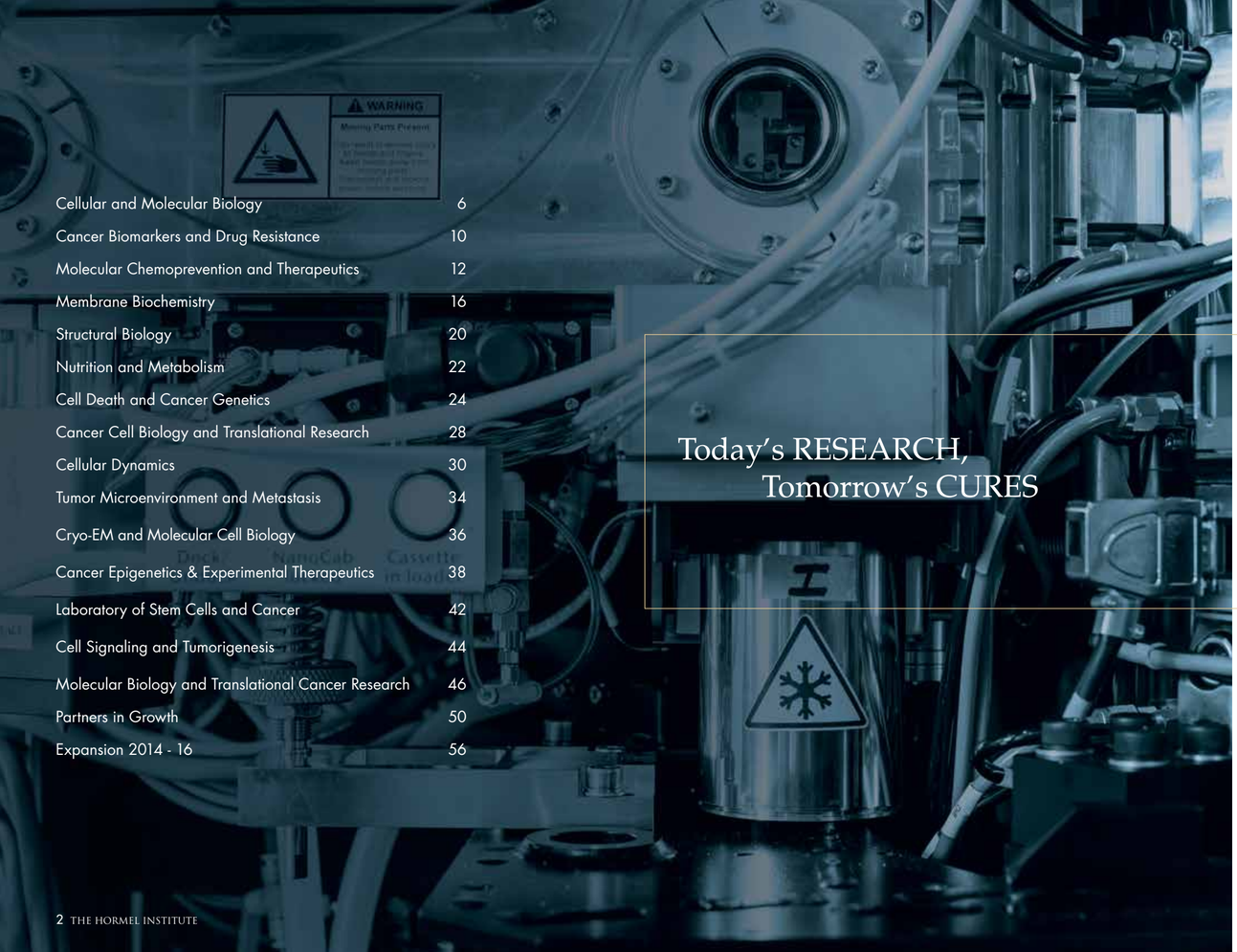
The Hormel Institute

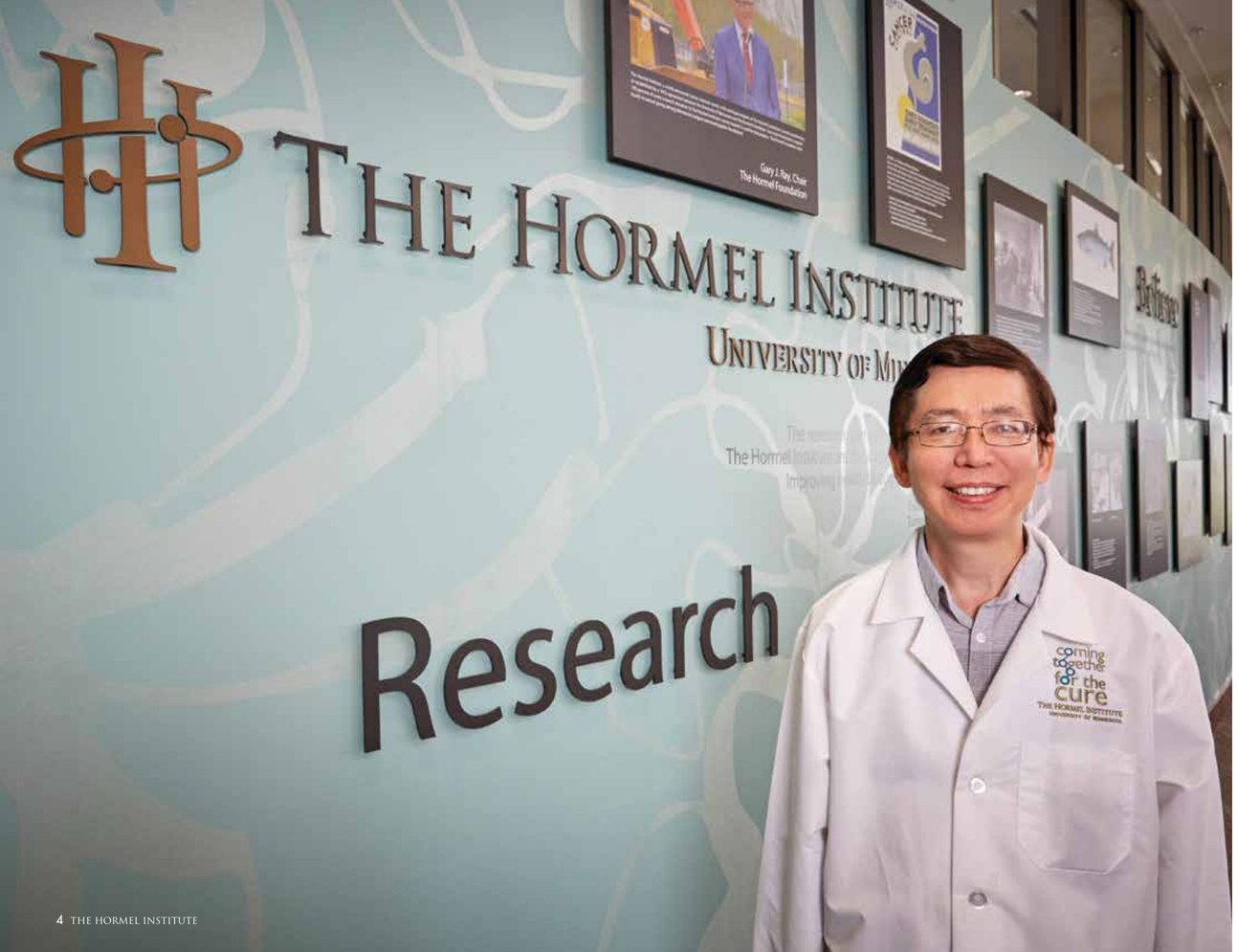
University of Minnesota

ANNUAL REPORT 2015-16



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.



Message from the Executive Director Dr. Zigang Dong

Dear Friends,

Throughout 2015-16, milestone progress continued at The Hormel Institute, University of Minnesota.

Our focus on making major contributions to cancer research and discoveries aimed at preventing cancer and extending lives again made major leaps forward this year. We had a historic record for grant funding and we became partners with one of the most respected scientific journals in the world - Nature.

Again our Institute grew, thanks to the support of The Hormel Foundation, and again we doubled the size of The Hormel Institute by adding another 20 state of the art labs and a global communications center named "Ray Live Learning Center" in recognition of the significant contribution of Gary and Pat Ray. This is great progress, especially in light of tripling in size just 8 years ago.

The expansion celebration brought leaders and supporters from throughout the state, country and world to tour the beautiful expanded facility and new state of the art technologies. The new labs house the world's most cutting edge imaging technology - the Cryo-Electron microscope - that captures and develops 2-D and 3-D images at the subatomic level. This technology is available at very few institutes in the country and will be used for cancer drug development.

The Hormel Institute's lab sections increased to 15 this year, making our center more comprehensive in our study of cancer development and prevention. In this report you will hear from our growing number of scientific research leaders, each outstanding in their investigations.

We are thankful for our growing partnerships and collaborations that bring like-minded dedicated scientists and leaders of organizations together to fight our common enemy, cancer.

Thank you for your faithful support as together we work for answers to cancer. We will enjoy a brighter, healthier tomorrow because of today's research and your dedicated friendship.

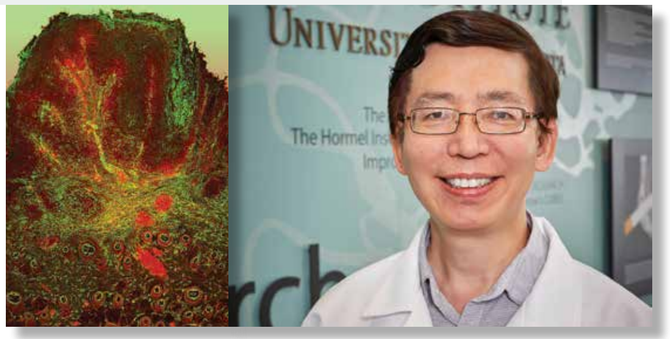
"Most human cancers are preventable, or treatable, if discovered at an early stage."

Dr. Zigang Dong
Executive Director

Cellular and Molecular Biology

ZIGANG DONG, M.D., DR. P.H.

Executive Director/Section Leader
McKnight Presidential Professor in Cancer Prevention
Hormel/Knowlton Professor



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

Cancer is one of the leading causes of human death worldwide. By focusing on molecular mechanisms, we continue to discover the key molecular events in cancer development as well as agents for cancer prevention and therapy.

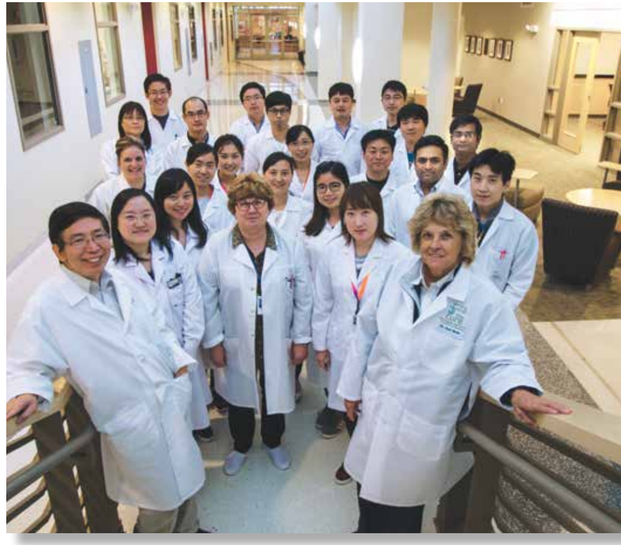
1. Discovery of key molecular events in cancer development.
We found that the prostaglandin thromboxane A2 (TXA2) level is correlated with colorectal cancer progression and this may be used as a marker for early diagnosis of colon cancer. The TXA2 pathway is constitutively activated during colorectal tumorigenesis and required for anchorage-independent growth of colon cancer cells. Our work lays the foundation for introducing a TXA2-targeting strategy for the prevention, early detection and therapy of colon cancer. We further discovered that human colorectal cancer progression is accompanied by an elevation in epidermal growth factor receptor (EGFR) levels. These high levels of EGFR can be attenuated by aspirin intake. The widespread overexpression of EGFR occurs as a consequence of COX-2 activation in familial adenomatous polyposis (FAP) patients. This study revealed a functional association between COX-2 and EGFR expression during colon carcinogenesis and provided new strategies for colon cancer prevention and therapy.

2. Discovery of novel targets and agents for skin cancer prevention and therapy.
Solar UV (SUV) irradiation is a major factor in skin carcinogenesis, the most common form of cancer in the United States. The mitogen-activated protein kinase (MAPK) cascades are activated by SUV irradiation. We found that p38 signaling is critical for skin carcinogenesis. The 90 kDa ribosomal S6 kinase (RSK) and mitogen and stress-activated protein kinase (MSK) proteins constitute a family of protein kinases that mediate signal transduction downstream of the MAPK cascades. Phosphorylation of RSK and MSK1 was upregulated in human squamous cell carcinoma (SCC) and SUV-treated mouse skin. Kaempferol – a natural flavonol found in tea, broccoli, grapes, apples, and other plant sources – is known to have anticancer activity, but its mechanisms and direct target(s) in cancer chemoprevention are unclear. Kinase array results revealed that kaempferol inhibited RSK2 and MSK1. Pull-down assay results, ATP competition, and in vitro kinase assay data revealed that kaempferol interacts with RSK2 and MSK1 at the ATP-binding pocket and inhibits their respective kinase activities. Mechanistic investigations showed that kaempferol suppresses RSK2 and MSK1 kinase activities to attenuate SUV-induced phosphorylation of cAMP-responsive element binding protein (CREB) and histone H3 in mouse skin cells. Kaempferol was a potent inhibitor of SUV-induced mouse skin carcinogenesis. Further analysis showed that skin from the kaempferol-treated mice exhibited a substantial reduction in SUV-induced phosphorylation of CREB, c-Fos, and histone H3. Overall, our results identify kaempferol as a safe and novel chemopreventive agent against SUV-induced skin carcinogenesis that acts by targeting RSK2 and MSK1.

Caffeic acid (3,4-dihydroxycinnamic acid) is a well-known phenolic phytochemical in coffee that reportedly has anti-cancer activities. The underlying molecular mechanisms and targeted proteins involved in the suppression of carcinogenesis by caffeic acid, however, are not fully understood. We reported that caffeic acid significantly inhibits colony formation of human skin cancer cells and EGF-induced neoplastic transformation of HaCaT cells dose-dependently. Caffeic acid topically applied to dorsal mouse skin significantly suppressed tumor incidence and volume in a solar UV-induced skin carcinogenesis mouse model. A substantial reduction of phosphorylation in mitogen-activated protein kinase signaling was observed in mice treated with caffeic acid either before or after solar UV exposure. Caffeic acid directly interacted with ERK1/2 and inhibited ERK1/2 activities in vitro. Importantly, we resolved the co-crystal structure of ERK2 complexed with caffeic acid. Caffeic acid interacted directly with ERK2 at amino acid residues Q105, D106 and M108. Moreover, A431 cells expressing knockdown of ERK2 lost sensitivity to caffeic acid in a skin cancer xenograft mouse model. Taken together, our results suggest that caffeic acid exerts chemopreventive activity against solar UV-induced skin carcinogenesis by targeting ERK1 and 2.

The Pim-1 kinase regulates cell survival, proliferation, and differentiation, and it is overexpressed frequently in many malignancies, including leukemia and skin cancer. We used kinase profiling analysis to demonstrate that 2′-hydroxycinnamicaldehyde (2′-HCA), a compound found in cinnamon, specifically inhibits Pim-1. Co-crystallography studies determined the hydrogen bonding pattern between 2′-HCA and Pim-1. Notably, 2′-HCA binding altered the apo kinase structure in a manner that shielded the ligand from solvent, thereby acting as a gatekeeper loop. Biologically, 2′-HCA inhibited the growth of human erythroleukemia or squamous epidermoid carcinoma cells by inducing apoptosis. The compound also was effective as a chemopreventive agent against EGF-mediated neoplastic transformation. Lastly, 2′-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. Overall, our results offered preclinical proof of concept for 2′-HCA as a potent anti-cancer principle arising from direct targeting of the Pim-1 kinase.

3. Discovery of novel agents for lung cancer prevention and therapy.
Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality



(Left to right) Front row: Zigang Dong, Ann M. Bode

Second row: Qiushi Wang, Ge Gao, Tatiana Zykova, Yaping Han, Eunmiri Roh

Third row: Tara Adams, Ting Wang, GuoGuo Jin, Ruihua Bai, Lichan Chen, Hiroyuki Yamamoto, Srinivasa Reddy, Seung Ho Shin

Fourth row: Wei-Ya Ma, Zhenjiang Zhao, Joohyun Ryu, Kibeom Bae, Souren Paul

Fith row: Christopher Dong, Keke Wang, Tianshun Zhang, Xiaoyu Chang

worldwide. Despite progress in developing chemotherapeutics for the treatment of NSCLC, primary and secondary resistance limits therapeutic success. NSCLC cells exhibit multiple mutations in the epidermal growth factor receptor (EGFR), which causes aberrant activation of diverse cell signaling pathways. Suppression of the inappropriate amplification of EGFR downstream signaling cascades, therefore, is considered to be a rational therapeutic and preventive strategy for the management of NSCLC. Our initial molecular target–oriented virtual screening revealed that the ginger components – including [6]-shogaol, [6]-paradol, and [6]-gingerol, and butein – a USP8 inhibitor, and 3,6,2′,4′,5′-pentahydroxy-flavone seem to be potential candidates for the prevention and treatment of NSCLC. Among the compounds, [6]-shogaol showed the greatest inhibitory effects against NSCLC cell proliferation and anchorage-independent growth. [6]-Shogaol induced cell cycle arrest (G1 or G2/M) and apoptosis. Furthermore, [6]-shogaol inhibited Akt kinase activity, a downstream mediator of EGFR signaling, by binding with an allosteric site of Akt. Other inhibitors, such as butein, a USP8 inhibitor and 3,6,2′,4′,5′-pentahydroxy-flavone, all showed potent inhibitory effects against lung cancer cells in vitro and in vivo. These inhibitors can overcome EGFR inhibitor resistance in lung cancer.

4. Discovery of novel targets and agents for inhibition of colon cancer.
Recent clinical trials raised concerns regarding the cardiovascular toxicity of selective cyclooxygenase-2 (COX-2) inhibitors, and cyclooxygenase-1 (COX-1) now is being reconsidered as a chemoprevention target. Our aims were to determine whether selective COX-1 inhibition could delay or prevent cancer development as well as clarify the underlying mechanisms. We showed that COX-1 was required for maintenance of malignant characteristics of colon cancer cells or tumor promoter-induced transformation of preneoplastic cells. We also successfully applied a ligand-docking computational method to identify a novel selective COX-1 inhibitor, 6-C-(E-phenylethenyl)-naringenin (designated herein as 6CEPN). 6CEPN could bind to COX-1 and specifically inhibited its activity both in vitro and ex vivo. In colorectal cancer cells, it potently suppressed anchorage-independent growth by inhibiting COX-1 activity. 6CEPN also effectively suppressed tumor growth in a 28-day colon cancer xenograft model without any obvious systemic toxicity. Taken together, COX-1 plays a critical role in human colorectal carcinogenesis, and this specific COX-1 inhibitor merits further investigation as a potential preventive agent against colorectal cancer.

Further, we found that naproxen, a COX1 and COX2 inhibitor, induces cell-cycle arrest and apoptosis by downregulation of Bcl-2 and upregulation of Bax.

