THE HORMEL INSTITUTE
UNIVERSITY OF MINNESOTA

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The Hormel Institute are dedicated to a single purpose:
Improving health through medical research.

Today's **RESEARCH**,
Tomorrow's **CURES**

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THE HORMEL INSTITUTE
UNIVERSITY OF MINNESOTA

2014 - 2015 Annual Report

eliminate cancer

believe hope unite research cure

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.

support

Message from the Executive Director Dr. Zigang Dong

During the 2014-15 year, we continued our focus on cancer research because cancer already has surpassed heart disease as the No. 1 killer of Americans under age 80. In fact, cancer is the leading cause of death worldwide. Cancer affects all of us: women and men; poor and rich; old and young; and all races.

The Hormel Institute is a leading medical research institute making contributions to the identification and discovery of novel targets and agents for cancer prevention and therapy. We experienced continued success during 2014-2015 in obtaining research funding and producing major research breakthroughs, even in a national environment of overall decreased funding for research.

On May 28, 2014, we finished the design of a new building expansion and held a groundbreaking ceremony with numerous local, state, and national leaders. This 20-laboratory expansion is funded in part by $13.5 million in State of Minnesota bonding funds included in a bill supported by State Senator Dan Sparks and State Representative Jeanne Poppe, and signed by Governor Mark Dayton. The Hormel Foundation matched the state's $13.5 million commitment to construct the laboratory space on our east side and was a major contributor to the $4.5 million Live Learning Center on our west side, featuring a multi-purpose room and 250-seat lecture hall with theater-style seating and state-of-the-art global communications technology. Both additions are scheduled for completion by January 2016. All of us from The Hormel Institute are very thankful for the generous support from the State of Minnesota, The Hormel Foundation, Hormel Foods Corporation, University of Minnesota, Mayo Clinic, 5th District Eagles Cancer Telethon, Paint the Town Pink, and many other individuals and groups. In particular, I would like to thank Mr. Gary Ray, Mr. Jeff Ettinger, Mr. Richard Knowlton, Mr. Joel Johnson, Mrs. Bonnie Rietz, Mr. Jerry Anfinson, and Mr. Steve Rizzi. We thank Drs. Eric Kaler and Brian Herman (University of Minnesota); and Drs. John Noseworthy, Glenn Forbes, Robert Diasio, and Greg Gores (Mayo Clinic) for their leadership and support. We thank our elected leaders, Minnesota Governor Mark Dayton; U.S. Senators Amy Klobuchar and Al Franken; U.S. Representative Tim Walz; Minnesota State Senator Dan Sparks; Minnesota State Representative Jeanne Poppe; Minnesota State Senator David Senjem; and Austin Mayor Tom Stiehm for their continued support. We remain deeply grateful to our community, our partners, and our collaborators for giving us the gift of being able to work here. Their support and gifts allow today's research to flourish and pave the way for tomorrow's progress to continue.

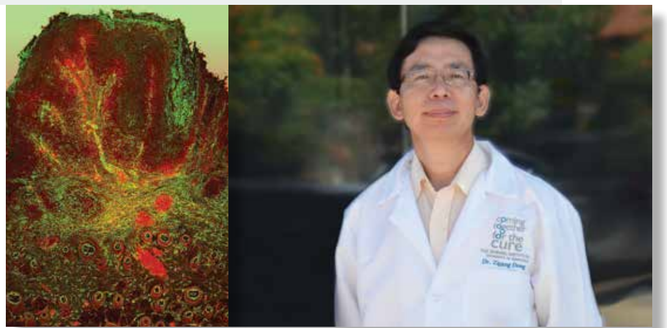
"Most human cancers are preventable, or treatable, if discovered at an early stage."

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.

a. The discovery of circulating prostaglandin biosynthesis in colorectal cancer. We found that the prostaglandin thromboxane A2 (TXA2) level is unexpectedly correlated with colorectal cancer progression. 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 over-expression 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.

b. Discovery of novel mechanisms of RNF2 in cell death.

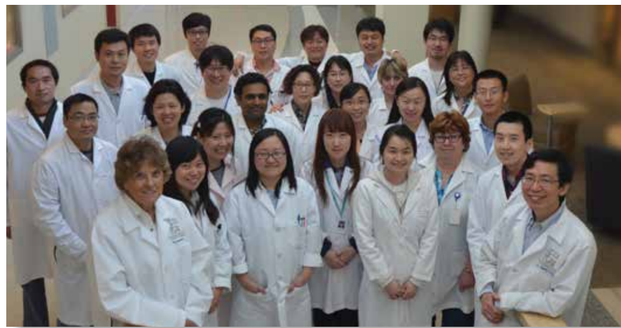
RNF2, also known as Ring1B/Ring2, is a component of the polycomb repression complex 1. RNF2 is highly expressed in many tumors, suggesting it might have an oncogenic function, but the mechanism of action is unknown. We showed that knocking down RNF2 expression significantly inhibits both cell proliferation and colony formation in soft agar and induces apoptosis in cancer cells. Knockdown of RNF2 in HCT116 p53+/+ cells resulted in significantly more apoptosis than was observed in RNF2 knockdown HCT116 p53−/− cells, indicating that RNF2 knockdown-induced apoptosis is at least partially, dependent on p53. Various p53-targeted genes were increased in RNF2 knockdown cells. Further studies revealed that in RNF2 knockdown cells, the p53 protein level was increased, the half-life of p53 was prolonged, and p53 ubiquitination was decreased. In contrast, cells over-expressing RNF2 showed a decreased p53 protein level, a shorter p53 half-life, and increased p53 ubiquitination. Importantly, we found that RNF2 directly binds with both p53 and MDM2 as well as promotes MDM2-mediated p53 ubiquitination. RNF2 over-expression also could increase the half-life of MDM2 and inhibit its ubiquitination. The regulation of p53 and MDM2 stability by RNF2 also was observed during the etoposide-induced DNA damage response. These results provide a possible mechanism explaining the oncogenic function of RNF2, and, because RNF2 is important for cancer cell survival and proliferation, it might be an ideal target for cancer therapy or prevention.

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.

Chrysin (5,7-dihydroxyflavone), a natural flavonoid widely distributed in plants, reportedly has chemopreventive properties against various cancers. The anti-cancer activity of chrysin observed in vivo studies, however, has been disappointing. A chrysin derivative, referred to as compound 69407, more strongly inhibited EGF-induced neoplastic transformation of JB6 P+ cells compared with chrysin. It attenuated cell-cycle progression of EGF-stimulated cells at the G1 phase and inhibited the G1/S transition. Compound 69407 reduced tumor growth in the A431 mouse xenograft model and retinoblastoma phosphorylation at Ser795 and Ser807/811. Overall results indicated that compound 69407 is an ATP-noncompetitive cyclin-dependent kinase inhibitor with anti-tumor effects, that acts by binding inside the Cdk2 allosteric pocket.

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.



(Left to right) Front row: Ann M. Bode, Ge Gao, Naomi Hamada, Qiushi Wang, Eunmiri Roh, Do Young Lim, Tatyana Zykova, Seung Ho Shin, Zigang Dong

Second row: Hanyong Chen, Ke Yao, Srinivasa Reddy Kanamata Reddy, Lichan Chen, Chengcheng Shi, Yi Zhang

Third row: Yan Li, Wei He, JongBin Kim, Kun Yeong Lee, Sung-Young Lee, Margarita Malakhova, Wei Ya Ma
Fourth row: KiBeom Bae, Joohyun Ryu, Hong-Gyum Kim, Hiroyuki Yamamoto, Tianshun Zhang, Tae-Gyu Lim.

Not pictured: Xiaoyu Chang, HyoSun Kim, Jihye Kim, Haitao Li, Kang Dong Liu, Mi Hee Park, Katrina Plueger, Yuqiao Sheng, DongHoon Yu, Cheng Juan Zhang

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.

"We discovered critical factors in cancer development and significant targets for cancer prevention and treatment."

Dr. Zigang Dong

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

We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of tyrosine kinase inhibitor (TKI)-sensitive and -resistant NSCLC cells and elucidated its underlying mechanisms. Treatment with ILQ inhibited growth and induced apoptosis in both TKI-sensitive and -resistant NSCLC cells. ILQ-induced apoptosis was associated with the cleavage of caspase-3 and poly-(ADP-ribose)-polymerase, increased expression of Bim, and reduced expression of Bcl-2. In vitro kinase assay results revealed that ILQ inhibited the catalytic activity of both wild-type and double-mutant (L858R/T790M) EGFR. Treatment with ILQ inhibited the anchorage-independent growth of NIH3T3 cells stably transfected with either wild-type or double-mutant EGFR with or without EGF stimulation. ILQ also reduced the phosphorylation of Akt and ERK1/2 in both TKI-sensitive and -resistant NSCLC cells and attenuated the kinase activity of Akt1 and ERK2 in vitro. ILQ directly interacted with both wild-type and double-mutant EGFR in an ATP-competitive manner. A docking model study showed that ILQ formed two hydrogen bonds (Glu762 and Met793) with wild-type EGFR and three hydrogen bonds (Lys745, Met793, and Asp855) with mutant EGFR. ILQ attenuated the xenograft tumor growth of H1975 cells, which was associated with decreased expression of Ki-67 and diminished phosphorylation of Akt and ERK1/2. Taken together, ILQ suppresses NSCLC cell growth by directly targeting wild-type or mutant EGFR.

4. Discovery of Src as a novel potential off-target of RXR agonists, 9-cis-UAB30 and Targretin, in human breast cancer cells
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. It's unclear, however, whether the anti-mammary cancer effects of UAB30 or Targretin originate from the activation of RXR. 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 showed 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 p70s6k, 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.

5. 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.

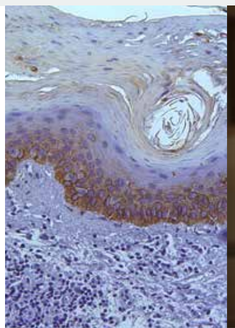
Further, we found that naproxen, a COX1 and COX2 inhibitor, induces cell-cycle arrest and apoptosis by downregulation of Bcl-2 and upregulation of Bax.

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 substantial 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. 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.

Cancer Biomarkers and Drug Resistance

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 (NIH) to identify biomarkers important in drug resistance to cancer prevention and treatment. During 2014-2015, we published a number of papers in collaboration with NIH and the University of Alabama.

