and our current instrument we can readily measure 50 pM of a fluorescently-labeled antigen in a fluid stream.

MEMBRANE BIOCHEMISTRY

SECTION LEADER
RHODERICK E. BROWN, PH.D.
PROFESSOR

Biomembranes are barriers that maintain the integrity of cells, while enabling desired substances to enter and toxic by-products to exit. Biomembranes also divide the cell interior into different specialized compartments. Biomembrane assembly results from insoluble lipid 'building blocks' being oriented to form films that are two lipid molecules thick, called bilayers or bimolecular leaflets. Interestingly, there are many more varieties of lipids in membranes than are needed to form the basic bilayer structure. Recent discoveries have shown that certain kinds of membrane lipids can function as messenger signals within cells, while other membrane lipids can cluster together to form microdomains able to control the spatial distribution and lateral interactions of specific membrane proteins that regulate cell growth, proliferation, and programmed cell death processes. The recognition of these new functionalities for membrane lipids has energized the field of biomembrane research and provided clearer links to the important and targeted roles of biomembranes in infectious diseases and cancer.

Over the past several years, research in this lab has provided fundamental insights into how different lipids mix together to change the physical environment in the membrane in ways that can either facilitate or impede interaction with proteins. Our research has focused on a specific class of membrane lipids known as sphingolipids and their interactions with other membrane lipids such as cholesterol. These two lipid types appear to be key components of membrane microdomains, sometimes referred to as rafts. The involvement of rafts in various cell biological processes has led to a tremendous surge of interest in the membrane processes and placed special importance on rigorously defining the understanding the physical basis for raft microdomain functionality. We have developed ways to measure quantitatively the lateral elasticity within model membranes and to very accurately assess the physical changes that occur within the membrane 'raft environment' when the content and structure of sphingolipids and sterols are altered. Our research has led to an increased understanding of the structural features of sphingolipids that affect their interactions with other membrane lipids and defined the physical nature of the membrane environment produced by compositional changes involving sphingolipids. This new knowledge is especially important for understanding how the raft microdomain environment regulates the membrane translocation of

Front row: Helen Pike, Rick Brown, Xiuhong Zhai
Back row: Young-Guang Gao, Ravikanth Kamlekar, Asif Zakaria, Xianqiong Zou

proteins that have 'affinity' for sphingolipids.

The processes by which sphingolipid-enriched domains are formed and maintained are not well understood but are likely to involve specific proteins that can bind and transfer sphingolipids between membrane surfaces. Thus, much recent effort in the lab has been directed towards a family of mammalian proteins, called glycolipid transfer proteins (GLTPs), that specifically bind and transfer glycosphingolipids between membranes. We have found that the ability of GLTPs to function *in vitro* depends upon the composition and packing of lipids within membranes. Use of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry) has enabled fundamental insights to be gained into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids in phospholipid membranes. We are applying this basic knowledge to decipher the functional regulation of GLTP. Exactly how GLTPs accomplish the intermembrane transfer of glycolipids is being actively studied with the long range goal of determining whether GLTPs actively participate in the assembly and maintenance of sphingolipid-enriched rafts within biomembranes. Our molecular biological studies have resulted in the first molecular cloning of human GLTP and related homologs from porcine and bovine brain and mouse skin fibroblasts. We found that mammalian GLTP transcripts encode very highly conserved amino acid sequences. Use of genetic engineering approaches enabled us to produce human GLTP using bacterial expression systems and purify in sufficient quantities to successfully crystallize the protein. In collaboration with structural biologists at Memorial Sloan Kettering Cancer Center in New York City, we solved the conformational structure of GLTP in its glycolipid-free form (1.65 Å) and complexed with lactosylceramide (1.95 Å). The folding motif of GLTP is completely novel among lipid binding proteins,

enabling publication of our findings in *Nature* and resulting in GLTP now being defined as the founding and prototypical member of the new GLTP protein superfamily, with orthologs occurring in many eukaryotes. New structural data, reported in a recent paper in *PLoS Biology* and involving resolution of GLTP complexed with five different glycolipids, has led to new insights into how GLTP adapts to accommodate different glycolipids within its liganding site.

The elucidation of the structure-function relationships governing GTLP action is expected to facilitate the development of the means to pharmacologically modulate GLTP and enhance its potential use as a biotechnological resource, i.e. nanotool, for targeted manipulation of cellular glycolipid composition. Such strategies could provide new ways to introduce specific GSL antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to the development new therapeutic approaches to treat disease processes involving glycolipids.

Our findings emphasize the need for continuing investigations into the workings of GLTP, and other proteins containing GLTP-like motifs, using a combination of biophysical, cell, and molecular biological approaches. Our very recent investigations of *GLTP* gene organization and transcriptional status in humans and other mammals are expected to provide a firm foundation for the future identification and characterization of inherited diseases involving GLTP. Our research efforts are possible because of longstanding support from the National Institute of General Medical Sciences division of NIH and The Hormel Foundation as well as recent new funding from the NIH National Cancer Institute.

Other Professional Activities
Rhoderick E. Brown

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

NUTRITION AND METABOLISM

Section Leader

Margot P. Cleary, Ph.D.

Professor

This section's major focus is the study of the interaction of breast cancer, caloric intake and changes in body weight. In addition, we are also applying our intervention strategies to prostate cancer. Several different approaches are being used to assess the effects of caloric restriction, as well as body weight changes and/or weight gain/loss on tumorigenesis with a focus on several serum factors, leptin and IGF-I, as mediators of the effects on tumor development. In the past year we have expanded our interest to an additional protein, adiponectin. Similar to leptin, adiponectin is synthesized in adipose tissue, however, in contrast to leptin, its synthesis declines with increasing body weight and body fat. Furthermore, recent studies indicate that lower serum adiponectin levels are associated with the development of several malignancies, including breast and prostate cancers. Additionally, cell culture studies show that addition of adiponectin reduces cell proliferation of both breast and prostate cancer cells and may also enhance cell death.

For our mammary tumor studies, both transgenic mice and xenograft mice models are used. We are currently expanding on our earlier studies, which indicated that intermittent caloric restriction was more protective than was the same degree of caloric intake imposed by chronic (evenly spaced) restriction in the prevention of mammary tumors. We have completed a longitudinal study whereby serum samples were obtained before tumors were detected in order to identify possible biomarkers indicative of early tumor growth. Serum analyses are now underway and we will begin tumor and mammary tissue protein determinations shortly, In addition, a cross-sectional study is almost completed where blood and tissue samples are being obtained over the course of mammary tumor development. In the past year, we have enrolled mice in an additional study to evaluate the effects of a high fat diet during refeeding on mammary tumor prevention.

We have also investigated the effects of this intermittent restriction protocol in a model for prostate cancer, TRAMP mice. Ongoing evaluation of results indicates that this intervention also protects against prostate cancer development as reflected by a delay in the age at initial detection of tumors as well as a later age at death. Furthermore, the intermittent restriction was far superior to chronic calorie restriction which had little effect on prevention of prostate cancer in TRAMP mice. Serum analyses are complete and one of the most interesting aspects of this was that during the intermittent calorie restriction phase the leptin:adiponectin ratio is reduced compared to the other groups suggesting that this may enhance the protective effect of intermittent versus chronic restriction. Thus, the serum environment that cells are exposed to may control cell proliferation. We are now analyzing tissue samples to determine the effects of these interventions on leptin and adiponectin receptors.

Additional studies are focused on the effect of leptin as a growth factor that could provide a link between obesity and postmenopausal breast cancer. These ongoing studies are based on our earlier findings that genetically obese mice that are either leptin-deficient or leptin receptor-deficient do not develop oncogene-induced mammary tumors. In

Front row: Melissa Bonorden, Margot Cleary, Nancy Mizuno

Back row: Katai Nkhata, Dmitry Malakhov, Olga Rogozina, Michael Grossmann, Amitabha Ray, Soner Dogan