Importantly, we found the direct cellular target of curcumin. Curcumin, the yellow pigment of turmeric found in Southeast Indian food, is one of the most popular phytochemicals for cancer prevention. Numerous reports have demonstrated modulation of multiple cellular signaling pathways by curcumin and its molecular targets in various cancer cell lines. To identify a new molecular target of curcumin, we used shape screening and reverse docking to screen the Protein Data Bank against curcumin. Cyclin-dependent kinase 2 (CDK2), a major cell-cycle protein, was identified as a potential molecular target of curcumin. Indeed, in vitro and ex vivo kinase assay data revealed a dramatic suppressive effect of curcumin on CDK2 kinase activity. Furthermore, curcumin induced G1 cell-cycle arrest, which is regulated by CDK2 in HCT116 cells. Although the expression levels of CDK2 and its regulatory subunit, cyclin E, were not changed, the phosphorylation of retinoblastoma (Rb), a well-known CDK2 substrate, was reduced by curcumin. Given that curcumin induced cell-cycle arrest, we investigated the anti-proliferative effect of curcumin on HCT116 colon cancer cells. In this experiment, curcumin suppressed HCT116 cell proliferation effectively. To determine whether CDK2 is a direct target of curcumin, CDK2 expression was knocked down in HCT116 cells. As expected, HCT116 sh-CDK2 cells exhibited G1 arrest and reduced proliferation. Due to the low levels of CDK2 in HCT116 sh-CDK2 cells, the effects of curcumin on G1 arrest and cell proliferation were not substantially relative to HCT116 sh-control cells. From these results, we identified CDK2 as a direct target of curcumin in colon cancer cells.

The c-Jun N-terminal kinases (JNKs) play an important role in many physiologic processes induced by numerous stress signals. Each JNK protein appears to have a distinct function in cancer, diabetes, and Parkinson's disease. Herein, we found that licochalcone A – a major phenolic constituent isolated from licorice root – suppressed JNK1 activity but had little effect on JNK2 in vitro activity. Although licochalcone A binds with JIP1 competitively with either JNK1 or JNK2, a computer simulation model showed that after licochalcone A binding, the ATP-binding cleft of JNK1 was distorted more substantially than that of JNK2. This could reduce the affinity of JNK1 more than JNK2 for ATP binding. Furthermore, licochalcone A inhibited JNK1-mediated, but not JNK2-mediated, c-Jun phosphorylation in both ex vivo and in vitro systems. We also observed that in colon and pancreatic cancer cell lines, JNK1 is highly expressed compared with normal cell lines. In cancer cell lines, treatment with licochalcone A or knocking down JNK1 expression suppressed colon and pancreatic cancer cell proliferation and colony formation. The inhibition resulted in G1 phase arrest and apoptosis. Moreover, an in vivo xenograft mouse study showed that licochalcone A treatment effectively suppressed the growth of HCT116 xenografts, without affecting the body weight of mice. These results show that licochalcone A is a selective JNK1 inhibitor. We, therefore, suggest that because of the critical role of JNK1 in colon cancer and pancreatic carcinogenesis, licochalcone A might have preventive or therapeutic potential against these devastating diseases.

5. Discovery of key regulators of chromosome missegregation
In collaboration with Dr. Edward H. Hinchcliffe, We have studied the role of histone H3.3 Ser31 phosphorylation in the cell cycle. Maloriented chromosomes can evade the spindle assembly checkpoint and generate aneuploidy, a common feature of tumorigenesis. But chromosome missegregation in non-transformed cells triggers a p53-dependent fail-safe mechanism that blocks proliferation of normal cells that inadvertently become aneuploid. How this fail-safe is triggered is not known. We identify a conserved feedback mechanism that monitors missegregating chromosomes during anaphase through the differential phosphorylation of histone H3.3 at Ser31. We do this by inducing transient chromosome missegregation in diploid cells. During anaphase, H3.3 Ser31 ins phosphorylated along the arms of lagging or misaligned chromosomes. Within minutes, Ser31 phosphorylation (Ser31P) spreads to all of the chromatids of both daughter cells, which persists into G1. Masking H3.3 Ser31P by antibody microinjection prevents nuclear p53 accumulation in the aneuploidy daughters. Our study provides insight into how aneuploidy caused by chromosome missegregation is normally monitored and suppressed.

"By focusing on molecular mechanisms, we continue to discover the key molecular events in cancer development as well as agents for cancer prevention and therapy."

Dr. Zigang Dong

ANN M. BODE, PH.D.
Associate Director/Section Leader
Professor

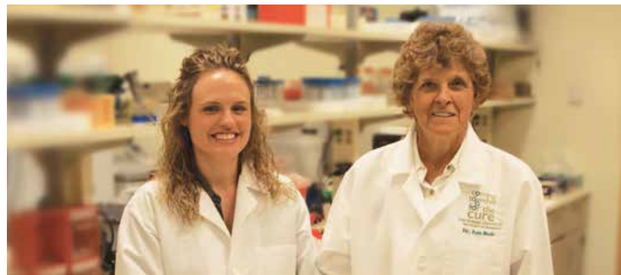
Immunohistological staining of Cox2 in squamous cell carcinoma

We continue to work with the National Institutes of Health to identify biomarkers important in drug resistance to cancer prevention and treatment. During 2015-2016, we published a number of papers in collaboration with NIH and University of Alabama.

9-cis-UAB30 (UAB30) and Targretin are well-known retinoid X receptor (RXR) agonists. They were highly effective in decreasing the incidence of methylnitrosourea (MNU)-induced mammary cancers. However, whether the anti-mammary cancer effects of UAB30 or Targretin originate from the activation of RXR is unclear. In the present study, we hypothesized that UAB30 and Targretin not only affect RXR, but likely influence one or more off-target proteins. Virtual screening results suggest that Src is a potential target for UAB30 and Targretin that regulates extracellular matrix (ECM) molecules and cell motility and invasiveness. In vitro kinase assay data revealed that UAB30 or Targretin interacted with Src and attenuated its kinase activity. We found that UAB30 or Targretin substantially inhibited invasiveness and migration of MCF-7 and SK-BR-3 human breast cancer cells. We examined the effects of UAB30 and Targretin on the expression of matrix metalloproteinases (MMP)-9, which are known to play an essential role in tumor invasion. We show that activity and expression of MMP-9 were decreased by UAB30 or Targretin. Western blot data showed that UAB30 or Targretin decreased AKT and its substrate molecule p70(s6k), which are downstream of Src in MCF-7 and SK-BR-3 cells. Moreover, knocking down the expression of Src effectively reduced the sensitivity of SK-BR-3 cells to the inhibitory effects of UAB30 and Targretin on invasiveness. Taken together, our results demonstrate that UAB30 and Targretin each inhibit invasion and migration by targeting Src in human breast cancer cells. (Thompson MD, Grubbs CJ, Bode AM, Reid JM, McGovern R, Bernard PS, Stijleman IJ, Green JE, Bennett C, Juliana MM, Moeinpour F, Steele VE, Lubet RA. Lack of effect of metformin on mammary carcinogenesis in nondiabetic rat and mouse models. Cancer Prev Res (Phila). 2015;8(3):231-9. doi: 10.1158/1940-6207.CAPR-14-0181-T. PubMed PMID: 25681088; PMCID: PMC4355096).

The COX inhibitors (NSAID/Coxibs) are a major focus for the chemoprevention of cancer. The COX-2-specific inhibitors have progressed to clinical trials and have shown preventive efficacy in colon and skin cancers. However, they have significant adverse cardiovascular effects. Certain NSAIDs (e.g., naproxen) have a good cardiac profile, but can cause gastric toxicity. The present study examined protocols to reduce this toxicity of naproxen. Female Fischer-344 rats were treated weekly with the urinary bladder-specific carcinogen hydroxybutyl(butyl)nitrosamine (OH-BBN) for 8 weeks. Rats were dosed daily with NPX (40 mg/kg body weight/day, gavage) or with the proton pump inhibitor omeprazole (4.0 mg/kg body weight/day) either singly or in combination beginning 2 weeks after the final OH-BBN. OH-BBN-treated rats, 96% developed urinary bladder cancers. While omeprazole alone was ineffective (97% cancers), naproxen alone or combined with omeprazole-prevented cancers, yielding 27 and 35% cancers, respectively. In a separate study, OH-BBN -: treated rats were administered naproxen: (A) daily, (B) 1 week daily naproxen/1week vehicle, (C) 3 weeks daily naproxen/3 week vehicle, or (D) daily vehicle beginning 2 weeks after last OH-BBN treatment. In the intermittent dosing study, protocol A, B, C, and D resulted in palpable cancers in 27%, 22%, 19%, and 96% of rats ($P < 0.01$). Short-term naproxen treatment increased apoptosis, but did not alter proliferation in the urinary bladder cancers. Two different protocols that should decrease the gastric toxicity of NSAIDs in humans did not alter chemopreventive efficacy. This should encourage the use of NSAIDs (e.g., naproxen) in clinical prevention trials (Lubet RA, Scheiman JM, Bode A, White J, Minasian L, Juliana MM, Boring DL, Steele VE, Grubbs CJ. Prevention of chemically induced urinary bladder cancers by naproxen: protocols to reduce gastric toxicity in humans do not alter preventive efficacy. Cancer Prev Res (Phila). 2015;8(4):296-302. doi: 10.1158/1940-6207.CAPR-14-0347. PubMed PMID: 25762530; PMCID: PMC4383706).

Epidemiologic studies have shown that diabetics receiving the biguanide metformin, as compared with sulfonylureas or insulin, have a lower incidence of breast cancer. Metformin increases levels of activated AMPK (AMP-activated protein kinase) and decreases circulating IGF-1; encouraging its potential use in both cancer prevention and therapeutic settings. In anticipation of clinical trials in nondiabetic women, the efficacy of metformin in nondiabetic rat and mouse mammary cancer models was evaluated. Metformin was administered by gavage or in the diet, at a human equivalent dose, in standard mammary cancer models: (i) methylnitrosourea (MNU)-induced estrogen receptor-positive (ER(+)) mammary cancers in rats, and (ii) MMTV-Neu/p53KO ER(-) (estrogen receptor-negative) mammary cancers in mice. In the MNU rat model, metformin dosing (150 or 50 mg/kg BW/d, by gavage) was ineffective in decreasing mammary cancer multiplicity, latency, or weight. Pharmacokinetic studies of metformin (150 mg/kg BW/d, by gavage) yielded plasma levels (Cmax and AUC) higher than humans taking 1.5 g/d. In rats bearing small palpable mammary cancers, short-term metformin (150 mg/kg BW/d) treatment increased levels of phospho-AMPK and phospho-p53 (Ser20), but failed to reduce Ki67 labeling or expression of proliferation-related genes. In the mouse model, dietary metformin (1,500 mg/kg diet) did not alter final cancer incidence, multiplicity, or weight. Metformin did not prevent mammary carcinogenesis in two mammary cancer models, raising questions about metformin efficacy in breast cancer in nondiabetic populations (Kim MS, Lim do Y, Kim JE, Chen H, Lubet RA, Dong Z, Bode AM. Src is a novel potential off-target of RXR agonists, 9-cis-UAB30 and Targretin, in human breast cancer cells. Mol Carcinog. 2015;54(12):1596-604. doi: 10.1002/mc.22232. PubMed PMID: 25328014; PMCID: PMC4402118).



(Left to right) Alyssa Langfald, Dr. Ann M. Bode

"We continue to work with the National Institutes of Health to identify biomarkers important in drug resistance to cancer prevention and treatment."
Dr. Ann M. Bode

Molecular Chemoprevention and Therapeutics

MOHAMMAD SALEEN (BHAT), PH.D.

Section Leader
Assistant Professor

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

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

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

Research Projects Underway

1. Investigation of mechanisms of chemoresistance in prostate cancer patients

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

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

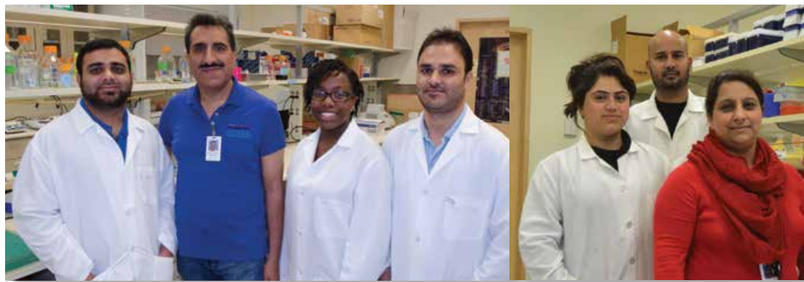
The critical pathological processes that occur during the development and progression of human prostate cancer and are known to confer aggressiveness to cancer cells are (1) abolishment of senescence of normal prostate epithelial cells, (2) self-renewability of prostate cancer cells even after chemotherapy and radiation, and (3) dysregulated cell cycle resulting in unchecked proliferation of cancer cells. Cellular senescence is physiologically important because it is a potent tumor suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumor cells is an essential defining property of a pluripotent stem cell–like phenotype of cancer cell which distinguishes it from other cell types. Stem cell–resembling population of cancer cells among the heterogeneous mix of cells constituting a tumor have been reported to be essential for tumor progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells which do not respond to chemotherapy or radiotherapy possess the traits of stem cells thus regenerating themselves even after chemo or radiotherapy treatment. Polycomb group (PcG) family of proteins (which form multimeric gene-repressing complexes) has been reported to be involved in self-renewability, cell cycle regulation, and senescence. BMI-1 is a transcription repressor and has emerged as an important member of PcG family. We are investigating the role for Bmi-1 protein in prostate cancer development. We hypothesize that BMI-1 protein could be developed as a diagnostic and prognostic of prostate cancer.

3. Reactivation of tumor supperrosor genes

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

4. Role of S100A4 in the development of prostate cancer

S100A4, also known as mts1, CAPL, p9Ka, and metastasin, belongs to the S100 super-family of calcium-binding proteins and is located in a 2.05 Mbp segment of the genomic DNA of chromosome 1q21 region where most of the S100 family of gene cluster occurs. S100A4 protein has been reported to be associated with invasion and metastasis of cancer cells and has been reported to be frequently over-expressed in metastatic tumors, normal cells with uninhibited movement, such as macrophages, transformed cells and in various cancer types such as breast, ovary, thyroid, lung, esophageal squamous cell carcinoma, gastric, colon, and prostate. Earlier, we reported that S100A4 is overexpressed during progression of prostate cancer in humans and in TRAMP mouse,



(Left to right) Arsheed Ganaie, M. Saleem Bhat, Kayla Turner, Rafiq Rather
Syed Umbreen, Fridous Beigh, Neelofar Bhat

an autochnhonous transgenic model that develops prostate cancer in a manner similar to human disease. Recently, we showed that S100A4 regulates the events leading to proliferation and invasion of prostate cancer cells. We showed that S100A4 guides the invasive phenomenon of prostate cancer cells by regulating transcription and function of matrix metalloproteinase (MMP-9) in prostate cancer cells. S100A4 is notably known for its role in metastasis. By creating a transgenic mouse model of prostate cancer lacking S100A4, we, for the first time, provide evidence that S100A4 protein, both in its intracellular and extracellular form plays a tumor promoting role in the development of prostate cancer by regulating the function of Nuclear Factor kappa B/Receptor for Advanced Glycation End products molecular circuitry.

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

Aberrant Androgen receptor (AR) expression and activation promoted by mutations, and binding partner mis-regulation is presented in several clinical manifestations

including androgen insensitivity syndrome, acne vulgaris, androgenetic alopecia, benign prostate hyperplasia (BPH), and different types of cancers in humans. AR has been found to be a principal driver of initiation and progression of prostate cancer. The initial stage of prostate cancer is dependent on androgen and can be managed by a series of therapies that are antagonist to AR or suppress AR signaling. However, the success of these therapies is temporary and after a short remission period, tumors reappear as androgen-independent or commonly known as castration-resistant prostate cancer (CRPC). It is noteworthy that FDA-approved agents (androgen receptor signaling inhibitors) such as Bicalutamide which are widely used in clinics to treat cancer show dismal results in men with advanced prostatic malignancy. Recently, it has been observed that overexpression of AR is the most common event associated with CRPC. AR (which generally responds to androgen) remains active and functional in CRPC disease. We are studying the mechanism through which AR becomes functional in prostate cancer patients exhibiting CRPC disease. Emergence of CRPC phenotype depends on different mechanism such as activation of receptor tyrosine kinase, uncontrolled cell growth, genomic mutation of AR that allows response to nonspecific AR-ligands. We are testing whether isoforms or splice variants of androgen receptor play a role in the CRPC disease. It has been reported that AR splice variants activate genes involved in the metabolism of androgens and provide a survival advantage for cells in a low-androgen environment. Our laboratory has identified the mechanism through which AR-variants induce their pro-growth activity in tumor cells. Notably, we have identified an agent that inhibits the activity of AR-variants in CRPC cells. The validation of this mechanism-based agent in animal models is expected to provide an excellent alternative or adjuvant modality for the treatment of advanced prostate cancer, particularly of CRPC phenotype.

6. Investigating the causes of racial disparity in prostate cancer

According to American Cancer Society, the higher overall cancer death rate among African American men is due largely to higher mortality rates from prostate, lung, and colorectal cancers. Although the overall racial disparity in cancer death rates has decreased, the death rate for all cancers combined continues to be 32% higher in African American men than in Caucasian men. African American men with prostate cancer have worse disease, with a higher incidence, are younger in age with more advanced disease at diagnosis, and a worse prognosis, compared to Caucasian men. In addition to socioeconomic factors and lifestyle differences, molecular alterations have been reported to contribute to this discrepancy. Recent developments in genetics, proteomics, and genomics, among other molecular biotechnologies are anticipated to greatly aid the advancement of translational research on prostate cancer racial disparity and hopefully will culminate in the discovery of novel mechanisms of disease, in addition to prognostic markers and novel therapeutic approaches. The research project running in our section is aimed to investigate the molecular mechanisms that cause the failure of therapy of cancer in African American men. Though widely used in clinics, the PSA has been reported to be insufficient as a reliable biomarker for prognosis of prostate cancer in African American men. The larger aim is to identify novel biomarkers which could be used for prostate cancer prognosis in Caucasians as well as in African American men. We recently showed that BMI1, a stem cell protein, could be developed as a sensitive and reliable blood-biomarker for prostate cancer disease in Caucasian as well as African American men.

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

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

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

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

Our Research Partner Institutions

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

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

Sponsors/ Funding Agencies Supporting our Research Activities:

1. National Cancer Institute, NIH, USA
2. National Institute of Minority and Health Disparity Research, NIH, USA
3. Austin Community-sponsored "Paint the Town Pink" Funding

Other Professional Activities

(A) Scientific expert in review panels of grant funding agencies (national & international):

1. Molecular Biology panel on Prostate cancer awards (CDMRP) Department of Defense
2. Pathology Biomarkers panel on Prostate cancer awards (CDMRP) Department of Defense
3. Rolex Research Awards, Rolex Corporation, Geneva, Switzerland
4. Arthritis-Research UK, United Kingdom
5. Prevention panel on breast cancer awards (CDMRP) Department of Defense
6. Special Emphasis Panel (ZCA1 SRLB-J (O1)S) National Cancer Institute, NIH

(B) Adhoc-reviewer of Scientific Journals

(1) J Biol Chem, (2) Oncogene, (3) Neoplasia, (4) Cancer Research, (5) Clinical Cancer Research, (6) Oncotarget, (7) PLOSE-one, (8) Biochemical Pharmacology, (9) Biochemica Biophysica Acta (BBA), (10), Melanoma Pigment research (11) Cancer Letters, (12) Toxicology Applied Pharmacology; (13) Life Sciences (14) Photochemistry and Photo biology; (15) Chemosphere (16) Clinica Chemica Acta (17) Molecular Cellular Biochemistry (18) Phytotherapy Research (19) Journal of Pharmacy and Pharmacology (20) Food Chemical Toxicology (21) Molecular Carcinogenesis, (22) International Journal of Cancer (23) Molecular Cancer Therapeutics (24) Carcinogenesis (25) British J of Breast Cancer

(C) Editorial Board Member of Scientific Journals

PLOSE ONE;
American Journal of Stem Cell,
Nutrition and Medicine;
American Journal of Clinical Experimental Urology

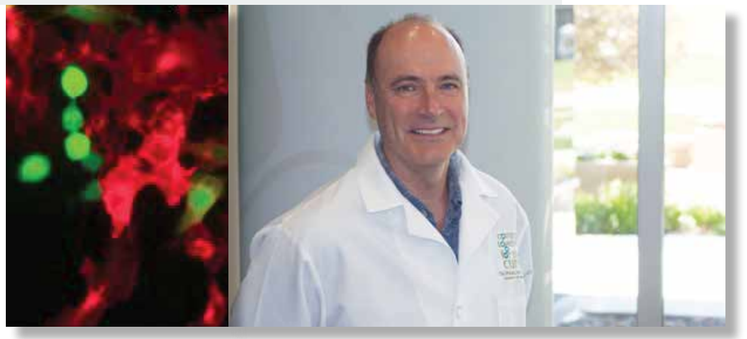
"A major goal of our laboratory is to identify novel and non-toxic agents that could be developed as chemopreventive and chemotherapeutics agents for either inhibiting cancer development or treating cancer in humans."