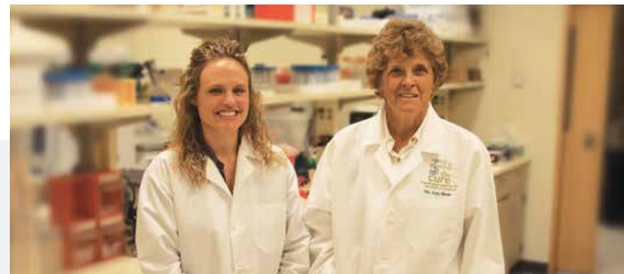
1. Epidemiologic studies have shown that diabetics receiving the biguanide metformin, compared with sulfonylureas or insulin, have a lower incidence of breast cancer. Metformin reportedly increases the levels of activated AMPK (AMP-activated protein kinase) and decreases circulating insulin growth factor-1 (IGF-1), which has encouraged its potential use in both cancer prevention and therapeutic settings. In anticipation of clinical trials in nondiabetic women, we evaluated the efficacy of metformin in nondiabetic rat and mouse mammary cancer models. 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 phosphorylated AMPK and phosphorylated p53 (Ser20), but failed to reduce Ki-67 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. Our immunohistochemistry results were a cover image for Cancer Prevention Research.

2. 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 shown preventive efficacy in colon and skin cancers. They, however, 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 naproxen's toxicity. Female Fischer-344 rats were treated weekly with the urinary bladder-specific carcinogen hydroxybutyl(butyl)nitrosamine (OH-BBN) for eight weeks. Rats were dosed daily with naproxen (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 two weeks after the final OH-BBN. With the OH-BBN-treated rats, 96 percent developed urinary bladder cancers. While omeprazole alone was ineffective (97 percent cancers), naproxen alone or combined with omeprazole-prevented cancers, yielded 27 and 35 percent cancers, respectively. In a separate study, OH-BBN-treated rats were administered naproxen: (A) daily; (B) one week daily naproxen/1week vehicle; (C) three weeks daily naproxen/three-week vehicle; or (D) daily vehicle beginning two weeks after last OH-BBN treatment. In the intermittent dosing study, protocol A, B, C, and D resulted in palpable cancers in 27 percent, 22 percent, 19 percent, and 96 percent 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. This study was a press release from the University of Michigan and the University of Minnesota.

3. Urinary bladder cancer prevention studies were performed with the nonsteroidal anti-inflammatory drugs (NSAID) naproxen (a standard NSAID with a good cardiovascular profile), sulindac, and their nitric oxide (NO) derivatives. In addition, we examined the effects of the ornithine decarboxylase inhibitor, difluoromethylornithine (DFMO), alone or combined with a suboptimal dose of naproxen or sulindac. Agents were evaluated at their human equivalent doses (HED) as well as at lower doses. In the hydroxybutyl(butyl) nitrosamine (OH-BBN) model of urinary bladder cancer, naproxen (400 or 75 ppm) and sulindac (400 ppm) reduced the incidence of large bladder cancers by 82 percent, 68 percent, and 44 percent, respectively, when the agents initially were given three months after the final dose of the carcinogen; microscopic cancers already existed. NO-naproxen was highly effective, whereas NO-sulindac was inactive. To further compare naproxen and NO-naproxen, we examined their effects on gene expression in rat livers following a seven-day exposure. Limited but similar gene expression changes in the liver were induced by both agents, implying that the primary effects of both are mediated by the parent NSAID. When agents were initiated two weeks after the last administration of OH-BBN, DFMO at 1,000 ppm had limited activity, and a low dose of naproxen (75 ppm) and sulindac (150 ppm) were highly and marginally effective. Combining DFMO with suboptimal doses of naproxen had minimal effects, whereas the combination of DMFO and sulindac was more active than either agent alone. Thus, naproxen and NO-naproxen were highly effective, whereas sulindac was moderately effective in the OH-BBN model at their HEDs.

> *"Our work funded by NIH has focused on biomarker identification in breast and bladder cancer."*
>
> Dr. Ann M. Bode

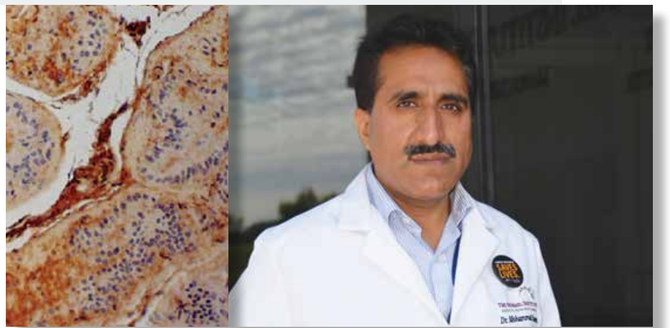
4. Naproxen [(S)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid] is a potent nonsteroidal anti-inflammatory drug that inhibits both COX-1 and COX-2 and is widely used as an over-the-counter medication. Naproxen exhibits analgesic, antipyretic, and anti-inflammatory activities. Naproxen, as well as other nonsteroidal anti-inflammatory drugs, has been reported to be effective in the prevention of urinary bladder cancer in rodents. Potential targets other than the COX isozymes, however, have not been reported. We examined potential additional targets in urinary bladder cancer cells and rat bladder cancers. Computer kinase profiling results suggested that phosphoinositide 3-kinase (PI3K) is a potential target for naproxen. In vitro kinase assay data revealed that naproxen interacts with PI3K and inhibits its kinase activity. Pull-down binding assay data confirmed that PI3K directly binds with naproxen in vitro and ex vivo. Western blot data showed that naproxen decreased phosphorylation of Akt, and subsequently decreased Akt signaling in UM-UC-5 and UM-UC-14 urinary bladder cancer cells. Furthermore, naproxen suppressed anchorage-independent cell growth and decreased cell viability by targeting PI3K in both cell lines. Naproxen caused an accumulation of cells at the G1 phase mediated through cyclin-dependent kinase 4, cyclin D1, and p21. Moreover, naproxen induced significant apoptosis, accompanied with increased levels of cleaved caspase-3, caspase-7, and PARP in both cell types. Naproxen-induced cell death was mainly due to apoptosis that involved a prominent downregulation of Bcl-2 and up-regulation of Bax. Naproxen also caused apoptosis and inhibited Akt phosphorylation in rat urinary bladder cancers induced by N-butyl-N-(4-hydroxybutyl)-nitrosamine.



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

Molecular Chemoprevention and Therapeutics

MOHAMMAD SALEEM (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. Understand the biochemical, cellular and molecular processes crucial for the development of hormone-related (prostate and breast cancer) and lethal (pancreatic & colon cancer) cancers.
2. Identify potential agents that could be used to treat and prevent cancer in humans.
3. Identify novel tissue, serum and urine-based diagnostic and predictive biomarkers for prostate and breast cancer.
4. Understand 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) also will be excellent candidate targets for staging the disease as well as 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 benchside research to the bedside use in clinics.

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

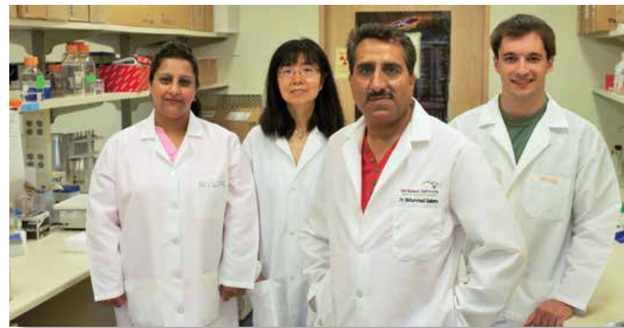
The critical pathological processes that occur during the development and progression of human prostate cancer and are known to confer aggressiveness to cancer cells are (1) abolishment of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cell cycle resulting in unchecked proliferation of cancer cells. Cellular senescence is physiologically important because it is a potent tumor suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumor cells is an essential defining property of a pluripotent stem cell–like phenotype of cancer cell that 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 that do not respond to chemotherapy or radiotherapy possess the traits of stem cells, thus regenerating themselves even after chemotherapy 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 Suppressor 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 aimed at delineating 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. Our current focus is to test our hypothesis in prostate, pancreatic, and skin cancer (melanoma). We are running this program in collaboration 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. We earlier reported that S100A4 is overexpressed during progression of prostate cancer in humans and in TRAMP mouse, an autochthonous transgenic model that develops prostate cancer in a manner similar to human disease. We recently 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, provided 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.



(Left to right) Neelofar Jan Bhat, Xiaodong Guo, Mohammad Saleem (Bhat), Chris Koppa
Not pictured: Firdous Beigh, Kate Soiney

5. Transition of androgen-dependent 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. The success

of these therapies, however, 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, that are widely used in clinics to treat cancer, show dismal results in men with advanced prostatic malignancy. It recently has been observed that over-expression 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 mechanisms, 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.

"Identification of new predictive biomarkers will be important for improving clinical management, leading to improved survival of patients with prostate cancer."

Dr. Mohammad Saleem (Bhat)

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 percent 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 that 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" that exhibits 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 NFκB signaling pathway. We are testing cocoa polyphenol in animal models evaluating its preventive as well as therapeutic value against cancer. For our studies, we have collaborated with Barry Calibaut (Belgium), one of the leading companies in the world producing functional foods including functional chocolates. We are seeking funds for support of this research study.

Our 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 of the Section Leader (Mohammad Saleem) in year 2014-2015:

(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

Membrane Biochemistry & Biophysics

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

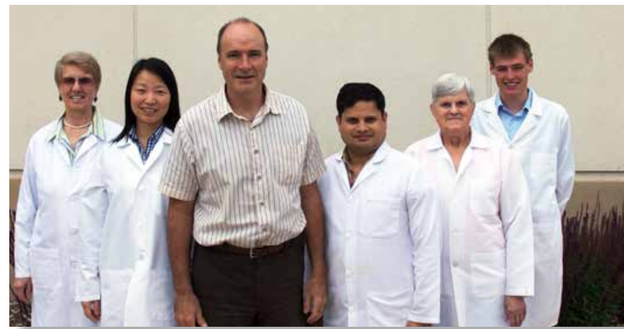
Cholera toxin B endosytosis was affected by the over-expression of GLTP.

When people read or hear the word "lipid", the picture that often comes to mind is the fat or grease associated with meat or body tissue. Generally unappreciated and misunderstood is the fact that many lipids play other key roles that are fundamental for healthy cell function and survival. For instance, formation of the thin, flexible barriers that surround cells and divide the cell interior into specialized compartments depends on lipids. These lipids are specially modified at the molecular level so that they are polar at one end and nonpolar at the opposite end. As the polar ends prefer to be in contact with water and the nonpolar ends do not, these special lipids readily form layers only two molecules thick, i.e. bilayers, commonly known as cell membranes. The thin, flexible nature of cell membranes enables them to act as selective permeability barriers to control what gets in and out of cells. Interestingly, there are many more varieties of lipids found in membranes than are needed to form bilayers. Over the past two decades or so, it has become clear that some membrane lipids can function as intracellular messenger signals that regulate cell growth, proliferation, and programmed cell death and survival processes, while other membrane lipids can cluster together to form membrane microdomains that control the spatial distribution and lateral interactions of certain membrane proteins. The discovery of these new functions for membrane lipids underscores why biomembranes so often come under direct attack during cancer and infectious disease.