Not shown: Emily J. Kain Quealy

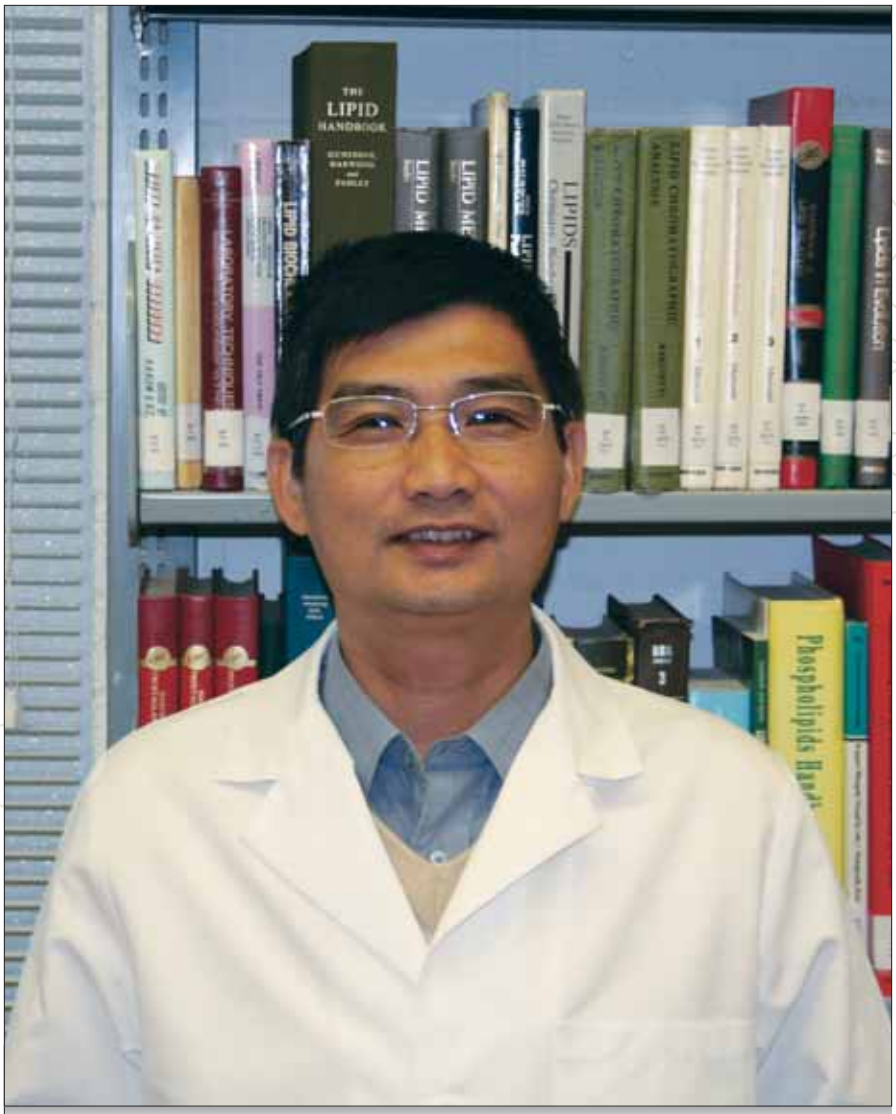
contrast, mice with diet-induced obesity that carry the same transgene develop mammary tumors with shortened latency. An additional study has shown that these mice with diet-induced obesity have elevated serum leptin levels and their tumors express the leptin receptor. These findings led us to hypothesize that leptin, a cytokine (protein) which is synthesized in fat tissue usually in relationship to the amount of body fat, may be a growth factor for breast tumor development. Results of cell culture studies provide further evidence to support this hypothesis. We have reported that a human breast cancer cell line expresses the leptin receptor form responsible for signal transduction. The addition of leptin increases cell proliferation and affects the appropriate signal pathways. More extensive studies have been conducted using breast cancer cell lines that are estrogen receptor negative and/or overexpress another protein associated with poor prognosis, HER2/neu. Our results indicate that different cell characteristics impact how the cells respond to the addition of leptin. Additionally, we are also now assessing the effects of adiponectin and shortly will combine the two adipokines to assess their interrelationship on cell proliferation and cell growth. We are also determining the effect of obesity on tumor development from human breast cancer cell lines in relationship to these cell characteristics and with respect to these serum factors. In particular we have tested the hypothesis that diet-induced obesity promotes the growth of estrogen receptor positive but not estrogen receptor negative breast cancer. Recently, because the human breast cancer cell lines have a number of different characteristics, we have created our own estrogen receptor positive cell line whereby we used an estrogen receptor negative cell line and added this receptor. Now we can conduct studies directly comparing two cell lines where only the estrogen receptor status is different. Initial studies have shown that these cells respond to estrogen *in vitro* and inoculation of the cells into mice results in tumor formation. Furthermore, tumor growth is enhanced by estrogen treatment. We hope to conduct a study in the near future using obese mice.

We are also trying to assess 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, with the chemical agent that we were using, there have been technical difficulties inducing obesity. We are now working on an alternative approach. We have also recently started a diet-induced obesity study in the TRAMP mice. In both these studies, we will assess the roles of leptin and adiponectin in the development of prostate cancer. Additional prostate cancer studies are being done in collaboration with Dr. Johnny Lu's Cancer Biology laboratory.

Other Professional Activities

Margot P. Cleary

DOD Grant Reviewer
NIH Grant Reviewer
Invited Participant at The Breast Cancer Research Foundation Fifth Annual Scientific Conference, New York, NY
Consultant for Georgetown University's U54 grant-Timing of Dietary Exposures and Breast Cancer Risk Lombardi Cancer Center, Washington, DC
CDC Grant Reviewer



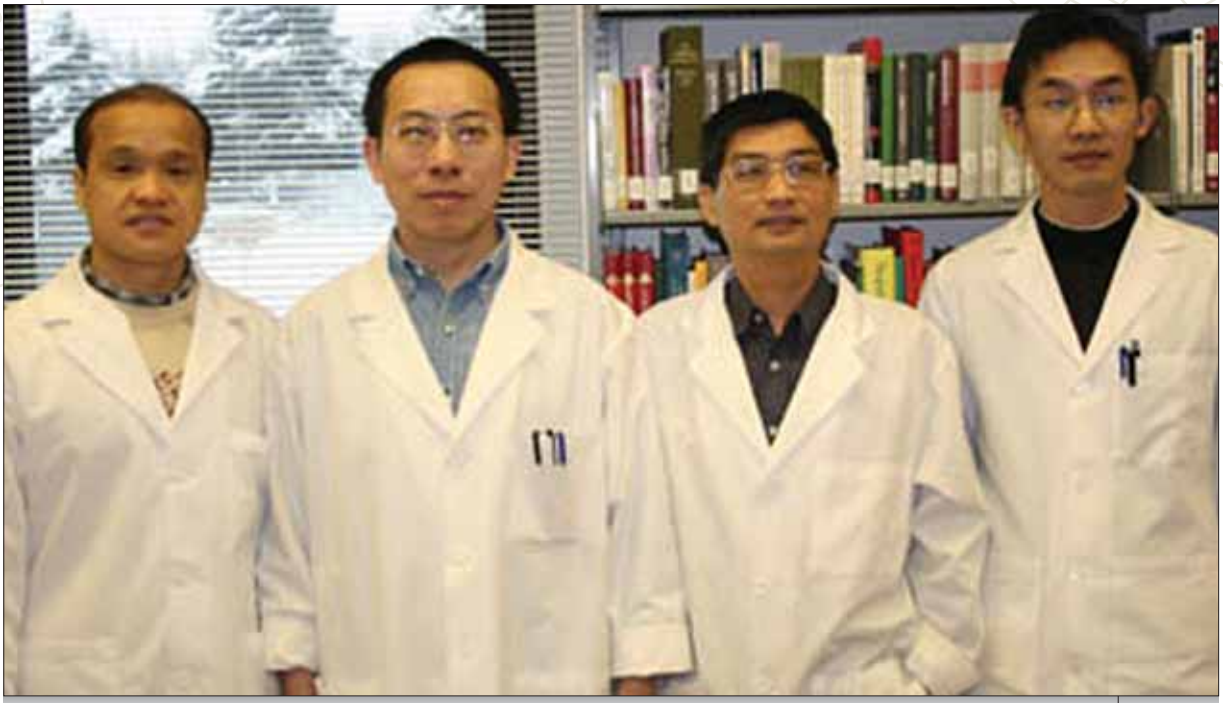
TRANSLATIONAL CANCER RESEARCH

SECTION LEADER
D. JOSHUA LIAO, PH.D.
ASSOCIATE PROFESSOR

Our section, new to The Hormel Institute in December of 2006, is currently funded by an NIH R01 grant to study the molecular mechanisms by which aberrant expression of c-myc and TGF-alpha synergistically induces early formation of an aggressive breast cancer phenotype, and whether inhibition of both c-myc and certain TGF-alpha target genes can result in a better therapeutic outcome. Two other projects are funded by the Elsa Pardee Foundation. One involves identification of genes relevant to the liver metastasis of pancreatic cancer. The most recent project studies the roles of certain clusters of microRNAs in breast cancer.

Experimental research results

P53 is one of the most important tumor suppressor genes that affects almost all aspects of cellular function. Although the functions of p53 are extremely complicated, for a long time scientists were somewhat relieved that at least p53 expression did not undergo alternative splicing and give rise to different mRNA variants, despite the fact that over 50% of



Houqing Zhou, Dong Qing Liu, D. Joshua Liao, Jiusheng Wu

the genes encoded by the human genome undergo alternative splicing. Unfortunately, this relief ended in 2005 when two laboratories found that human p53 also underwent alternative splicing to produce several mRNA variants, which seem to be tissue specific. This milestone finding triggers a novel area of research on p53, and quickly other groups also identified p53 mRNA variants in several types of human cancer. We recently identified nine p53 mRNA variants in mouse mammary epithelial cells that are derived from alternative splicing. Four of these variants are novel because they have not yet been reported in humans or other species. We have cloned the full length cDNA of two of the four novel variants and are currently analyzing their functions, including their possible effects on the response of breast cancer cells to chemotherapies. Preliminary results show that treatments with several chemotherapeutic agents significantly down regulate the expression of these novel p53 mRNA variants while the wild type form of p53 is induced, which suggests a possibility that these novel variants may have biomarker values for cancer chemotherapy.

Results of our research have most recently been published in *Clinical Cancer Research*, *Molecular Cancer Research*, *Cancer Research*, and other scientific journals.