Dr. Mohammad Saleem (Bhat)

Membrane Biochemistry

RHODERICK E. BROWN, PH.D.

Section Leader
Professor



Cholera toxin B endosytosis was affected by the over-expression of GLTP.

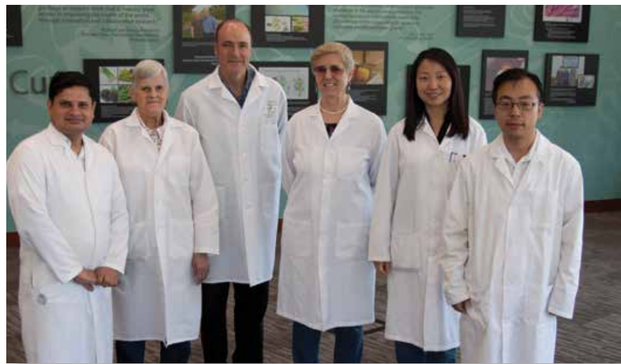
Essential for the existence of cells are barriers to envelope their contents. The barriers must be selectively permeable for nutrient entry and toxic by-product export. To meet this need, cells produce specialized lipids that are polar at one end and nonpolar at the opposite end. The polar ends are well-suited for contact with water but the nonpolar ends are not. As a result, they readily form thin, flexible layers only two molecules thick, i.e. bilayer, which forms the basic structural platform for cell membranes. In addition to corralling the cell contents, membranes serve as internal partitions that enable formation of functionally-specialized compartments within cells. Interestingly, there are many more varieties of lipids found in membranes than are needed to form bilayers. What is clear is that certain membrane lipids can function as messenger signals that regulate cell growth, proliferation, inflammation, and programmed cell death processes, while other membrane lipids appear to cluster together in bilayers to form microdomains that regulate the spatial distribution and lateral interactions of membrane proteins. The discovery of these membrane lipid functions under scores why biomembranes so often come under direct attack during cancer and infectious disease.

Our research focuses on membrane lipids known as sphingolipids. Certain sphingo¬lipids along with cholesterol can form 'raft' microdomains in membranes. Rafts appear to function as organizing regions for certain signaling kinases as well as target sites for certain viruses and bacteria. In earlier investigations, we focused on rigorously defining the physical basis for raft micro¬domain functionality. To gain insights into lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we have used a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR). We developed ways to quantitatively measure the lateral elasticity within model membranes, to accurately assess the physical changes that occur within the 'raft environment' when the content and structure of sphingolipids and sterols become altered, as well as assess changes in sphingolipid lateral and transbilayer distribu¬tions. Our research has elucidated structural features of sphingolipids that regulate their interactions with other membrane lipids and provided insights into the unique physical features at the heart of the lateral organizing functionality of sphingolipid-enriched microdomains. The findings have proved to be important for understanding how the spatial organization of lipids in membranes can regulate proteins that translocate onto membranes to function.

Formation and maintenance of sphingolipid-enriched microdomains in cells likely involves specific proteins that can bind and transfer sphingolipids between membrane surfaces. Hence, much recent effort in our lab has been directed toward a protein family known as glycolipid transfer proteins (GLTPs) that can specifically bind and transfer glycosphingolipids between membranes. We found that GLTP functionality is regulated by lipid composition and packing within membranes. We applied this basic knowledge to begin elucidating exactly how GLTPs accomplish glycolipid intermembrane transfer. To do so, we cloned human GLTP and showed the existence of closely related homologs in mammals, plants, and fungi. Polymerase chain reaction (PCR) approaches enabled amplification of mRNA transcript open reading frames encoding human GLTP and related homologs followed by expression in bacterial expression systems, and purification of sufficient quantities to crystallize the proteins. Our efforts led to the molecular structural determination of GLTP and related homologs both in glycolipid-free form and complexed with different glycolipids, in collaboration with the D.J. Patel lab at Memorial Sloan Kettering Cancer Center in New York and the L. Malinina lab at CIC bioGUNE in Derio/Bilbao, Spain. Our studies shed light on: i) how GLTP adapts to accommodate different glycolipids within its binding site; ii) the functional role played by intrinsic tryptophan residues in glycolipid binding and membrane interaction; iii) the structural basis for the more focused glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2 . More importantly, our work revealed that human GLTP forms a novel structural fold among known proteins. As a result, the Protein Data Bank has designated human GLTP as the founding member and prototype of the new GLTP superfamily, enabling our findings to be published in Nature, PLoS Biology, Structure, The Journal of Biological Chemistry, Biophysical Journal, Biochemistry, Journal of Lipid Research, and Quarterly Reviews of Biophysics.

In very recent investigations also published in Nature, we reported the discovery of a new GLTP structural homolog in human cells. Remarkably, the lipid specificity of the new protein has evolved for binding/transfer of ceramide-1-phosphate rather than glycolipids even though the new protein still forms a GLTP-fold encoded by a completely different gene than GLTP. For this reason, the protein is named ceramide-1-phosphate transfer protein (CPTP). In collaboration with Ted Hinchcliffe here at the UMN-Hormel Institute, we have tracked the location of CPTP in mammalian cells using state-of-the-art fluorescence microscopy approaches. With collaborating investigators in the Charles Chalfant lab at Virginia Common¬wealth University, we have shown that depletion of CPTP levels in human cells by RNA interference leads to over-accumulation of newly synthesized ceramide-1-phosphate in the trans-Golgi. The over-accumulation triggers cytoplasmic phospholipase A2 action, generating arachidonic acid that then is further metabolized into pro inflammatory eicosanoids.

In studies of the model plant, Arabidopsis thaliana, carried out in collaboration with the John Mundy at the University of Copenhagen, we showed that a gene originally identified by its ability to induce accelerated cell death, known as acd11, actually encodes a plant GLTP ortholog. X-ray structural determinations revealed that ACD11 is a GLTP-fold that has evolved to bind and transfer ceramide-1-phosphate. Disruption of the acd11 gene results in impaired development and dwarfed plants in which the ceramide-1-phosphate and ceramide levels are severely altered. This research study was published in Cell Reports.



(Left to right) Shrawan Mishra, Helen Pike, Rhoderick Brown, Lucy Malinina, Xiuhong Zhai, Yong-Guang Gao

We anticipate that elucidation of the fundamental structure-function relationships governing GTLP and CPTP action will facilitate development of the means to pharmacologically modulate GLTP and enhance their potential use as biotechnological resources, i.e. nanotools, for targeted manipulation of cellular sphingolipid composition. Such strategies could provide new ways to introduce specific sphingolipid antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new

therapeutic approaches to treat disease processes involving sphingolipids. Our exciting progress to date emphasizes the need for continuing studies into the workings of GLTP, CPTP, and other proteins containing GLTP-like motifs using comprehensive strategies involving biophysical, cell, and molecular biological approaches. Our recent investigations of the gene organization and transcriptional status in humans and other mammals now provide a firm foundation for identification and characterization of inherited diseases involving GLTP and CPTP. Our ongoing efforts benefit from collaborations with researchers at Memorial Sloan Kettering Cancer Center in New York, The University of Copenhagen in Denmark, Virginia Commonwealth University in Richmond, The Russian Academy of Sciences in Moscow, CIC bioGUNE in Derio/Bilbao, Spain and the Mayo Clinic. Our research continues because of financial support received from the National Institute of General Medical Sciences, the National Cancer Institute of NIH and The Hormel Foundation.
For more details regarding research expertise and scientific publications of our lab, please visit the following web sites:

Experts-UMN (REB):
http://experts.umn.edu/en/persons/rhoderick-e-brown%28b67653a3-667a-4e50-a17c-202e43bc0884%29.html

Experts-UMN (REB publications):
http://experts.umn.edu/en/persons/rhoderick-e-brown%28b67653a3-667a-4e50-a17c-202e43bc0884%29/publications.html

"The discovery of these membrane lipid functions underscores why biomembranes so often come under direct attack during cancer and infectious disease."

Dr. Rhoderick E. Brown

Photo submitted by, Harlan Johnsrud

Structural Biology

YOUNG-IN CHI, PH.D.

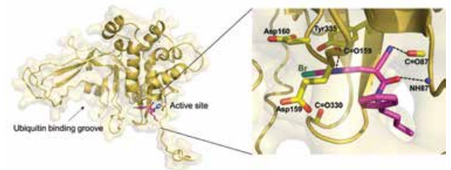
Section Leader
Assistant Professor

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

Structural biology is a branch of biomedical science concerned with molecular structures of biological macromolecules such as proteins and nucleic acids. Since their biological functions are tightly coupled to the molecular structures, elucidating atomic details of their structures is crucial to understanding the molecular mechanisms underlying their physiological functions. These biomolecules are too small to be seen even with the most advanced electron microscope. So special techniques have to be employed and we particularly harness X-ray crystallography as a main experimental tool to elucidate three-dimensional structures. This technique involves various disciplines of modern biomedical research such as molecular biology, nucleic acid/protein chemistry, biophysics, and various computations. We also perform eukaryotic cell-based functional studies to complement the structural studies. Our long term goal is to facilitate structure-based drug designs against the target biomolecules and their complexes as means of providing new avenues for developing therapeutics.

Currently, our research is focused on elucidating the atomic details and understanding the molecular mechanisms of the key biomolecules and their interactions involved in human diseases, especially various cancers and diabetes. In particular, we are focusing on (i) the key proteins involved in tumor progression and metastasis and (ii) the transcriptional regulators involved in diabetes development. We apply structural biology to gain a better understanding of their normal function and dysfunction in the disease state and an opportunity to discover or design structure-based functional modulators.

For cancer-related projects, we have embarked several new projects. First, Dub3 is an ubiquitin hydrolase (de-ubiquitinase) and a key protein that relays extrinsic signals to regulate epithelial-mesenchymal transition (EMT) and metastasis in breast cancer,



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

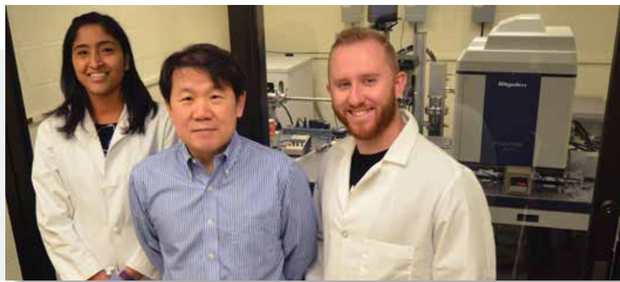
Secondly, hexokinase II (HK2) which catalyzes the first committed step in glucose metabolism is exclusively expressed in human prostate cancer cells, particularly elevated in human lethal castration-resistant prostate cancer (CRPC) harboring PTEN/p53 deletions. Thus, HK2 has emerged as an attractive target for currently incurable CRPC. We, together with Dr, Yibin Deng, have assembled a multidisciplinary research team targeting this protein from different angles. One way to inhibit oncogenic activity of HK2 is to suppress its gene expression. Recently, it has been reported that HK2 expression is regulated by untranslated RNAs such as the G-quadruplex structure in the 3′ untranslated region (3′UTR). We seek to elucidate the molecular mechanism of HK2 gene regulation by RNA local structures at the untranslated region, in particular its association with the human translation initiation factors such as eIF4a. Successful outcomes from these studies including the crystal structure of the complex will help identify novel anti-prostate cancer therapeutic compounds.

"We seek to understand how the molecules carry out their bioactivities and how their normal functions are disrupted in the disease state. We mainly harness X-ray crystallography to elucidate the atomic details of their molecular architectures and physiological molecular interactions."

Dr. Young-In Chi

Thirdly, the leukemic fusion protein AML1-ETO occurs frequently in human acute myeloid leukemia (AML) and has received much attention over the past decade. Currently we seek to understand the critical roles of the EZH1/AML1-ETO and HIF1a/AML1-ETO axes in acute myeloid leukemia cell formation and growth. This multifaceted project is in internal collaboration with Dr. Shujun Liu and we participate in crystal structure determination of the complexes and virtual screening of the library compounds for potential functional modulator discovery.

As part of diabetes-related projects, we have been studying monogenic causes of diabetes. HNF1(Hepatocyte Nuclear Factor1) and HNF4 are are the master regulators of pancreatic-cell development and function, and their mutations are the most common monogenic causes of diabetes referred to as MODY. Over the years, we have determined the crystal structures of the functional complexes made by HNF1 and HNF4. These structures provided valuable information on the molecular basis of target gene recognition, ligand-mediated activation, and functional disruption by disease-causing mutations. However, these structures provided only partial answers as to how their full transcriptional activities arise, and how these proteins are involved in additional protein-protein interactions and physiological functions. Therefore, we set out to identify previously unknown functional binding partners of HNF1 and HNF4 in -cells, and study the physiological implications of these interactions, especially on insulin secretion that is impaired in MODY patients, and perform structural studies of the complexes and functional characterization of MODY mutations. We previously published the findings on the mediator component of the main transcriptional machinery, MED25, as functional binding partner of HNF4 and its implication to-cell function. Currently, we are in the process of following-up additional binding partners and their physiological implications, such as novel transcriptional



(Left to right) Puja Singh, Young-In Chi, Thomas Olmsted

co-repressors AES and EBP1 for HNF1 and HNF4, respectively. The findings from these studies will advance the current understanding of the transcription regulatory network in-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.

One other diabetes-related project we have been working on is the structural basis of Glucose-6-phosphatase (G6pase) gene regulation, especially by the transcription factors FoxO1 and Creb. G6pase is a key regulating enzyme for gluconeogenesis in the liver and considered to be an attractive target for diabetes treatment. Last year, we finally finished the FoxO1/DNA complex structure and we have submitted the manuscript for publication, in which we have identified a new Foxo1 binding site and novel biding modes on G6pase promoter.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41374771/?sort=date&direction=descending

MARGOT P. CLEARY, PH.D.
Section Leader
Professor

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

Research in the Nutrition and Metabolism section focuses on the effects of body weight and food intake on the development of breast cancer using mouse models. Findings from our lab have include identifying that leptin a protein made in adipose tissue is an important growth factor for mammary tumor development. This was accomplished by conducting experiments that showed that genetically obese mice which do not produce leptin or do not have the receptor for leptin do not develop mammary tumors. In contrast mice with dietary-induced obesity that have elevated serum leptin levels develop mammary tumors at an earlier age than mice fed the same high fat diet that stay in the normal body weight range. Cell culture studies further provided evidence to the importance of leptin as a growth factor.

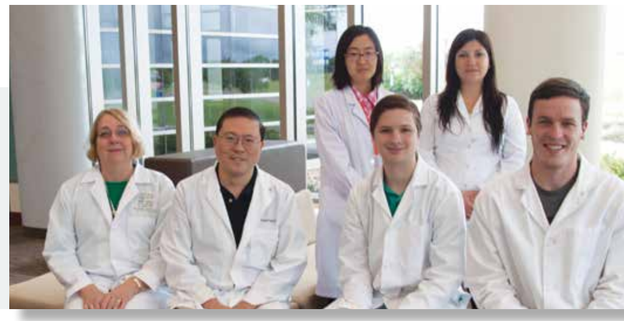
Other studies have assessed the impact of calorie restriction on the prevention of mammary tumors in several mice models of breast cancer. Of particular interst, we consistently find that periods of moderately severe calorie restriction followed by ad libitum refeeding, which we term intermittent calorie restriction, results in much greater reduction in mammary tumor incidence than does the same degree of restriction implemented chronically. These two interventions result in the same overall calorie reduction of 20-25%. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the IGF-axis. Based on results of our studies, we hypothesize 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 decreased mammary tumor incidence in comparison to ad libitum feeding as well as to 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. Intermittent calorie restriction may provide an easier approach for individuals to reduce caloric intake either for disease prevention. In fact several recent weight loss programs utilize this approach.

Although calorie restriction has an incredible effect on cancer prevention in many rodent models, 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. Our 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 was started when the mice were middle-aged to also reflect what would occur in at risk women. We have now completed this long term study – following the mice until they were 90 weeks of age. We did not find that metformin had a cancer preventing effects in either lean or obese mice. In contrast 25% calorie restriction resulted in a significant decrease in mammary tumor incidence and delayed age when tumors were detected. 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. We anticipate that these ongoing studies will provide valuable insights into ways to prevent mammary tumor development and to slow disease progression.

"We focus on the effects of body weight and food intake on the development of breast cancer and findings from our lab have included identifying that leptin a protein made in adipose tissue is an important growth factor for mammary tumor development."

Dr. Margot P. Cleary

Other studies in the lab under the direction of Dr. DaQing Yang include the investigation of two important proteins, ATM and p53, which are critical for multiple physiological processes, including cell cycle progression, DNA damage repair, insulin signal transduction, and glucose metabolism. Signal transduction of the ATM protein kinase in response to insulin and metformin is known to be linked to both cancer and diabetes. The investigation of the abnormal glucose metabolism in cancer cells using LC-MS-based targeted metabolomics has led to the discovery of potential biomarkers for early detection of pre-invasive breast cancer. The study of the translational regulation of p53 induction following DNA damage provides better understanding regarding how defective synthesis of the p53 tumor suppressor is involved in the development of cancer, which may lead to novel diagnosis and treatment strategies for various types of cancer, including breast, prostate, and pediatric cancer.



(Left to right) Margot Cleary, Daqing Yang, Bai Ji, Brett Cornforth, Marina Ferrari, Ben Harris

Other Professional Activities
Margot P. Cleary

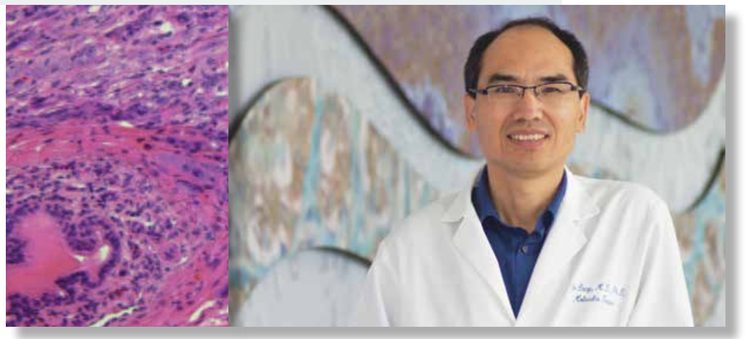
Presentations:
Noon Seminar Series, Hormel Institute, Austin, MN. July 2015.
University of Louisville, Louisville, KY. October 2015.
San Antonio Breast Cancer Symposium, San Antonio TX December 2016

Grant Review Committees:
NIH Study Section January 2016. ORAU-Florida 2015. PEER NEW 2015, AICR

Member of working group for the International Agency for Research on Cancer (IARC), Lyon, France April 2016 to reassess the preventive effects of weight control on cancer risk

Cell Death and Cancer Genetics

YIBIN DENG, M.D., PH.D.
Section Leader
Associate Professor



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

The tumor suppressor TP53 gene encodes p53 protein that maintains genomic integrity and prevents tumorigenesis in response to a variety of genotoxic stresses. The importance of p53 in tumor suppression is highlighted by mutations identified in more than half of human cancers that lead to the loss of wild-type p53-mediated tumor suppressive function and/or the gain-of-oncogenic-function (GOF) in vivo. The comprehensive genomic/whole exons sequencing analyses sponsored by The Cancer Genome Atlas (TCGA) consortium confirmed the high frequency of TP53 mutations in all the sequenced human cancers. TCGA studies, for example, revealed 96 percent of ovarian cancers, 37 percent of breast cancers, 54 percent of colorectal cancers, and 81 percent of lung squamous cell carcinomas display TP53 mutations. Mouse genetic studies provide compelling evidence that TP53 mutations play a causal role in tumorigenesis. However, the mechanisms that underlie wild-type p53-mediated tumor suppression and mutant p53-driven tumorigenesis remain incompletely understood.