Our research focuses on membrane lipids known as sphingolipids. Certain sphingolipids serve as key components needed for formation of "raft" microdomains in membranes. Rafts appear to function as organizing regions for some signaling kinases as well as target sites for certain viruses and bacteria. In earlier investigations, our research focused on rigorously defining the physical basis for raft microdomain functionality. To do so, we developed ways to quantitatively measure the lateral elasticity within model membranes as well as accurately assess and quantify physical changes that occur within the raft microdomain environment when the content and structure of sphingolipids and sterols becomes altered. This research helped identify structural features of sphingolipids that regulate their interactions with other membrane lipids and provided fundamental insights into the unique physical features of membrane microdomains at the heart of their lateral organizing functionality. The findings have been proven to be important for understanding how changes in membrane lipid composition can regulate interaction with proteins that need to translocate onto membranes to function.

Formation and maintenance of sphingolipid-enriched microdomains in cells are likely to involve 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 have found that GLTP functionality is regulated by lipid composition and packing within membranes. To gain insights into the lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we have used a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balances, NMR, microcalorimetry). We have applied this basic knowledge to decipher the functional regulation of GLTP, i.e. exactly how GLTPs accomplish the intermembrane transfer of glycolipids. To do so, we carried out the first molecular cloning of human GLTP and showed the existence of related homologs in mammals, plants, and fungi. Molecular biological approaches involving polyermase chain reaction (PCR) enabled amplification of mRNA transcript open reading frames and production/purification of human GLTP and related homologs using bacterial expression systems. The successes enabled application of X-ray crystallographic approaches that led to molecular structure determination of GLTP and related homologs in glycolipid-free form and complexed with different glycolipids in collaboration with structural biologists in the D.J. Patel lab at Memorial Sloan Kettering Cancer Center in New York and in the L. Malinina lab at CIC bioGUNE in Derio/Bilbao, Spain. Our work showed that human GLTP forms a novel structural fold among known proteins. The Worldwide Protein Data Bank has designated human GLTP as the founding member and prototype of the GLTP superfamily, enabling our research findings to be published in Nature, PLoS Biology, Structure, The Journal of Biological Chemistry, Biophysical Journal, Biochemistry, and Journal of Lipid Research. The studies have shed light on the: i) structural adaptation used by GLTP to accommodate different glycolipids within its binding site; ii) functional role played by intrinsic tryptophan residues in glycolipid binding and membrane interaction; and iii) structural basis for the more focused glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2.

In studies of the model plant, Arabidopsis thaliana, carried out in collaboration with Dr. 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 showed 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 recently was published in Cell Reports.
In other recent investigations, we reported the discovery of a new GLTP structural homolog in human cells that we named ceramide-1-phosphate transfer protein (CPTP). Remarkably, the lipid specificity of CPTP has evolved for binding/transfer of ceramide-1-phosphate rather than glycolipids even though CPTP still forms a GLTP-fold encoded by a completely different gene than GLTP. In collaboration with Dr. Ted Hinchcliffe at The Hormel Institute, University of Minnesota, we have tracked the location of CPTP in mammalian cells using state-of-the-art fluorescence microscopy approaches. In collaboration with the Charles Chalfant lab at Virginia Common¬wealth University, we showed 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. CPTP previously was unknown and unstudied prior to our investigations. The recent successful CPTP research efforts, published in Nature, have stimulated a new research project on sepsis with our collaborators at Virginia Commonwealth University; Memorial Sloan Kettering Cancer Center in New York; and The Hormel Institute, University of Minnesota focused. Investigations now are underway to decipher the molecular means to control and reverse inflammation, which is critically important for successful resolution and recovery from sepsis.



(Left to right) Liudmila (Lucy) Malinina, Xiuhong Zhai, Rick Brown, Shrawan Kimar Mishra, Helen Pike, Tommy Dvergsten

We anticipate that elucidation of the fundamental structure-function relationships governing GTLP and CPTP action will facilitate the development of pharmacological ways to modulate GLTP and CPTP while enhancing 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; Virginia Commonwealth University in Richmond; The Russian Academy of Sciences in Moscow; The University of Copenhagen in Denmark; CIC bioGUNE in Derio/Bilbao, Spain; and the Mayo Clinic in Rochester, MN. Our research continues because of financial support received from the National Institute of General Medical Sciences; the National Cancer Institute of NIH; the National Heart, Lung, and Blood Institute of NIH; and The Hormel Foundation.

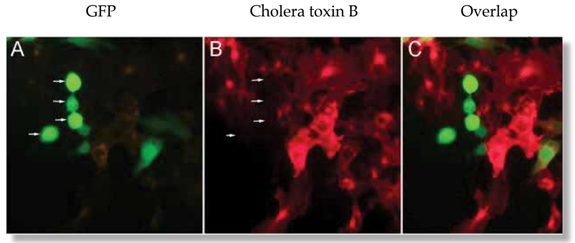
> *"The discovery of these new functions for membrane lipids under-scores the reasons why biomembranes come under direct attack during cancer and infectious disease."*
>
> Dr. Rhoderick E. Brown

For more details regarding research expertise and scientific publications of our lab, please visit the following web sites:

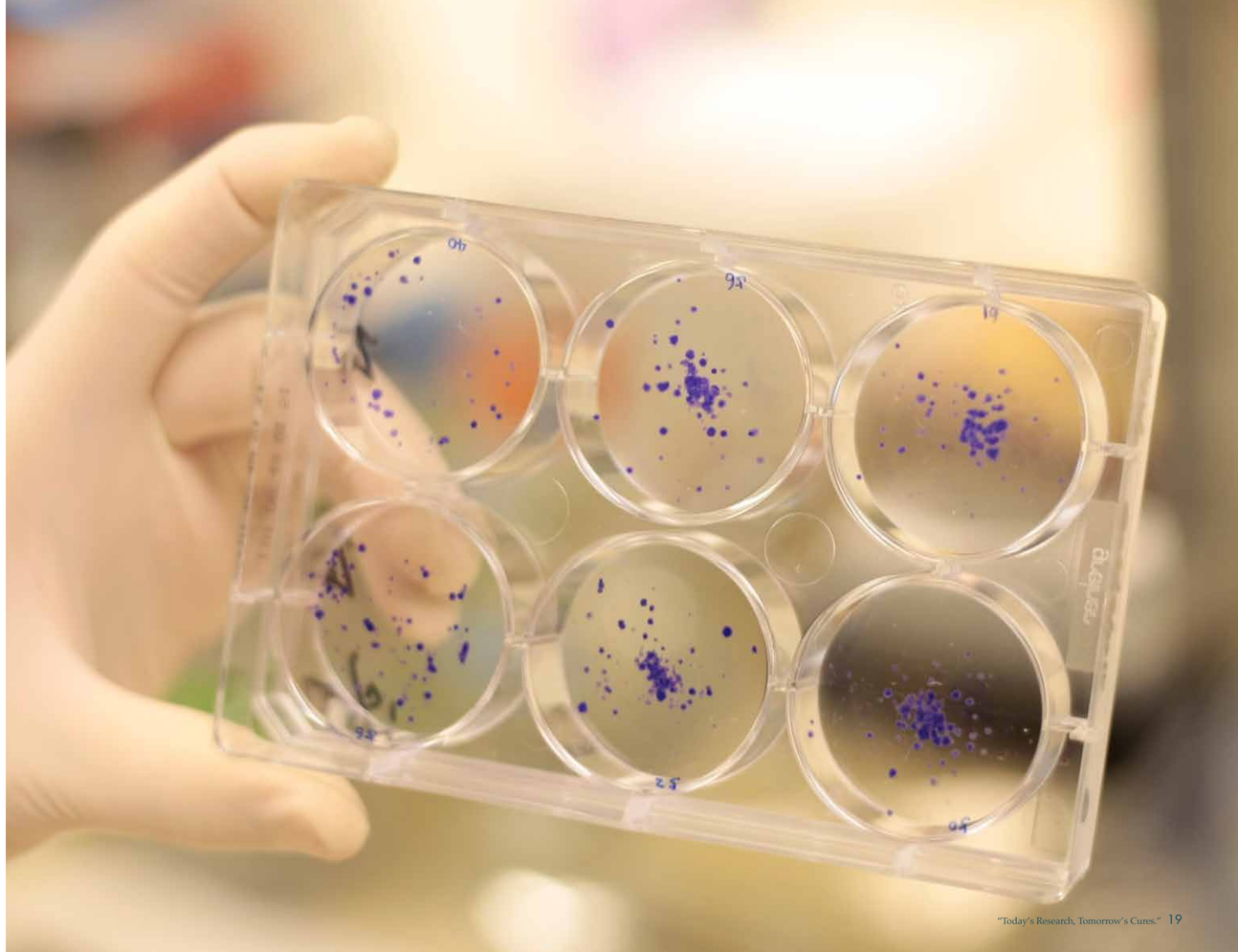
My NCBI Collections (REB): http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/42052948/?sort=date&direction=descending

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



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



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. Given that their biological functions are tightly coupled to their molecular structures, elucidating atomic details of their structures is crucial to understanding the molecular mechanisms underlying their physiological functions. Biomolecules are too small to be seen even with the most-advanced electron microscope. Special techniques need to be employed. 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 elucidate how biomolecules work and identify new avenues for developing therapeutics.

Our research focuses on elucidating atomic details of key molecular interactions involved in diseases, especially diabetes and cancer. In particular, we focus on transcriptional regulators involved in diabetes and protein functional modulators involved in tumor progression and metastasis. We apply structural biology to better understand their normal function and dysfunction in the disease state as well as discover or design structure-based functional modulators.

HNF1α (Hepatocyte Nuclear Factor1α) and HNF4α are the master regulators of pancreatic β-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 HNF1α and HNF4α. These structures provided valuable information on the molecular basis of target-gene recognition, ligand-mediated activation, and functional disruption by disease-causing mutations. These structures, however, provided partial answers as to how their full transcriptional activities arise and how these proteins are involved in additional protein-protein interactions and physiological functions. We set out to identify previously unknown functional binding partners of HNF1α and HNF4α in β-cells and study these interactions' physiological implications – 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 findings on the mediator component of the main transcriptional machinery, MED25, as the functional binding partner of HNF4α and its implication to β-cell function. We are following up on additional binding partners and their physiological implications, such as novel transcriptional co-repressors AES and EBP1 for HNF1α and HNF4α, respectively. These studies will advance the understanding of the transcription regulatory network in β-cells and provide a new avenue for diabetes prevention/treatment by discovering novel, more-effective target sites for designing and further improving partial agonists selectively against them.

Another diabetes-related project 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 an attractive target for diabetes treatment. We finished the Foxo1/DNA complex structure and have submitted the manuscript for publication in which we identified a new Foxo1 binding site and novel binding modes on G6pase promoter.