CANCER BIOLOGY

SECTION LEADER
JUNXUAN (JOHNNY) LÜ, PH.D.
PROFESSOR

Our 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 & medicinal foods or drug approaches. Our research program has continued to focus on the following two areas:

- sustaining our research excellence in understanding the cellular and molecular mechanisms by which the trace element nutrient selenium affects cancer chemoprevention and treatment.
- identifying and developing novel cancer chemopreventive and therapeutic agents based on Chinese and Oriental medicinal herbs.

Mechanisms of cancer chemoprevention and treatment by selenium

We elucidated the role of reactive oxygen species (ROS) and DNA damage in cell death induced by the inorganic sodium selenite. In earlier studies, we have shown that selenite induces DNA single strand breaks (SSBs), p53 Ser15 phosphorylation and caspase-dependent and -independent apoptosis, whereas a methylselenol precursor methylseleninic acid (MSeA) induces caspase-mediated apoptosis regardless of p53 status. We addressed three main questions:

- What types of ROS are induced by selenite vs. MSeA in LNCaP (p53 wild type, androgen-responsive) and DU145 (mutant p53, androgen-independent) prostate cancer cells?
- Does ROS generation depend on androgen signaling?
- What are the relationships among ROS, DNA SSBs, p53 and caspases?

We showed that selenite (5 microM) induced superoxide and hydrogen peroxide in LNCaP cells much more than in DU145 cells and the ROS generation was not affected by physiological androgen stimulation. MSeA (10 microM) induced apoptosis without either type of ROS in both cell lines. In LNCaP cells, we established superoxide as a primary mediator for selenite-induced DNA SSBs, p53 activation and caspase-mediated apoptosis. Furthermore a p53-dominant negative mutant attenuated selenite-induced ROS, leading to a proportionate protection against apoptosis. The results support the p53-mitochondria axis in a feedback loop for sustaining superoxide production to lead to efficient caspase-mediated apoptosis by selenite. In contrast, caspase-mediated apoptosis induced by MSeA does not involve ROS induction. Because p53 is frequently mutated or deleted in prostate cancer and many other cancers, our results suggest that

Front row: Melissa Bonorden, Junxuan (Johnny) Lu, Hyo Jeong Lee

Back row: Qiu Ziang, Hongbo Hu, Guang-Xun Li, Zhe Wang

Not pictured: Lei Wang

genotoxic vs. nongenotoxic classes of selenium may exert differential apoptosis efficacy depending on the p53 status of the cancer cells.

In addition to cell culture studies, we have developed several xenograft models of human prostate cancer in nude mice and initiated efforts to compare the anti-cancer efficacy of methyl-selenium compounds vs. selenomethionine and selenite as well as the impact of methyl-selenium on taxol efficacy in therapy. These studies are a crucial first step to validate the cell culture findings to prepare the way for translational studies in the future.

Identification of novel cancer chemopreventive and therapeutic agents

A novel class of anti-androgen pyranocoumarin compounds for prostate cancer prevention and treatment: In collaboration with Professor Sung Hoon Kim of Kyung Hee University, South Korea, we discovered that decursin from the ethanol extract of Korean Angelica gigas Nakai (AGN) root possesses strong and long lasting anti-androgen receptor (AR) signaling activities in the androgen-dependent LNCaP human PCa cell model.

We reported the structure-activity relationship by comparing decursin with its naturally occurring structural isomer decursinol angelate (DA), decursinol to identify the structural determinants and mechanisms of actions. These studies have shown that decursin and DA are prototype members of a novel class of anti-androgen receptor agents. Mechanistically, this class of agents inhibited androgen-stimulated AR translocation to the nucleus and down regulated AR protein abundance without affecting the AR mRNA level. They do not have androgen agonist activity like many of the currently used anti-androgen drugs such as flutamide and bicalutamide. It is anticipated that these novel agents will have significant implications for the chemoprevention and treatment of prostate cancer and other androgen-dependent diseases. Because

ligand-independent AR signaling is still crucial for hormone refractory prostate cancer survival and growth, their ability to block AR signaling in the absence of androgen may be quite attractive for preventing and managing this stage of the prostate cancer in conjunction with or after hormone ablation treatment. We carried out work funded by the Prostate Cancer Foundation to test these hypotheses in preclinical animal models.

This research demonstrates the feasibility for drug discovery from complex herbal mixtures and has built the technological platform for us to expand efforts into additional Oriental medicinal herbs for prostate and breast cancer prevention.

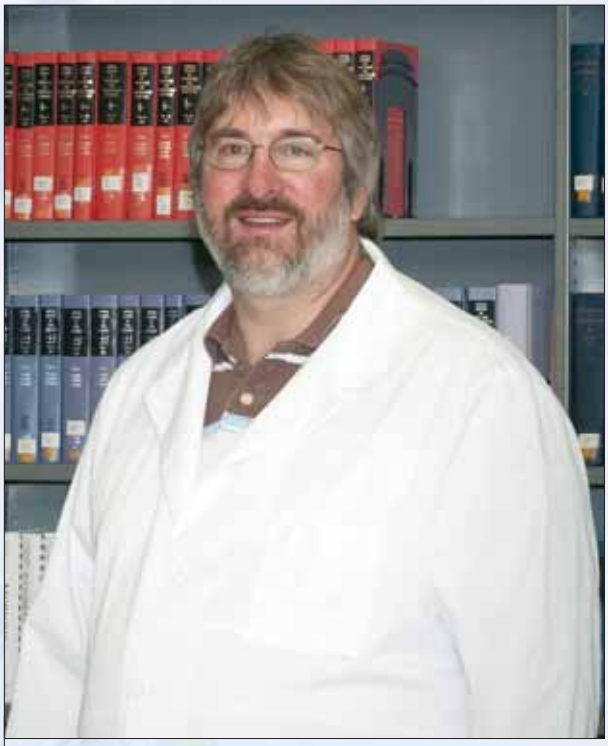
Anticancer efficacy of an Oriental herbal formula

Rigorous and systematic pre-clinical studies are necessary and essential to establish the efficacy and safety of Oriental herbs and formulas in order to transform traditional herbal practices into evidence-based medicine. Together with Prof. Kim's group, we evaluated the anti-cancer activities of the ethanol extract of Ka-mi-kae-kyuk-tang (KMKKT), a formula of ten Oriental herbs, with a battery of *in vitro* and *in vivo* mechanism-based biomarkers involving angiogenesis, apoptosis and metastasis. The results show that KMKKT suppressed the vascular endothelial responses by inhibiting basic fibroblast growth factor (bFGF)-induced ERK1/2 phosphorylation, cell migration as well as tube formation in the human umbilical vein endothelial cell model, and decreased the hypoxia-induced HIF1alpha and vascular epithelial growth factor (VEGF) expression in the mouse Lewis lung carcinoma (LLC) cells in vitro, and inhibited the bFGF-induced angiogenesis in chick chorioallantoic membrane model, and in the Matrigel plugs in mice. Intraperitoneal delivery of KMKKT potently inhibited the growth of the subcutaneously inoculated LLC cells in syngenic mice. In addition, KMKKT inhibited the invasion ability of the mouse colon 26-L5 cancer cells in vitro and decreased their formation of liver metastasis when intraportally inoculated in syngenic mice. Furthermore, KMKKT suppressed the growth of the human PC-3 prostate cancer xenografts in athymic nude mice and averted the cancer-related body weight loss. The *in vivo* cancer growth suppression was associated with a decreased microvessel density and VEGF abundance as well as an increased PARP cleavage and the TUNEL-positive apoptosis. Together, our data support broad-spectra in vivo anti-cancer activities of KMKKT targeting angiogenesis, apoptosis and metastasis without any adverse effect on the body weight. This formula merits serious consideration for further evaluation for the chemoprevention and treatment of cancers of multiple organ sites.

In addition to institutional support from The Hormel Foundation, our work is supported by grants from the Department of Defense and the Prostate Cancer Foundation and two R01 grants from the National Cancer Institute.

Other Professional activities
Junxuan (Johnny) Lü

Grant Reviewer, National Institutes of Health



Todd Schuster
Senior Lab Technician

Schuster operates, maintains and instructs scientists about the shared instruments used at The Hormel Institute for cancer research.