Our laboratory, therefore, focuses on understanding how the wild-type p53 suppresses tumorigenesis and why the oncogenic "GOF" of mutant p53 found in cancer patients promotes tumor development. To translate our bench work to bedside, we have been utilizing genomic, proteomic, and metabolomics approaches, bioinformatics, computational modeling, structural biology, RNAi- and CRISPR/Cas9 or Cpf1-based screening, and genetically engineered mouse models (GEMMs) that recapitulate the salient characteristics of human cancers to discover the crucial "druggable" targets for cancer cells. Our ultimate goal is to find the Achilles' heel of cancer cells to selectively and efficiently kill them while leaving the normal cells unharmed. In the past year, our laboratory has made progress in the following three major areas:

1. Understanding wild-type p53-mediated signaling pathways in tumor suppression in vivo

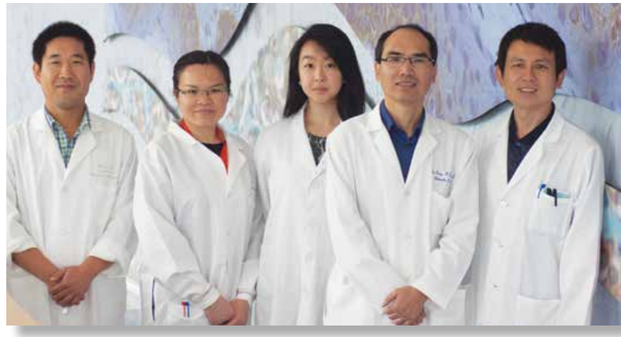
While many studies have focused on the role of apoptosis and/or senescence in p53-mediated tumor suppression, recent findings suggest that p53 induces DRAM (Damage-Regulated Autophagy Modulator)-dependent autophagy. To study the role of DRMA-dependent autophagy in tumorigenesis, we generated conditional Dram knockout mice. Our findings suggest that Dram potentially functions as a tumor suppressor because deletion of Dram promotes spontaneous tumor development in mouse models. Currently, we are trying to dissect the molecular basis underlying Dram-deficiency-driven tumorigenesis in vivo. We are also exploring whether and how the crosstalk between p53-initiated autophagy and p53-mediated cell metabolism leads to tumor initiation, progression and metastasis.

To answer the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing tumor development in vivo, we have generated "triple" mutant mice utilizing the conditional Dram knockout mice to breed with mice deficient in p53-mediated apoptosis (p53R172P knock-in or Puma knockout) and senescence-deficient mice (p21 knockout). We expect that by utilizing these complex genetic engineered mouse models, we will be able to address the critical question how the p53-regulated signaling axis contributes to its tumor suppressive function in vivo.

2. Gain-of-function of mutant p53 in telomere uncapping-driven breast tumorigenesis

Human sporadic breast carcinomas are characterized by the presence of complex cytogenetic aberrations. One of the foremost challenges for breast cancer researchers is to develop experimental model systems that identify pathogenetic events driving breast tumor development. Our long-term goal in this project is to establish "chromosomal instability" mouse breast cancer models and discover the "causal" genomic events driving breast tumorigenesis in vivo. One important mechanism that can give rise to the unstable breast cancer genome is the dysfunction of telomeres.

Telomeres are nucleoprotein caps that protect chromosomal ends from being recognized as aberrant damaged DNA and prevent chromosome end-to-end fusions. Telomeres that no longer can exert end-protective functions are said to be dysfunctional, and these telomeres could arise either from progressive telomere attrition (telomere shortening) or when components of the telomeric DNA-binding proteins – termed "shelterin complex" – are perturbed (telomere uncapping). In human breast carcinomas, chromosomal instability fueled by dysfunctional telomeres is associated with the transition from benign ductal hyperplasia to malignant ductal carcinoma in situ. This strongly supports the notion that telomere dysfunction-induced chromosome instability initiates the development of breast cancers. Our laboratory has been engineering a novel mouse breast cancer model harboring telomere uncapping-induced chromosomal instability without affecting the activity of telomerase. Importantly, the mouse model also carries "hot spot" mutant p53 found in breast epithelium of cancer patients. We believe that this mouse model will faithfully recapitulate the genetic abnormality commonly observed in human sporadic breast carcinomas. We have been establishing and utilizing this novel mouse breast cancer model to identify the key genetic pathways perturbed in chromosomal instability-driven mammary tumorigenesis and target these pathways with novel therapeutics that potentially could suppress human breast cancer.



(Left to right) Changwei Qui, Yan Cai, Annie Sun, Yibin Deng, Lei Wang

3. Exploring the molecular targets involved in selective killing of prostate cancer cells

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

We recently have made progresses in our study on prostate cancers. Prostate cancer strikes one in six men and is the second leading cause of cancer-related deaths in men after lung cancer in the United States. Prostate cancer arises mainly from prostatic intraepithelial neoplasia (PIN), a precursor lesion that ultimately progresses to adenocarcinoma and systemic metastasis. Conventional androgen deprivation therapy

(ADT) by surgical and/or chemical castration remains the gold standard-of-care therapy for metastatic prostate cancer. Unfortunately, these prostate cancers invariably develop resistance to conventional ADT and progress to a more aggressive castration-resistant prostate cancer (CRPC) within 18-24 months. The discovery that persistent androgen receptor (AR) signaling plays a crucial role in the progression of CRPC leads to "second generation" ADT treatments, such as the recently Food and Drug Administration-approved androgen synthesis blocker abiraterone (2011, FDA) and the second generation of AR signaling inhibitor enzalutamide (formerly MDV3100) (2012, FDA), which have demonstrated efficacy against chemotherapy-resistant CRPC with median increase in survival of 4-5 months. However, nearly all CRPC patients inevitably develop acquired resistance to the "second generation" anti-AR signaling axis treatments within ~6-12 months. Currently, no therapeutic options exist for CRPC patients who have developed resistance to the second generation of anti-androgen receptor (AR) signaling axis therapy. We found that co-deletion of Pten and p53 in prostate epithelium, often observed in human lethal CRPC, leads to AR-independent CRPC and thus confers de novo resistance to "second generation" androgen deprivation therapy (ADT) in multiple independent yet complementary preclinical mouse models. In striking contrast, mechanism-driven co-targeting hexokinase 2 (HK2)-mediated Warburg effect with 2-deoxyglucose (2-DG) and ULK1-dependent autophagy with chloroquine (CQ) selectively kills cancer cells through intrinsic apoptosis to cause tumor regression in xenograft and lead to a near-complete tumor suppression in Pten-/p53-deficiency-driven CRPC mouse model. Given that 2-DG is recommended for phase II clinical trials for prostate cancer and CQ has been clinically used as an anti-malaria drug for many decades, the preclinical results from our "proof-of principle" studies in vivo are imminently translatable to clinical trials to evaluate the therapeutic efficacy by the combination modality for a subset of currently incurable CRPC patients. Through collaborations with clinicians, we are translating our experimental studies in CRPC mouse models into clinical trials and hopefully our studies will benefit CRPC patients harboring PTEN and TP53 mutations.

Our laboratory also is utilizing multiple genetic and pharmacological approaches to identify targets that can be selectively targeted in human lung and colon cancers.

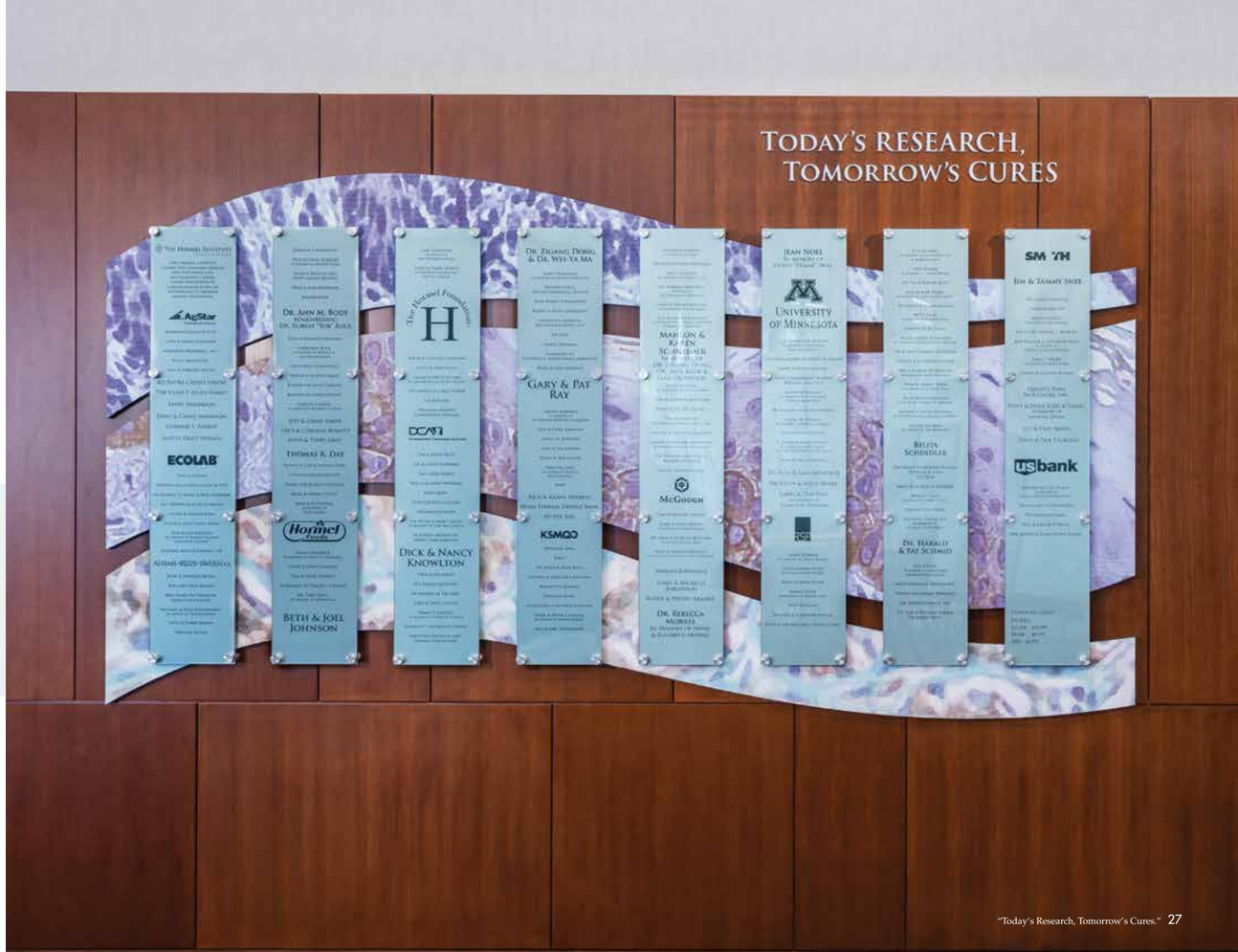
Our ongoing projects are collaborating with researchers from Penn State College of Medicine in Hershey, PA; The University of Texas M.D. Anderson Cancer Center in Houston, TX; The University of Minnesota Masonic Cancer Center in Minneapolis, MN, and Mayo Clinic College of Medicine in Rochester, MN. Our research projects are supported by the grants from National Cancer Institute of NIH and The Hormel Foundation.

Other Professional Activities

Grant Reviewer, National Cancer Institute

Our ultimate goal is to find the Achilles' heel of cancer cells to selectively and efficiently kill them while leaving the normal cells unharmed."

Dr. Yibin Deng



Cancer Cell Biology and Translational Research

SERGIO GRADILONE

Section Leader
Assistant Professor

Sensing the environment. This confocal immunofluorescence shows a cross-section of a bile duct, where the nuclei of cholangiocytes lining the duct are stained in blue, and a primary cilium extending into the ductal lumen in red

The "Cancer Cell Biology and Translational Research" section focuses on understanding the basic biological processes involved with a normal cell transforming into a cancerous one. By understanding these mechanisms, potential therapeutic interventions may be envisioned. Right now we are investigating the role of the primary cilium in tumor biology. Primary cilia are multisensory organelles – similar to a cell antenna – that sense and receive signals from the environment surrounding the cells. We've found that these antennae are lost in tumor cells; therefore, we are trying to understand the mechanisms of ciliary loss, and what are the consequences of such a loss. Furthermore, as we gain knowledge on these mechanisms, we are now able to induce the restoration of primary cilia in tumor cells and bring back the malignant cells to a more normal phenotype, which may contribute to the development of new therapeutic strategies based on the rescue of primary cilia integrity.

Our research is focused on "cholangiocarcinoma", an aggressive and lethal form of liver cancer that derives from the epithelial cells of the bile ducts. But the loss of primary cilia also has been described in other solid tumors, including pancreatic, prostate, breast and kidney cancers, broadening the spectrum of potential applications of this research.

We established several collaborations, both intra- and extramural, with prestigious investigators and institutions including: Dr. Saleem Bath (The Hormel Institute), Drs. Nicholas LaRusso, and Steven Alberts (Mayo Clinic Rochester, MN), Drs. Kabir Mody (Mayo Clinic, Jacksonville, FL), Dr. Jesus Banales (Biodonostia Research Institute -Donostia University Hospital, San Sebastian, Spain), Dr. Raul Marinelli (National University of Rosario, Argentina), and Acetylon Pharmaceuticals Inc (Boston, MA) among others.

Our laboratory first federal grant started in July 2015. This research grant from the National Cancer Institute (National Institutes of Health) brings over 1.2 million dollars to support our research at The Hormel Institute for five years. This R01 CA183764 entitled "The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle" supports our main line of research focused on bile duct cancer.

Furthermore, we stablished several collaborations including: Dr. Kabir Mody, from Mayo Clinic in Florida to explore the role of HDAC6 in pancreatic cancer; Dr. Jesus Banales, from the Biodonostia Research Institute -Donostia University Hospital, San Sebastian, Spain, to pursue our common interest in cholangiocarcinoma; Dr. Raul Marinelli, from the National University of Rosario, Argentina, to explore the role of aquaporin water channels in the biogenesis of cilia and their role in cholangiocarcinoma; and Dr. Nicholas LaRusso, from Mayo Clinic Rochester to investigate the role of autophagy in the regulation of ciliaexpression.

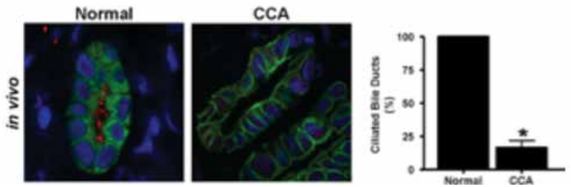
Dr. Sergio Gradilone has been honored as an external advisor for the European Network for the Study of Cholangiocarcinoma (ENS-CCA) and was awarded a travel grant to represent the Hormel Institute and the University of Minnesota in the first International Monothematic Congress in Cholangiocarcinoma celebrated last May in San Sebastian, Spain.

"The results of our research is uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilia architecture and function."

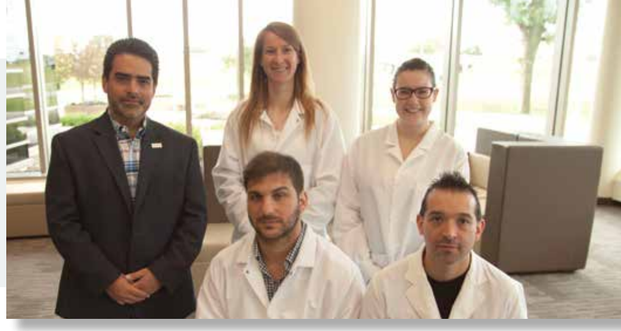
Dr. Sergio Gradlione

The results of our research is uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilia architecture and function. By partnering with collaborators directly engaged in the treatment of patients and with pharmaceutical industries, our ultimate goal is to translate our basic research to the bedside by developing new clinical trials for these diseases. Importantly, in collaboration with Acetylon Pharmaceuticals Inc and Mayo Clinic oncologists, our basic research is moving from the bench to the bedside through a Phase 1b Clinical trial is starting patient's recruitment soon.

Our section also initiated and organized a new biweekly seminar series "Thursdays HI Research Seminar Series" that fosters the internal discussion of experimental results and collaboration between the different sections of our Institute.



Primary cilia are loss in tumor cells. This confocal immunofluorescence shows the albescence of primary cilia in human cholangiocarcinoma samples (CCA) compared to normal liver samples.



(Left to right) Sergio Gradilone, Kristen Thelen, Cesar Gaspari, Stephanie Holtorf, Adrian Mansini

Dr. Sergio Gradilone organizes a biweekly Research Seminar Series at The Hormel Institute which features internal and external speakers who share their work on current research projects. The seminar series aims to serve as a great way to learn what other researchers are doing; get input from others on unpublished scientific data; and, most importantly, foster collaborations, which Dr. Gradilone says is "the key to surviving in today's research environment and doing more meaningful research."

Cellular Dynamics

EDWARD H. HINCHCLIFFE, PH.D.

Section Leader
Associate Professor

In vitro assembly of a frog nucleus and centrosome.

We study the regulation of cell division, the process by which cells proliferate. We have several ongoing research projects in the lab, including understanding the molecular mechanisms underlying the generation of mitotic spindle bipolarity, and the gain/loss of whole chromosomes during mitotic division, a process which is associated with tumor progression.

Our research section is funded by grants from the National Institutes of Health, and the Department of Defense CDMRP (Congressionally Directed Medical Research Programs).

Cell division lies at the heart of normal tissue development and maintenance. The division of cells must occur in a strict one-to-two fashion, in order to ensure genomic stability. The loss or gain of whole chromosomes during abnormal cell division leads to aneuploidy, where daughter cells have variable chromosome number. 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 failsafe 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 inoperable. The result is the inadvertent missegregation 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 chromatid disjunction, and centrosome separation errors. However, despite an increasingly mechanistic understanding of how CIN is generated, we know relatively little about how chromosome missegregation becomes transduced into cell transformation and tumorigenesis. A major unresolved question is the role of cell cycle checkpoints and failsafe devices in preventing chromosome missegregation in the first place. The question of how a single missegregated chromosome can trigger the p53/p21 pathway and induce durable cell cycle arrest – a molecular failsafe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is part of the answer. However, to date, no mechanisms have been identified that monitor chromosome mispositioning – either before or after anaphase – at the single chromosome level.

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

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

"A detailed understanding of the regulation of cell division, cytokinesis and chromosome instability will advance our knowledge of the biology of cancer – itself a disease characterized by unregulated cell proliferation and chromosome missegregation."

Dr. Edward H. Hinchcliffe

Experimental research results

1. Chromosome missegregation: Contributing to the onset of tumorigenesis

Our long-term goal is to understand the cell cycle regulation of bipolar mitotic spindle assembly and function. Proper bipolar mitotic spindle assembly ensures that each daughter cell receives an exact set of chromosomes. Chromosome instability (CIN) – the loss or gain of individual chromosomes during mitosis – generates aneuploidy, and correlates with the aggressive behavior of advanced tumor cells. Recent studies have linked chromosome segregation errors to merotelic kinetochore attachments caused by transient defects in spindle geometry, often mediated by supernumerary centrosomes. Yet despite our increasingly mechanistic understanding of the causes of CIN, the important question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood.

To this end we have recently identified a novel biochemical pathway that monitors chromosome missegregation. We find that misaligned chromosomes (i.e. those well away from the metaphase plate) activate a dynamic positional "sensor", involving phosphorylation of the highly conserved histone variant H3.3. H3.3 differs from the canonical H3.1 by 5 AA substitutions; one of which, Ser 31 is phosphorylated only during mitosis (Ser31-P). Whereas all congressed chromosomes have Ser31-P confined to their peri-centromeric regions, we find that misaligned chromosomes

(Left to right) Sela Fadness, Alyssa Langfald, Charles Day, Edward Hinchcliffe

accumulate Ser31-P along their arms. H3.3 Ser31 hyper-phosphorylation persists after anaphase, and is found on both lagging chromosomes in the bridge, and disjoined pairs of chromatids syntelicly-attached to one pole. Thus, Ser31-P serves as a dynamic mark for CIN in both mitotic and post-mitotic cells. We are characterizing the Ser31 phosphorylation pathway used to recognize misaligned chromosomes. We are determining the mechanism used to generate the Ser31-P proximity sensor on misaligned chromosomes, and identify both the kinase and the phosphatase responsible for generating this dynamic mark. We are using live-cell imaging assays to determine the fate of cells that exit mitosis with missegregated chromosomes, while simultaneously using biochemical/genetic methods to inactivate Ser31 phosphorylation in these cells. We are testing whether H3.3 Ser31P affects cell fate or proliferation in CIN cells. Recent work has shown that single nucleotide somatic mutations in the tail of the H3.3 gene (K27M and G34R) are associated with human cancers. Both mutations flank Ser31. We

will test the role of these flanking AA substitutions in modulating H3.3 Ser31-P, and in the ability of H3.3 to bind potential regulatory elements. Our work is innovative, because is capitalizes on a novel pathway to identify chromosome missegregation in individual cells. It is also important, because for the first time, it allows for the biochemical manipulation of basic cellular responses to chromosome missegregation and aneuploidy.