We also have embarked on new cancer research projects. Dub3 is an ubiquitin hydrolase (de-ubiquitinase) and key protein that relays extrinsic signals to regulate epithelial-mesenchymal transition (EMT) and metastasis in breast cancer. It can serve as a druggable target for treating triple negative/basal-like breast cancers. We started determining the crystal structure of the Dub3 catalytic domain alone and/or its complex ubiquitin, its substrate. We have made sufficient progress and are improving the crystals as well as finishing the structure determination. Once complete, we will start computer-assisted 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 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 lead to new therapeutic interventions.

> *"Our research currently is focused on elucidating the atomic details of key molecular interactions involved in human diseases, especially diabetes and cancer."*
>
> Dr. Young-In Chi

Another study is on the leukemic fusion protein AML1-ETO that occurs frequently in acute myeloid leukemia (AML) and has received much attention over the past decade. We want 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 collaboration with The Hormel Institute's Dr. Shujun Liu as we work on crystal structure determination of the complexes and virtual screening of compounds for potential functional modulator discovery.

Thirdly, hexokinase II (HK2), which catalyzes the first committed step in glucose metabolism, is expressed exclusively in prostate cancer cells, particularly elevated in lethal castration-resistant prostate cancer (CRPC) harboring PTEN/p53 deletions. HK2 has emerged as an attractive target for incurable CRPC. Together with Dr. Yibin Deng of The Hormel Institute, we have assembled a multidisciplinary research team targeting this protein from different angles. One way to inhibit HK2's oncogenic activity is to suppress its gene expression. It recently was reported that HK2 expression is regulated by untranslated RNAs.

(Left to right) Puja Singh, Young-In Chi
Not pictured: Shu-Ping Tung

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 translation initiation factors, such as eIF4a. These studies' successful outcomes, including the complex's crystal structure, will help identify novel, anti-prostate cancer therapeutic compounds.

Additional cancer-related projects with therapeutic values include FABP/inhibitor complexes, novel protein kinases/inhibitor complexes, and small RNA molecules for drug delivery. Our lab will continue this work and expand target molecules to include more cancer-related proteins leading to additional preliminary data for sustaining grant applications. Crystal structure determination, functional studies, and drug discovery will provide a critical basis for human physiology, dysfunction in the disease state, and a better strategy for therapeutic intervention.

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

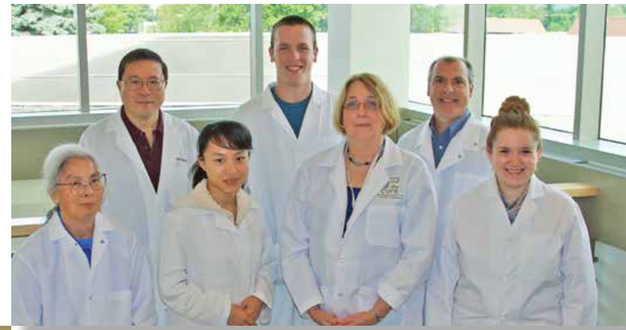
Pictured is an estrogen receptor from a series of images showing the staining of mammary tumors for adipokine (made in fat tissue) growth factors. Brown staining are the proteins of interest.

Primary interests of the Nutrition and Metabolism section are the effects of body weight and food intake on the development of breast cancer using mouse models. Past studies have included effects of genetic and dietary induced obesity on breast/mammary tumor development, particularly with respect to body fat and serum IGF-I, leptin and adiponectin levels. Other studies have assessed the effect of calorie restriction on the prevention of mammary tumors in several mouse models of breast cancer. Of particular interest, we consistently find that periods of moderately severe calorie restriction followed by refeeding – which we term "intermittent calorie restriction" – results in much greater reduction in mammary tumor incidence than the same degree of restriction implemented chronically with both interventions resulting in 20 to 25 percent calorie reduction. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors, and the IGF-axis. Based on results of our studies, we hypothesized that the altered (i.e. reduced) adiponectin:leptin ratio that 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 result 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 of The Hormel Institute 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 might provide an easier approach for individuals to reduce caloric intake for disease prevention. In fact, several recently promoted 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 successful. This has led to interest in identifying compounds that act like calorie restriction, such as calorie-restriction mimetics. One such compound is metformin, a commonly used type 2 diabetic drug. Our most recent work focuses on directly comparing moderate calorie restriction (25 percent reduction) to metformin treatment on the prevention of mammary tumors. This study is being conducted in a transgenic mouse model to mimic post-menopausal breast cancer and includes obese- as well as normal-weight subjects. The intervention was started when the mice were middle-age to reflect also what would occur in at-risk women. We also are conducting studies related to metformin's effects on cancer progression. We have 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 effect in either lean or obese mice. NEEDS MORE TEXT/EDITING In contrast, 25 percent calorie restriction resulted With respect to mechanisms of action of these interventions not only are we assessing alterations in the AMPK pathway but also on aspects of altered glucose metabolism that may result. We anticipate our ongoing studies will provide valuable insights into ways to prevent mammary tumor development and slow disease progression. In contrast 25% calorie restriction resulted in a significant decrease in mammary tumor incidence and delayed age when tumors were detected.

Other Professional Activities
Presentations
Minnesota Chemoprevention Consortium, June 2015

Attended
Obesity Week 2014, Boston, Mass., November 2014
Grant Review Committees
NIH Study Section Meetings (October 2014 and March 2015)



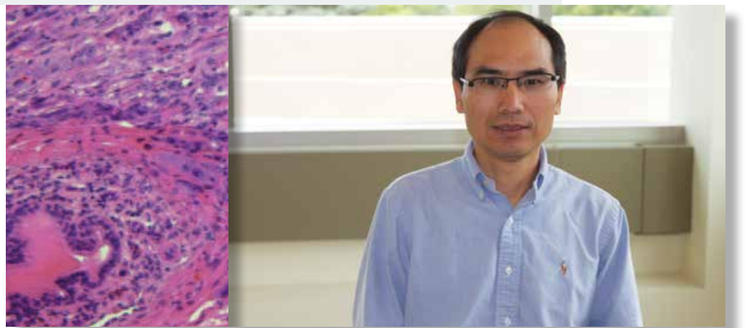
(Left to right) Nancy Mizuno, DaQing Yang, Xi Pan, Ben Harris, Margot Cleary, Michael Grossmann, Brenna Nordeng
Not pictured: Jingfei Chen, Shuxia (Susan) Jiang, Defeng Wang

"We anticipate that these ongoing studies will provide valuable insights into ways to prevent mammary tumor development and to slow disease progression."

Dr. Margot P. Cleary

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 the 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 that lead to the loss of wild-type p53 function and/or oncogenic gain of function (GOF) identified in more than half of human cancers. The comprehensive genomic/whole exons sequencing analyses sponsored by The Cancer Genome Atlas (TCGA) consortium confirmed the high frequency of TP53 mutations in all of 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. The mechanisms that underlie wild-type, p53-mediated tumor suppression and mutant p53-driven tumor development, however, 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 and proteomic approaches, bioinformatics, computational modeling, RNAi-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. We currently are trying to dissect the molecular basis underlying Dram-deficiency-driven tumorigenesis in vivo. We also are exploring whether and how the crosstalk between p53-initiated autophagy and p53-mediated cell metabolism leads to tumor initiation, progression, and metastasis.

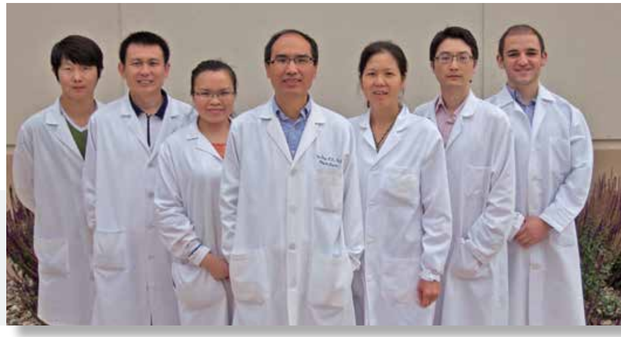
To answer the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing tumor development in vivo, we have generated "triple" mutant mice utilizing the conditional Dram knockout mice to breed with mice deficient in p53-mediated apoptosis (p53R172P knock-in or Puma knockout)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

"Finding effective and selective means of killing prostate cancer cells carrying Pten/p53 deficiency is critical to successfully treat currently incurable CRPC."

Dr. Yibin Deng

Telomeres are nucleoprotein caps that protect chromosomal ends from being recognized as 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 expresses "hot spot" mutant p53 protein found in cancer patients in breast epithelium. We believe that this mouse model will faithfully recapitulate the genetic abnormality commonly observed in human sporadic breast carcinomas. We are 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) Yingjie Zhang, Lei Wang, Yan Cai, Yibin Deng, Lingli Hou, Ji Wang, Mark Mizrachi
Not pictured: Tian Lan, Huanan Wang, Fengxia Wu

Our studies currently suggest that endogenous expression of "hot spot" mutant p53 promotes breast tumor development in comparison with the loss of p53 in breast epithelial cells. To understand the molecular mechanism underlying mutant p53-mediated GOF, we found that "hot spot" mutant p53 protein cooperates with CCCTC-binding factor (CTCF) to transcriptionally downregulate PHLPP2 resulting in activation of AKT1-mTORC1 signaling to exert its oncogenic GOF in multiple independent, yet complementary, mouse models. Surprisingly, the activated AKT1-mTORC1 signaling generates a positive feedback loop to sustain mutant p53 protein expression through 4EBP1-eIF4E translation axis. Accordingly, genetic and pharmacologic targeting of the AKT1-mTORC1 signaling axis not only strikingly blocks mutant p53-driven GOF properties but also dramatically diminishes mutant p53 protein. Given that mutant p53 is essential for its GOF but targeting the mutant p53 protein for cancer therapy has proved

challenging, our novel findings provide a potential and effective therapeutic strategy for human cancers carrying mutant p53.

3. Exploring the molecular targets involved in selective killing of 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 made progress 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 to 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 androgen synthesis blocker abiraterone recently approved by the Food and Drug Administration (2011, FDA); and the second generation of AR signaling inhibitor enzalutamide (formerly MDV3100) (2012, FDA), which has demonstrated efficacy against chemotherapy resistant CRPC with median increase in survival of four to five months. Nearly all CRPC patients, however, inevitably develop acquired resistance to the "second generation," anti-AR signaling axis treatments within about six to 12 months. No therapeutic options currently 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 kill cancer cells through intrinsic apoptosis to cause tumor regression in xenograft and lead to near-complete tumor suppression in Pten-/p53-deficiency-driven CRPC mouse model. Mechanistically, 2-DG causes AMPK phosphorylation, which, in turn, inhibits mTORC1-S6K1 translation signaling to preferentially block anti-apoptotic protein MCL-l synthesis to prime mitochondria-dependent apoptosis while simultaneously ULK1-driven autophagy for cell survival to counteract the apoptotic action of anti-Warburg effect. Inhibition of autophagy with CQ, accordingly, sensitizes cancer cells to apoptosis upon 2-DG challenge. Given that 2-DG is recommended for phase II clinical trials for prostate cancer and that CQ has been used clinically 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.