SIGNAL TRANSDUCTION AND APOPTOSIS

Section Leader

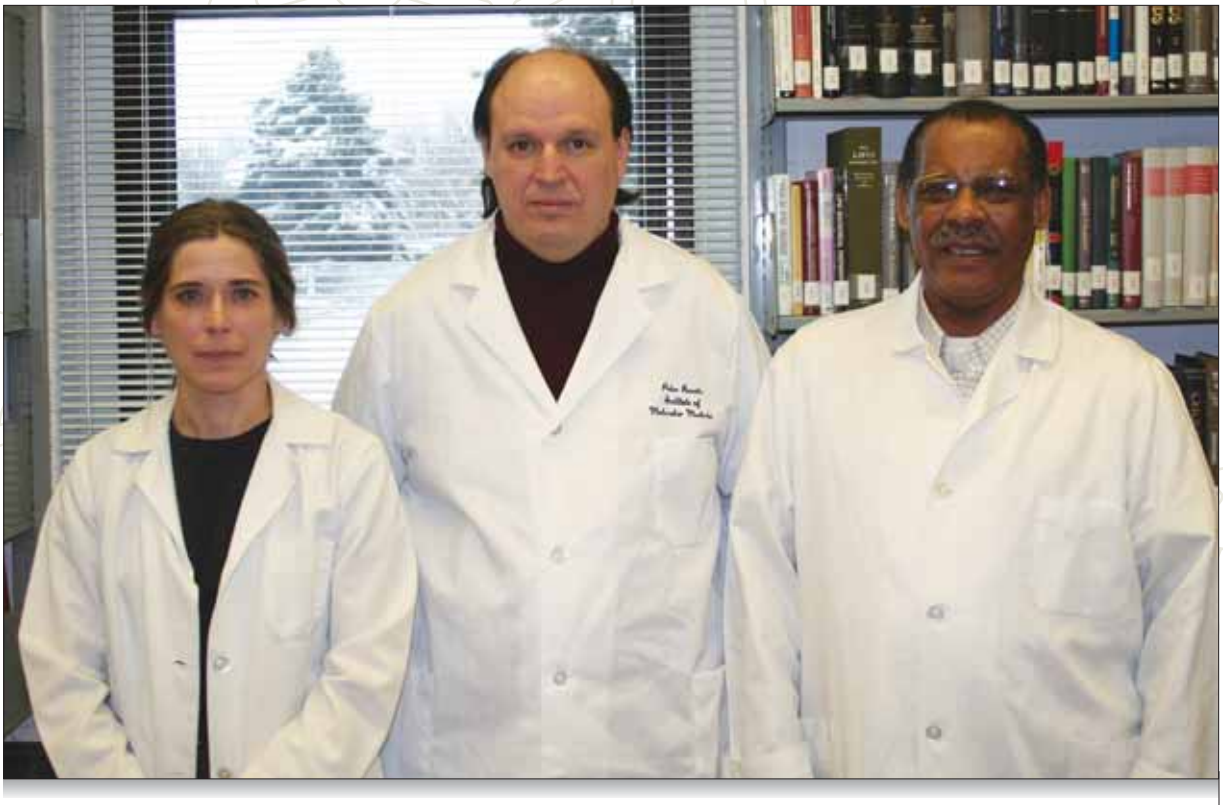
Peter Ruvolo, Ph.D.

Associate Professor

This section, in operation since January 2007, is committed to understanding the cell signaling mechanisms that regulate cell death and ultimately influence tumor development and drug resistance in cancer and tissue destruction in diseases such as emphysema. A major focus of our research is the characterization of signal transduction pathways that are regulated by the sphingolipid ceramide. The Hormel Institute has a long history as a leader in lipid biology, so it is fitting that ceramide is at the center of many of the Section's projects. Ceramide is a potent second signal molecule and its production in most cells results in the induction of programmed cell death (also known as apoptosis). The production of ceramide is so common during cell death induced by diverse stress stimuli (including chemotherapy) that it is considered a near universal feature of apoptosis. Our major project, funded by the National Cancer Institute, involves the regulation of the Bcl2 oncogene by phosphorylation, particularly those pathways involving ceramide activated protein phosphatase 2A (PP2A).

Bcl2 is the founding member of a family of proteins that regulate apoptosis. Bcl2 was discovered as the cellular oncogene product associated with the t(14,18) translocation commonly seen in B-cell lymphomas. While other oncogenes known at the time of Bcl2's discovery were found to affect cell proliferation, Bcl2's function to prolong cell survival represented a novel mechanism for tumorigenesis. In recent years it has become apparent that post-translational modification of Bcl2 affects its anti-apoptotic function. Recently, we have examined Bcl2 phosphorylation patterns in blast cells from patients with acute myeloid leukemia (AML) in collaboration with Michael Andreeff's group at MD Anderson Cancer Center in Houston, Texas (published in Leukemia in 2006). We were the first group to determine that Bcl2 is phosphorylated in blast cells from AML patients (nearly half of patients exhibited phosphorylated Bcl2). Furthermore, we determined that AML patients with blast cells expressing phosphorylated Bcl2 exhibit shorter overall survival (~ 79 days on average) compared to patients with blast cells expressing unphosphorylated Bcl2 (~ 198 days on average). In other studies with the Andreeff group, we discovered further evidence that phosphorylated Bcl2 might render cells more resistant to chemotherapy when we found that phosphorylation of Bcl2 promoted resistance to ABT-737. This finding is important since ABT-737 is a novel compound that targets the Bcl2 BH3 domain and is currently being developed for clinical trials for AML and other cancers.


Owl



Vivian Ruvolo, Peter Ruvolo, Tilahun Jiffar

Bcl2 phosphorylation is a dynamic process that involves both kinases and protein phosphatases. Our laboratory previously determined that the Bcl2 phosphatase was activated by ceramide and involved a mitochondrial PP2A isoform. The finding that Bcl2 function is inhibited by a ceramide-activated mitochondrial PP2A has important potential for our understanding of chemoresistance in leukemia considering the effect of phosphorylation on Bcl2's anti-apoptotic function. Indeed, our laboratory has found that inhibition of PP2A with low dose okadaic acid prevented Bcl2 dephosphorylation while protecting cells from apoptosis by ceramide or chemotherapeutic drug treatment (such as araC which is commonly used for the treatment of AML). Current efforts in the laboratory are focused on characterizing how ceramide activates the Bcl2 phosphatase. The identification of which PP2A isoform acts as the Bcl2 phosphatase was critical since PP2A is not really a single enzyme but rather a family of enzymes. PP2A is a hetero-trimer containing a catalytic subunit (subunit C), a scaffold subunit (subunit A) and regulatory subunit (subunit B). Because PP2A function is controlled by the B subunit (of which there are at least 21 proteins from 3 major families), it was necessary to determine which B subunit was responsible for Bcl2 phosphatase function. Our laboratory determined that the B56 · subunit is the regulatory subunit comprising the physiologic Bcl2 phosphatase. Recent studies in our laboratory have shown that ceramide appears to promote up-regulation of the B56 · PP2A subunit by a post-translational mechanism involving double stranded dependent protein kinase (PKR). These findings represent a novel role for this kinase in stress signaling and may be a new target for chemotherapy.

In the next year, we will pursue our studies to characterize the Bcl2 phosphatase and to determine its role in chemoresistance in leukemia. We will continue our studies on how the ABT-737 compound kills leukemia cells and the role Bcl2 phosphorylation plays in ABT-737-induced cell death. We also plan to begin investigations into how a novel PKC inhibitor promotes apoptosis in acute leukemia cells and which PKC isoforms are involved.

The Expansion

The Hormel Institute expansion, announced in 2005, catapulted The Hormel Institute into the limelight of the emerging Bioscience Corridor in southern Minnesota. The unique research partnerships between The Hormel Institute, University of Minnesota and Mayo Clinic Rochester result in research opportunities found no where else in the world.

The collaboration with Mayo Clinic was officially forged on August 21, 2006 between leaders from The Hormel Institute, University of Minnesota and Mayo Clinic Rochester. The growth, and the official collaborative research agreement, will propel The Hormel Institute to a new level of scientific achievement.

The $20 million project will triple the size of the 1960 facility, building a new two-story addition which houses 20 state-of-the-art science labs and a major conference room and library. The added space allows for 100 more scientists and support staff to be added over the next few years, which will create a significant economic benefit for the Austin and Mower County area.

Under the leadership of Richard L. Knowlton, The Hormel Foundation paved the way for The Hormel Institute expansion with a historic gift of $10 million. This was followed by major gifts from Hormel Foods Corporation of $5 million and substantial long-term, low interest loans and funding for infrastructure provided by the City of Austin and Mower County.

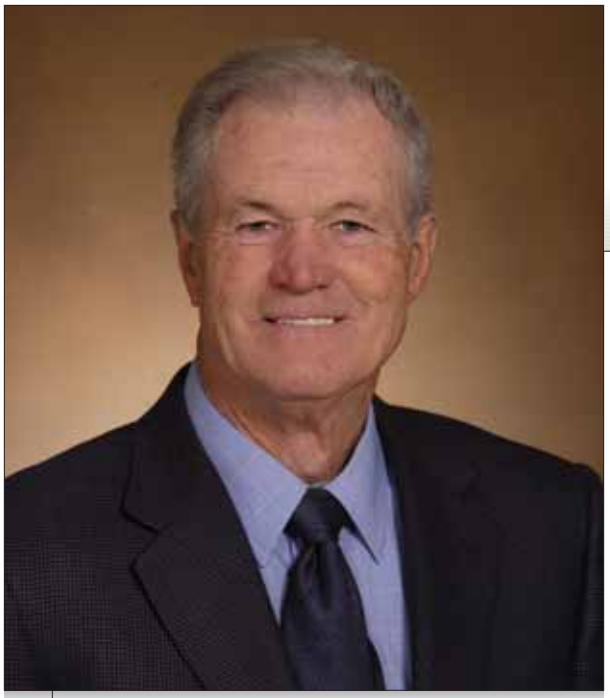
The local community showed its support for the expansion of The Hormel Institute by the generous response to a fundraising campaign called "Grow Science, Grow Austin." With a goal of $1 million, over $1.5 million was donated by individuals, businesses, organizations and associations in support of The Hormel Institute Expansion Project.