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

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

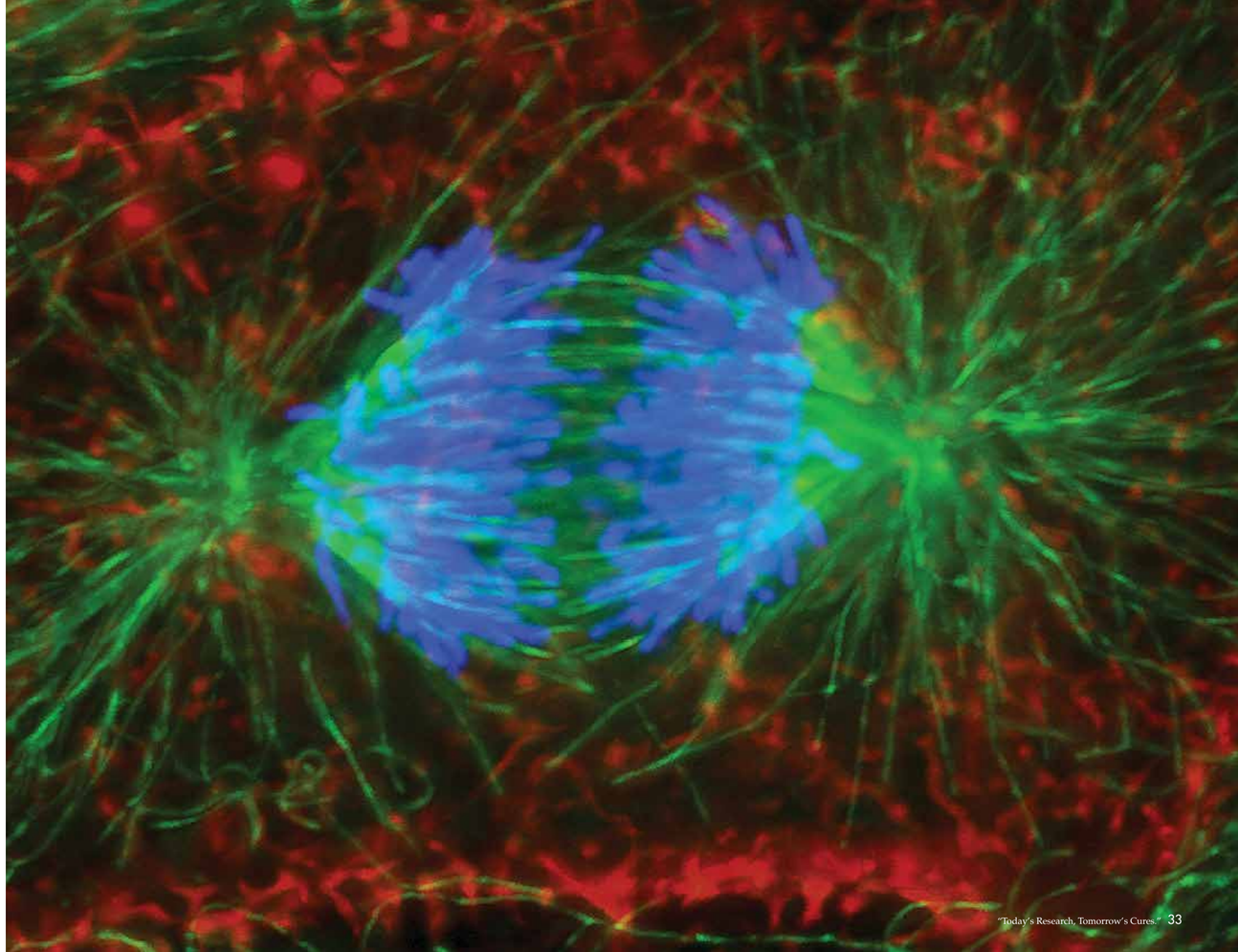
3. Coordinating cytokinetic furrow formation with anaphase onset
The cell division furrow – created by the recruitment of actin filaments and the motor protein myosin II – is formed between the separating sister chromatids at anaphase. This furrow constricts the dividing cell into two daughters. In order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

We have found that there is a period following the onset of anaphase where the cell cortex can respond to furrow-inducing signals, and this period is sensitive to the loss of microtubules, and the activity of Polo-like kinase 1. However, once cells progress beyond this point, the furrow will form, regardless of whether or not 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.

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

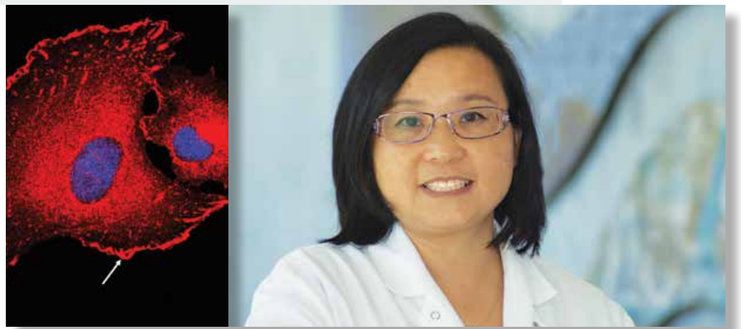
Funding
Department of Defense (CDMRP), CA130436
National Institutes of Health, R01HL125353

Other activities:
Mentor, American Society for Cell Biology Minorities Affairs Committee FRED program
Ad hoc review for: MRC UK, Wellcome Trust UK, Biotechnology and Biological Sciences Research Council UK.



NINGLING KANG, PH.D.

Section Leader
Assistant Professor



Heptic stellate cells were subjected to immunofluorescence staining for VASP (red) and cell nuclei were stained blue.

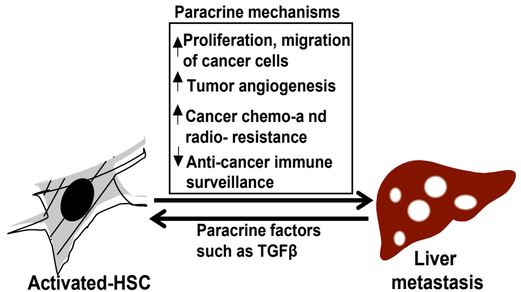
The major focus of our program is to understand how liver resident pericytes, hepatic stellate cells (HSCs), interact with gastrointestinal (GI) cancer cells disseminated in the liver to promote their metastatic growth. Under cancer invasion of the liver, cancer cells and other components of the hepatic tumor microenvironment produce growth factors and inflammatory cytokines, which act together to induce activation of quiescent HSCs into myofibroblasts (MFs). HSCs activated by cancer cells express alpha-smooth muscle actin (αSMA) and fibronectin, and they in turn promote cancer cell implantation and proliferation by paracrine mechanisms, including release of growth factors, cytokines, extracellular matrix proteins, and matrix metalloproteinases. Thus, the bidirectional interactions between cancer cells and HSCs in the liver represent a therapeutic target for suppressing liver metastasis of GI cancer. This research program has been continuously funded for more than 10 years by grants of various funding agencies, including American Association for the study of liver diseases (AASLD, Sheila Sherlock Clinical and Translational Research in Liver Diseases Award, 2006-2008), Mayo Clinic (Research Early Career Development Award, 2009-2011), and NIH (NCI K01 2007-2012 and R01 2011-2016). With these grant support, we have studied the role of IQ motif containing GTPase activating protein 1 (IQGAP1), vasodilator-stimulated phosphoprotein (VASP) and PDGF receptor-alpha (PDGF-α) in the intracellular trafficking of TGF-αreceptors of HSCs (Liu C et al. J Clin Invest. 2013; Tu K. et al. Hepatology, 2015; Liu C et al. Am J Physiol Gastrointest Liver Physiol.). Consequently, we have developed expertise in the field of the hepatic tumor microenvironment. Since the phenotypes of activated-HSCs are defined by both cytoplasmic signaling and nuclear gene transcription programs, we now shift our focus on epigenetic mechanisms of HSC activation. Our data, demonstrating that p300 acetyltransferase is required for TGF-αinduced MF activation of HSCs, were presented at the Liver Meeting AASLD in Nov. 2015. Additionally, our program will be continuously funded for next 5 year by a NIH R01 grant.

In addition to aforementioned NIH funded program, we are also working on a new direction aiming at the prometastatic signaling cascades of GI cancer cells. Our most recent data, demonstrating that VASP is required for α-intergrin activation in GI cancer cells and liver metastasis, were presented at the AACR Annual Meeting in April 2016.

Presentation at National or International Meeting (July 2015 –June 2016)

1. Luyang Guo, Vijay H. Shah and Ningling Kang. P300 acetyltransferase promotes TGF-αstimulated nuclear translocation of SMADs and activation of hepatic stellate cells into liver metastasis promoting myofibroblasts. The Liver Meeting, AASLD. Nov. 13-17, 2015, San Francisco, CA.

2. Xiaoyu Xiao, Jinhua Piao, Selvaraj Muthusamy, Lei Wang, Yibin Deng, Shengbing Huang, Raul Urrutia, Jinping Lai, and Ningling Kang. Vasodilator-stimulated phosphoprotein promotes liver metastasis of GI cancer via activating α-integrin-FAK-YAP1/TAZ signaling axis. AACR Annual Meeting. April 16-20, 2016, New Orleans, LA



Bidirectional tumor/HSC ineractions promoting liver mestastic

Figure 1. Dynamin and BAR proteins regulate pathways involved in carcinogenesis and metastasis. A closer look at cellular mechanisms involved in carcinogenesis and metastasis, namely, receptor signaling, cell migration, cell growth, cell cycle progression, DNA repair, autophagy, and apoptosis, reveal significant involvement of membrane remodeling members of the dynamin and BAR protein families. Although the exact molecular mechanisms control- ling their functions in these diverse fundamental processes are not fully elucidated, this indicates that dynamins and BAR proteins may serve important safeguarding roles in the cell's fight against cancer via their membrane remodeling properties.

(Left to right) John Luebbe, Ningling Kang, Hongbin Zahn

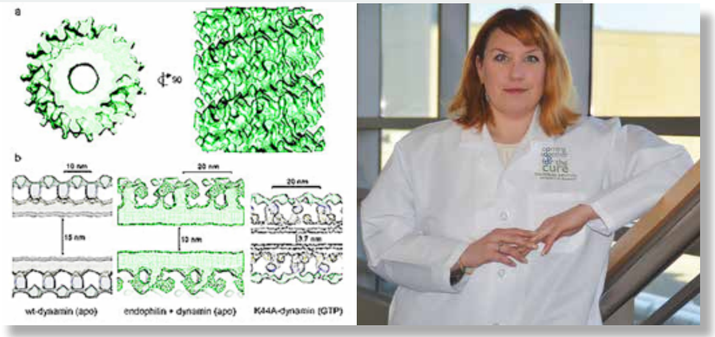
"Liver metastasis remains a principal cause of patient death despite significant advances in the treatment of cancer and this metastatic lever disease." (this is from last year's AR, but I can't find anything from this year's AR to pull out, at least anything that's not too technical)

Dr. Ningling Kang

Cryo-EM and Molecular Cell Biology

ANNA SUNDOBORGER, PH.D

Section Leader
Assistant Professor



Membrane remodeling as a mechanism of tumor suppression

I joined the Hormel Institute and established the laboratory of Cryo-Electron Microscopy and Molecular Cell Biology in March of 2016. In my lab, we're interested in how membrane bending BAR domain proteins and members of the dynamin family of large GTPases, responsible for membrane fission and fusion, assemble into large complexes and regulate fundamental membrane remodeling events, such as apoptosis, autophagy and mitochondrial dynamics. Our primary focus is to determine how dysregulation of these pathways contributes to infectious diseases and cancer. Equipped with a Titan Krios electron microscope (FEI) fitted with phase plates and a direct electron detector, we are able to solve the 3D structure of key proteins and protein complexes at atomic resolution, in the ultimate effort to identify key players that contribute to regulation of cell death and to identify novel drug targets.

There is a strong link between intracellular pathways that regulate cell death and cancer. Remodeling of cellular membranes is a key feature during these processes and there is emerging evidence that membrane-remodeling members of the dynamin super family and BAR domain-containing proteins (BAR proteins) serve important tumor suppressor functions in the cell, though their exact mechanisms are unknown. Dynamins mediate membrane fission and fusion events in the cell, while endophilins are BAR proteins that sense and induce high membrane curvature. During clathrin-mediated endocytosis, endophilin A1 is critical for recruitment of dynamin 1 to sites of plasma membrane fission. Our previous work shows that dynamin and endophilin co-localize on necks of clathrin-coated pits (CCPs) in vivo, where endophilin A1 acts as a membrane template for dynamin 1, promoting optimal CCP neck curvature for dynamin scaffold assembly. Short dynamin 1 scaffolds undergo GTP-dependent conformational changes that constrict the underlying membrane, evoke fission and disassemble with release of the vesicle. Dynamin 1 also assembles into a complex with endophilin A1 on tubulated liposomes in vitro. Endophilin B1 localizes to sites of dynamin family member Drp1-mediated mitochondrial fission and Dynamin 2-dependent trafficking of Atg9 vesicles from Golgi during autophagy. Endophilin B1 also interacts with dynamin family member IRGM, which may facilitate xenophagy, and thus prevent propagation of intracellular pathogens.

These observations suggest that a close relationship between dynamins and endophilins is important for their functions in intracellular membrane trafficking events that regulate cells death. It further indicates that the mechanism controlling their functions is complex formation.

Our hypothesis is that a potential tumor suppression mechanism of dynamins and endophilins is complex formation in effort to spatially and temporally coordinate membrane curvature with membrane fission and/or fusion. We speculate that this complex formation is a common mechanism utilized in the cell in various membrane trafficking pathways. Outstanding questions we are addressing are:

- What are the molecular mechanisms underlying the functions of dynamins and endophilins during apoptosis and autophagy/xenophagy?
- Do endophilins and dynamins form distinct complexes that mediate their membrane remodeling functions in the cell?
- How are endophilin-dynamin complexes assembled?
- Are specific lipids involved, potentially to trigger complex formation?
- How does complex formation regulate the GTPase activity of dynamin family members and the membrane curvature activity of endophilins, respectively?

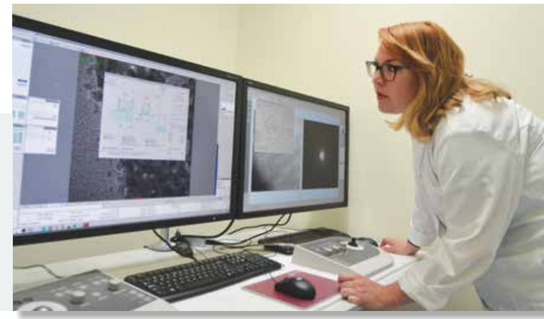
I have previously dissected the function of dynamin 1 and elucidated the step-by-step mechanisms of plasma membrane fission using a combination of cryo-EM, X-ray crystallography and biochemical assays. Therefore, the Cryo-EM and Molecular Cell Biology will answer our outstanding question using a similar approach.

Figure 2. Preliminary 3D reconstruction of the dynamin 1-endophilin A1 fission complex a) Top and side views of 3D reconstruction of dynamin-endophilin complex on lipid tubes obtained by cryo-EM and IHRSR image processing. b) Cross section through dynamin polymer 3D reconstructions shows differences in inner luminal diameter and spiral pitch. In absence of nucleotide, the inner luminal diameter of the WT-dynamin 1-decorated lipid tubes is 15 nm and the helical pitch 10 nm. In presence of GTP, K44A-dynamin super-constricts the underlying lipid to the theoretical limit for spontaneous fission (4 nm). In the presence of endophilin A1, the protein scaffold has a wider pitch than WT-dynamin 1 and achieves semi-constriction. This suggests that endophilin may regulate dynamin stimulated GTPase activity by inhibiting G domain dimerization across rungs of the helix (Sundborger et al, manuscript in preparation).

Our preliminary 3D reconstruction of the endophilin A1-dynamin 1 fission complex has been obtained by Iterative Helical Real Space Reconstruction (IHRSR) of cryo-EM data collected on a Tecnai 12 (FEI) operated at 200kV. This 3D EM density map shows that the inner luminal diameter of dynamin 1-endophilin A1 decorated lipid tubes is significantly smaller than that of tubes decorated by dynamin alone (10 nm vs. 15 nm), while the helical pitch is wider. Stimulated GTPase activity of dynamin is promoted by dimerization of dynamin G domains across rungs of the dynamin helix. This suggests that endophilin may regulate dynamin fission by preventing G domain dimerization across rungs of the helix and thus inhibiting dynamin stimulated GTPase activity. Furthermore, complex formation between endophilin B1 and dynamin 2 (in solution) has been confirmed by size exclusion chromatography. A peak corresponding to a ~600kDa protein complex has been sent for crystal trails and preliminary EM analysis of samples visualized by negative stain shows a helical structure with a discernable diffraction pattern. Additional data indicate that recombinant endophilin B1 also forms a complex with IRGM.

"Equipped with a Titan Krios electron microscope (FEI) fitted with phase plates and a direct electron detector, we are able to solve the 3D structure of key proteins and protein complexes at atomic resolution, in the ultimate effort to identify key players that contribute to regulation of cell death and to identify novel drug targets."

Dr. Anna Sundborger



Presentations 2015-2016
Keynote Speaker
FEI Women in Microscopy Annual Breakfast
Microscopy & Microanalysis Meeting 2016, Columbus, OH

Invited Speaker
Karolinska Institute, Cell and Molecular Biology Seminar Series, November 2015, Stockholm
"Dynamin at the brink of fission"

Invited Speaker
National Institutes of Health Protein Trafficking Interest Group, September 2015, Bethesda, MD
"Dynamin regulates a two-step membrane fission process"
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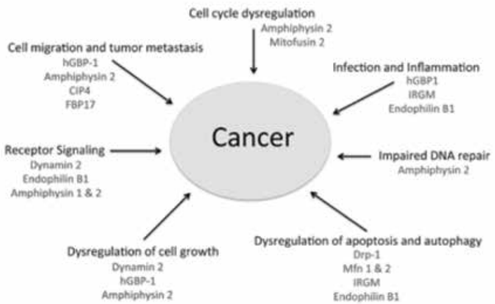

Cancer Epigenetics & Experimental Therapeutics

SHUJUN LIU, PH.D.

Section Leader
Associate Professor

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

Primary interests of our research section are to understand the molecular mechanisms and the roles of aberrant epigenetics and protein kinase activity in cancer pathogenesis and drug resistance, and to translate the discoveries from bench to bedside by means of characterizing novel therapeutic reagents and developing innovative vehicles to efficiently and specifically deliver the drugs to the disease sites. In our laboratory, studies have included the cause of DNA hypermethylation and abnormal protein kinase activity, the mechanistic link between obesity and leukemia, the dissection of molecular basis underlying resistance to molecular-targeted therapies and the development of innovative nanoparticles for drug delivery.