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

Our ongoing projects involve collaborations with researchers from Texas Tech University Health Sciences Center School of Pharmacy in Amarillo, Texas; The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Roswell Park Cancer Institute in Buffalo, N.Y.; and Mayo Clinic College of Medicine in Rochester, Minn. Our research projects are supported by grants from the National Cancer Institute of the National Institutes of Health and The Hormel Foundation.

Other Professional Activities
Grant Reviewer, National Cancer Institute

Cancer Cell Biology and Translational Research

Sergio Gradilone
Section Leader
Assistant Professor

This shows a cross section of a bile duct, where the nuclei of cholangiocytes lining the duct are stained in blue and a primary cilium (shown in red) extending into the ductal lumen.

Our section started in November 2014 and we equipped the new laboratory, putting together a small team to start moving our research forward. 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 might be envisioned. We currently 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 now are able to induce the restoration of primary cilia in tumor cells and bring back the malignant cells to a more normal phenotype, which might contribute to the development of new therapeutic strategies based on the rescue of primary cilia integrity.

The lab primary cilia research is focused now on an aggressive, lethal form of liver cancer known as "cholangiocarcinoma" that derives from epithelial cells of the bile ducts. Its incidence has been increasing worldwide in recent decades and there is no effective treatment for it. 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.

During our time at The Hormel Institute, our section brought a federal grant form NIH/NCI (R21 CA166635) and secured new funding for the coming five years (R01 CA183764), also from the National Cancer Institute, part of the National Institutes of Health.

We established several collaborations, both intra- and extramural, with prestigious investigators and institutions including: Dr. Mohammad Saleem Bhat (The Hormel Institute); Drs. Nicholas LaRusso and Steven Alberts (Mayo Clinic Rochester, MN); Drs. Kabir Mody and Debabrata Mukhopadhyay (Mayo Clinic, Jacksonville, FL); Dr. Aram Hezel (University of Rochester School of Medicine, Rochester, NY); Dr. Mina Komuta (Cliniques Universitaires Saint-Lu, Brussels, Belgium); Dr. Jesus Banales (Biodonostia Research Institute -Donostia University Hospital, San Sebastian, Spain); and Acetylon Pharmaceuticals Inc. (Boston, MA), among others.

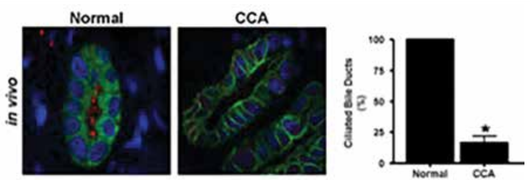
The results of our research are uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilia architecture and 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 that hopefully will start patient recruitment in early 2016. 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.

Publications/Meetings

1. Gradilone SA*, Lorenzo Pisarello MJ, LaRusso NF. "Primary Cilia in Tumor Biology: The Primary Cilium as a Therapeutic Target in Cholangiocarcinoma". Curr Drug Targets, 2015. [Epub ahead of print]. *Corresponding author.
2. Gradilone SA*, O'Hara SP, Masyuk TV, Lorenzo Pisarello MJ, LaRusso NF. "miRNAs and Benign Biliary Tract Diseases". Semin Liver Dis, 35(1):26-35, 2015. *Corresponding author.
3. Lorenzo Pisarello MJ, Howard BN, Trussoni CE, Gradilone SA*. "Exportin-5 downregulation induces miRNA dysregulation and HDAC6 over-expression in cholangiocarcinoma" [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18–22; Philadelphia, PA. Abstract nr 192. *Corresponding author.

"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."
Dr. Sergio Gradlione

(Left to right) Kristen Thelen, Sergio Gradilone, Adrian Mansini, Maetzin Cruz-Reyes



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.

Cellular Dynamics

Edward H. Hinchcliffe, Ph.D.
Section Leader
Associate Professor

In vitro assembly of a frog nucleus and centrosome.

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

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 to ensure genomic stability. The loss or gain of whole chromosomes during abnormal cell division leads to aneuploidy in which daughter cells have variable chromosome numbers. This is a major problem for cells because there is a change in the dosage of essential gene products. The cell has developed multiple biochemical checkpoints and 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. To date, no mechanisms, however, 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 also is relevant to identifying potential targets for chemotherapy agents
Experimental research results

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

Dr. Edward H. Hinchcliffe

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 recently have 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 accumulate Ser31-P along their arms. H3.3 Ser31 hyper-phosphorylation persists after anaphase, and is found on both lagging

(Left to right) Charles (Charlie) Day, Edward Hinchcliffe, Alyssa Langfald, Sela Fadness
Not pictured: Kul Karanjeet

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 currently are using microsurgery coupled with time-lapse videomicroscopy of living acentrosomal cells to investigate the role of the centrosome in cell cycle regulation. To directly visualize the role of microtubules, and regulatory molecules during the acentrosomal cell cycle, we have generated 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 to ensure fidelity during mitotic spindle assembly.

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

In addition to the tektins, we are exploring the role of two highly conserved proteins called EFHC 1 & 2. These Ca2+-binding proteins also are involved in centriole assembly and the formation of midbodies. Importantly, mutations in these proteins lead to abnormal cell division, associated with neurological birth defects.

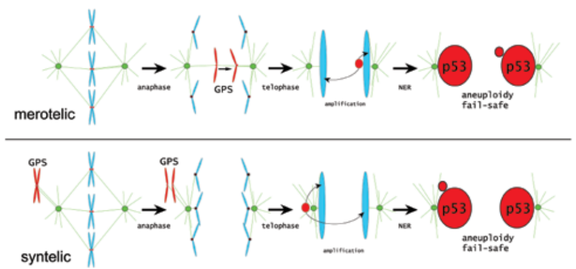
We are interested in uncovering the molecular mechanisms underlying these observations. We currently are examining the motility of several key regulators of midzone function: PRC1 and Kif4, in response to experimental loss of tektin 2 and or EFHC 1&2. We are using live-cell imaging, and FRAP analysis to examine the role played by tektins in regulating these important components of the cell division apparatus.

4. Coordinating cytokinetic furrow formation with anaphase onset
The cell-division furrow – created by the recruitment of actin filaments and the motor protein myosin II – is formed between the separating sister chromatids at anaphase. This furrow constricts the dividing cell into two daughters. To ensure that cytokinesis 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 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. Once cells progress beyond this point, however, the furrow will form, regardless of whether or not microtubules persist. Polo-like kinase 1 activity also is 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 also will provide a source of potential targets for future anti-cancer drugs.

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

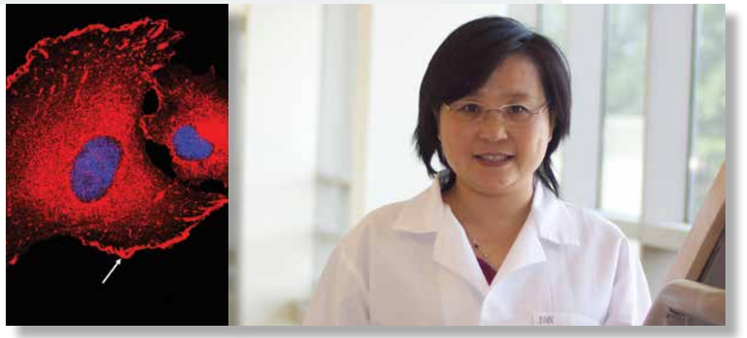


Other professional activities
Review panel, National Science Foundation, USA
Mentor, American Society for Cell Biology Minorities Affairs Committee, FRED mentor

Ad hoc reviewer:
European Research Council
Medical Research Council, UK
Wellcome Trust, UK

Tumor Microenvironment and Metastasis

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 liver is a preferred organ for cancer metastasis, and liver metastasis remains a principal cause of patient death. Our research program is focused on bidirectional interactions between cancer cells and the liver's microenvironment that critically regulate the development of liver metastasis. We specifically are interested in the interactions between cancer cells and hepatic stellate cells (HSCs), which are liver resident cells. We study how cancer cells induce activation of hepatic stellate cells into cancer-promoting fibroblasts and how activated HSC/fibroblasts promote implantation and proliferation of cancer cells in the liver.

We have identified three critical mechanisms that control TGF-β-mediated activation of HSCs, which might present important therapeutic targets to inhibit HSC activation. 1) We found that vasodilator-stimulated phosphoprotein (VASP) promotes HSC activation by regulating the targeting of TGF-β receptors to the plasma membrane. VASP forms a protein complex with Rab11, a key molecule regulating recycling of TGF- β receptors, and VASP is required for Rab11-dependent recycling of TβRII to the plasma membrane. VASP of HSCs promotes cancer cell proliferation and growth in a cancer/HSC coculture and coimplantation mouse model. In patients, high VASP expression levels in hepatocellular carcinoma correlate with poor survival of patients. These data led us to an extended study focusing on the role of VASP in cancer cells. We found that VASP of cancer cells is required for adhesion and proliferation of cancer cells disseminated in the liver, requisite for the development and progression of liver metastasis. Together, these data highlight VASP as a therapeutic target for liver metastasis. 2) PDGF receptor alpha (PDGFRα) promotes HSC activation via regulating TGF-β receptors. HSCs express both PDGFRα and PDGFRβ receptors. PDGFRα but not PDGFRβ, however, is required for TGF-β-mediated activation of HSCs. PDGFRα forms a protein complex with TGF-β receptors, which is required for internalization of TGF-β receptors and TGF-β downstream signaling. PDGFRα of HSCs promotes colorectal cancer cell proliferation and migration in vitro, and it is upregulated when cancer cells invade the liver in a liver metastasis mouse model and colorectal cancer patients. Thus, PDGFRα can cross-talk with TGF-β receptors to promote activation of HSCs. 3) One ongoing study is focused on the role of E1A-binding protein p300 (p300) in HSC activation; p300 is an acetyltransferase with a poorly defined role in HSCs and amenable to inhibition by small molecule. Our preliminary data demonstrate that p300 facilitates transcription of TGF-β-induced target genes in the nucleus, thereby promoting HSC activation. Thus, p300 presents another important target to inhibit HSC activation and the prometastatic liver microenvironment.

Presentations (7/1/2014 – 6/30/2015)

Oral Presentation at The Liver Meeting, AASLD, Nov. 7-11, 2014, Boston. VASP mediates plasma membrane targeting of TGF-beta receptor II and myofibroblastic activation of hepatic stellate cells.

