The research, partnerships and resources of The Hormel Institute are dedicated to a single purpose: Improving health through medical research.

Today’s RESEARCH.  
Tomorrow’s CURES
The mission of The Hormel Institute is to conduct research and provide education in the biological sciences with applications in medicine and agriculture. In pursuit of this mission, and as intended by its founders, The Hormel Institute generates fundamental knowledge and disseminates it to the scientific community worldwide. It also serves as a center of technical and educational expertise for the benefit of the Austin community, the surrounding region and the State of Minnesota.
Cancer affects all of humankind: women and men, poor and rich, old and young, and all races. Cancer is the leading cause of death worldwide. Most human cancers are preventable or treatable. History has proven that only research will lead to new methods for prevention and therapy of human cancer. The Hormel Institute is a leading medical research institute making major contributions to the identification and characterization of novel molecular and cellular targets and agents for cancer prevention and therapy. During 2013-14, The Hormel Institute experienced continued success obtaining research funding and producing major research breakthroughs, even in a national environment of overall decreased funding for research.

With the support of State Senator Dan Sparks and State Representative Jeanne Poppe, as well as State Senator David Senjem, the State of Minnesota bonding bill, signed by Governor Mark Dayton, included $13.5 million in funding to the City of Austin Port Authority to lead the construction project for The Hormel Institute’s next expansion. The Hormel Foundation, led by Chairman Gary Ray, announced $23 million in funding to support the project. The construction is currently in the design process and groundbreaking was held on May 28, 2014. The new building will be home to the International Center for Research Technology (ICRT) and The Hormel Institute.

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

We are thankful for the generous support of The Hormel Foundation, Hormel Foods Corporation, University of Minnesota, and Mayo Clinic. In particular, I would like to thank Mr. Gary Ray, Mr. Jeff Ettinger, Mr. Richard Kuehlow, Mr. Joel Johnson, Mrs. Bonnie Rietz, Mr. Jerry Albinson, and Mr. Steve Rizzi.

We thank Drs. Eric Kaler and Brian Herman (University of Minnesota) and Drs. John Noseworthy, Glenn Forbes, Robert Daiso, and Greg Corcoran (Mayo Clinic) for their leadership and support.

We thank our elected leaders, Minnesota Governor Mark Dayton, U.S. Senators Al Franken and Amy Klobuchar, U.S. Representative Tim Walz, Minnesota State Senator Dan Sparks, Minnesota State Representative Jeanne Poppe, State Senator David Senjem, and Mayor Tom Stiehm for their continued support.

We remain deeply grateful to our community, our partners and our collaborators for giving us the gift of allowing us to work here. Their support and gifts allow today’s research to flourish and pave the way for tomorrow’s progress to continue.

“We most human cancers are preventable, or treatable, if discovered at an early stage.”

Dr. Zigang Dong
Executive Director
Cancer is one of the leading causes of human death worldwide. Throughout history, humankind has seen the battle against deadly diseases, including smallpox and polio, by devoting enormous efforts to the discovery of new medicines. However, little progress was made against malignancies until the 1960s, when Atomic Energy provided the first in vivo evidence that the antitumor effects of retinoids are mediated by blocking the retinoic acid receptor (RAR) and RAR-related orphan receptor (ROR). We were one of the first groups to systematically elucidate these signal transduction pathways in cancer cell lines. We also have tested the efficacy of many natural products in the prevention of skin cancer and identified their molecular targets. Today, the skin cancer can be treated by surgery, and the incidence of skin cancer is decreasing. We were the first to elucidate key signals/proteins that play functional roles in human carcinogenesis, especially hormone-targeted cancer therapy. We have discovered critical proteins and their targeted signaling pathways in cancer development and prevention. We have shown that natural compounds, found in fruit, vegetables, and traditional medicinal herbs have been shown to be effective chemopreventive agents in multiple animal models. We have also shown that UV irradiation directly activates signal transduction pathways induced by SUV irradiation is critical for SUV-induced skin cancer. We also measured the molecular mechanism(s) and direct target(s) of taxifolin in skin cancer chemoprevention. The discovery that natural compounds, found in fruit, vegetables, and traditional medicinal herbs have been shown to be effective chemopreventive agents in multiple animal models. We have also shown that UV irradiation directly activates signal transduction pathways induced by SUV irradiation is critical for SUV-induced skin cancer. We also measured the molecular mechanism(s) and direct target(s) of taxifolin in skin cancer chemoprevention.

1. The discovery that signal transduction pathways induced by UV, UVB, and solar UV are major etiologic factors for human skin cancer and other diseases. We were the first to elucidate key signals/proteins that play functional roles in human carcinogenesis, especially hormone-targeted cancer therapy. We have discovered key proteins, transcription factors, and other signaling molecules that are critical in cancer development and are significant targets for cancer prevention and treatment. We were the first to elucidate key signals/proteins that play functional roles in human carcinogenesis, especially hormone-targeted cancer therapy. We have discovered key proteins, transcription factors, and other signaling molecules that are critical in cancer development and are significant targets for cancer prevention and treatment.

2. The discovery that protein kinases and their target transcription factors, including activator protein-1 (AP-1) and nuclear factor kappa B (NFkB), are major etiologic factors for human skin cancer and other diseases. We were the first to elucidate key signals/proteins that play functional roles in human carcinogenesis, especially hormone-targeted cancer therapy. We have discovered key proteins, transcription factors, and other signaling molecules that are critical in cancer development and are significant targets for cancer prevention and treatment.

3. The discovery that natural compounds, found in fruit, vegetables, and traditional medicinal herbs have been shown to be effective chemopreventive agents in multiple animal models. We have also shown that UV irradiation directly activates signal transduction pathways induced by SUV irradiation is critical for SUV-induced skin cancer. We also measured the molecular mechanism(s) and direct target(s) of taxifolin in skin cancer chemoprevention.
Dr. Dong and his group have, therefore, evaluated the potential of tea polyphenols to alter molecular targets within cancer cells. This research, focusing on cell signaling, to EGCG. In collaboration with scientists at IBM, Dr. Dong’s group used the world’s fastest supercomputer, the Blue Gene/L, to establish a docking method for EGCG-receptor complex. What is more, EGCG can directly bind EGCG. Identification of this cellular receptor represents the first, most critical step in understanding molecular and biochemical mechanisms of polyphenols’ anticancer effect. Such studies have also provided a powerful new technology for studying molecular targets of other cancer chemopreventive agents.”

The discovery that histones – proteins with a critical role in cell division – are regulated at the transcriptional level by numerous protein kinases has advanced our knowledge of how cells communicate and govern cellular growth and differentiation. We have discovered that many protein kinases phosphorylate histone to play critical roles in cell growth, cell transformation and apoptosis. We reported a function of H2A.X in cellular apoptosis. Our data indicated that H2A.X phosphorylation is required for DNA ladder formation, but not for the activation of caspase-3. The RSK 2/H2A.X signaling pathway negatively regulates the RSK 2/histone H3 pathway and, therefore, maintains normal cell proliferation.

In this study, we investigated the role of such modifications in cell apoptosis, cell cycle, and tumorigenesis. We have discovered three novel MEK inhibitors, and novel use of FDA-approved drugs for new uses, such as anti-cancer, anti-inflammatory.