Interplay of epigenome and kinome determines cancer cell fate

DNA methylation occurs at the 5-position of cytosine in a CpG dinucleotide context and is a major epigenetic mechanism regulating chromosomal stability and gene expression. DNA methylation is under control of DNA methyltransferases (DNMTs) that are highly expressed in cancers. Our findings suggest that DNMT overexpression is attributed to Sp1/miR29 network, miR101, nucleolin, and recently, cytokines (e.g., IL-6/IL-15). In addition, abnormal kinase activities are essential in cancer initiation and metastasis. While kinase mutations are crucial, our main focus is shifted to kinase overamplification, which significantly contributes to the development, progression and drug resistance of cancers. Our discoveries support the idea that receptor tyrosine kinases are regulated by Sp1/miR29 network. Because Sp1/miR29 is also involved in DNMT gene regulation, we proposed that aberrant DNMT activities may control kinase signaling. Indeed, we demonstrated that KIT and DNMT1 form a regulatory circuit, in which KIT regulates DNMT1 expression through STAT3 pathway, whereas DNMT1 modulates KIT expression through Sp1/miR29 loop. Functionally, KIT and DNMT1 synergistically enhance cancer cell survival and proliferation, implicating the effectiveness of dual inhibition. These findings identify the regulatory and functional interactions between kinases and DNA methyltransferases, and suggest that crosstalk between the dysregulated KIT signaling and DNA hypermethylation is a key regulator of cancer cell survival and proliferation.

Protein kinases and DNA methyltransferases cooperatively promote drug resistance

Since aberrant DNA methylation and abnormal KIT function critically contribute to cancer pathogenesis, as independent practice, KIT and DNMT1 have been extensively used for therapeutic targets and their inhibitors have been tested in various pre- and clinical models. However, resistance of tumor cells to kinase inhibitors or DNA hypomethylating agents poses huge limitations to their use in treatment. Our findings suggest that resistance to decitabine and PKC412 eventually results from simultaneously re-methylated DNA and re-activated kinase cascades, as evidenced by the upregulation of DNMT1, DNMT3a, DNMT3b and tyrosine-protein kinase KIT, the enhanced phosphorylation of KIT and its downstream effectors and the increased global and gene-specific DNA methylation with the downregulation of CDH1. Interestingly, the resistant cells had higher capability of colony-formation and wound-healing than parental cells in vitro, with stronger tumorigenicity in vivo. Reciprocal inactivation of DNMT1 and KIT eradicates drug-resistant cells. In addition to the molecular targeted therapy, we recently showed that resistance to cisplatin in small cell lung cancer takes place through a new signaling network, DNMT1-KIT-PD1. Theoretically, our findings shed light on the molecular biology of drug resistance; practicably, our studies provide a sound rationale in clinical trials for using inhibitors of new signaling network to override drug resistant phenotypes, and also identify new opportunities for early therapeutic intervention against the emergence of drug-resistance.

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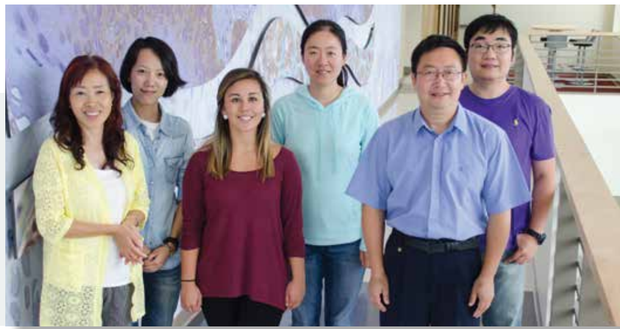
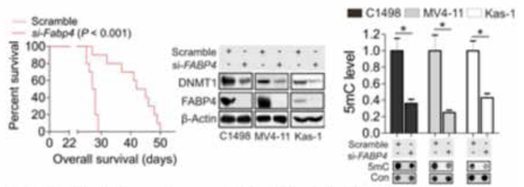
Dr. Shujun Liu

Mechanistic links between obesity and leukemia

Cancer is the representatively systemic lesions taking over the first place of lethal diseases throughout the world. Obesity is a "disease" with abnormal body fat accumulation. The World Health Organization estimates that approximately one quarter of population worldwide are obese. While it is a well-established concept that obesity is a major risk factor for breast cancer, colon cancer and prostate cancer etc., whether and how obesity contributes to leukemia remain unexplored. Our findings showed that dietary-induced obesity mediates aggressive leukemia growth in vitro and in vivo, thus, for the first time, experimentally demonstrating obesity-leukemia association. Mechanistic investigations showed that a family of fatty acid binding protein (Fabps) could be responsible for obesity-associated aggressive leukemic phenotypes, because a single change of Fabp4 in obese host or in leukemia cells is sufficient to alter leukemia cell fate. Importantly, the deregulated Fabp4 in obese host or leukemia cells abnormally modifies the epigenetic landscape in leukemia cells, leading to further silencing of tumor suppressor genes followed by uncontrollable leukemia growth. Mechanistically, we are the first to demonstrate lipid chaperone Fabp4 as an epigenetic modulator, and to identify Fabp/DNMT1 regulatory circuit as a hitherto unknown molecular link behind obesity-cancer association; in terms of practical use, our findings



(Left to right) Jiuxia Pang, Na Zhao, Emily Johannsen, Liping Dou, Shujun Liu, Fei Yan



Left: Fabp4 depletion prolongs survival; middle: Fabp4 knockdown suppresses DNMT1 expression; right: Fabp4 disruption leads to DNA hypomethylation

open a novel window of targeting Fabp4/DNMT1 axis for treating leukemia, and potentially, other types of cancers.

Developing multifunctional drug and gene delivery nanoparticles for cancer therapy

The current chemotherapeutic drugs (i.e., small molecules, siRNA or miRs), although they display promising anti-cancer activity, suffer from a variety of drawbacks when administered particularly in vivo, including rapid clearance, lack of tissue selectivity, high affinity to plasma proteins and poor cellular uptake. We have developed new liposomal formulations and synthesized nanoparticles to efficiently deliver the aforementioned drugs. We demonstrated the synergy between bortezomib and miR29b, which were delivered by liposomal nanoparticles, in promoting DNA hypomethylation in vitro. We have successfully delivered bortezomib, miR29 and Sp1 siRNA by nanoparticles in vivo. As a consequence of efficient delivery, we observed that liposomal bortezomib has a decrease of clearance and thereby an increase of drug exposure to leukemia cells existing in blood, compared to those of free bortezomib in mice. We also evidenced the synergistic effects of combined liposomal bortezomib with nano-miR29b on leukemia cell growth in mice. Recently, we synthesized HDL/AuNP nanoparticle and successfully delivered small molecule compounds into leukemia cell lines, patient primary cells and in leukemic mice, which was demonstrated by the inhibition of leukemia cell colony formation, the reduction of DNA methylation and the blockage of leukemia growth in mice. These results revealed that nano-drug delivery displays huge potential to improve therapeutic efficacy while reducing its side effects, including decreased drug toxicity, altered pharmacokinetics, improved drug solubility and more specific target binding.

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

List of Published Work in MyBibliography
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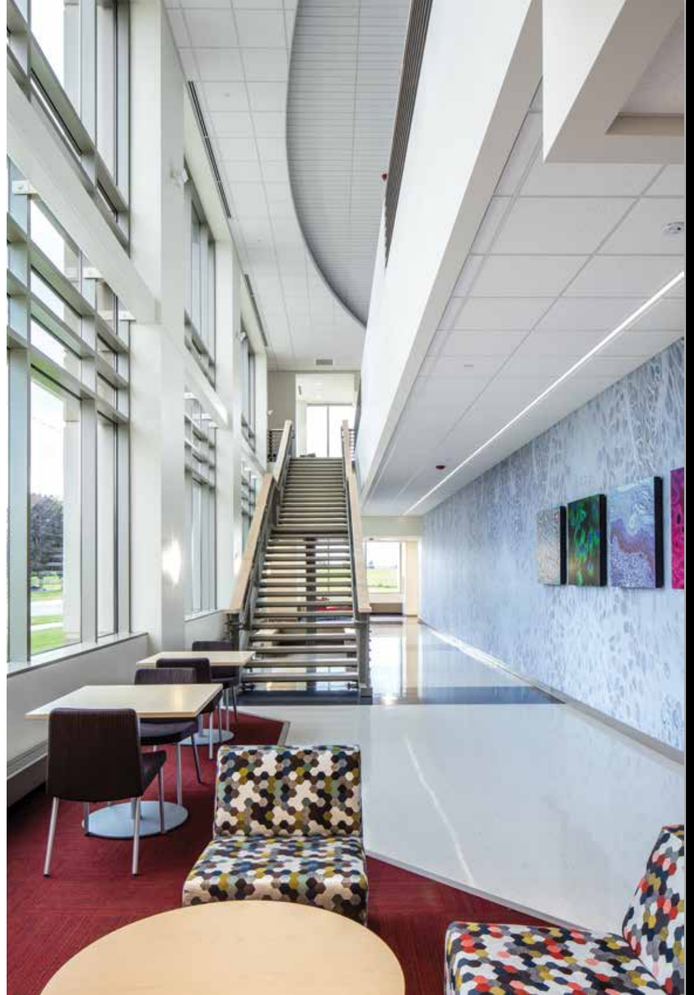

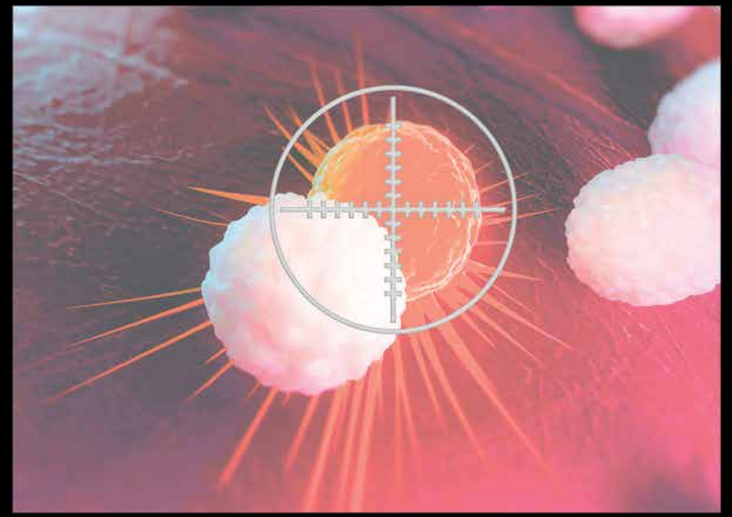

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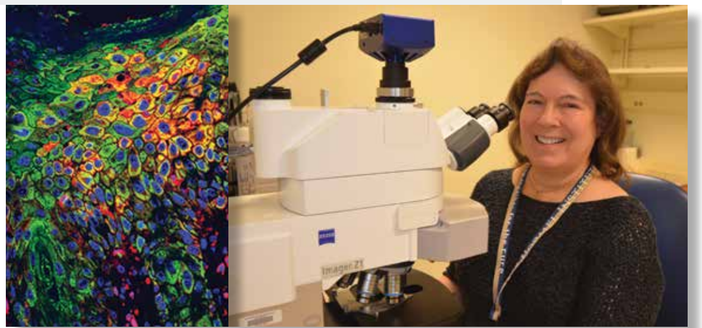
- Springer Nature announced the launch of *"npj Precision Oncology"* in partnership with The Hormel Institute University of Minnesota in Austin, Minnesota, United States.
- *npj Precision Oncology*, is a new open access, international, peer-reviewed journal that will publish cutting edge scientific research in all aspects of precision oncology, from basic science to translational applications to clinical medicine.
- Precision oncology is the growth area of precision medicine.
- A need exists for a journal where both preclinical and early clinical studies can be published together to help support this rapidly advancing field.
- The Hormel Institute is partnering with Springer Nature to establish *npj Precision Oncology* as a leading journal that supports and assists dissemination of knowledge in this rapidly growing field.
- In addition to publishing original basic science, translational and clinical research articles, *npj Precision Oncology* will also publish case reports, brief communications, commentaries, perspectives, and review articles.

Stem Cells and Cancer

REBECCA MORRIS, PH.D.

Section Leader
Professor



Skin keratinocytes

Skin cancer as seen in the clinic is the culmination of molecular damage to the stem cells. Human non-melanoma skin cancers (NMSCs) occur more frequently than any other malignancy, and approximately 1 million new cases are diagnosed in the United States annually with a heavy burden on society. An estimated one-third to one-half of all human cancers originate in the skin; skin cancers exceed all others combined; and the lifetime risk of skin cancer the US is 1 in 5. Solar ultraviolet radiation (UV) is the major known cause of NMSCs and is directly relevant to the etiology as demonstrated by epidemiological evidence and the tight correlation between NMSC in humans and UV-induced skin carcinogenesis in murine models. These cancers progress through an orderly sequence in which genetic, biochemical, and cellular abnormalities accumulate in target cells over time. Mild alterations initially seen within keratinocytes can only be identified histologically. Increased cellular atypia occurs with further sun damage, and hyperkeratotic, pre-malignant actinic keratoses develop. Of these 1-10% will progress to squamous cell carcinomas (SCCs). Because avoiding exposure to sunlight is more easily said than done, the Morris laboratory is focusing on three specific projects.

Evidence for expression of epidermal keratin and mRNA in blood and bone marrow. Cytokeratins are frequently found in the blood and bone marrow of patients with epithelial cancers and are attributed to metastasis. We wondered whether we could find keratin expression in blood and bone marrow in untreated adult mice. To address this problem, we have used classical immunoreactivity, Krt1-14;mTmG transgenic mice together with fluorescence activated cell sorting, and quantitative reverse transcriptase polymerase chain reaction. We have made several novel findings. First, we discovered, rare but distinctive, keratin-14 and keratin-15 immunoreactive cells the size of small lymphocytes in blood and bone marrow of untreated mice. Second, using Krt1-14;mTmG transgenic mice, we found low (8.6 GFP positive cells per 10^6 cells analyzed), but significant numbers ($p<0.0005$) of GFP positive cells in bone marrow of normal adult mice when compared with negative controls. Third, qRT-PCR demonstrated very low but reproducibly detectable expression of keratin-14 mRNA in blood and bone marrow when compared with epidermal keratinocytes: with blood expressing one thousand times, and bone marrow, one hundred thousand times, less than epidermal keratinocytes. Moreover, FACS analysis of fresh bone marrow disclosed a subpopulation of keratin-14 immunoreactive cells that was negative for hematopoietic lineage markers. We conclude from these observations that keratin-14 protein and mRNA are expressed at low, but detectable levels in the blood and bone marrow of mice. These observations should further our understanding of cutaneous biology, non-melanoma skin cancer, and other epithelia and their cancers.

Identification of two novel differentially expressed genes in murine keratinocyte stem cells and their possible roles in sensory perception. The hair follicle bulge provides a home for keratinocyte stem cells (KSCs) involved in epidermal renewal and formation of new hair. Identifying key regulators of KSCs can help in discovering new pathways in proliferation, carcinogenesis and other skin inherited diseases. In this study, we harvested cutaneous epithelial cells and FACS sorted CD49f+/CD34+ KSCs and CD49f+/CD34- KSC-depleted basal cells from 11 pairs of 54+/-1 day old C57BL/6 female mice. We performed RNA-sequencing on these two cell populations to identify the differentially expressed genes and performed functional analysis on them. Krt15, CD34, Bmp4 and other known KSC markers were significant, along with genes involved in Wnt signaling pathway that maintains homeostasis of the cutaneous epithelium. We further validated the data set by performing qRT-PCR on CD34, Col6A2, Adamts3, Fabp4 and four other genes that showed higher expression in KSCs. Two of the genes, Egflam, has been implicated in retinal signaling as a photoreceptor, and Il31ra, also overexpressed in KSCs, is associated with an itchy skin disorder, Primary Cutaneous Amyloidosis (PCA). Ongoing investigation of these genes and their isoforms will facilitate discovery of new therapeutic targets and contribute to our understanding of the skin as a sensory organ.

"Our research 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."

Dr. Rebecca J. Morris

(Left to right) Yong Li, Xiangying Pi, Rebecca Morris, Sonali Lad, Brett Sterk

The role of Hmga2 nuclear translocation in skin tumorigenesis. High mobility group AT-hook 2 (Hmga2) is a member of the HMG family of proteins. Hmga2 mRNA is differentially expressed in hair follicle stem cells however; the protein is preferentially expressed in non-stem epidermal cells. Hmga2 has always been considered as nuclear architectural protein. The molecule is widely expressed in undifferentiated cells during embryogenesis, but becomes more restricted as fetal development progresses, and has been limited to the mesenchyme at normal development. Hmga2 is always regulated through promoter region containing Sp1, Sp3 and RUNX1 binding sties and 3'UTR containing Let-7, miR 33b, miR101 et al binding sites. ROCK inhibition was also found to be mediated by shortening the poly A length of Hmga2 mRNAs by Let-7. Recently several groups found histone deacetylase inhibitors (HDACI) such as panobinostat, sirtuin-6, and trichostatin-A significantly reduced steady-state level of endogenous Hmga2 through Let-7 or Sp1 and Sp3 in cell lines and pancreatic cancer. Previously published studies have established Hmga2 as a critical player in neuronal- and hair follicle- stem cells self-renewal, and adult somatic reprogramming associated with skin squamous cell carcinoma stemness, and metastasis. The importance of Hmga2 was further validated by its prevalence in a variety of benign and malignant tumors including cancers of the lung, breast, colon, prostate, bladder, and melanoma. Hmga2 overexpression in the tumors of mesenchymal and epithelial origin is considered necessary for rearrangements and mutations of Hmga2 following chromosomal translocation involving HMG loci. However, whether Hmga2 is required in skin tumor initiation and promotion has largely remained unexplored. To this end, we identified Hmga2 expression is significantly increased by binding its own promoter following nuclear translocation during keratinocyte culture in vitro and carcinoma development in vivo. Hmga2 translocation and expression can be inhibited by panobinostat through the inhibition of Hmga2 promoter activity. We established that Hmga2 translocation is an important mechanism to induce the mouse skin tumor formation.

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 probe the interactions between epidermal stem cells and bone marrow derived cells as tumor initiating- and propagating- cells.

Cell Signaling and Tumorigenesis

JAMES ROBINSON, PH.D.

Section Leader
Assistant Professor

Immunohistochemical staining of ß-Catenin expression of a tumor in the small intestine.

My section is primarily interested in the molecular mechanisms by which oncogenic signaling regulates tumorigenesis with the ultimate goal of developing and improving existing therapeutic approaches to eliminate cancer. Our current primary focus is on melanoma and colon cancer. We employ two experienced postdoctoral fellows, Kwan Hyun Kim, Ph.D., and Hana Yang, Ph.D., and Lab Technician Selena Hataye. This summer, we are joined by Annie Holtz, whose summer undergraduate research experience (SURE) internship was generously funded by an Orville S. Privett Scholarship. Our former SURE intern, Celeste Underriner, has been accepting to the molecular and cellular pharmacology doctoral degree program at the University of Wisconsin-Madison. We, as part of the University of Minnesota and a member of the Masonic Cancer Center (MCC), have and will continue to collaborate with worldwide experts in the fields of cell signaling, cancer research, comparative pathology, and genetics. In his final State of the Union address, the President of the United States tasked Vice President Joe Biden with heading up a new national effort to end cancer, and I was honored to participate as an expert panelist at the Minnesota Moonshot summit in June. Last November, we were also honored to present our novel model of melanoma at the International Congress of the Society for Melanoma Research in San Francisco. 2015-2016

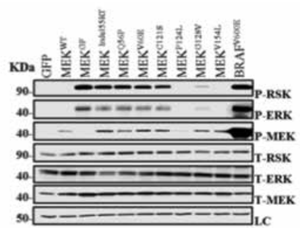
Publications 2015-16:
'AKT1 Activation Promotes Development of Melanoma Metastases' - Cell Reports
'In vitro visualization and characterization of wild-type and mutant IDH homo- and heterodimers using Bimolecular Fluorescence Complementation'- Cancer Research Frontiers.