Publications (7/1/2014 – 6/30/2015)

1. Tu K, Li J, Verma VK, Liu C, Billadeau DD, Lamprecht G, Xiang X, Guo L, Dhanasekaran R, Roberts LR, Shah VH, Kang N. Vasodilator-stimulated phosphoprotein promotes activation of hepatic stellate cells by regulating Rab11-dependent plasma membrane targeting of transforming growth factor beta receptors. Hepatology. 2015 Jan;61(1):361-74. doi: 10.1002/hep.27251. Epub 2014 Sep 19.
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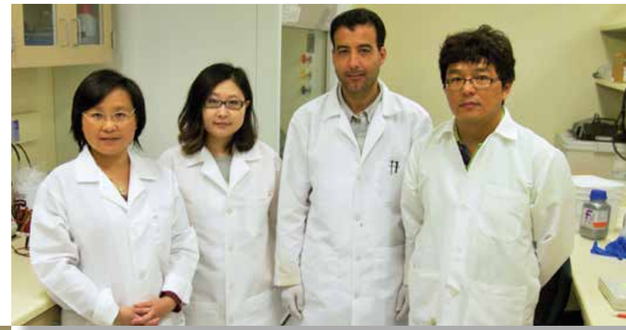
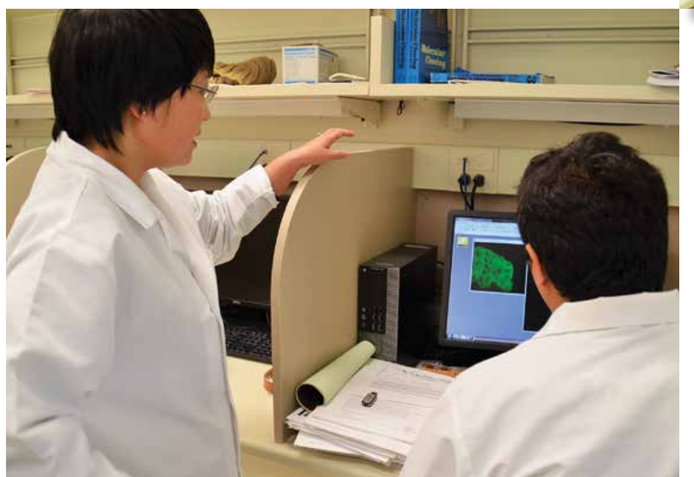


(Left to right) Ningling Kang, Luyang Guo, Ahmed Chahdi, Xiaoyu Xiang
Not pictured: Jiachu Li, Yali Xu



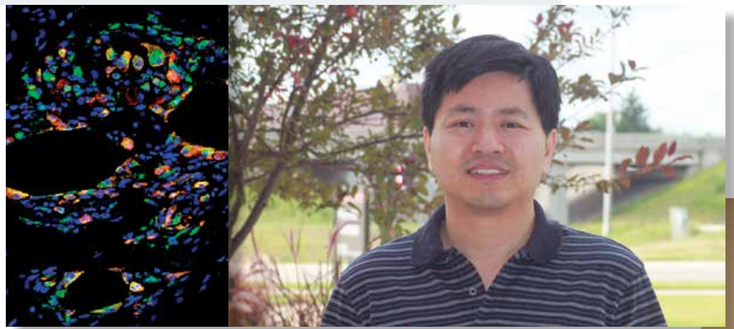
"Liver metastasis remains a principal cause of patient death despite significant advances in the treatment of cancer and this metastatic liver disease."

Dr. Ningling Kang

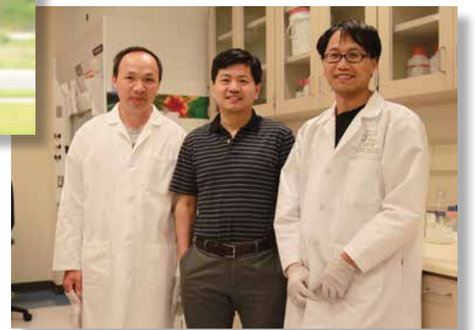
Immunoregulation of Autoimmune Diseases and Cancer

BING LI, PH.D.
Section Leader
Assistant Professor

Our studies have revealed that FABPs play essential roles in regulating cellular metabolism and immune functions. While A-FABP is more critical in regulating functions of macrophages and adipocytes in tumor development, E-FABP exhibits a unique role in T cell differentiation in inflammatory autoimmune diseases. These results will have significant implications in their potential applications.



A-FABP (red color) is abundantly expressed in tumor infiltrated macrophages (green color) in breast cancer.



(Left to right) Yuwen Zhang, Bing Li, Enyu Rao

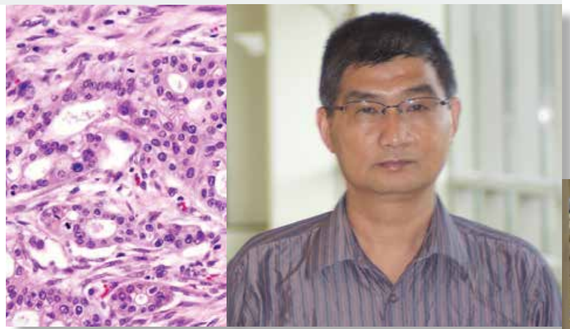
The main focus of this section is to understand the role of fatty acid binding proteins (FABPs) in autoimmune diseases and cancer development. FABPs constitute a family of small, highly homologous intracellular lipid chaperones that have been recognized as central regulators of both metabolic and inflammatory pathways. We have shown that adipose FABP (A-FABP) and epidermal FABP (E-FABP) play important roles in autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) model, a mouse model of human multiple sclerosis (MS), and in different types of cancer, including breast, skin and colon cancers. The exact mechanisms underlying these observations, however, remain undetermined. My laboratory's research currently strives to understand how FABPs regulate cellular metabolism and intracellular signal transduction pathways in leukocytes; determine the mechanisms by which FABPs link metabolism and complex diseases; and identify specific inhibitors of FABPs for potential drug discovery.

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

Dr. Bing Li

Translational Cancer Research

D. JOSHUA LIAO, M.D., PH.D.
Section Leader
Associate Professor



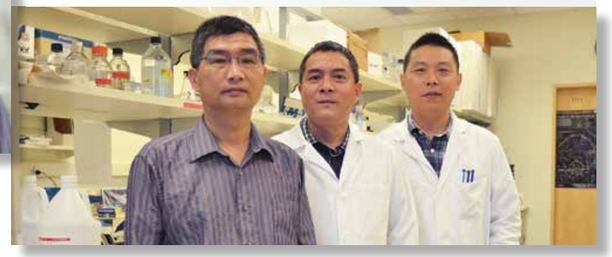
Micrograph of pancreatic ductal adenocarinoma (the most common type of pancreatic cancer).

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

We also have initiated a new project to develop a new cancer therapeutic regimen. Whole body hyperthermia (i.e. systemic increase in the body temperature) has been used clinically for decades to treat cancer, either alone or adjuvant to chemotherapy or irradiation. In almost all cases, however, the whole body temperature is raised by sophisticated warming devices to a high, feverish range for only a short period (a few hours). In addition, there are many attempts aiming to develop chemical inhibitors of heat-shock proteins (HSPs) as anticancer drugs because most cancers manifest elevated levels of HSPs to survive not only heat but also many other forms of stress. Besides,

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

Dr. D. Joshua Liao

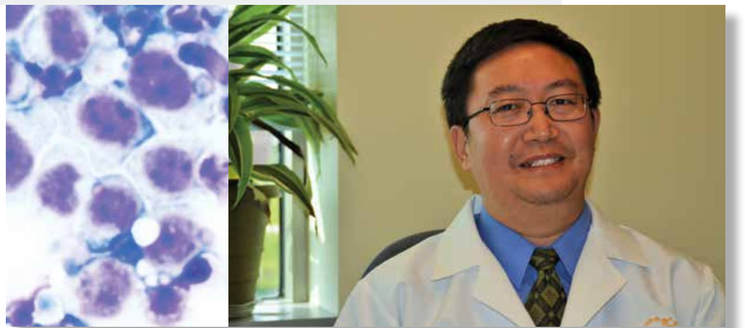


(Left to right) Joshua Liao, Jiangang Wang, Shengming Zhu
Not pictured: Wu Chen, Didacus Eze, Lewis Ezeogu, Lingli Hou, Yongchang Ouyang

hyperthermia can enhance the innate immunity against cancer cells. We hypothesize that combined hyperthermia, HSP inhibition and chemotherapy, abbreviated as HHIC, may be a better regimen for cancer treatment because cancer cells no longer can further raise their HSP levels during hyperthermia while normal cells have low basal levels of – and, thus, still can raise – HSPs for cytoprotection. Our preliminary studies on culture cancer cells show promising results that a feverish temperature (39 °C) can enhance the killing effects of several chemo drugs on different cancer cell lines. Moreover, KRIBB11, an inhibitor of heat shock factor-1 that is a master activator of many HSPs, also enhances chemotherapeutic effects, especially at a feverish (39 °C) temperature. These results lead us to the proposal of HHIC as a better cancer treatment regimen.

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 roles of aberrant epigenetics and protein kinase activity in cancer pathogenesis. We also work 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 the anti-cancer actions of bioactive compounds and the development of innovative nanoparticulates 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 over-expression 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. These findings identify the regulatory and functional interactions between kinases and DNA methyltransferases, and suggest that crosstalk between the misregulated KIT signaling and DNA hypermethylation regulates cancer cell fate.

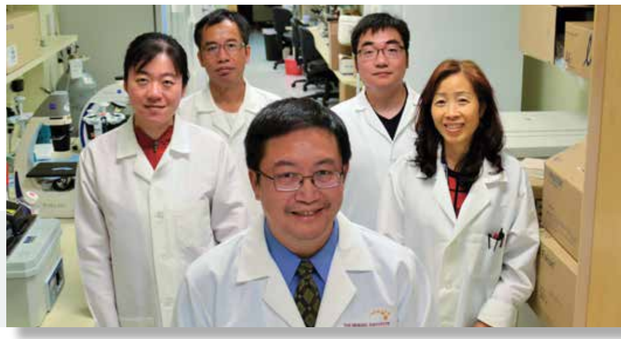
Protein kinases and DNA methyltransferases cooperatively promote drug resistance
Given that aberrant DNA methylation and abnormal KIT function critically contribute to cancer pathogenesis, as independent practice, KIT and DNMT1 have been extensively used for therapeutic targets and their inhibitors have been tested in various pre- and clinical models. However, resistance of tumor cells to PKC412 (PKC412R) or decitabine (decitabineR) poses huge limitations to their use in treatment. Our recent 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. Theoretically, our findings shed light on the molecular biology of drug resistance; practicably, our studies provide a sound rationale in clinical trials for overriding decitabine resistance by kinase inactivation or vice versa and identify an innovative opportunity for early therapeutic intervention against the emergence of drug-resistance.