Inhibitors targeting DNA damage and cellular repair. The mitogen-activated protein kinase (MAPK) cascade is a major component of the Ras (rat sarcoma)/RAF (rapidly accelerated fibrosarcoma)/MEK (mitogen-activated protein kinase) signaling pathway. In normal cells, the MAPK cascade is activated by extracellular signals and regulates tumorigenesis and cancer cell growth. MEK is frequently activated in various cancers that have mutations in the RAS and RAF kinases. Therefore, the MEK and WNT pathways have been suggested as therapeutic targets for inhibitor development against tumorigenesis. We have discovered novel MEK inhibitors, reduced tumor growth in A431 xenograft tumor model and the 秋水仙素-induced tumor growth in the A431 xenograft model.

Our work was highly recognized on the National Cancer Institute (NCI) website. "Dr. Dong and his group have, therefore, evaluated the potential of tea polyphenols and other dimeric EGCG to inhibit cell growth. They focused on human and mouse ESC self-renewal activity, and we further found that EGCG also binds and phosphorylates Nanog. We demonstrated that ERK-activated Nanog phospho- proteomics identifies a role for Nanog in self-renewal of ESCs through FDDasso-medi- ated Nanog protein stability.

Computational biology directed molecular biology study in cancer research. Working with IBM’s Blue Gene supercomputer team, my group has developed cutting-edge methods of computational biology to study protein targets for cancer prevention and therapy. Our group was the first to use such methods to study protein targets for cancer prevention and therapy. The manuscript was published in Molecular and Cellular Biology.

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Cloning of 5′-dehydroflavone, a natural flavonoid widely distributed in plants, to determine the amino acid residues critical for the activity of chymotrypsin observed in in vitro studies, however, has been disappointing. A chymotrypsin derivative, referred to as compound 6940 7, more strongly inhibited EGF-induced neoplastic transformation of JB6 P+ cells compared with chrysin. It inhibited cell cycle arrest (G 1  or G 2/M ) and apoptosis. Further-more, 6-shogaol inhibited A kt kinase activity, a downstream mediator of EGF receptor signaling, by binding with an allosteric site of A kt. Other inhibitors such as butein, a flavonoid, and 3,6,2′,4′,5′-pentahydroxy-flavone seem to be potential candidates for the prevention of lung cancer cell growth.

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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 cancer patients.

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

1. Understanding the biochemical, cellular and molecular processes that are crucial for the development and progression of prostate cancer and are known to confer aggressiveness to cancer cells are (1) androgen receptor signaling, (2) metabolic reprogramming, (3) hypoxia and (4) immune suppression of tumour-suppressor genes (tumour-suppressor action).

2. Reactivation of Tumour Suppressor Genes

Early development of cancer is largely dependent upon androgens, and simultaneous suppression of tumour-suppressor genes predispose the initiated and premalignant prostate epithelial cells to acquire malignancy 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 and its receptor Roundabout (Robo) 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. SLIT/ROBO 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 tumour-suppressor system in humans. We have discovered a critical role of normal prostate epithelial cells in mediating the mechanism of action of androgen deprivation therapy. In early stages of prostate cancer treatment, SLIT/ROBO expression is physiologically important because it is a potent tumour suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumour cells is an essential defining property of a potent stem cell-like phenotype of cancer cells that allows for the disease-free existence of heterogeneous cell populations of cancer cells among the heterogenous mix of cells constituting a tumour has been reported to be essential for tumour progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells that do not respond to chemotherapy or radiotherapy possess the traits of stem cells, thus, regenerating themselves even after chemotherapeutic treatment. The polycystic kidney (PKC) family of proteins (which form multifunctional, gene-regulating 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 the PKC family. We are investigating the role for BMI-1 in prostate cancer development.

We hypothesize that the BMI-1 protein could be developed as a diagnostic and prognostic marker of prostate cancer.

3. Reactivation of Tumour Suppressor Genes

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

Research projects underway

1. Investigation of mechanisms of chemoresistance in prostate cancer patients

Prostate cancer is the most common visceral cancer diagnosed in men. It is the second-leading cause of cancer-related death 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 predilection, resistance of the disease and survival of cancer cells (even after chemotherapy) shall be excellent candidate targets for staging the disease and establishing effectiveness of therapeutic and chemotherapeutic interventions of prostate cancer. We investigate the molecular mechanisms that cause the failure of chemotherapy and radiotherapy in cancer patients. We have identified several markers (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 gene and stem cell marker), SLIT-ROBO (a growth-inhibitory and maturation-inhibiting protein) and various studies suggest the SLIT-Robo network acts as a tumour-suppressor system in humans. We have discovered a critical role of normal prostate epithelial cells in mediating the mechanism of action of androgen deprivation therapy. In early stages of prostate cancer treatment, SLIT-Robo expression is physiologically important because it is a potent tumour suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumour cells is an essential defining property of a potent stem cell-like phenotype of cancer cells that allows for the disease-free existence of heterogeneous cell populations of cancer cells among the heterogenous mix of cells constituting a tumour has been reported to be essential for tumour progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells that do not respond to chemotherapy or radiotherapy possess the traits of stem cells, thus, regenerating themselves even after chemotherapeutic treatment. The polycystic kidney (PKC) family of proteins (which form multifunctional, gene-regulating 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 the PKC family. We are investigating the role for BMI-1 in prostate cancer development.

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4. 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) androgen receptor signaling, (2) metabolic reprogramming, (3) hypoxia and (4) immune suppression of tumour-suppressor genes (tumour-suppressor action). Among the phenotypic changes, the premalignant cancer cells acquire increased motility, changes in cytoskeleton, changes in cell adhesion characteristics, and increased tendency for clonal expansion. The interaction between SLIT and its receptor Roundabout (Robo) 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. SLIT/ROBO 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 tumour-suppressor system in humans. We have discovered a critical role of normal prostate epithelial cells in mediating the mechanism of action of androgen deprivation therapy. In early stages of prostate cancer treatment, SLIT-Robo expression is physiologically important because it is a potent tumour suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumour cells is an essential defining property of a potent stem cell-like phenotype of cancer cells that allows for the disease-free existence of heterogeneous cell populations of cancer cells among the heterogenous mix of cells constituting a tumour has been reported to be essential for tumour progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells that do not respond to chemotherapy or radiotherapy possess the traits of stem cells, thus, regenerating themselves even after chemotherapeutic treatment. The polycystic kidney (PKC) family of proteins (which form multifunctional, gene-regulating 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 the PKC family. We are investigating the role for BMI-1 in prostate cancer development.

We hypothesize that the BMI-1 protein could be developed as a diagnostic and prognostic marker of prostate cancer.
metastatic tumors, normal cells with uninhibited movement, such as macrophages, transformed cells, and in various cancer types, such as breast, ovary, lung, and skin. Metastatic cells have been shown to arise through the release of androgen-dependent tumor cells. Notably, we have identified a novel inhibitor that inhibits the activity of AR variant in CRPC cells.