Melanoma: The incidence of melanoma increased 690% from 1950 to 2001, and it continues to increase at a greater rate than any other cancer. Most melanoma patients are under 60; it is the most common form of cancer for ages 25-29 and the second for ages 15-29. Five-year survival for patients with metastatic disease is less than 16%. The rapidly rising incidence, coupled with the high rate of mortality associated with advanced disease, is particularly troubling. The increased incidence of melanoma, combined with the poor prognosis of patients with advanced disease, make it imperative that we increase our understanding of the underlying causes of resistance to targeted therapies so that better therapeutic strategies can be developed. The mitogen-activated protein kinase pathway is constitutively activated in the majority of cutaneous melanomas, predominantly due to NRAS and BRAF mutations. We have developed a novel retroviral gene delivery mouse model of melanoma that allows for targeted delivery to melanocytes in vivo. The mice are immune-competent, and tumors evolve from developmentally normal somatic cells in an unaltered microenvironment. Multiple genetic alterations can be introduced into the same cell without the time and costs associated with crossing multiple strains of transgenic mice. We established the validity of our model by delivering NRASQ61R and Cre to melanocytes in vivo to study the role of NRAS in melanoma. Because of the renewed interest in the development of RAS inhibitors (The National Cancer Institute RAS Initiative), we adapted our model to permit the temporal control of oncogene expression using tetracycline to mimic pharmacological NRAS inhibition. We found that while NRAS tumors respond fully to NRAS inhibition, many reoccur after a prolonged latency. We then determined several of the possible resistance mechanisms involved. Using this model, we determined that PTEN loss and AKT activation increases the frequency of brain and lung metastasis. Vemurafenib and dabrafenib are FDA-approved drugs for the treatment of advanced metastatic melanomas with BRAFV600E mutations. Although the initial response to these inhibitors can be dramatic, sometimes causing complete tumor regression, the majority of these melanomas eventually become resistant and reoccur. Resistance to BRAFV600E kinase inhibitors is frequently associated with the reactivation of the MAPK pathway. For this reason, BRAF inhibitors are combined with MEK inhibitors; however, after a period of response and dormancy, the tumors still reoccur. We recently demonstrated that gain of function MEK mutants found in drug-resistant BRAF melanoma drive the de-novo development of malignant melanoma with high penetrance (Figure 1). Using this wealth of preliminary data, we now plan to define and validate the mechanisms of tumor dormancy and recurrence following BRAF and MEK inhibition.

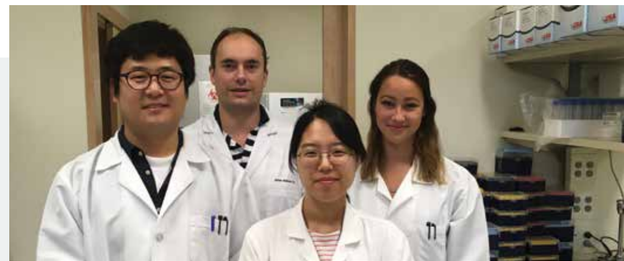
"The increased incidence of melanoma, combined with the poor prognosis of patients with advanced disease, make it imperative that we increase our understanding of the underlying causes of resistance to targeted therapies so that better therapeutic strategies can be developed."

Dr. James Robinson

Figure 1. A comparison of the activity of MEK mutants found in BRAFV600E inhibitor-resistant melanoma.
(A) An immunoblot for MAPK pathway components in 293 HEKs cells transfected with plasmid DNA containing wildtype MEK, MEKIndel55RT, MEKQ56P, MEKV60E, MEKC121S, MEKP124L, MEKG128V, MEKV154L, and BRAFV600E or empty vector controls. Both the transfections and immunoblotting were performed in triplicate. Tubulin was used as a loading control (LC).



Colon Cancer: Our work on colon cancer is funded by the National Institutes of Health (NIH). Colorectal cancer (CRC) is one of the most common cancers worldwide and, after lung and prostate cancer, is the leading cause of cancer deaths in the United States, with 132,770 new cases and 49,700 deaths anticipated in 2015. About 75% of cases are sporadic, with no obvious evidence of an inherited disorder. The remaining 25% of patients have a family history of CRC that suggests a hereditary contribution, common exposures among family members, or a combination of both. Familial adenomatous polyposis (FAP) is one of the most clearly defined and well understood of the inherited colon cancer syndromes. Our preliminary data has demonstrated that loss of APC is insufficient for tumorigenesis and additional growth signals, or mutations are also required for nuclear accumulation of αCatenin and intestinal polyposis. Since mouse models of FAP develop a multitude of intestinal polyps without additional genetic alterations, these additional signals are likely to arise from adjacent stromal cells (Figure 2). If we can show that stromal signaling plays a driving role in tumorigenesis, following or pre-empting epithelial LOH of APC, it should be possible to develop targeted therapeutics to block this signaling. Our studies will contribute to the development of novel therapies and improve the outcome for patients with colon cancer A major preliminary finding is that heterozygous mutation of APC in adult mice is not sufficient to cause tumor formation.

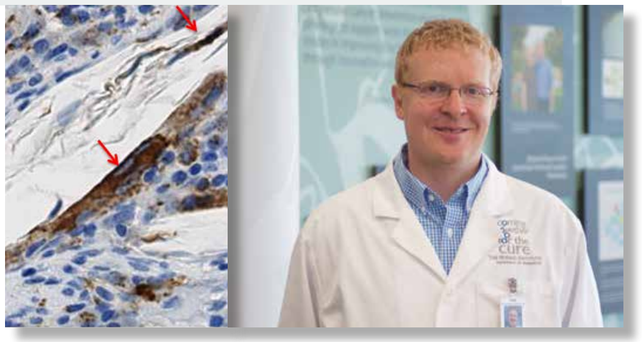


(Left to right) Kwan Hyun Kim, James Robinson, Hana Yang, Selena Hataye

Molecular Biology and Translational Cancer Research

LUKE HOEPPNER PH.D.

Section Leader
Assistant Professor



Dopamine D2 receptor positive endothelial cells in human lung cancer tissue.

Our "Molecular Biology and Translational Cancer Research" section began in September of 2015. We established our laboratory, initiated a new zebrafish facility, and assembled a talented team to accelerate our research. Our work is funded by the National Institutes of Health to study the molecular mechanisms and signal transduction pathways involved in vascular permeability, cancer progression/metastasis, and cancer drug resistance.

One goal of our research is to develop new therapies to inhibit lung cancer progression and prevent tumor cells from acquiring resistance to current treatments. We accomplish these goals through the use of a variety of models as well as utilization of lung cancer patient samples. Such translational studies will be important for the development of new cancer therapies. Our research aims to improve the dismal survival rate of lung cancer patients and seeks an innovative approach to combatting tumor drug resistance. This research will have collective impact because its studies will identify novel therapeutic targets to help the multitude of Americans suffering from lung cancer.

Vascular endothelial growth factor (VEGF) is required for blood vessel formation and promotes permeability in veins. Tumors produce VEGF because they require their own vasculature to grow, obtain nutrients and oxygen, and eliminate waste products. The permeability induced by VEGF enables cancer cells to escape their primary site, enter the bloodstream, and metastasize to other tissues. Dopamine (DA) and dopamine D2 receptor (D2R) agonists inhibit VEGF-mediated blood vessel development (angiogenesis) and vascular permeability by inhibiting VEGF binding, VEGF receptor phosphorylation and subsequent downstream signaling. Dopamine and D2R agonists completely block accumulation of tumor ascites fluid and cancer growth in mice. My recent studies demonstrated D2R agonists, including FDA approved cabergoline, inhibit lung cancer growth in mouse models by reducing angiogenesis and tumor infiltrating immune suppressor cells. Pathological examination of human lung cancer tissue revealed a positive correlation between endothelial D2R expression levels and tumor stage as well as patient smoking history.

1. Triggering the dopamine pathway to inhibit lung cancer progression
Interestingly, DARPP-32, a cyclic-AMP-regulated phosphoprotein (a signaling molecule downstream of D2R), and its truncated splice-variant, t-DARPP, are overexpressed in many adenocarcinomas and mediate drug resistance in cancer cells. Our current goal is defining the role of DARPP-32 and t-DARPP in lung cancer growth. To this end, we are modulating DARPP-32 and t-DARPP protein expression in human lung cancer cell lines using three distinct techniques, including overexpression and knockdown through viral and genome editing procedures. We then evaluate the consequences of altered DARPP-32 and t-DARPP levels through molecular biology methods and mouse models to determine their effect in lung cancer progression. We are in the process of assessing differential DARPP-32 and t-DARPP expression in human lung adenocarcinoma tissues (various grades/stages) using an antibody that exclusively detects DARPP-32 as well as an antibody that recognizes both isoforms. Additionally, we seek to elucidate the role of DARPP-32 and t-DARPP in lung cancer drug resistance. We are studying whether upregulation of DARPP-32 or t-DARPP contributes to lung tumor cells developing resistance to commonly used molecular targeted anti-cancer drugs. We recently identified a molecular pathway regulated by DARPP-32 that may enable lung tumor cells to evade current therapies, which we are currently investigating. These studies will help overcome lung tumor drug resistance as well as contribute to the development of innovative lung cancer treatment approaches.

2. Development of zebrafish models of vascular permeability and cancer metastasis
VEGF induces vascular permeability in stroke, heart attack, and cancer leading to many pathophysiological consequences. Following cerebral or myocardial infarction, VEGF induces gaps between adjacent endothelial cells in ischemic tissue and the resulting vessel leakiness causes deleterious edema formation and tissue damage. In cancer, VEGF-mediated permeability promotes tumor angiogenesis and metastasis. The molecular mechanisms by which VEGF acts to induce hyperpermeability are poorly understood and in vivo models that easily facilitate real-time, genetic studies of permeability do not exist. We developed a heat-inducible VEGF transgenic zebrafish model through which vascular permeability can be monitored in real-time. Using this approach with morpholino-mediated protein knockdown, as well as knockout mice, we described a novel role of phospholipase Cβ3 (PLCβ3) as a negative regulator of VEGF-mediated vascular permeability by tightly regulating intracellular calcium release. We have also used this zebrafish model to elucidate the role of RhoC and other molecules in vascular homeostasis. The zebrafish vascular permeability model represents a straightforward method for identifying genetic regulators of VEGF-mediated vascular as promising targets for cancer, heart disease and stroke therapies. We also developed a zebrafish xenograft model of human cancer cell metastasis, which was used in two separate studies to support our findings from murine cancer models.

"Our research aims to improve the dismal survival rate of lung cancer patients and seeks an innovative approach to combatting tumor drug resistance."
Dr. Luke Hoeppner

Funding
National Institutes of Health, National Cancer Institute, R00CA187035

Publications (2015-2016)
1. Hoeppner LH, Wang Y, Sharma A, Javeed N, Van Keulen VP, Wang E, Yang P, Roden AC, Peikert T, Molina JR, Mukhopadhyay D. Dopamine D2 receptor agonists inhibit lung cancer progression by reducing angiogenesis and tumor infiltrating myeloid derived suppressor cells. Molecular Oncology. 9:270-81; 2015.
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Editorial Board
Nature Partner Journals: Precision Oncology

(Left to right) Erin Dankert, Sk Kayum Alam, Luke Hoeppner, Stephanie Hall

Ad Hoc Reviewer
Cancer Research, Gene, American Journal of Pathology, Journal of Thoracic Oncology, Scientific Reports, PLOS One

Our "Molecular Biology and Translational Cancer Research" section began in September of 2015. We established our laboratory, initiated a new zebrafish facility, and assembled a talented team to accelerate our research. Our work is funded by the National Institutes of Health to study the molecular mechanisms and signal transduction pathways involved in vascular permeability, cancer progression/metastasis, and cancer drug resistance.

One goal of our research is to develop new therapies to inhibit lung cancer progression and prevent tumor cells from acquiring resistance to current treatments. We accomplish these goals through the use of a variety of models as well as utilization of lung cancer patient samples. Such translational studies will be important for the development of new cancer therapies. Our research aims to improve the dismal survival rate of lung cancer patients and seeks an innovative approach to combatting tumor drug resistance. This research will have collective impact because its studies will identify novel therapeutic targets to help the multitude of Americans suffering from lung cancer.

Vascular endothelial growth factor (VEGF) is required for blood vessel formation and promotes permeability in veins. Tumors produce VEGF because they require their own vasculature to grow, obtain nutrients and oxygen, and eliminate waste products. The permeability induced by VEGF enables cancer cells to escape their primary site, enter the bloodstream, and metastasize to other tissues. Dopamine (DA) and dopamine D2 receptor (D2R) agonists inhibit VEGF-mediated blood vessel development (angiogenesis) and vascular permeability by inhibiting VEGF binding, VEGF receptor phosphorylation and subsequent downstream signaling. Dopamine and D2R agonists completely block accumulation of tumor ascites fluid and cancer growth in mice. My recent studies demonstrated D2R agonists, including FDA approved cabergoline, inhibit lung cancer growth in mouse models by reducing angiogenesis and tumor infiltrating immune suppressor cells. Pathological examination of human lung cancer tissue revealed a positive correlation between endothelial D2R expression levels and tumor stage as well as patient smoking history.

1. Triggering the dopamine pathway to inhibit lung cancer progression
Interestingly, DARPP-32, a cyclic-AMP-regulated phosphoprotein (a signaling molecule downstream of D2R), and its truncated splice-variant, t-DARPP, are overexpressed in many adenocarcinomas and mediate drug resistance in cancer cells. Our current goal is defining the role of DARPP-32 and t-DARPP in lung cancer growth. To this end, we are modulating DARPP-32 and t-DARPP protein expression in human lung cancer cell lines using three distinct techniques, including overexpression and knockdown through viral and genome editing procedures. We then evaluate the consequences of altered DARPP-32 and t-DARPP levels through molecular biology methods and mouse models to determine their effect in lung cancer progression. We are in the process of assessing differential DARPP-32 and t-DARPP expression in human lung adenocarcinoma tissues (various grades/stages) using an antibody that exclusively detects DARPP-32 as well as an antibody that recognizes both isoforms. Additionally, we seek to elucidate the role of DARPP-32 and t-DARPP in lung cancer drug resistance. We are studying whether upregulation of DARPP-32 or t-DARPP contributes to lung tumor cells developing resistance to commonly used molecular targeted anti-cancer drugs. We recently identified a molecular pathway regulated by DARPP-32 that may enable lung tumor cells to evade current therapies, which we are currently investigating. These studies will help overcome lung tumor drug resistance as well as contribute to the development of innovative lung cancer treatment approaches.

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Supporting Departments

Research Support Group

KIM KLUKAS
Supervisor

(Left to right) Chris Boruff, Kim Klukas, Michelle Jacobson. Back row: Teri Johnson, Melissa Deml

The Hormel Institute's Research Support Group has grown this year with the expansion. We have begun to add more staff and have incorporated weekly sessions to provide procedural training for scientists. We also aid in maintaining research compliance standards for each department and offer research operational support on a day to day basis. We are excited to be able to offer our skill sets to the research sections and aid in helping to find a cure for cancer.

Instrument Core Facility

TODD SCHUSTER
Senior Lab Technician

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

Library

ANDY LUCAS
Librarian

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.

Office

ANN M. BODE, PH.D.
Supervisor / Associate Director

(Left to right) Ann Bode, Betsy Mentel, Nicki Brickman, Jessica Swanson, Julie Gerstner

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.

Development and Public Relations Departments

GAIL DENNISON, M.A., CFRE
Director of Development and Public Relations

(Left to right) Mandie Siems, Gretchen Ramlo, Gail Dennison, Brenna Gerhart, Michelle Phillips

We are extremely grateful to all who dedicated their time, efforts and caring hearts to support the cancer research of The Hormel Institute, University of Minnesota.

It is truly amazing to be part of a historic era of accelerated growth at The Hormel Institute. This is only possible because of each of you, with special recognition to The Hormel Foundation, for making such rapid progress possible. We also thank the dedicated faculty and staff of The Hormel Institute for their research achievements - representing them indeed is a privilege and an honor.

The "Coming Together for the Cure" capital campaign came to a successful close, exceeding our goal of $4.5 million dollars to develop the Ray Live Learning Center. The center includes a beautiful multipurpose event room and a 250-seat auditorium. It provides the necessary space to hold seminars, research meetings and conferences for the faculty who will grow to 250 over the next few years.

The Hormel Foundation and University of Minnesota provided the major gifts that developed the beautiful Ray Live Learning Center. A special thanks to Gary and Pat Ray, Richard and Nancy Knowlton, Joel and Beth Johnson, Hormel Foods Corporation, Mahlon and Karen Schneider, U.S. Bank and Ecolab and the hundreds of people and organizations who generously donated to make this important part of the expansion possible and equip it with state of the art communications technology.

Our guiding principle is to win support for The Hormel Institute's quest to improve the health of the world through scientific research. Together, we know that for a healthier tomorrow, research must be funded today.

The Hormel Institute

The new logo for The Hormel Institute was designed and donated by Troy Doyle and Smyth Company. The logo is an "H" and "I" made up of test tubes and molecules, and is a celebration of The Hormel Institute's incredible contributions to cancer research as well as its continuing mission to find answers to cancer.

The Hormel Foundation
University of Minnesota & Masonic Cancer Center
Hormel Foods Corporation
Mayo Clinic
Gary & Pat Ray
Richard & Nancy Knowlton
Joel & Beth Johnson
Vice President Joseph Biden
Minnesota Governor Mark Dayton
U.S. Senator Amy Klobuchar
U.S. Senator Al Franken
The Honorable Norm Coleman
U.S. Representative Tim Walz
State Senator Dan Sparks
State Senator David Senjem
State Representative Jeanne Poppe
Mayor of Austin – Tom Stiehm
Mayor of Rochester – Ardell Brede
Mahlon & Karen Schneider
Dr. Harald & Pat Schmid
Adams, Rizzi & Sween, P.A.
Belita Schindler
5th District Eagles Cancer Telethon
Lyle Area Cancer Auction
U.S. Bank
Ecolab
Development Corporation of Austin (DCA)
Austin Park & Rec
Austin Bruins' "Paint the Rink Pink"
Paint the Tow Paint the Town Pink – Austin, Adams, Brownsdale, Rose Creek
"Plunging for Pink" Polar Plunge
Pink Pumpkin Patch Foundation
Karl R. Potach Foundation
Dr. Kurt and Brenda Potach
Austin Eagles Club – Aerie 703
Hoot & Ole's
Thomas & Patricia Wiechmann
Reichel Foods
Minnesota VFW Ladies Auxiliary
AgStar Fund for Rural America
Austin Area Chamber of Commerce
Minnesota Chamber of Commerce
Austin Area Foundation
Austin Convention & Visitors Bureau
City of Austin – Austin Port Authority
GRAUC – Greater Rochester Advocates of Universities and Colleges
IBM Rochester
University of Minnesota – Rochester
Mower County
Riverland Community College
Austin Public Schools
Pacelli Catholic Schools
Southern Minnesota Initiative Foundation
Bowling for the Battle – A Fight Against Prostate Cancer
Deryl Arnold Memorial Golf Tournament
Fishing for a Cure
Mower County USBC Association's "Bowl for a Cure"
The Hormel Institute Mentor Group
Mower County Fair Board
YMCA of Austin
Austin Vision 2020
Norma Foster Memorial "Ride for a Reason"
Jim & Vicky King/Spiritually Motivated
Larry Anderson
Sharon Lewis
Blooming Prairie Cancer Group
St. Marks Lutheran Home
Hormel Historic Home
Austin ArtWorks Festival
Gretchen and Mark Ramlo
Sterling Drug/Astrup Drug/Astrup Family Foundation
Ryan Gordon Memorial Golf Tournament
Joel & Beth Johnson
Helen S. Mears
John F. Scallon
Jean Noel
McGough Construction Company
Jim & Tammy Snee
RSP Architects
Tom Day
Dr. Phillip & Gail Minerich
Randy & Wendy Kramer
Home Federal Savings Bank
Dr. Richard & Karen Herreid
Dr. Kevin & Aleta Myers
Jeff & Diane Baker
Clair F. Allen
Corrine Astrup
SKB Environmental

Thank You . . . Partners in Growth

Lyle Area Cancer Auction

Karl's Tourney Golf Tournament

Hormel Foods, Deryl Arnold Memorial Golf Tournament

Eagles Fifth District Cancer Telethon

Agstar for Rural America

(Left to right) Top: Tom Gillard "Bowling for the Battle" Bottom: Norma Foster "Ride for a Reason"

PAINT THE TOWN
PINK

Community Outreach

Thank you

hope
support
research
progress

"Your donation is extremely important. Through research, you help create a world where cancer is better prevented, detected, and controlled."