Above: August 21, 2006 – Signing of the official collaboration agreement between The Hormel Institute, University of Minnesota and Mayo Clinic Rochester. Left to right: Dr. Zigang Dong, Executive Director, The Hormel Institute, Richard L. Knowlton, Chairman, The Hormel Foundation, former President, CEO and Chairman of the Board, Hormel Foods Corporation, Dr. Glenn S. Forbes, Chief Executive Officer, Mayo Clinic Rochester, Dr. Robert Bruininks, President,University of Minnesota

GROUNDBREAKING

AUGUST 21, 2006

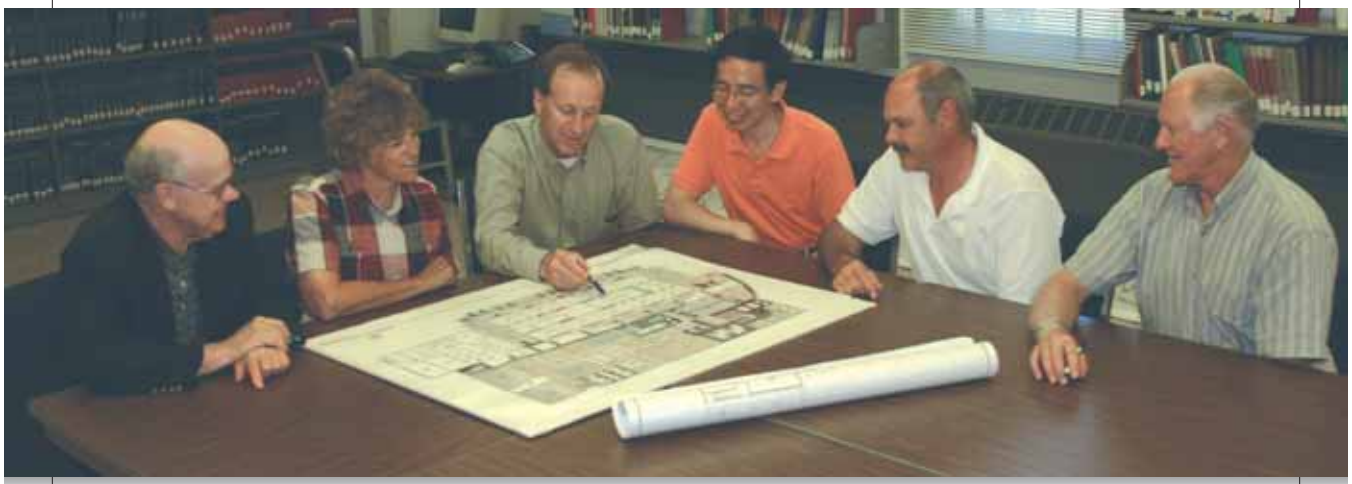
MAKING HISTORY



EXPANSION PROJECT
LEADERSHIP

"The major Hormel Institute expansion brings national and international science to our community and to our state. Our commitment is that these state-of-the-art resources, joining the University of Minnesota and Mayo Clinic, will lead to discoveries that improve the health of the world. The new science laboratories will provide a platform for significant breakthroughs, especially in cancer research."

— Richard. L. Knowlton
Chairman, The Hormel Foundation
former President, CEO and Chairman
of the Board
Hormel Foods Corporation

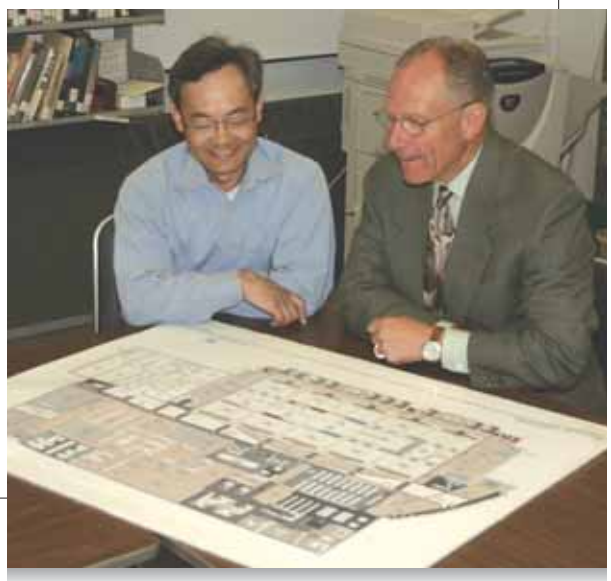


Expansion Project Steering Committee

Pictured above: George Brophy, President, Development Corporation of Austin, Dr. Ann Bode, Associate Director of The Hormel Institute, Larry Pfeil, Vice President, Hormel Foods Corporation, Dr. Zigang Dong, Executive Director, The Hormel Institute, Craig Jones, Supervisor, Research Support Services, The Hormel Institute, Ron Skjeveland, Supervisor, Building Operations and Maintenance, The Hormel Institute.

Right: Dr. Johnny Lu, Professor, Cancer Biology, The Hormel Institute, and Gary J. Ray, Executive Vice President, Hormel Foods Corporation, Chairman of The Hormel Institute Expansion Project Steering Committee

Not pictured: Richard L. Knowlton, Chairman, The Hormel Foundation, Scot Ramsey, Mayo Clinic Rochester.



— Photo submitted by Austin Daily Herald —

grow SCIENCE
grow AUSTIN

In November of 2006, the "Grow Science, Grow Austin" campaign was launched in an effort to provide additional support for The Hormel Institute Expansion Project. Conducted by volunteers and under the leadership of The Hormel Foundation and The Hormel Institute, the campaign had two goals: 1) Educate the community about The Hormel Institute's research and expansion plans, and 2) Raise $1 million in donations from local citizens. The campaign exceeded its $1 million goal by raising over $1,500,000 in donations from area individuals, businesses, clubs and associations. This generous financial support from all parts of the community will be instrumental in securing future, more significant funding for The Hormel Institute Expansion Project.

$1,500,000

Public Relations and Development
Gail Dennison

The Public Relations and Development office of The Hormel Institute is designed to encourage interest in our research, build supportive constituents and solicit financial support for new facilities, faculty, equipment and supplies. The impact of The Hormel Institute Expansion Project resulted in statewide visibility for The Hormel Institute and the emerging Bioscience Corridor collaborations between The Hormel Institute, University of Minnesota and Mayo Clinic Rochester.

Key partnerships this year included the following:

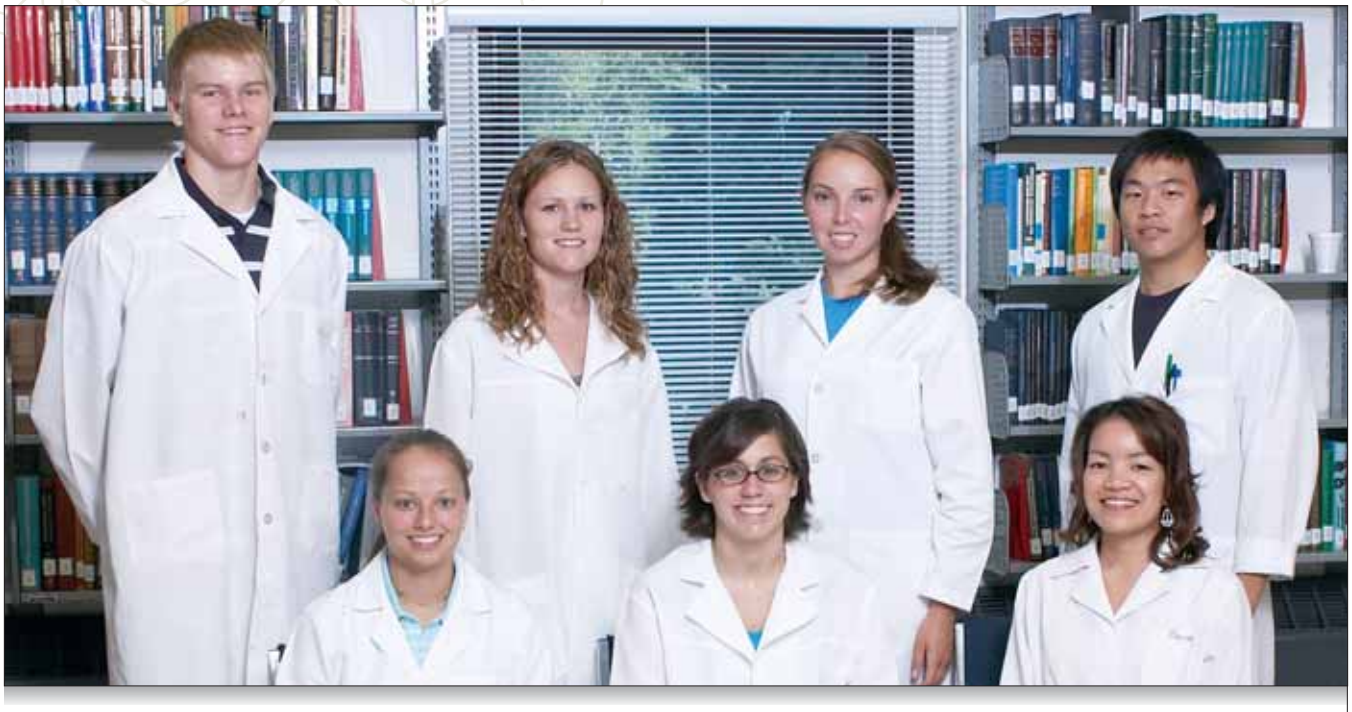
- The Hormel Foundation
- Hormel Foods Corporation
- Development Corporation of Austin
- Mayo Clinic Rochester
- City of Austin
- Mower County
- Grow Science, Grow Austin Volunteer Committee
- Southern Minnesota Initiative Foundation
- University of Minnesota-Rochester
- DECA Business Club – Austin High School
- Austin City Science Fair

Building Operations and Maintenance
Supervisor: Ronald Skjeveland

The maintenance support unit's main goal is to provide all personnel with a comfortable and safe working environment. Regular inspections 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 rearrangment 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.