The validation of this mechanism-based agent in animal models is expected to be insufficient as a reliable biomarker for prognosis of prostate cancer in African American men. Though widely used in clinics, PSA has been reported at investigating the molecular mechanisms that cause the failure of cancer treatment for both xenografts and in vivo models, including the presence of chemoresistant cells, molecular alterations have been reported to contribute to this discrepancy. Recent developments in genetics, proteomics, and genomics, among other molecular biotechnologies, are anticipated to greatly aid in the advancement of translational research on prostate cancer racial disparity and hopefully will culminate in the development of novel molecular markers in African American men. The larger aim is to identify novel biomarkers that could be used for prostate cancer prognosis in Caucasian as well as African American men. We recently showed that BMI-1, a stem-cell protein, could be developed as a sensitive and reliable marker for prostate cancer disease in Caucasian and African-American men.

Lupus, a fruit- and vegetable-based intervention, is found in clove, garlic, cucumbers, carrots, and onions as well as in herbs, such as aloe vera. Our laboratory has shown that reduced risk of developing cancer develops in Capan-1 xenograft tumor model module. We further have shown that lupin treatment inhibits the growth of prostate, pancreatic, and skin tumors (of human origin) using relevant mouse models. These studies provide strong evidence that lupin may be a potential agent for cancer prevention and treatment. We have recently observed that lupin has the potential of improving chemotherapy in cancer. Our pharmacokinetic studies have shown that lupin is bioavailable in human colon cancer cells after oral consumption (as a oral adminstration).  

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

According to the American Cancer Society, the higher overall cancer death rate among African American men also is due largely to higher mortality rates from lung, breast, colorectal, prostate, and pancreatic cancers. Cancer death rates have decreased, the death rate for all cancers combined continues to be 52% higher in African American men than in Caucasian men, even after adjusting for age at diagnosis. Our studies have shown that epicatechin-rich cocoa polyphenol supplementation has been associated with improved survival in a NIH CTSA--funded study of familial adenomatous polyposis (FAP) patients. S100A4 regulates the events leading to proliferation and invasion of prostate cancer, particularly the CRPC phenotype.

6. Investigating the causes of racial disparity in prostate cancer  

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

Abnormal Androgen receptor (AR) expression and activation is frequently observed in different tumors. It has been observed that abnormal AR expression and activation are involved in the metabolism of androgens and provide a survival advantage for cells in a low-androgen environment. Our laboratory has identified the mechanism through which androgen plays a role in the development of prostate cancer. We recently have shown that lupin treatment inhibits the growth of prostate, pancreatic, and skin tumors (of human origin) using relevant mouse models. These studies provide strong evidence that lupin may be a potential agent for cancer prevention and treatment. We have recently observed that lupin has the potential of improving chemotherapy in cancer. Our pharmacokinetic studies have shown that lupin is bioavailable in human colon cancer cells after oral consumption (as a oral administration).

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Our laboratory is funded by a National Institutes of Health (NIH) contract and Pediatric Pharmaceuticals. The purpose of the NIH-studies is to identify and measure specific cellular signal transduction endpoints with the purpose of identifying potential biomarkers and mechanisms of action of the various anticancer agents. The work funded by Pediatric Pharmaceuticals focuses on the anti-skin cancer effects of ginger compounds. The NIH-funded work focuses on studies with mammary tumors and normal mammary glands, and effects of chemopreventive agents in in vivo mammary models. The primary purpose of this work is to determine whether specific signal transduction molecules can serve as reliable endpoint biomarkers (or clinical trial as well as provide insight into the mechanism(s) by which selected anticancer agents modulate their prophylactic effects. The development and identification of reliable biomarkers will allow us to 1) assess the efficacy of potential chemopreventive or therapeutic agents for clinical trials, 2) identify patients who will respond to specific drug treatments, and 3) determine the mechanisms of action of specific agents or mixtures of agents in e.g., liver cancer. These are major objectives in the field of chemoprevention and cancer therapeutics. To identify biomarkers, we use a variety of techniques, including immunohistochemistry, Western blot analysis, protein array analysis, and cell culture. The use of Neu expressing or ER positive breast cancer cell lines to test the effect of RXR inhibitors, targretin and UAB, on migration and invasion, along with other characteristics of cancer, is being investigated. Our work funded by Pediatric Pharmaceuticals has focused on developing a ginger-based formulation to treat and/or prevent solar UV-induced skin cancer.

“Our work funded by NIH has focused on biomarker identification in breast and bladder cancer.”

Dr. Ann M. Bode
Cells envelope their contents by means of thin, flexible barriers called “membranes” that enable selective import of nutrients and export of toxic by-products. Assembly of membranes relies on the polar at one end and nonpolar at the opposite end. With the polar ends facing to be in contact with water and the nonpolar ends wanting to avoid water, these lipids readily orient and arrange themselves as thin, flexible layers, i.e. bilayers. These membrane bilayers not only surround cells but also form internal partitions that enable regions of specialized function inside of cells. Interestingly, there are many more varieties of lipids found in membranes than are needed to form bilayers. Some membrane lipids also function as messenger signals that regulate cell growth, proliferation, and programmed cell death processes. While other membrane lipids appear to cluster together in bilayers to form microdomains that are capable of containing specific signaling molecules within the bilayer and the opposite end of these signaling molecules. These microdomains can function as organizing regions for certain biological processes.

Our research is focused on a membrane lipid class known as “sphingolipids and proteins” that can bind and transfer sphingolipids between membranes. Certain sphingolipids, along with cholesterol, serve as key components needed for formation of membrane “raft” microdomains. Rafts appear to function as organizational regions for certain signaling processes as well as target sites for certain viruses and bacteria. Earlier efforts focused on rigorously defining the physical basis for raft formation and proliferation. To do so, we developed ways to quantitatively measure the lateral elasticity within model membranes to accurately assess the physical changes that occur within the “raft environment” as the content and structure of sphingolipids and sterols are systematically altered. Our research continues because of the need for continuing studies into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids. Our ongoing efforts benefit from collaborations with researchers at Memorial Sloan Kettering Cancer Center in New York, Virginia Commonwealth University in Richmond, The Russian Academy of Sciences in Moscow, CIBER-BioENGINEERING, and the Mayo Clinic.

GLTP function. Our molecular biological studies resulted in the first molecular cloning of human GLTP and showed that related homologs originating from mRNA transcripts of other mammalian, plant, and fungal G protein-coupled receptors. We used a combination of biophysical, cell biological, and chemical approaches to understand the expression, intracellular distribution, and regulation of GLTP function. Our recent investigations of the gene organization and transcriptional status in humans as well as other mammals now provide a firm foundation for the identification and characterization of inherited diseases involving GLTP and CPTP. Our ongoing efforts benefit from collaborations with researchers at Memorial Sloan Kettering Cancer Center in New York, Virginia Commonwealth University in Richmond, and the Mayo Clinic.

The discovery of these new functions for membrane lipids underscores the reasons why biomembranes come under direct attack during cancer and infectious disease. To gain insights into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we use a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR). We apply these resources, i.e. nanotools, for manipulation of targeted sphingolipid levels in cells. Such strategies could provide new ways to introduce specific sphingolipids antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new therapeutic approaches to treat disease processes involving sphingolipids.