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. Emerging data indicate that obesity is a major risk factor for human malignancies. It can increase the occurrence of cancerous lesions and decrease the benefit of therapy. The molecular mechanisms behind these phenomena, however, are poorly defined. We observed that higher BMI (body mass index) associates with shorter overall survival in leukemia patients. When leukemia cells were transplanted into obese or lean mice, we found that, compared to the lean counterparts, obese mice display exacerbated leukemic disease; thus, experimentally demonstrating the contribution of obesity to leukemogenesis in mice. Mechanistically, a family of fatty acid binding protein (FABPs) could mediate obesity-associated leukemia through the reversal of the adverse epigenetic alterations. In fact, leukemia cells abundantly express FABP4 (aP2) that is highly expressed in obesity. Treatment with FABP4 recombinant protein accelerates leukemia cell growth. The future directions are to delineate the molecular pathways controlling the FABP4-induced aggressive leukemia growth.

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

Dr. Shujun Liu

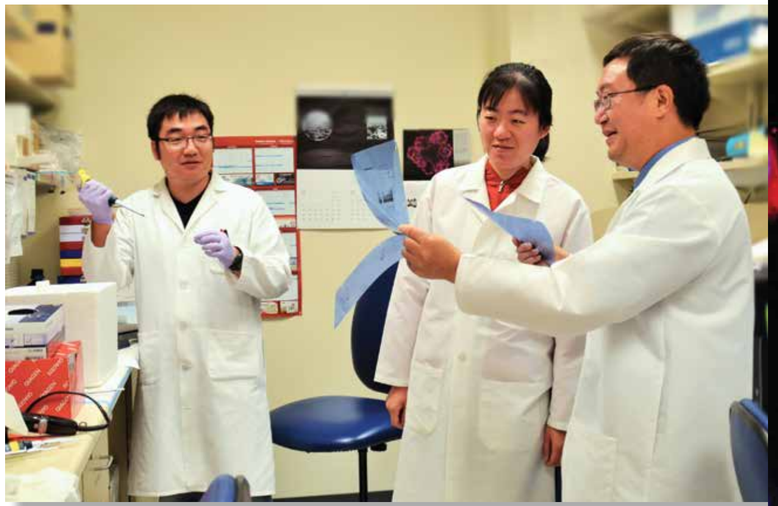
Molecular mechanisms of anti-cancer actions of bioactive compounds
Due to the essential roles of aberrant DNA methylation in cancers, DNA hypomethylating agents have been in clinical use for decades. While some positive response has been achieved, the majority of leukemia patients relapse and eventually die of their disease, arguing for the new type of DNMT inhibitors with different structure and distinct mechanisms
Due to their anti-cancer activity and lower toxicity to normal cells, numerous plant extracts have been tested in vitro and in vivo with huge therapeutic potentials. We have demonstrated that certain types of bioactive compounds [i.e., thymoquinone (TQ), echinomycin or emetine] suppress the expression of DNMT1, DNMT3a and DNMT3b resulting in global DNA hypomethylation and the re-expression of TSGs by promoter DNA hypomethylation. Functionally, these compounds block cancer cell proliferation in cell lines, patient primary cells, and metastatic growth in vivo. While the underlying molecular mechanisms remain elusive, these compounds may hold a promising in human cancer therapy.



(Left to right) Liping Dou, Shengcai Wei, Shujun Liu, Fei Yan, Jiuxia Pang
Not pictured: Lijun Wang

Developing multifunctional drug and gene delivery nanoparticles for cancer therapy

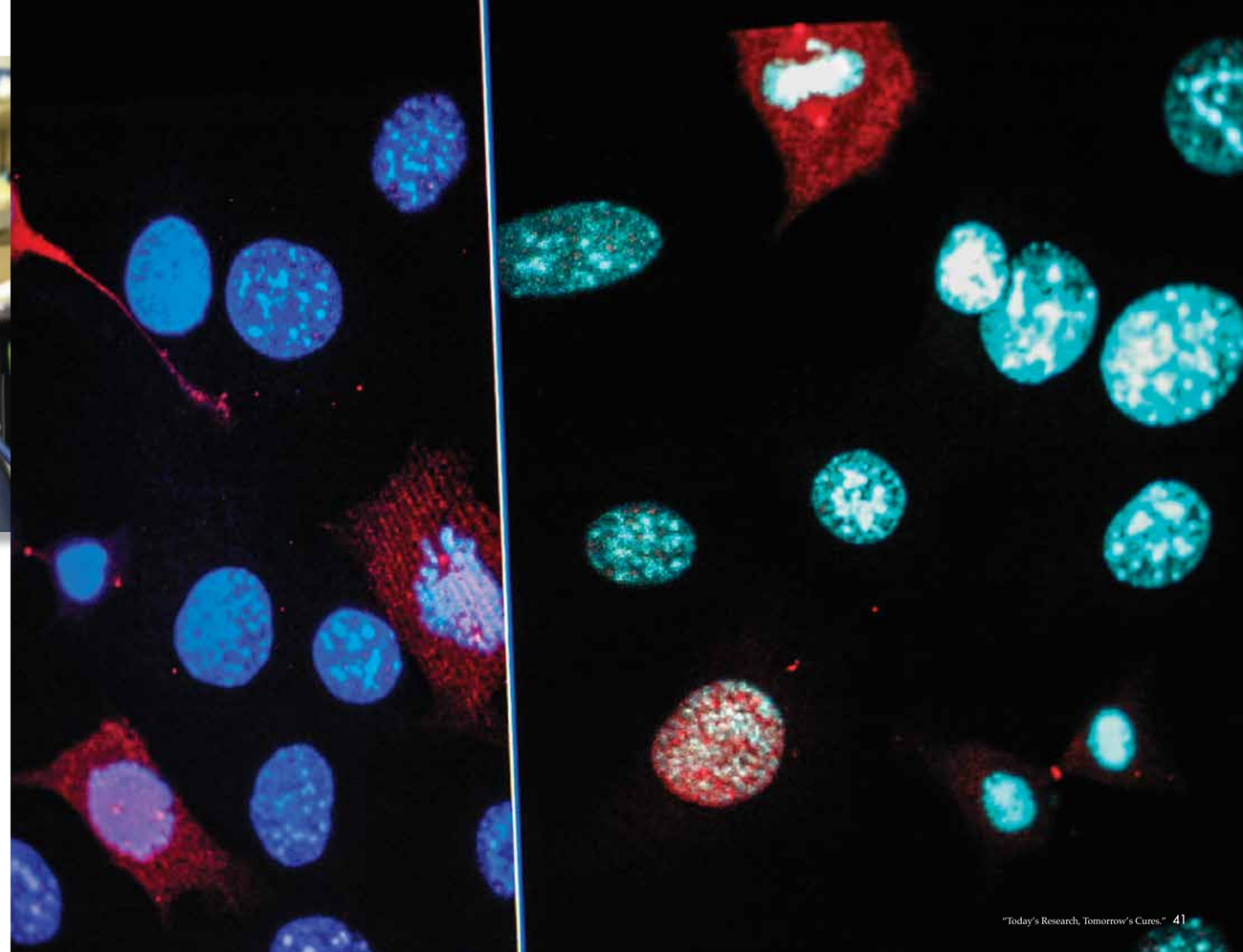
The current chemotherapeutic drugs (i.e., small molecules, siRNA or miRs), although they display promising anti-cancer activity, suffer from a variety of drawbacks when administered particularly in vivo, including rapid clearance, lack of tissue selectivity, high affinity to plasma proteins and poor 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, 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:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1vURyczXn9gkz/bibliography/48071365/public/?sort=date&direction=ascending



Stem Cells and Cancer

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

Skin keratinocytes

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, and skin cancers exceed all others combined. In the United States, the lifetime risk of skin cancer 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 only can be identified histologically. Increased cellular atypia occurs with further sun damage, and then the development of hyperkeratotic, pre-malignant actinic keratoses. Of these, 1 to 10 percent will progress to squamous cell carcinomas (SCCs). Given that avoiding sunlight exposure is more easily said than done, the Morris laboratory is focusing on two specific projects.

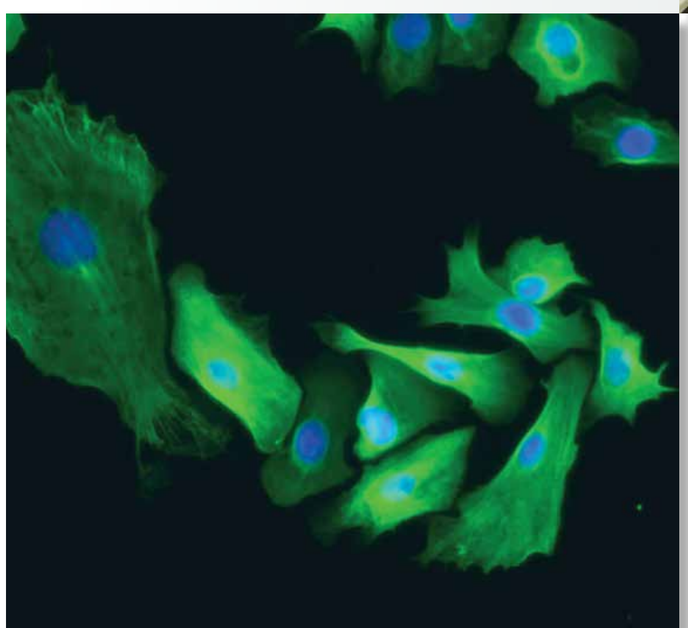
The first project is related to the interactions between cutaneous epithelial cells and bone marrow cells. We are employing both in vitro models of co-culture and migration as well as in vivo models, using transplantation of genetically labeled bone marrow. Although these experiments remain in progress, we have found evidence of a dynamic interaction between the epidermis and bone marrow-derived cells in vitro and in vivo. We now are working on the mechanism of these interactions as well as the identification and isolation of the involved cells.

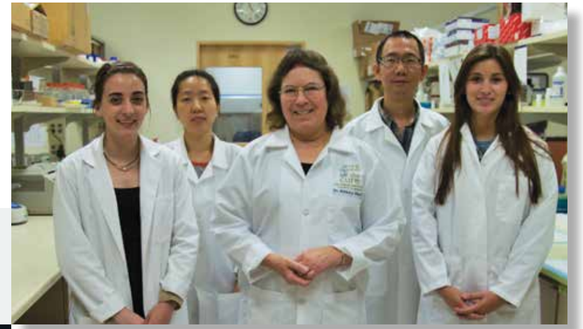
In the second project, we are working to identify novel keratinocyte stem cell regulatory genes. Keratinocyte stem cells have an unquestioned role in maintaining the normal structure and function of the epidermis and hair follicles, and they are thought to be important players in inherited and acquired skin diseases. Hence, identification of genes regulating their number and proliferative potential is a critical problem in cutaneous biology. To address this problem, we proposed a novel strategy for identifying genes involved in keratinocyte stem cell regulation. We made the surprising discovery that an innate immunity gene might play a role in regulating hair follicle stem cells. We now are working toward defining the mechanism and determining whether other genes are involved similarly.