Norm Johnson, Duane Graff, Ron Skjeveland, Tom Wobschall



Front: Rebecca LeVan, Krista Ryan, Danh "Jane" Voong.
Back: Tyler Conway, Brittany Alms, Amy Jencks and Jonathan Song.

S.U.R.E.
Summer Undergraduate Research Experience

Seven college students worked in the **S**ummer **U**ndergraduate **R**esearch **E**xperience (S.U.R.E.) Program with The Hormel Institute scientists during the summer of 2007. The S.U.R.E. interns work on research projects to expand their knowledge of basic research and learn about equipment and techniques that are not generally available in undergraduate academic programs. The students were selected based on their academic achievement as well as their plans to pursue careers in science or medically-related fields.

Brittany Alms is a Biology major at the University of Minnesota-Minneapolis with plans to earn a Doctorate of Pharmacy. Brittany worked in the Molecular and Cellular Biology lab of Dr. Zigang Dong.

Tyler Conway attends the University of Wisconsin-Stevens Point, majoring in Biology with a minor in Chemistry. After graduation, he plans to attend either medical or dental school. Tyler worked in the Cellular and Molecular Biology lab of Dr. Zigang Dong.

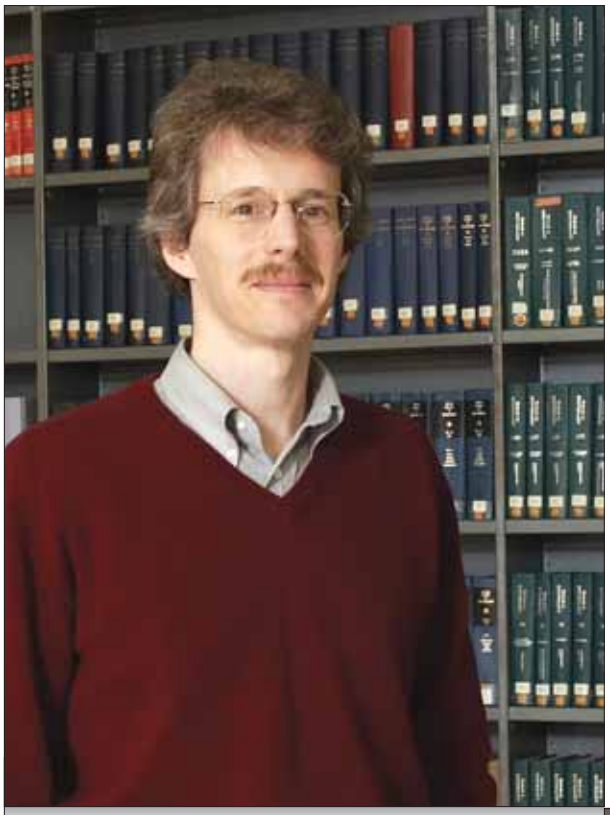
Amy Jencks attends the University of Wisconsin-LaCrosse, majoring in Biology with Chemistry and Spanish minors. She plans to pursue a Doctorate degree in medicine after obtaining her Bachelor of Arts degree. Amy worked in the Cancer Biology lab of Dr. Junxuan Lü.

Rebecca LeVan attends Wartburg College (Waverly, Iowa) where she is majoring in Biochemistry with a Chemistry and Biology minors. She plans to pursue a career in a health-related field. Rebecca worked in the Nutrition and Metabolism lab of Dr. Margot Cleary.

Krista Ryan attends Winona State University, where she is a pursuing Bachelor of Science degree in Biology. After graduation, Krista plans to attend medical school. Krista worked in the Nutrition and Metabolism lab of Dr. Margot Cleary.

Jonathan Song is pursuing a Bachelor of Science degree in Biochemistry at the University of Wisconsin-LaCrosse. His future plans are to pursue a Doctorate in Medicine. Jonathan worked in the Translational Cancer Research lab of Dr. Joshua Liao.

Danh "Jane" Voong is majoring in Molecular Biology at Winona State University. Jane plans to become a Physician's Assistant in the future and worked in the Cellular and Molecular Biology lab of Dr. Zigang Dong.



LIBRARY
Supervisor: Andy Lucas

The library serves as the information resource center for The Hormel Institute. We provide print and online materials to support faculty and staff research as well as special projects. Our collection contains approximately 10,250 volumes of bound journals and 2,900 volumes of books and serials comprising the areas of chemistry, biology, biophysics, medicine, and related subjects, including electronics, relevant to The Hormel Institute's research mission.

The library is a member of both the MINITEX and SELS consortiums. MINITEX Library Information Network is a program of the Minnesota Higher Education Services Office (HESO) with the mission of facilitating resource sharing among libraries and reducing the cost of providing access to information for residents throughout Minnesota, North Dakota and South Dakota. Book and journal articles not available online or in our library are requested as interlibrary loans through MINITEX. SELS (Southeast Library System) is a cooperative library network that facilitates sharing of informational resources among its multitype libraries in southeastern Minnesota.

OFFICE
Supervisor: Ann 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

Andria Hansen, Office Support Assistant
Jodi Loverink, Executive Accounts Specialist
Betsy Mentel, Executive Office & Administrative Specialist
Jeanne Ruble, Personnel Specialist

Andria Hansen, Betsy Mentel, Ann Bode, Jodi Loverink, Jeanne Ruble

Front row: Ryan Bonorden, Rose Srock, Theresa Tucker,

Back row: Ryan Wiersma, Craig Jones, Gary Bush, Tim Lastine

Not pictured: Mike Conway

Research Support Services (RSS)
Distance Outreach and Education (DOE)
Supervisor: Craig Jones

The RSS group provides instrument maintenance, computer, graphics, telecommunication, network, and internet support for The Hormel Institute. Maintenance of scientific instruments includes a wide variety of instruments from complex to the very simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our work load. The network is an absolute necessity for world wide communications and submission of research papers for publication and continues to become even more important every year.

Our DOE program, in cooperation with the Southern Minnesota Internet Group (SMIG), is making technology available to many rural citizens throughout a large area of Southern Minnesota. The DOE program is configured to be entirely self-sustaining, which gives us the growth potential and flexibility required to provide community based education and technical support now and in the future. SMIG is a non-profit Minnesota corporation with expressed goals consistent with the Institute. A seven-member board of directors is selected from the community to govern SMIG, ensuring that our DOE program remains true to the community and its mission. Our efforts with many of the local school districts, non-public schools, small libraries and non-profit organizations have improved network technology and internet availability for public use. We also provide web page space and creation assistance to area organizations.

Building coordination for the new facility has been very challenging and rewarding this year. The new addition has provided many opportunities to plan for the future. Our philosophy has been that the only reasonable approach to future planning is to design flexibility into the new facility. In this way, we will be able to adapt to the ever-changing world of scientific research and information technology. With the new addition completion planned for December 2007, RSS will have a lot of responsibility to keep the facility running smoothly during the move and remaining construction process.

THE HORMEL INSTITUTE
Board of Directors

Left to right:
Gary L. Nelsestuen, Ph.D.
Professor, Department of Biochemistry, College of Biological Sciences, University of Minnesota, St. Paul, MN

R .Timothy Mulcahy, Ph.D., Chair
Vice President for Research, University of Minnesota, Minneapolis, MN

Allen S. Levine, Ph.D.
Professor, Department of Food Science & Nutrition, University of Minnesota, St. Paul, MN

Gary J. Ray
Executive Vice President Operations, Hormel Foods Corporation, Austin, MN

Andre Terzic, M.D., Ph.D.
Professor of Medicine, Molecular Pharmacology & Experimental Therapeutics, Mayo Clinic College of Medicine, Rochester, MN

THE HORMEL FOUNDATION
Board of Directors

Chairman, Richard L. Knowlton – former President, CEO and Chairman of the Board, Hormel Foods Corporation

Vice Chairman, Joel W. Johnson – former President, CEO and Chairman of the Board, Hormel Foods Corporation

Secretary, Steve T. Rizzi, Jr. – partner in Adams, Rizzi & Sween P.A.

Treasurer, Jerry A. Anfinson – former partner of LarsonAllen LLP

Marlys K. Anderson, The Salvation Army

Mark T. Bjorlie, YMCA Austin

Donald R. Brezicka, Austin Medical Center

Zigang Dong, The Hormel Institute, University of Minnesota

Jeffrey M. Ettinger, President, CEO and Chairman of the Board, Hormel Foods Corporation

Kermit F. Hoversten, Hoversten, Johnson, Beckmann & Hovey

Mandi D. Lighthizer-Schmidt, United Way of Mower County

James R. Mueller, Cedar Valley Services, Inc.