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

The formation and maintenance of sphingolipid-enriched microdomains are likely to involve specific protein interactions and lateral transfer of sphingolipids between membranes. Much effort in our lab has been directed toward a protein family known as “glycosylceramide transfer proteins” (GLTVP) that can specifically bind and transfer glycosylceramide between membranes. We found that GLTP functionality is regulated by lipid composition and packing within membranes. To gain insights into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we use a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR). We apply these resources, i.e. nanotools, for manipulation of targeted sphingolipid levels in cells. Such strategies could provide new ways to introduce specific sphingolipids antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new therapeutic approaches to treat disease processes involving sphingolipids.

“Discovering new functions for membrane lipids underscores the reasons why biomembranes come under direct attack during cancer and infectious disease.”

Dr. Blacklock E. Brown
One other diabetes-related project we have been working on is the structural basis of Glucagon-like-peptide (GLP) gene regulations, especially through the transcription factors Foxo1 and Creb. GLP is a key regulating enzyme for glucagonogenesis in the liver. It has been considered to be an attractive target for diabetes treatment. Last year, we finally finished the Foxo1-DNA complex structure and now have submitted the manuscript for publication, in which we have identified a new Foxo1 binding site and novel binding modes on Creb promoter.

As part of cancer-related projects, Dub3 is an ubiquitin hydrolase (de-ubiquitinase) and a key protein that mediates extrinsic signals to regulate epithelial-mesenchymal transition (EMT) and metastasis in breast cancer, which can serve as a drug-gable target for treating triple negative/basal-like breast cancers. To gain the ground work for structure-based rational drug design against this protein, we set out to determine the crystal structures of the Dub3 catalytic domain alone and/or in complex with the functional inhibitors. These findings will validate the effectiveness of Dub3 target strategy and could open new doors for therapeutic intervention.

Additional cancer-related projects in the lab with therapeutic values include Fabp7 inhibitor complexes, leukemia-associated histone modifiers, novel protein kinase inhibitors complexes, and small RNA molecules for drug delivery. Research in our laboratory will continue to this end, and target molecules so far discovered will be expanded to include more cancer-related proteins that will lead to additional preliminary data for sustaining grant applications. Crystal structure determination, functional studies, and drug discovery will provide a critical basis for human physiology, dysfunction in the disease state, and a better strategy for therapeutic intervention.

Our research currently is focused on elucidating the atomic details of key molecular interactions involved in human disease, especially diabetes and cancer. We, in particular, are focusing on (i) transcriptional regulators involved in diabetes and (ii) protein functional modulators involved in tumor progression and metastasis. We aim to apply structural biology to gain a better understanding of their normal function and dysfunction in the disease state as well as an opportunity to discover or design structure-based functional modulators.

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

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HNF1α (Hepatocyte Nuclear Factor1 α) and HNF4α (Hepatocyte Nuclear Factor4 α) are the master regulators of pancreatic β-cell development and function, and their mutations are the most common causes of diabetes referred to as MODY. Over the years, we have determined the crystal structures of the functional complexes made by HNF1α and HNF4α. These structures provided valuable information on the molecular basis of target gene recognition, ligand-mediated activation, and functional dysregulation by disease-causing mutations. These structures, however, proved only partial answers as to how their full transcriptional activities arise, and how these proteins are involved in additional protein-protein interactions and physiological functions. Therefore, we set out to identify previously unknown functional binding partners of HNF1α and HNF4α in β-cells, and study the physiological implications of these interactions, especially on insulin secretion that is impaired in MODY patients. We performed structural studies of the complexes and functional characterization of MODY mutations. We previously published the findings on the mediator component of the main transcriptional machinery, MED25, as a functional binding partner of HNF1α and its implication to β-cell function. We currently are in the process of follow-up additional binding partners and their physiological implications, such as novel transcriptional co-activator class II (IP3) for HNF1α and HNF4α, respectively. The findings from these studies will advance the current understanding of the transcriptional regulatory network in β-cells and provide a new avenue for diabetes treatment/prevention strategies by discovering novel and more effective target sites for designing and further improving partial agonists selectively against them.

Critical species of a protein/DNA complex used for structure determination by X-rays.
Primary interests of the Nutrition and Metabolism section are the effects of body weight and food intake on the development of breast cancer using mouse models. Past studies have included effects of genetic and dietary induced obesity on breast/mammary tumor development, particularly with respect to body fat and serum IGF-I, leptin and adiponectin levels. Other studies have assessed the effect of calorie restriction on the prevention of mammary tumors in several mouse models of breast cancer. Of particular interest, we consistently find that periods of moderately severe calorie restriction followed by refeeding – which we term “intermittent calorie restriction” – results in much greater reduction in mammary tumor incidence than the same degree of restriction implemented chronically with both interventions resulting in 20-25% calorie reduction. Mechanisms of the protective effect of calorie restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the IGF-axis. Based on results of our studies, we have hypothesized that the altered i.e., reduced adiponectin:leptin ratio, which is characteristic of obesity, provides a permissive environment for tumor development. In contrast, the reductions of IGF-I and leptin and increased adiponectin:leptin ratio resulting from intermittent calorie restriction results in reduced mammary tumor development and increased mammary tumor incidence in comparison to ad libitum feeding as well as chronic calorie restriction. These studies have been expanded by Dr. Michael Grossmann to include the interaction of an omega-3 fatty acid in combination with intermittent calorie restriction on the development of mammary tumors. The intermittent calorie restriction approach may provide an easier approach for individuals to reduce caloric intake for disease prevention.

Although calorie restriction has an incredible effect on cancer prevention in rodent models of many kinds of cancer, the practical aspects of implementing and maintaining this intervention in human populations has not been very successful. This has led to interest in identifying compounds that act like calorie restriction (i.e. calorie restriction mimetics). One such compound is the commonly used type 2 diabetic drug, metformin. The most recent work focuses on directly comparing moderate calorie restriction (25% reduction) to metformin treatment on the prevention of mammary tumors. This study is being conducted in a transgenic mouse model to mimic postmenopausal breast cancer and includes obese as well as normal-weight subjects. The intervention is being started when the mice are middle-aged to also reflect what would occur in at-risk women. We also are conducting studies related to the effects of metformin on cancer progression. With respect to mechanisms of action of these interventions, not only are we assessing alterations in the AMPK pathway but also on aspects of altered glucose metabolism that may result. We anticipate that these ongoing studies will provide valuable insights into ways to prevent mammary tumor development and to slow disease progression.

Other Professional Activities

Margot P. Cleary

Invited speaker
Georgia Regents University - Cancer Center

Presentations

4th Annual Masonic Cancer Center Research Symposium (Dr. Yang)

Attended
AACR 12th Annual Frontiers in Cancer Prevention Meeting – Washington, DC

Grant Review Committees

3 NIH Study Section Meetings (July, October and May)

NUTRITION AND METABOLISM

Section Leader
Margot P. Cleary, Ph.D.
Professor

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Identification of p53-targeted therapeutic strategies for prostate cancer.