Dr. Zigang Dong
Executive Director

"Today's RESEARCH, Tomorrow's CURES"

Research Support Services

CRAIG M. JONES
Supervisor

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

Research Support Services has had another exciting year as we have continued to provide instrument maintenance along with 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 network security needs keep us busy. The Linux cluster CAL42 (Computational Analysis of Life-sciences 42) has been calculating away simulating protein molecules in our supercomputer room, part of The Hormel Institute's International Center of Research Technology. As building coordinator, I also have been extremely busy with The Hormel Institute's 2014-16 Expansion on our east and west sides – an overall $31.5 million project. The east expansion of 20 research laboratories was supported by The Hormel Foundation, Austin Port Authority and the State of Minnesota. Construction started in summer 2014 and was completed in summer 2016. In spring 2015, we broke ground on the Institute's west side for our future Live Learning Center that features innovative, global-communication technology in a 250-seat lecture hall with an adjacent multipurpose room. This has been another great year for our department, and next year is looking to be even more exciting as the expansion is now complete.

Building Operations and Maintenance

MARK SEVERTSON
Supervisor

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

The maintenance support unit's main goal is to provide all personnel with a comfortable and safe working environment. Regular inspection and maintenance of all buildings and equipment is performed to assure continuous, efficient operation and comfort. All safety equipment is routinely checked to assure proper operation in the event of an emergency. This unit also is responsible for the receiving, recording and delivering of all incoming supplies and equipment delivered to the Institute. Also occasional minor laboratory and office rearrangement is done to maximize efficient use of space. This unit has regular contact with University building and safety officials to be certain that various building alterations, repairs and functions are completed according to required code and safety regulations. Local professional tradesmen are also contacted for minor repairs or alterations necessary to keep operations running safely, smoothly and efficiently within the facility. The Building Operations and Maintenance department is very proud of our new addition and remodeled facility. We will all strive to keep it looking and operating with the upmost of efficiency.

Education . . . Changing lives through research progress

Throughout each year, The Hormel Institute's faculty and staff conducts an extensive educational outreach that reaches children from elementary age to graduate students. Some of the main annual outreach activities include the SURE internship program; scientist judges at local science fairs; scientists visiting Austin's Ellis Middle School and IJ Holton Intermediate School to talk about science and work with students in labs; and hosting all Austin sixth-graders for a full day of tours.

SURE Intern (Summer Undergraduate Research Experience)

Front row (left to right) Annie Sun, Teigan Petersen, Emily Johannsen, Kjersten Monson, Stephanie Holtorf

Back row (left to right) Brett Sterk, Brett Cornforth, John Luebbe, Erin Dankert, Annie Holtz

Not Pictured Syed Umbreen, Thomas Olmsted

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

GRAND OPENING 2016 Expansion

"The Hormel Foundation believes by continuing the investments we make in our community, we support and benefit our families, students, employees and buisiness and organizational leaders. By providing vital resourcees to deserving organizations, we will continue to positively impact the world"

Gary J. Ray, Chair, The Hormel Foundation

The Hormel Foundation Executive Board

Gary Ray, Chair | Bonnie Rietz, Vice Chair | Jerry Anfinson, Treasurer | Steve Rizzi, Secretary

The Hormel Institute's 2016 expansion and exciting new Ray Live Learning Center tripled the size of the rapidly growing cancer research facility. The 20 new labs allow space for innovative new research departments and world-class faculty to join The Hormel Institute over the next few years.

The expansion collaboration between The Hormel Foundation, State of Minnesota, University of Minnesota and generous private donors showed a great success in "Coming Together For the Cure" to support and further cancer research discoveries. The outcome - cutting edge labs, recruitment resources, space and technologies - makes The Hormel Institute poised to become increasingly a world leader in research aimed to prevent and control cancer.

coming together for the cure

75 YEARS The Hormel Foundation
SUPPORTING AUSTIN, IMPACTING THE WORLD

research

progress

expansion

coming together for the cure

GRAND OPENING 2016

After tripling in size in 2008, to double in size just eight years later is an amazing feat. We thank The Hormel Foundation and our community/state leaders for The Hormel Institute's continuing transformation designed to further cancer research progress. The June 1st expansion celebration brought friends from the community, state, country and from throughout the world to celebrate an investment that will result in new discoveries, greater contribution to science and improved health for all humanity.

It was through The Hormel Foundation's matching grant of $13.5 million that the State of Minnesota bonding bill $13.5 million grant was successfully awarded. This effort was championed by Austin Port Authority and supported strongly by Governor Mark Dayton and bill authors, State Senator Dan Sparks and Representative Jean Poppe. We also thank Senator David Senjem and all our legislators for working together as their bi-partisan support led to a successful outcome.

RSP Architect and McGough Construction designed and built the expansion on both the east and west sides of the 2008 building. The Hormel Foundation invested in technology that includes the world's most powerful microscope, the Titan CryoElectron microscope - that will be used for cancer drug development.

"The new labs and new technologies will expand the research capabilities of The Hormel Institute and paves the way for continued cutting edge research," said Gary J. Ray, chair of The Hormel Foundation, whose overall support of the expansion was in excess of $40 million. "We are thankful to have played a key role in establishing and equipping the facility with state of the art labs and the world's most advanced technologies."

The Ray Live Learning Center, named for major benefactors Gary and Pat Ray, was supported through hundreds of donations generously given by individuals, businesses and organizations from the community and beyond. Ray Live Learning Center includes a beautiful multi-purpose Event Room used for gatherings such as scientific symposium meetings, poster sessions, and event meals. Ray Live Learning Center also includes a stunning new 250-seat auditorium, fully equipped with the most advanced communications technology to enhance global communications so The Hormel Institute can connect with scientists around the world.

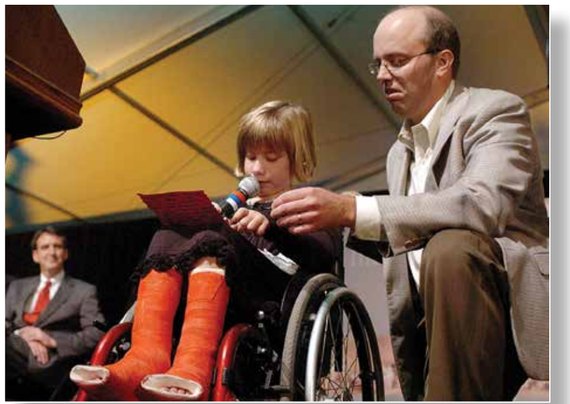
"This would be an amazing facility if it were located in New York City," said former U.S. Senator Norm Coleman, who gave the keynote address at the Grand Opening's first International Cancer Research Conference, and personally shared his own journey as a cancer survivor. "The fact that this facility and outstanding research is done in Austin, Minnesota is something we can all be very proud of."

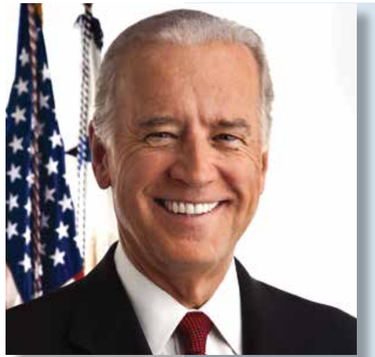
Congratulatory messages were sent from Vice President Joe Biden and Minnesota Governor Mark Dayton, and the ceremony included speakers U.S. Senator Amy Klobuchar, U.S. Representative Tim Walz, Vice Governor Wang Yanling of Henan Provincial People's Government, The Hormel Foundation chair Gary J. Ray, University of Minnesota President Eric Kaler and Hormel Foods' CEO and Chairman of the Board Jeffrey M. Ettinger. Meaningful messages were shared by those whose lives have been affected by cancer and those who champion and fundraise for cancer research to benefit The Hormel Institute, University of Minnesota. A three day international cancer conferenced launched the first use of Ray Live Learning Center, bringing hundreds of scientists to Austin, Minnesota and The Hormel Institute from around the world.

The Hormel Institute thanks all who contributed to and supported our continuing growth and progress with the 2014-16 expansion. Truly, we are Coming Together for the Cure.

"Today's RESEARCH, Tomorrow's CURES"

Abby Bauleke was the 2008 Expansion Cancer Research Ambassador. Thanks to research, Abby is a 10-year leukemia survivor. She returned for the 2016 Expansion to celebrate The Hormel Institute's continued research progress.





"We need to stop talking and start doing. The Hormel Institute has been doing just that for more than 70 years. I am confident that this new expansion will allow you to accelerate your progress, fund more research, and provide much-needed space for our brightest minds and cutting-edge technology."

U.S. Vice President Joe Biden

"There is ground-breaking cancer research going on here. And you can see how this works when people believe in each other and believe that we can actually get a cure for cancer."

"This research means something. It means something 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."

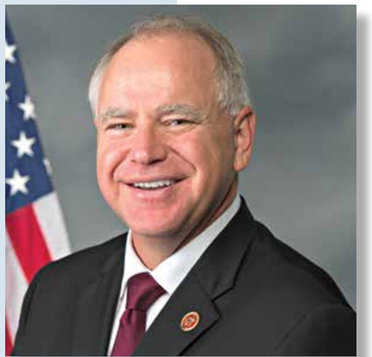
U.S. Senator Amy Klobuchar

"I am proud to have been the Chief Senate Author for the state's investment of $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."

State Senator Dan Sparks

"At the University of Minnesota, we are committed to the fight against cancer, which is one part of our mission to enrich and save lives in Minnesota and around the world, Our critical and extraordinary partnership with The Hormel Institute helps the university to move that mission forward."

University of Minnesota president Eric Kaler



"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. Representative Tim Walz

"The Hormel Foundation's early vision and commitment to research has grown exponentially and created opportunities in all aspects of scientific discovery and research through The Hormel Institute. Expanding its footprint enhances the possibilities for discovery."

"Our community is stronger and our outlook for good health is better thanks to the scientists, researchers, faculty and staff of "our" Hormel Institute. Thanks to their dedication and for the leadership by the Hormel Foundation board we achieved a synergy of focus, commitment and results which continues to serve our community and our health into the future."

State Representative Jeanne Poppe

EXPANSION 2016

Cryo-Electron Microscope

The Hormel Institute continues to add state-of-the-art technology to its International Center of Research Technology. The new east addition is now home to the most powerful and flexible high-resolution electron microscope available today and captures 2 dimensional (2D) and 3D images using cryo-electron microscopy (EM). As part of the recent building expansion, a specialized laboratory was designed to accommodate the new FEI Titan Krios G2 microscope.

Dr. Anna Sundborger joined The Hormel Institute to lead the CRYO-EM lab, coming from National Institutes of Health, Bethesda, Maryland.

CANCER CONFERENCE

The Ray Live Learning center includes an innovative multipurpose room and 250-seat auditorium that offers Institute scientists state-of-the-art global communication technologies to support and accelerate cancer research discoveries. The Ray Live Learning Center was first used The Ray Live Learning Center was first used at the Grand Opening for the 7th China-U.S. for the 7th China-U.S. Forum on Frontiers of Cancer Research and 4th Hormel Institute International Cancer Research Conference.

EXPANSION 2016

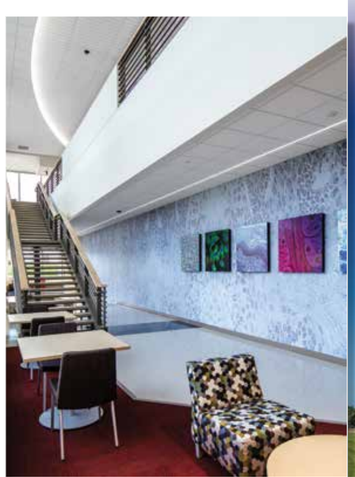
Ray Live Learning Center

- 250 seat auditorium and multipurpose room
- Distance Learning Education collaborations are key to accelerating progress in medical research
- High-resolution/HD video conferencing with global reach, including to researchers in China, South Korea, India and throughout the United States and world
- Required space needed to seat the 250 faculty and staff that will be working at The Hormel Institute within 3 - 5 years

NEW LABS

East Expansion

- Added another 20 state-of-the-art cancer research labs to The Hormel Institute and translational doctor/patient rooms for first stage clinical trials
- The Hormel Institute tripled in size in 2008 and this expansion doubles the size
- Vital space created for Institute's cutting-edge technology to accelerate discoveries
- Will add 130 jobs and up to 15 new research sections over the next few years



"RAY OF HOPE"

Donated by Gary and Pat Ray as part of their donation for the 2016 expansion, the sculpture reflects the anticancer agent silybin found in milk thistle.

The Hormel Institute named the piece "Ray of Hope" in honor of the Ray's dedication to research and hope for a cancer free world.

It is a representation of combining supercomputer technology and laboratory methods for identifying natural compounds to prevent and control cancer.

"Ray of Hope" is collaboration between The Hormel Institute, Visual Communications and Archetype.

SCIENCE PARK APARTMENTS

The Hormel Institute recently completed a major expansion that doubled its existing size and includes a promise of 120 new faculty and staff hired over the next few years.

Science Park Housing LLC, a wholly owned subsidiary of The Hormel Foundation, owns a new 42-unit facility called "Science Park Housing," managed by a new local business, Innovative Housing Concepts. Joseph Construction was the builder for the three-story project that includes 30 one-bedroom units, 11 two-bedroom units and one four-bedroom quad. The RSP designed plan blends The Hormel Institute's current cancer research center design creating a "Science Park" that includes reception area, property management office and a common residential lounge space, along with an outdoor plaza for tenants and their families.

"With 90% of The Hormel Institute's current scientists living and working in Austin, adding another 120 scientists will only increase the expected demand for rental housing which is why The Hormel Foundation approved this project," said Gary Ray, Chair of The Hormel Foundation.

"Cancer researchers have non-traditional work hours and the easily accessible 'Science Park' complex will serve to support cancer research and provide a quality living experience for them in Austin," said Jerry Anfinson, Treasurer of The Hormel Foundation.

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Fyn is a redox sensor involved in solar ultraviolet light-induced signal transduction in skin carcinogenesis. Kim, JE, Roh, E, Lee, MH, Yu, DH, Kim, DJ, Lim, TG, Jung, SK, Peng, C, Cho, YY, Dickinson, S, Alberts, D, Bowden, GT, Einspahr, J, Stratton, SP, Curiel-Lewandrowski, C, Bode, AM, Lee, KW, & Dong, Z. Oncogene, 35(31), 4091-4101. (2016).

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Clusterin induced by N,N'-dinitrosopiperazine is involved in nasopharyngeal carcinoma metastasis. Li, Y, Lu, J, Zhou, S, Wang, W, Tan, G, Zhang, Z, Dong, Z, Kang, T, & Tang, F. Oncotarget, 7(5), 5548-5563. (2016).

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JULY 1, 2015 - JUNE 30, 2016

July 21, 2015
Qiu-Xing Jiang, Ph.D.
Assistant Professor
University of Texas Southwestern Medical Center
"Nanoscale chemical engineering for studying lipid effects on ion channels and cryoEM imaging of human telomerase complexes"

July 30, 2015
Prasad G. Iyer, M.D.
Consultant, Division of Gastroenterology and Hepatology
Associate Professor, College of Medicine
Mayo Clinic
"Role of Obesity in Esophageal Carcinogenesis"

September 9, 2015
Geou-Yarh Liou, Ph.D.
Postdoctoral Senior Research Fellow
Mayo Clinic Cancer Center (Jacksonville, FL)
"Signaling mechanisms that regulate acinar-to-ductal metaplasia to initiate pancreatic cancer and the formation of pancreatic intraepithelial neoplasia"

September 16, 2015
Walden Ai, Ph.D.
Assistant Professor
University of South Carolina School of Medicine
"Function of Kruppel-like factor 4 (KLF4) in cancer development"

September 16, 2015
Chuanshu Huang, M.D., Ph.D.
Professor, Department of Environmental Medicine and Biochemistry and Molecular Pharmacology
New York University School of Medicine
"Novel Function of XIAP and Its RING Domain in Regulation of RhoGDI SUMOylation, Cancer Cell Motility and Metastasis

September 24, 2015
Jennifer Isaacs, Ph.D.
Associate Professor
Medical University of South Carolina
'Misbehaving- Heat Shock Protein 90 (Hsp90) running amuck in cancer'

October 6, 2015
You Jeong Lee, M.D., Ph.D.
Post-doctoral Fellow, Center for Immunology
University of Minnesota
"iNKT cells regulate IL-4 cell homeostasis"

January 27, 2016
Gary A. Piazza, Ph.D.
Chief, Drug Discovery Research Center
Professor of Oncologic Sciences and Pharmacology
University of South Alabama, Mitchell Cancer Institute
"Phosphodiesterase 10A, A Novel Anticancer Target."

February 25, 2016
Steven P. O'Hara, Ph.D.
Associate Consultant in Research, Division of Gastroenterology and Hepatology
Assistant Professor of Medicine
Assistant Professor of Biochemistry and Molecular Biology
Mayo Clinic, Rochester, MN
"The dynamic biliary epithelia: Molecules, pathways, and disease"

March, 24, 2016
Aaron Sarver, Ph.D.
Masonic Cancer Center
University of Minnesota
"Bone tumors in Man, Dog, and Mouse: a Summary Score Deconstruction Analyses of Osteosarcoma RNA-Seq Transcriptomics across three species"

April 7, 2016
Gina Razidlo Ph.D.
Assistant Professor, Biochemistry & Molecular Biology
Division of Gastroenterology and Hepatology
Mayo Clinic, Rochester, MN
"Targeting Metastatic Invasion in Pancreatic Cancer"

June 21, 2016
Bob Ashley, A.A.S.
Electron Microscopist
PennState
"Transmission Electron Cryo-Microscopy of Biological Macromolecules"

National Institutes of Health

National Cancer Institute

Prevention of Mammary Tumors by Metformin in Comparison to Calorie Restriction (M. Cleary)	*75,448*
Gain of Function Mutant p53 Telomere Uncapping-driven Breast Tumorigenesis (Y. Deng)	*144,048*
Targeting Aberrant Epigenetics by Nanomedicine (S. Liu)	*41,313*
Developing New Ornithine Decarboxylase Inhibitors to Prevent Skin Cancer (Z. Dong)	*153,449*
Prevention of Prostate Carcinogenesis by Next-generation Selenium (Y. Deng)	*21,767*
Modulation of p53 Induction by Targeting Cap-dependent Translation in Cancer (D. Yang)	*16,856*
Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver (N. Kang)	*182,720*
The Role of Stromal APC Haploinsufficiency in Colorectal Tumorigenesis (J. Robinson)	*196,774*
Novel Gene That Determines Metastasis in African-American Men (M. Bhat)	*109,228*
Novel Targeted Chemo/immunotherapy Approach for Localized and Metastatic CaP (M. Bhat)	*10,074*
Prevention of Colon Cancer by Targeting the Wnt/beta Catenin Pathway (Z. Dong)	*111,985*
Prevention of solar UV-induced Skin Cancer by Targeting LTZ4H (Z. Dong)	*144,200*
The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle (S. Gradilone)	*210,676*
Triggering the Dopamine Pathway to Inhibit Lung Cancer Progression (L. Hoeppner)	*124,548*

National Institute of General Medical Sciences

Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown)	*136,036*

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Identification of a Keratinocyte Stem Cell Regulatory Gene (R. Morris)	*244,440*

Department of Defense – U.S. Army

Defects in Histone H3.3 phosphorylation, and ATRX Recruitment to Misaligned Chromosomes During Mitosis Contribute to the Development of Pediatric Glioblastomas (E. Hinchcliffe)	*91,247*

AgStar Fund for Rural America

AgStar Research Project (A. Bode)	*8,749*

Mayo Clinic

S. Liu	*9,810*
S. Gradilone	*352*

University of Alabama at Birmingham

Preclinical in vitro and in vivo Agent Development Assays (A. Bode)	*61,158*

University of Arizona/NIH *NIH (Z. Dong)* *27,842*

University of Kentucky/NIH *(Y. Chi)* *24,123*

University of Louisville/NIH

M. Cleary	*36,756*
S. Liu	*12,515*

Virginia Commonwealth University/NIH

The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (E. Hinchcliffe)	*115,780*
The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (R. Brown)	*148,053*

Prairie Pharms (S. Liu) *9,262*

Other Resources

The Hormel Foundation	*5,704,013*
University of Minnesota	*440,873*
Indirect Cost Return	*1,209,943*
Other Resources	*745,734*
LLC Capital Campaign/Expansion	*3,705,009*

Total	**14,274,781**

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