J.D. Myers, former Superintendent, Austin Public Schools

John E. O'Rourke, former Mayor, City of Austin

Gary J. Ray, Executive Vice President, Hormel Foods Corporation

Mahlon C. Schneider, former Senior Vice President, Hormel Foods Corporation

Robert J. Thatcher, Austin Community Scholarship Committee

Hormel Institute Publications

July 1, 2006 — June 30, 2007

No. 1629
Enhancement of mammary carcinogenesis in two rodent models by silymarin dietary supplements
Barbara Malewicz, Zaisen Wang, Cheng Jiang, Junming Guo, Margot P. Cleary, Joseph P. Grande, and Junxuan Lü
Carcinogenesis 27, 1739-1747 (2006)

No. 1632
Involvement of the paxillin pathway in JB6 Cl41 cell transformation
Yasuaki Tatsumi, Yong-Yeon Cho, Zhiwei He, Hideya Mizuno, Hong Seok Choi, Ann M. Bode, and Zigang Dong
Cancer Res. 66, 5968-5974 (2006)

No. 1633
COOH-terminal Src kinase-mediated c-Jun phosphorylation promotes c-Jun phosphorylation and inhibits cell transformation
Feng Zhu, Bu Young Choi, Wei-Ya Ma, Zhongliang Zhong, Yiguo Zhang, Yong-Yeon Cho, Hong-Seok Choi, Ann M. Bode, and Zigang Dong
Cancer Res. 66, 5729-5736 (2006)

No. 1634
Cell apoptosis: requirement of H2AX in DNA ladder formation but not for the activation of caspase-3
Chengrong Lu, Feng Zhu, Yong-Yeon Cho, Faqing Tang, Tatyana Zykova, Wei-Ya Ma, Ann M. Bode, and Zigang Dong
Mol. Cell. 23, 121-132 (2006)

No. 1635
The role of histone H3 phosphorylation (ser10 and ser28) in cell growth and cell transformation
Zigang Dong and Ann M. Bode
Mol. Carcinog. 45, 416-421 (2006)

No. 1636
Molecular and cellular targets
Ann M. Bode and Zigang Dong
Mol. Carcinog. 45, 422-430 (2006)

No. 1638
Inorganic selenium sensitizes prostate cancer cells to TRAIL-induced apoptosis through superoxide/p53/Bax-mediated activation of mitochondrial pathway
Hongbo Hu, Cheng Jiang, Todd Schuster, Guang-Xun Li, Peter T. Daniel, and Junxuan Lü
Mol. Cancer. Ther. 5, 1873-1882 (2006)

No. 1640
Lactosylceramide: Lateral interactions with cholesterol
Xiuhong Zhai, Xin-Min Li, Maureen M. Momsen, Howard L. Brockman, and Rhoderick E. Brown
Biophys. J. 91, 2490-2500 (2006)

No. 1641
Using monomolecular films to characterize lipid lateral interactions
Rhoderick E. Brown and Howard L. Brockman
In "Methods in Molecular Biology" vol. 398: Lipids Rafts (T.J. McIntosh, ed.) Humana Press, Totowa, NJ, pp. 41-58 (2007)

No. 1643
Lymphokine-activated killer T-cell-originated protein kinase phosphorylation of histone H2AX prevents arsenite-induced apoptosis in RPMI7951 melanoma cells
Tatyana A. Zykova, Feng Zhu, Chengrong Lu, LeeAnn Higgins, Yasuaki Tatsumi, Yasuhito Abe, Ann M. Bode, and Zigang Dong
Clin. Cancer Res. 12, 6884-6893 (2006)

No. 1645
Potent inhibition of Lewis lung cancer growth by heyneanol A from the roots of Vitis amurensis through apoptotic and anti-angiogenic activities
Eun-Ok Lee, Hyo-Jeong Lee, K.S. Ahn, C. Chae, K.S. Kang, Junxuan Lü, and Sung-Hoon Kim
Carcinogenesis 27, 2059-2069 (2006)

No. 1646
An oriental herbal cocktail, ka-mi-kae-kyuk-tang, exerts anticancer activities by targeting angiogenesis, apoptosis, and metastasis
Hyo-Jeong Lee, Eun-Ok Lee, Yun-Hee Rhee, Guang-Xun Li, Cheng Jiang, Junxuan Lü, and Sung-Hoon Kim
Carcinogenesis 27, 2455-2463 (2006)

No. 1647
The enigmatic effects of caffeine in cell cycle and cancer
Ann M. Bode and Zigang Dong
Cancer Lett. 247, 26-39 (2007)

No. 1648
PROCEEDINGS—Targeting carcinogenesis: transduction, transcription, translation
Zigang Dong and Ann M. Bode
Mol. Carcinog. 45, 353-354 (2006)

No. 1649
(-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucose-regulated protein 78
Svetlana P. Ermakova, Bong Seok Kang, Bu Young Choi, Hong Seok Choi, Todd F. Schuster, Wei-Ya Ma, Ann M. Bode, and Zigang Dong
Cancer Res. 66, 9260-9269 (2006)

No. 1650
Identification of novel phosphoproteins in signaling pathways triggered by latent membrane protein 1 using functional proteomics technology
Guangrong Yan, Lili Li, Yongguang Tao, Sufang Liu, Yiping Liu, Wei Luo, Yong Wu, Min Tang, Zigang Dong, and Ya Cao
Proteomics 6, 1810-1821 (2006)

No. 1651
Arsenite inhibits p53 phosphorylation, DNA binding activity, and p53 target gene p21 expression in mouse epidermal JB6 cells
Faqing Tang, Guangming Liu, Zhiwei He, Wei-Ya Ma, Ann M. Bode, and Zigang Dong
Mol. Carcinog. 45, 861-870 (2006)

No. 1652
Direct inhibition of insulin-like growth factor-1 receptor kinase activity by (-)- epigallocatechin-3-gallate regulates cell proliferation and transformation
Ming Li, Zhiwei He, Svetlana Ermakova, Duo Zheng, Faqing Tang, Yong-Yeon Cho, Feng Zhu, Yuk Yin Sham, Ann M. Bode, Ya Cao, and Zigang Dong
Cancer Epidemiol. Biomarkers Prev. 16, 598-605 (2007)

No. 1653
RSK2 mediates muscle cell differentiation through regulation of NFAT3
Yong-Yeon Cho, Ke Yao, Ann M. Bode, H. Robert Bergen III, Benjamin J. Madden, Sang-Muk Oh, Svetlana Ermakova, Bong Seok Kang, Hong Seok Choi, Jung-Hyun Shim, and Zigang Dong
J. Biol Chem. 282, 8380-8392 (2007)

No. 1654
Differential involvement of reactive oxyden species in apoptosis induced by two classes of selenium compounds in human prostate cancer cells
Guang-Xun Li, Hongbo Hu, Cheng Jiang, Todd Schuster, and Junxuan Lü
Int. J. Cancer 120, 2034-2043 (2007)

No. 1655
The liganding of glycolipid transfer protein is controlled by glycolipid acyl structure
Lucy Malinina, Margarita L. Malakhova, Alex T. Kanack, Min Lu, Ruben Abagyan, Rhoderick E. Brown, and Dinshaw J. Patel
PLoS Biol. 4, e362 (2006)

No. 1657
Prevention of mammary tumorigenesis by intermittent caloric restriction: does caloric intake during refeeding modulate the response?
Margot P. Cleary, Xin Hu, Michael E. Grossmann, Subhash C. Juneja, Soner Dogan, Joseph P. Grande, and Nita J. Maihle
Exp. Biol. Med. 232, 70-80 (2007)

No. 1659
Effects of leptin on human breast cancer cell lines in relationship to estrogen receptor and HER2 status
Amitabha Ray, Katai J. Nkhata, and Margot P. Cleary
Int. J. Oncol. 30, 1499-1509 (2007)

No. 1660
p85· acts as a novel signal transducer for mediation of cellular apoptotic response to UV radiation
Lun Song, Jingxia Li, Jianping Ye, Gang Yu, Jin Ding, Dongyun Zhang, Weiming Ouyang, Zigang Dong, Sung O. Kim, and Chuanshu Huang
Mol. Cell. Biol. 27, 2713-2731 (2007)

No. 1667
T-lymphokine-activated killer cell-originated protein kinase functions as a positive regulator of c-Jun-NH2-kinase 1 signaling and H-ras-induced cell transformation
Sang-Muk Oh, Feng Zhu, Yong-Yeon Cho, Ki Won Lee, Bong Seok Kang, Hong-Gyum Kim, Tatyana Zykova, Ann M. Bode, and Zigang Dong
Cancer Res. 67, 5186-5194 (2007)

No. 1671
A novel class of pyranocoumarin anti-androgen receptor signaling compounds
Junming Guo, Cheng Jiang, Zhe Wang, Hyo-Jeong Lee, Hongbo Hu, Barbara Malewicz, Hyo-Jung Lee, Jae-Ho Lee, Nam-In Baek, Jin-Hyun Jeong, Dae-Keun Kim, Kyung-Sun Kang, Sung-Hoon Kim, and Junxuan Lü
Mol. Cancer Ther. 6, 907-917 (2007)

No. 1672
Glycolipid transfer proteins
Rhoderick E. Brown and Peter Mattjus
Biochim. Biophys. Acta 1771, 746-760 (2007)

No. 1673
Model of peripheral protein adsorption to the water/lipid interface
Istvan P. Sugar and Howard L. Brockman
J. Phys. Chem. B 111, 4073-4081 (2007)

Hormel Institute Seminars

2006 – 2007

Dr. Shi-Yuan Cheng
Hillman Cancer Center, Pittsburgh, PA
July 21, 2006
"Angiopoietin-2 induces human cancer invasion and metastasis through integrin-mediated pathways"