The TP53 gene encodes a tumor suppressor protein that functions as a stress response and cell cycle checkpoint regulator to maintain genomic integrity. The importance of p53 in prostate cancer is highlighted by the high frequency of mutations and the poor overall survival of p53-null tumors found in more than half of human cancers. The more comprehensive genetic sequencing studies sponsored by The Cancer Genome Atlas (TCGA) confirm the high frequency of TP53 mutations in many cancer types, for example, prostate cancer. Our laboratory has found that no longer can prostate cancer be viewed as a traditional tumor and that it now represents a spectrum of diseases, with the most important molecular target of TP53-null tumors now known to be the androgen receptor (AR). Alternatively, prostate cancer is a highly heterogeneous disease with different disease stages and treatment effects. Understanding prostate cancer is a complex process, and our research is focused on identifying molecular targets that can be selectively targeted in prostate cancer.

Our ongoing collaborations are with researchers from Texas Tech University Health Sciences Center School of Pharmacy in Amarillo, TX; the University of Texas MD Anderson Cancer Center in Houston, TX; Roswell Park Cancer Institute in Buffalo, NY; and the Fred Hutchinson Cancer Research Center in Seattle, WA.

Our research projects are supported by the grants from National Cancer Institute of NIH and The Hormel Foundation.

Note: This text is a summary of the identification of molecular targets in prostate cancer. For more information, please refer to the original research papers and publications.

Yibin Deng

Grant Reviewer, National Cancer Institute

Left to right: Austin Wang, Yibin Deng, Ji Wang, Lei Wang.

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CELL DEATH AND CANCER GENETICS
Section Leader
Yiling Deng, M.D., Ph.D.
Assistant Professor

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Loss of tumor suppressor genes Pten and p53 in prostate cancer can cause castration-resistant prostate cancer in genetically engineered mice. One of the foremost challenges for breast cancer researchers to develop effective therapeutic strategies for breast cancer is to identify potential therapeutic targets in breast cancer cells. In our studies, we have identified the role of p53 in breast cancer suppression in vivo. To answer the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing tumor progression and metastasis, our studies currently suggest that endogeous expression of mutant p53 promotes breast cancer in vivo. We also use genetic and pharmaceutical approaches in genetically engineered mice models to identify key genetic pathways associated with breast cancer that can give rise to the unstable breast cancer genome is the dysfunction of telomeres. Telomeres also function as the “end-protective” mechanism that prevents chromosomal end-to-end fusions. Telomeres that no longer can exert a telomere-capping activity give rise to unstable breast cancer genome.

We have made progress in our study on prostate cancers. Prostate cancer is the second-leading cause of cancer-related death in males after lung cancer and prostate cancer is one of the most common cancers in the United States. Recent advances in whole-genome and exome sequencing techniques show that alterations of tumor suppressors Pten and p53 occur frequently in lethal human breast cancer-resistant prostate cancer. Genetic studies in mouse models support that Pten and p53 deletions play a causal role in the development of CRPC. Thus, finding effective and selective means of killing prostate cancer cells carrying Pten/p53 deficiency is critical to successfully treat and cure human prostate cancer.

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Our section studies the molecular mechanisms that regulate normal cell division, the roles played by duplication of the centrosome in ensuring the integrity of this process, and defects in chromosome segregation in the gain/loss of whole chromosomes during mitotic cell division. A significant number of cells with more than two spindle poles and an increase in the abnormality of chromosome division. It is, therefore, important to understand the molecular mechanisms that drive normal centrosome duplication and restrict centrosome duplication to one per cell cycle.

In our lab, we use cultured mammalian cells and cytoplasmic extracts generated from Xenopus to examine the basic control mechanisms underlying metaphase, anaphase, cell division, and cytokinesis. We use advanced imaging techniques, such as live-cell confocal fluorescence microscopy, fluorescence recovery after photobleaching (FRAP), microscopy, and microscopy, 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. We also work in relevant to identifying potential targets for chemotherapeutic 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. To ensure that cytokinesis takes place in the right place and at the right time, the positioning of the cleavage furrow must be coupled to the segregation of the chromosomes. This occurs through signaling via the microtubule network, specifically the dynamic astral microtubules and the stable, overlapping midzone microtubules. Both of these classes of microtubules are important for signaling the formation of the cytokinetic furrow and ensuring that the furrow moves in response to the cell cortex, and that this movement is not allowed to proceed without cytokinesis. 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, the microtubules reassemble and the cell cycle proceeds in its way. Using this system and shrinking disk confocal microscopy, we are able to examine the role of candidate regulatory mechanisms, specifically the dynamism of astral microtubules. Our goal is to integrate molecular studies with live-cell physiology to understand the mechanisms underlying cell division.

We have found that there is a period following the onset of anaphase in which the cell cortex cannot respond to furrow-inducing signals, and that this period is sensitive to the loss of microtubules and the activity

"Mistakes in the cell-division process can have disastrous consequences for the cell, leading to aneuploidy, cellular transformation and tumorigenesis."

Dr. Edward H. Hinchcliffe

Our cell work with multiple microtubules, monitoring the centrosome at mitosis in red, centrosomes in green, chromosomes in blue.

We have identified that monitoring centrosome mispositioning – either before or after anaphase – at the single chromosome level.

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 the proper orientation of the cell division and the protection of the chromosomes.

Cell division has at the heart of normal tissue development and maintenance. The division of cells must occur in a strict one-to-two fashion to ensure genomic stability. The loss or gain of whole chromosomes during abnormal cell division leads to aneuploidy, in which daughter cells have variable chromosome numbers. This is a major problem for cells because there is a change in the dosage of essential gene products. The cell has developed multiple, biochemical checkpoints and fail-safe devices to ensure that cell division occurs with absolute fidelity. Unfortunately, DNA mutations – often caused by environmental factors – can render these molecular, quality-control mechanisms ineptible. The result is the inadvertent mispositioning of chromosomes during cell division, leading to genomic abnormalities and tumorigenesis.

Chromosome instability (CIN) is a hallmark of solid tumors and contributes to the genomic heterogeneity of tumor cells. There are multiple mechanisms believed to underlie the generation of CIN, including cell-cycle defects, abnormal centrosome duplication and function; premature chromosomal disjunction; and centrosome-separation errors. Despite an increasingly mechanistic understanding of how CIN is generated, however, very little is known relatively little about how chromosome missegregation becomes transduced into cell transformation and tumorigenesis. A major unresolved question is the role of cell-cycle checkpoints and progression beyond this point, regardless of whether microtubules persist. Polo-like kinase 1 activity is also not required after this “point of no return.” Adding kinase inhibitors after this point does not affect the ability of a furrow to assemble.

2. Centrosome duplication

When CHO cells are arrested in S-phase, they undergo repeated rounds of centrosome duplication without cell-cycle progression. While the increase in size and atherosclerotic, the number of centrosomes in these cells does not increase. To investigate mechanism controlling this duplication, we have arrested CHO cells in S-phase for up to 72 hours and inhibited centrosome formation by treating 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, the microtubules reassemble and the cell cycle proceeds in its way. Using this system and shrinking disk confocal microscopy, we are able to examine the role of candidate regulatory mechanisms, specifically the dynamism of astral and midzone microtubules. We find that, in such cells, the pre-existing centrosomes remain and a variable number of centrosomal microtubules – containing α/β-tubulin and centrin 2 – assemble at the nuclear periphery. If the centrosome is washed out, these nuclear-associated centrosomal loci 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 that does not occur for the number of nuclear-associated centrosomal foci. Importantly, the number of centrosomes that assemble following colcemid washout corresponds to the number of centrosomes that form during G2 phase arrest alone. This suggests that during G2 phase, a core centrosomal activity repeatedly replicates, even if centrioles themselves are prevented from replicating, 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 tumorigenesis. The centrosome is known to play a critical structural role in the cell division process. It organizes the microtubule network during interphase as well as astral microtubules at the spindle poles during mitosis. We currently are using microsurgery coupled with time-lapse videomicroscopy of living acentrosomal cells to investigate the role of the centrosome in cell-cycle regulation. To directly visualize the role of microtubules and regulatory molecules during the acentrosomal cell cycle, we have generated a pri-mate kidney cell line (BSC-1 cells) that constitutively express GFP. We find that, after several hours, acentrosomal cells reform their microtubule network into an organized array. Interestingly, the acentrosomal microtubule focus can separate into two, distinct poles prior to nuclear envelope breakdown. This demonstrates that the splitting of the microtubule network does not require a centrosome, contrary to previously held notions. We find, however, that in the absence of a centrosome, the splitting of the microtubule network is inefficient; approximately 40 percent of acentrosomal cells enter 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 lacks sufficient microtubules to interact with the cell cortex. Regardless of the mechanism, our work reveals that centrosomes are absolutely necessary to ensure fidelity during mitotic spindle assembly.

4. Tektins promote key to spindle pole and spindle midbody

We currently are investigating the role of the tektin proteins in establishing the spindle midzone. Tektins first were identified as components of axonemal microtubules, where they are thought to impart structural rigidity and complex periodic spacing to these highly stable microtubules. Our recent results suggest that tektins localize to the overlapping microtubules at the spindle midzone, where they also play an important role. This region of the mitotic spindle is responsible for initiating cytokinesis and required for the process to continue. Many key regulators of late-mitotic events, along with cytokinesis, localize to the spindle midzone. When tektin 2 (one of three distinct tektins found in vertebrates) is knocked down using shRNAs, the midzone microtubules fail to become compacted and appear to exhibit abnormal, plus-end microtubule motility. The result is failure of cytokinesis.

In addition to the tektins, we are exploring the role of two, highly conserved proteins called EFHC 1 & 2. These C2δ-binding proteins are involved in centriole assembly and the formation of midbodies. Importantly, mutations in these proteins lead to abnormal cell division associated with neurological birth defects.

We are interested in uncovering the molecular mechanisms underlying these observations. We currently are examining the motility of several key regulators of midzone function - PRC1 and KIF4 - in response to experimental loss of tektin 2 and/or EFHC 1 & 2. We are using live-cell imaging and FRAP analysis to examine the role played by tektins in regulating these important components of the cell-division apparatus.

A detailed understanding of the regulation of cell division, cytokinesis and chromosome instability will advance our knowledge of the biology of cancer – the disease characterized by unregulated cell proliferation and chromosome missegregation. Our work will provide a mechanistic understanding of key cell cycle events that may contribute to cancer progression. Together, these studies also will provide a source of potential targets for future anti-cancer drugs.
The liver is a preferred organ for metastasis of many malignant cancers, including gastrointestinal cancers, melanoma, breast and lung carcinomas, neuroendocrine tumors, and sarcomas. Liver metastasis accounts for a principal cause of patient death despite significant advances in the treatment of cancer and this metastatic liver disease.

My research program is focused on bidirectional interactions between cancer cells and the liver microenvironment critical for the development of liver metastases.

Specifically, we are interested in the interactions between cancer cells and hepatic stellate cells (HSCs), which are resident liver pericytes. Tumor-derived factors, such as TGF-beta, induce transactivation of quiescent HSCs into cancer associated fibroblasts (CAFs). In turn, CAF-activated HSCs promote tumor implantation and growth in the liver; tumor angiogenesis, and tumor chemo and radio resistance as well as suppress the anti-tumor immune responses. Furthermore, the bidirectional interactions between cancer cells and CAF-activated HSCs may function as an “amplification loop” to further enhance metastatic tumor growth in the liver. Understanding mechanisms governing tumor-HSC interactions is important for developing new interventions to target liver-specific mechanisms for preventing and treating tumors that have a predilection for liver metastases.

During the past year, we identified two critical factors that mediate myofibroblastic activation of HSCs under TGF-beta stimulation, which may present therapeutic targets for inhibiting tumor-HSC interactions, reducing tumor implantation and metastatic growth in the liver. Our studies’ main findings are summarized below:

1. Vasodilator stimulated phosphoprotein (VASP) of HSCs is required for recycling of TGF-beta receptors to the plasma membrane. In cell culture, VASP knockdown inhibited TGF-beta mediated activation of HSCs into myofibroblasts. VASP knockdown increased total protein levels of TGF-beta receptor II (βRII); however, it inhibited plasma membrane protein levels of TGF-beta receptors. As revealed by real-time RT-PCR, VASP knockdown suppressed TGF-beta receptor I (βRI) gene transcription. At the protein level, PDGF receptor β (PDGFRβ) of HSCs was recruited to TGF-βRII membrane complexes by TGF-β stimulation. PDGFRβ knockdown blocked TGF-β mediated activation of quiescent HSCs and subsequently induced accumulation of TGF-βRII at the plasma membrane, thereby inhibiting TGF-β downstream signaling. Functionally, knockdown of PDGFRβ reduced paracrine effects of HSCs on colorectal cancer cells proliferation and migration in vitro as well as in mice and patients. Colorectal cancer cell invasion of the liver induced upregulation of PDGFRβ of HSCs. Taken together, our findings highlight a convergence of PDGF and TGF-β signaling for HSC activation and PDGFRβ of HSCs as a therapeutic target for liver metastasis and other settings of HSC activation.

“Liver metastasis remains a principal cause of patient death despite significant advances in the treatment of cancer and this metastatic liver disease.”

Dr. Ningling Kang

TUMOR MICROENVIRONMENT AND METASTASIS

Section Leader
Assistant Professor
Ningling Kang, Ph.D.

were stained blue.

(red) and cell nuclei were subjected to immunofluorescence localization of β-actin and SMAD2 banding.

2. Molecular Cancer

3. Molecular and Cellular Biochemistry

Poster presentations
AASLD, The Liver Meeting, Nov. 1-5, 2013, Washington, DC
Journal Reviews
1. Journal of Hepatology

Other professional activities
1. GI Seminar Series, Basic GI Research Unit, Mayo Clinic
Feb. 26-March 1, 2014, San Diego, CA
2. AASLD, The Liver Meeting, Nov. 1-5, 2013, Washington, DC
Journal Reviews
1. Journal of Hepatology
2. Molecular Cancer
3. Molecular and Cellular Biochemistry

Not pictured: Jiachu Li, Yali Xu

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A. Summary of research directions and findings

B. Other professional activities

Labs open to uptake: Tashi Dhesa, Dongmei Peng, Ningling Kang. For present interest: Lab led
For the immunoregulation of autoimmun e diseases, we are focusing on the EAE model to dissect how E-FABPs regulate leukocyte differentiation and function, and to development of E-FABP inhibitors for treatment of EAE. MS continues to be a serious public health problem without a curative treatment. Although the development of MS is attributed to a combination of genetic and environmental factors, the exact cause of MS is not completely understood. The strategies of MS therapy are to modify the disease course and manage symptoms. Identification of new targets for MS prevention and management, therefore, are urgently needed. This project aims to identify E-FABP as a new risk factor for MS and produce mechanistic insights into modification of E-FABP activity. 