Dr. An-Sik Chung
Korean Advanced Institute of Science and Technology, Republic of Korea
July 31, 2006
"Antitumor effect of selenium by inducing apoptosis and blocking tumor invasion"

Dr. Stephen S. Hecht
University of Minnesota, Minneapolis, MN
January 5, 2007
"Tobacco and cancer: Chemical mechanisms, biomarkers, and chemoprevention"

Dr. Michel M. Sanders
University of Minnesota, Minneapolis, MN
January 17, 2007
"ZEB1 and the art of mesenchymal maintenance"

Dr. Joel Slaton
University of Minnesota, Minneapolis, MN
February 16, 2007
"Dietary phytoestrogens and prostate cancer prevention: results from the SoyCaP trial"

Dr. Donald Tindall
Mayo Clinic, Rochester, MN
March 23, 2007
"Molecular signaling in prostate cancer"

Dr. Zhiguo Zhang
Mayo Clinic, Rochester, MN
April 6, 2007
"Regulation of genome stability by a novel histone acetyltransferase"

Dr. Chinthalapally V. Rao
University of Oklahoma, Oklahoma City, OK
May 11, 2007
"COX-2 and beyond: Prevention of colorectal cancer"

Dr. Shivendra Singh
Hillman Cancer Center, Pittsburgh, PA
May 18, 2007
"Activation of a novel cell cycle checkpoint by garlic constituent diallyl trisulfide"

Dr. Paul Limburg
Mayo Clinic College of Medicine, Rochester, MN
June 6, 2007
"Looking over the fence: chemoprevention clinic trials"

Dr. Ajay Rana
Texas A & M University-HSC, Temple, TX
June 22, 2007
"Role for mixed lineage kinase 3 in stress signaling"

Hormel Institute Faculty and Staff

Research Sections

Biophysics
Howard L. Brockman, Jr., Professor
William E. Momsen, Scientist
Maureen M. Momsen, Junior Scientist

Cancer Biology
Junxuan (Johnny) Lü, Professor
Cheng Jiang, Senior Research Associate
Hongbo Hu, Research Assistant Professor

Hormel Fellows
Hyo Jeong Lee
Guang-Xun Li
Lei Wang
Zhe Wang
Qiu Xiang

Barbara Malewicz, Scientist
Kim, Sung-Hoon, Visiting Professor

Cellular and Molecular Biology
Zigang Dong, Professor and Executive Director
Ann M. Bode, Research Associate Professor and Associate Director
Yong Yeon Cho, Research Assistant Professor
Feng Zhu, Research Assistant Professor
Wei Ya Ma, Senior Research Associate
Margarita Malakhova, Research Associate

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Svetlana Ermakova
Bong Seok Kang
Hong-Gyum Kim
Myoungok Kim
Tao Yin Lau
Sung-Young Lee
Ming Li
Sang-Muk Oh
Cong Peng
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Evgeny A. Rogozin
Jung-Hyun Shim
Faqing Tang
Darya Urusova
Ke Yao
Ji-Shuai Zhang
Duo Zheng
Tatiana Zykova

Mara Ebeling, Junior Scientist
Merlene Stiles, Assistant Scientist
Andria Leyden, Junior Laboratory Technician

Visiting Scholars
Nam-Joo Kang
Ki Won Lee
Zheng-Yuan Su

Membrane Biochemistry
Rhoderick E. Brown, Jr., Professor

Hormel Fellows
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Ravikanth Kamlekar
Asif Zakaria
Xiuhong Zhai
Xianqiong Zou

Helen Pike, Principal Laboratory Technician
Nicolai Petersen, Visiting Scholar

Nutrition and Metabolism
Margot P. Cleary, Professor
Michael Grossmann, Research Assistant Professor

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Amitabha Ray
Olga Rogozina

Junior Scientists
Melissa Bonorden
Nancy Mizuno
Katai Nkhata

Junior Laboratory Technicians
Dmitry Malakhov
Emily J. Kain Quealy
Christina Kluczny

Signal Transduction & Apoptosis
Peter P. Ruvolo, Associate Professor
Tilahun Jiffar, Research Assistant Professor
Vivian Ruvolo, Senior Research Associate

Translational Cancer Research
Dezhong (Joshua) Liao, Associate Professor
Houqing Zhou, Hormel Fellow
Dongqing Liu, Junior Scientist
Jiusheng Wu, Junior Scientist
Yi Mo, Visiting Scholar

Support Units

RAR Facility
Miranda Goff, Lab Tech Specialist and Supervisor

Laboratory Technicians
Laura Hamersma
Michelle Jacobson
Lynn Leraaen
Amy Snider

Instrument Core Facility
Todd Schuster, Senior Laboratory Technician

Research Support Services
Craig Jones, Information Technology Supervisor
Ryan Bonorden, Technical Supplemental
Gary Bush, Technical Supplemental
Michael Conway, Senior Electronics Technician
Timothy Lastine, Information Technology Professional
Rose Srock, Data Processing Technician
Theresa Tucker, Information Technology Professional
Ryan Wiersma, Data Processing Technician

Building Operations and Maintenance
Ronald Skjeveland, Supervisor
Tommy Wobschall
Norman D. Johnson
Duane H. Graff

Office
Ann Bode, Associate Director and Area Manager
Jeanne Ruble, Personnel Specialist
Andria Hansen, Office Support Assistant
Jodi Loverink, Executive Accounts Specialist
Betsy Mentel, Executive Office & Administrative Specialist

Public Relations and Development
Gail Dennison
Interns: Andrew Dennison, Luke Green

Library
Andy Lucas

S.U.R.E. Students (Summer 2007)
Brittany Alms, Cellular and Molecular Biology
Tyler Conway, Cellular and Molecular Biology
Amy Jencks, Cancer Biology
Rebecca LeVan, Nutrition and Metabolism
Krista Ryan, Nutrition and Metabolism
Jonathan Song, Translational Cancer Research
Danh Voong, Cellular and Molecular Biology

Professors Emeriti
Wolfgang J. Baumann, Membrane Chemistry and Biology, NMR Facility
Ralph T. Holman, Nutritional Biochemistry
Harald H.O. Schmid, Physiological Chemistry

Income from Grants and Contracts

National Institutes of Health	
National Cancer Institute	
Anticarcinogenesis Mechanisms of Tea Constituents (Z. Dong)	182,252
Inhibition of Carcinogenesis by Tea and Tea Constituents Program Project (Z. Dong)	35,371
Study on Ultraviolet-induced Signal Transduction (Z. Dong)	160,381
Methyl Selenium Regulation of Angiogenic Switch Mechanism (J. Lü)	115,878
Intermittent Food Restriction Prevents Mammary Tumors (M. Cleary)	171,065
Molecular Basis of Arsenic-induced Cell Transformation (Z. Dong)	190,529
Selenium and Prostate Cancer Apoptosis Pathways (J. Lü)	160,788
Chemoprevention of Skin Cancer Program Project (Z. Dong)	199,187
Mechanisms of Chemopreventive Effect of Resveratrol (Z. Dong)	191,927
Inhibition of Carcinogenesis by Tea and Tea Constituents (Z. Dong)	176,213
Molecular Basis of Glycosphingolipid Binding Specificity (R. Brown)	71,000
Measurement of Specific Signal Transduction Endpoints to Identify Potential Biomarkers (A. Bode)	121,413
c-Myc,Growth Factor and Breast Cancer (D.J. Liao)	150,094
Regulation of Bcl12 Function Via Ceramide-activated PP2A (P .Ruvolo)	119,956
National Institute of General Medical Sciences	
Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown)	245,000
Department of Defense – U.S. Army	
Role of Obesity in Prostate Cancer Development (M. Cleary)	134,218
Alcon	
Mechanism of Membrane Stabilization and Disruption by Antihistamines (H. Brockman)	42,667
American Institute for Cancer Research	
Dietary Obesity and Prostate Cancer Development in TRAMP Mice (M. Cleary)	37,311
Breast Cancer Research Foundation	
Obesity, Leptin, and Hormone Responsive Breast Cancer (M. Cleary)	50,907
Body Weight Change, Leptin/Adiponectin and Breast Cancer (M. Cleary)	155,767
Mayo Clinic/MN DEED	
Selective Small-Molecule Inhibitors of JNK2 as Anti-Cancer Drugs (Z. Dong)	250,000
Pardee Foundation	
Identification of Genes Relevant to the Liver Metastatis of Pancreatic Cancer (D.J. Liao)	43,771
Roles of the mir-17 and mir-221 Clusters of MicroRNAs in Breast Cancer (D.J. Liao)	7,500
Prostate Cancer Foundation	
Novel Herbal Drug Candidates for Prostate Cancer Therapy (J. Lü)	58,333
Other Resources	
The Hormel Foundation	1,569,217
University of Minnesota	639,730
Indirect Cost Return	1,116,176
Other Income	140,259
Eagles Cancer Telethon	140,000
Southern Minnesota Internet Group	213,749
TOTAL	**$6,890,659**

Ron Skjeveland, Supervisor of Building Operations and Maintenance, with the original boiler installed in 1959. This boiler operated for 47 years and will be removed upon completion of the expansion.

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"The Hormel Institute is part of a team project. By working together, we will help to lead our university in realizing the goal of becoming a top research institute worldwide."

— Zigang Dong, M.D., Dr. P.H.
Executive Director