Fatty acids (FAs) are key substrates for cell surface presentation of antigens to T cells and are major signal molecules for immune cell function. For example, they are highly expressed in tumor cells and can regulate immune cell responses. E-FABPs are highly expressed in human breast and melanoma cancer cells. Our recent studies have demonstrated that E-FABPs can promote breast cancer cell growth and migration. In vitro and in vivo studies have shown that E-FABP-deficient cells display reduced proliferation and migration. E-FABP-deficient breast cancer cells and tumors exhibit reduced invasion and metastasis in animal models. These results suggest that E-FABP is a critical regulator of breast cancer cell growth and invasion. E-FABP may represent a new link between obesity and breast cancer.

For the immunoregulation of cancer development, we are focusing on mouse models of breast cancer. Each year, breast cancer kills nearly a half-million women, of whom about 90% die from distant metastases. Uncovering new mechanisms of breast cancer development and identifying anti-metastatic agents, therefore, is critically important for prevention and/or treatment of breast cancer. In addition to understanding breast cancer biology, it is important to develop new therapeutic strategies for breast cancer treatment. In this project, we aim to identify E-FABP as a new target for breast cancer treatment. E-FABP-deficient cells display reduced proliferation and migration. E-FABP-deficient breast cancer cells and tumors exhibit reduced invasion and metastasis in animal models. These results suggest that E-FABP is a critical regulator of breast cancer cell growth and invasion. E-FABP may represent a new link between obesity and breast cancer.

“Given the rising rates of obesity in the United States and worldwide, there is an urgent need to identify biological mediator(s) that can link obesity, immunosurveillance, and breast cancer development.”

Dr. Bing Li
In the past year, we continue working on a U.S. Department of Defense (DOD) funded project that aims to identify fusion RNAs as possible biomarkers for breast cancer. Our results achieved so far lead to a conclusion that the vast majority of over a million of putative fusion RNAs documented in the literature may be technical artifacts. In a paper we published recently, we propose major technical reasons for the possible inclusion of the artifacts. Of those truly existing fusion RNAs, most are associated with a corresponding fusion gene in the genome. In breast cancer, however, basically all fusion RNAs are not recurrent, and this feature emphasizes the importance of personalized diagnosis and treatment. Of some fusion RNAs that occur at the RNA level without a genomic base, mitochondrial RNAs may participate in their formation. In other words, human mitochondrial RNAs do undergo cis- and trans-splicing and fuse with nuclear RNAs to enlarge the cellular RNA repertoire, which implies a previously unawares mechanism for RNA fusion that may occur at the cytoplasm, but not in the nucleus.

Many of the fusion RNAs may be translated to proteins that differ from their wild-type protein in molecular weights. To test this hypothetical thinking, sophisticated LC-MS/MS technique for the first time is used to stratify proteins by their molecular weight from narrow stripes of the SDS-PAGE gel. The results show that only about one-fourth (24.5%) to one-third (36.2%) of the LC-MS/MS identified proteins have a molecular weight as calculated from the wild-type protein sequence while 8.4% to 26.0%, varying among cell types, of the proteins may have a larger molecular weight, in part because they are a larger isoform. Most of the remaining proteins (varying between 67.1% to 37.8%) may be smaller isoforms or pre-processed fragments, 42.1-47.5% of which – at least in one cell type – may have at least two smaller isoforms besides the wild-type protein. These startling figures – although they may vary among cell types – strongly indicate that a large number of genes produce different protein isoforms, some of which may be products of fusion RNAs. This information should be of importance not only to the researchers on determining protein expression but also to the antibody producers for their determination of the antibody specificity because selection of those antibodies that detect only the protein with anticipated molecular weight may be a bias in some situations.

In the past year, we also have initiated a new research project to develop a new cancer therapeutic regimen. Whole body hyperthermia (i.e. systemic increase in the body temperature) has been used clinically for decades to treat cancer, but startling figures – although they may vary among cell types – strongly indicate that there is a vast majority of cancers with high levels of – and, thus, less can raise – HSPs for cytoprotection. Our preliminary studies on culture cancer cells show promising results that a feverish temperature (39 ºC) can enhance the killing effects of several chemotherapeutic agents on different cancer cell lines. Moreover, KRR111, an inhibitor of heat shock factor-1 that is a master activator of many HSPs, also enhances chemotherapy effects, especially at a feverish (39 ºC) temperature. These results lead us to the proposal of HHIC as a better cancer treatment regimen, as illustrated in the figure.

“In the past year, we also have initiated a new research project to develop a new cancer therapeutic regimen.”

Dr. D. Joshua Liao
Cancer is the representative systemic lesion taking over the first place of lethal disease burden in the 21st century. Among the various ‘foci’ with advanced technology, we are currently facing is cancer. The World Health Organization estimates that one out of four persons in the world’s population is affected by cancer. Emerging data indicate that obesity is a major risk factor for human malignancies. It can increase the occurrence of cancerous lesion and decrease the benefit of therapy. The molecular mechanisms behind these phenomena, however, are poorly defined.

We observed that higher body mass index (BMI) associates with shorter overall survival in leukemia patients.

Molecular mechanisms of anti-cancer actions of bioactive compounds

Because of their anti-cancer activity and lower toxicity to normal cells, numerous plant extracts containing DNA methyltransferase (DNMT) inhibitors have been tested in vitro and in vivo with huge therapeutic potentials. We have demonstrated that certain types of bioactive compounds (i.e., thymoquinone (TQ), echinomycin or HDX/AnnV) and successfully delivered small molecule compounds into leukemic cells, primary patient cells and leukemia mice, which was demonstrated by the inhibition of leukemic cell colony formation, reduction of DNA methylation and blockage of leukemic cell growth in vivo. These results revealed that nano-drug delivery displays increased drug toxicity, altered pharmacokinetics, improved drug solubility and more specificity and target binding.

Overall, our discoveries offer new insights into the molecular biology of cancer, advance our understanding of nanotechnology with efficient delivery vehicles for small molecules and micro particles, and foster the translation of nanotechnology solutions to biomedical applications, thereby improving the management of cancerous lesions.
The Morris laboratory studies the role of stem cells in cancer. We focus on normal adult stem cells responsible for maintenance, replacement, and regeneration of all the body’s tissues. In particular, we study adult stem cells from hair follicles, mammary glands, and bone marrow. In the absence of disease, these stem cells maintain the normal tissues. They are known to be able to reconstitute a graft, heal wounds, and even give rise to non-melanoma skin-derived epithelial cells to a subset of cutaneous papillomas.

Keratinocyte stem cells have an unquestioned role in maintaining the normal structure and function of the epidermis and hair follicles and are thought to be important players in inherited and acquired skin diseases. Hence, identification of genes regulating their number and proliferative potential is a critical problem in cutaneous biology. To address this problem, we proposed a novel strategy for identifying genes involved in keratinocyte stem cell regulation. This strategy takes advantage of several important advances made in our laboratory: (1) identification of selectable markers in hair follicle cells; (2) development of sensitive and quantitative in vivo assays for donor keratinocyte stem cells; (3) genetic mapping of several loci with linkage to skin cancer susceptibility; and (4) analysis of keratinocyte stem cell gene expression. The objective is to identify major genes regulating the number of keratinocyte stem cells. Our hypothesis is that there are specific genes and pathways that regulate stem cells that may be different from those regulating transit-amplifying cells.

In summary, research in the Morris laboratory continues to highlight the role of hair follicle stem cells in the pathogenesis of non-melanoma skin cancer, and has documented an unexpected contribution of bone-marrow-derived cells. Going forward, we will continue to investigate the regulation of skin stem cells in cancer as well as the interactions between epidermal epithelial cells and bone-marrow-derived cells in tumor-initiating and -propagating cells.
The Hormel Institute’s Research Support Group (RSG), supervised by Ellen Kroc, provides vital operational support within the Institute’s 13 research sections for their many ongoing research projects. Each of the Institute’s cancer research departments is dedicated to preventing or controlling cancer.

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.

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 FACSAria II cell sorter, FACSAccuri flow cytometer, AB Sciex 5600 Triple TOF mass spectrometer and Exakt 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.

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

In 2013-2014, more individuals, businesses and organizations stepped forward than ever before to support The Hormel Institute’s groundbreaking cancer research. The visionary support of The Hormel Foundation, led by Chairman Gary Ray, places The Hormel Institute on a path where the future is truly limitless for what can only be called TRANSFORMATIVE CHANGE.

Our friends and collaborators know and understand the unique story of The Hormel Institute. Together we know for a healthier tomorrow, research must be funded today.

Thank you, one and all, for sharing our vision of “Today’s Research, Tomorrow’s Cures.”
Dr. Harald Schmid, who joined the Institute in 1962 and served as executive director from 1987 to 2001, gave $1 million for an endowed professorship from him and his wife, Pat. Schmid retired in 2004.
It has been another exciting year for RSS. The Linux cluster CAL42 (Computational Analysis of Life-sciences 42) has been calculating away, simulating protein molecules.

Research Support Services continues to provide instrument maintenance as well as computer, graphics, telecommunication, network, and Internet support for The Hormel Institute. Maintenance includes a wide variety of scientific instruments, from complex to simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our work load. As always, the security needs of the network keep us busy.

Plans are progressing extremely well for our $27 million expansion project supported by The Hormel Foundation, Austin Port Authority and the State of Minnesota. We are getting real excited about moving some dirt and actually getting started building. There will be 20 new laboratories to set up and all the new instrumentation that goes with them. It is scheduled to be completed by fall of 2015, so we will have a lot of infrastructure to get ready. This has been another great year for us, and next year is looking to be even more exciting.

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 monitoring, 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.

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

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

On May 28, 2014, The Hormel Institute hosted more than 350 state, federal and local leaders as well as many supporters to celebrate the start of the continuing historic progress of The Hormel Institute. This next exciting chapter in the Institute’s seven-decade history of helping the health of the world through cutting-edge scientific research was launched with the groundbreaking of the current expansion that will again double the size of The Hormel Institute.

Gary Ray, Chair of The Hormel Foundation

“In just the last 10 years, The Hormel Foundation has invested $70 million into this Institute. We believe in what it’s doing to beat cancer. The work of the Institute has benefited all of us here today. The real excitement, though, is going to be about the future that it brings to generations of families. The Institute is truly living up to the promise of its slogan, ‘Today’s Research, Tomorrow’s Cures.’”

The expansion bill was introduced for the 2012 Minnesota bonding bill by local legislators Senator Dan Sparks and Representative Jeanne Poppe, and supported by nearly all state legislators. Minnesota Governor Mark Dayton, U.S. Senator Amy Klobuchar, U.S. Senator Al Franken and State Senator Dave Senjem spoke during the May groundbreaking ceremony, launching this great achievement. Following an expansion in 2008 that tripled the size of The Hormel Institute, the current expansion will double the size of The Hormel Institute, adding 20 state-of-the-art laboratories and better space for The Hormel Institute’s International Center of Research Technology. The Hormel Foundation and expansion leaders are providing the space to support the hire of another 120 faculty and staff and to provide a stronger path to commercialization opportunities in Austin and southern Minnesota.

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LIVE LEARNING CENTER

A 250-seat, globally interactive learning center/lecture hall also is planned as an additional project to the 2014-2016 expansion at The Hormel Institute. Projected to be completed in late 2015 / early 2016, the expansion is paid for by $13.5 million in bonding funds from the State of Minnesota (an Austin Port Authority project) and $2 million from The Hormel Foundation to support construction, technology and the hiring of faculty. Fundraising continues for the $4.5 million Live Learning Center.
Minnesota Governor Mark Dayton  
“This is truly the beginning—the result is dou-
bling the size of the Institute, almost doubling the 
employment here. There are going to be great jobs.”

Dr. Brian Herman, University of Minnesota's  
Vice President for Research  
“Every day, this Institute makes good on its charge 
and helps sow the seeds of innovation around the 
globe. Here at the Institute, the quality of research is 
superb. The scientists engage in thoughtful and far-
reaching study, stimulated by unique, cross-disci-
plinary partnerships, many with industry.”

State Senator David Senjem  
“I’m not sure we can imagine today what might 
come out of these facilities but we know it’s good 
and we know it’s going to make our people better, 
our human race better, our world better.”

U.S. Representative Tim Walz  
“The Institute is one of the shining stars in medical 
research. I’m certainly honored to have it in the 1st 
District, and proud to work as a partner with the 
Institute. Some of the best and brightest minds in 
the world working towards a cure for cancer are 
right in Austin.”

U.S. Senator Amy Klobuchar  
“This research means something. It means some-
thing to people that have cancer and can go on 
another month knowing that Dr. Dong and his 
team are fighting for them. And it means something 
for jobs in Minnesota in a big way.”

Dr. Zigang Dong,  
Executive Director of The Hormel Institute, 
University of Minnesota  
“We are truly and just beginning the growth of the 
success and also for more cancer research because we 
learn the best way for us think open is to do more 
research, do better research, to fund a cure or preven-
tion may of the deadly disease that is human cancer.”

U.S. Senator Al Franken  
“This is a world leader in cancer research. And The 
Hormel Institute is bringing us one closer to 
groundbreaking prevention and treatment therapies. 
Our investment in research is the key to our coun-
try’s success.”

State Senator Dan Sparks  
“I am proud to have been the Chief Senate Author 
for the $13.5 million in the expansion project. The project gained wide support as legislators learned of The Hormel Institute’s 
world-class reputation and groundbreaking cancer 
research. It is exciting to see the project underway.”

State Representative Joanne Poppa  
“The Hormel Foundation’s early vision and com-
mittment to research has given exponentially and 
created opportunities in all aspects of cancer 
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tute. Expanding its footprint enhances the possibili-
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tion may of the deadly disease that is human cancer.”
"BCL2 signaling."

"BMI1 polycomb group protein acts as a master regulator in cancer."