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.

"Ultimately, these findings may provide potential targets for treatment of non-melanoma skin cancers."

Dr. Rebecca J. Morris





(Left to right) Kelsey Boland, Mi Sung Kim, Rebecca Morris, Yong Li, Taylor Picha
Not pictured: Kelly Johnson

Cell Signaling and Tumorigenesis Section

James Robinson, Ph.D.
Section Leader
Assistant Professor

Immunohistochemicak analysis of a mouse melanoma.

The Robinson laboratory primarily is 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 lab employs two experienced, full-time postdoctoral fellows Basak Celtikci, M.D. Ph.D.; and Hana Yang, Ph.D. This summer we also were joined by Celeste Underriner, whose Summer Undergraduate Research Experience (SURE) internship was generously funded with an Orville S. Privett Scholarship. As part of the University of Minnesota, The Hormel Institute has full access to the support service at the Masonic Cancer Center (MCC) and Genomics Center (UMGC), and we also have established collaborations with the MCC comparative pathology, bio-statistics and genomics center to assist in our research. We will continue to collaborate with worldwide experts in the fields of cell signaling, comparative pathology, and genetics

Areas of investigation

Colon Cancer

Our work on colon cancer is funded by a National Institutes of Health (NIH) grant. Colorectal cancer (CRC) is one of the most common cancers worldwide and – after lung and prostate cancer – the leading cause of cancer deaths in the United States, with 132,770 new cases and 49,700 deaths anticipated in 2015. About 75 percent of these cases are sporadic, with no obvious evidence of an inherited disorder. The remaining 25 percent of patients have a family history of CRC that suggests a hereditary contribution; common exposures among family members; or combination of both.

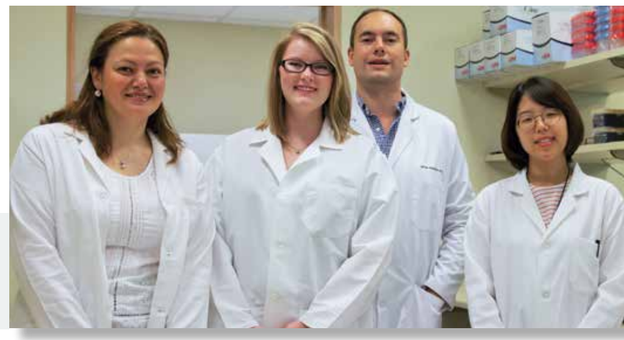
Familial adenomatous polyposis (FAP) is one of the most clearly defined and well understood of the inherited colon cancer syndromes. The vast majority of FAP cases result either from dominantly inherited or de-novo mutations in the Adenomatous polyposis coli gene (APC). FAP is characterized by the development of numerous adenomatous polyps of the large intestine, and it is an excellent model of colorectal tumorigenesis as each adenoma is representative of the first step in CRC: APC loss. Individually, these polyps are histologically indistinguishable from sporadic non-familial colonic adenomatous polyps, and – although the proportion that progress to carcinoma is low – progression is inevitable due to the high number of polyps. For this reason, removal of the colon (a "colectomy"), typically is performed.

The study of FAP has led to advances in the understanding of the genetics of colon cancer and human malignancy. Precise elucidation of steps in FAP tumorigenesis, however, remains elusive. Both human and mice polyps develop without additional genetic alterations other than loss/inactivation of the normal copy of APC. Polyp multicity in both humans and mice can be attenuated greatly by COX-2 inhibition or with anti-inflammatory drugs. Diet, pregnancy, and exercise also might affect polyp numbers and the incidence of sporadic cancer. Our preliminary data has demonstrated that APC loss is insufficient for nuclear accumulation of β-catenin in intestinal epithelial cells. Additional growth signals or mutations also are required for nuclear accumulation of b-catenin and intestinal polyposis. Given that 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. We currently are validating the role of key growth factors HGF and EGF while examining the role of IL17 in colorectal tumorigenesis by assessing if they can promote the nuclear accumulation of β-catenin. Aberrant stromal signaling following loss or haploinsufficiency of LKB1 or SMAD4 is known to drive polyposis in Peutz-Jeghers syndrome and juvenile polyposis syndrome. APC loss of heterozygosity (LOH) is detected in FAP polyp epithelium, and due to FAP not having a prominent stromal compartment, unlike the other syndromes, a proper assessment of stromal LOH was never attempted. 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 melanoma."
Dr. James Robinson

Melanoma

Melanoma incidence is increasing at a greater rate than any other cancer. In 2015, it is estimated that 73,870 Americans will be diagnosed with melanoma and about 9,940 will die of the disease. Melanoma typically can be cured through surgery if detected early; however, the five-year survival rate for patients with metastatic disease is less than 15 percent.
The MAPK signaling pathway (RAS>RAF>MEK>ERK) is constitutively activated in more than 85 percent of malignant melanomas. Recent advances in melanoma therapy have involved combinations of drugs that target this pathway. Vemurafenib treatment increases median survival by 6 months in approximately 50 percent of patients whose melanomas carry the BRAFV600E mutation. Although the initial response to BRAFV600E inhibition can be dramatic – sometimes causing complete tumor regression – melanomas eventually become resistant and reoccur. Combining MEK and BRAFV600E inhibition improves the response but the majority of patients still eventually experience disease progression (Figure 1). The U.S. Food & Drug Administration (FDA) recently approved humanized anti PD-1 antibodies (nivolumab, pembrolizumab, and opdivo) as a first line of treatment for melanoma, but most patients (about 80 percent) do not experience a clinical response and then are treated with BRAF and/or MEK inhibitors. Combining BRAF inhibition with PD-1 antibodies improves the response rate and overall survival; however, most patients still succumb to the disease. Other approved treatments for melanoma include dacarbazine interleukin-2 (IL-2) and ipilimumab (anti-CTLA-4). These agents, however, produce a response in only a small percentage of patients and their side effects can be pronounced. The increased incidence of melanoma, combined with the poor prognosis of patients with advanced disease, makes it imperative that we increase our understanding of the underlying causes of resistance to targeted therapies to enable the development of better therapeutic strategies.



(Left to right) Basak Celtikci, Celeste Underriner, James Robinson, Hana Yang
Not pictured: Shuxia (Susan) Jiang, Jaclyn Sweetapple

Mouse models that permit regulated expression of oncogenes are useful particularly for modeling the effects of targeted therapies because

abrogation of oncogene expression mimics pharmacological inhibition of the target. We have developed a novel, retroviral gene delivery mouse model of melanoma that permits control of oncogene expression using tetracycline. This model ideally is suited for testing the role(s) of specific genes in tumor initiation, progression, and maintenance. This model's versatility eliminates the need to create a new transgenic mouse for testing each new gene. In our model, melanomas can be induced by mutant NRAS, BRAF or MEK in the context of Ink4a/Arf and/or Pten loss.

Importantly, tumors in our model evolve from developmentally normal somatic cells in an unaltered microenvironment. We have used this system to assess the efficacy of targeting NRASQ61R as a therapy for malignant melanoma. Most tumors respond to NRAS inhibition but reoccur after a prolonged latency. Analysis of the recurrent tumors has revealed the most common mechanism of resistance to be over-expression of receptor tyrosine kinases (RTK). In our ongoing research, we seek to define the common mechanisms of resistance to NRAS, BRAF, and MEK inhibition as well as test preemptive and coordinate targeted therapeutic approaches by targeting resistance mechanisms (Figure 2). Our studies will contribute to the development of novel therapies and improve the outcome for patients with melanoma.

Figure 1. Scheme depicting mechanisms of acquired resistance observed in vitro and in vivo to BRAFV600E and MEK inhibitors. Resistance mechanisms are largely mediated by the emergence of MAPK-dependent mechanisms as an alternative means of pathway reactivation. Gain of function NRASQ61X mutations, alternative splice variants of BRAFV600E, and over-expression of BRAFV600E, CRAF, COT, and RTKs are capable of overcoming BRAF inhibition. Mutations in MEK1 and MEK2 that interfere with drug binding-pockets or that upregulate inherent kinase activity are also known to mediate resistance to both BRAF and MEK inhibitors.

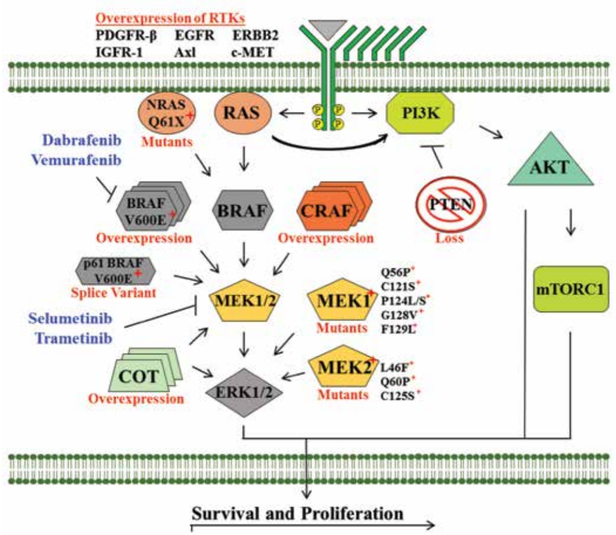


Figure 2.(full page image) Immunohistochemicak analysis of a mouse melanoma. Demonstrating BrafV600E expression and P-Erk activation while ki67 staining demonstrates tumor cells were actively dividing.

Research Support Group

MATT PLUEGER
Supervisor

(Left to right) Melissa Fortsch, Teri Johnson, Michelle Jacobson

The Hormel Institute's Research Support Group (RSG), supervised byMatt Plueger, provides vital operational support within the Institute's 13 research sections for their many ongoing research projects. Each of the Institute's cancer research departments is dedicated to preventing or controlling cancer.

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.

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.

Office

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

(Left to right) Jessica Swanson, Nicole (Nicki) Brickman, Betsy Mentel, Dr. Ann M. Bode

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.

Public Relations and Development

GAIL DENNISON, M.A., CFRE
Director

(Left to right) Jelena Maric, Tim Ruzek, Gail Dennison, Gretchen Ramlo, Mandie Siems, Michelle Phillips Not pictured: Tucker Mithuen

Our guiding principle is to win support for The Hormel Institute's quest to improve the health of the world through scientific research. Our focused team of expert researchers aim every day to discover the mechanisms of cancer as well as better ways to prevent, detect and control this devastating disease through healthier paths.

In 2014-2015, more individuals, businesses and organizations stepped forward than ever before to support The Hormel Institute's world-class cancer research. The visionary support of The Hormel Foundation, led by Mr. Gary Ray, places The Hormel Institute on a path where the future is truly limitless for what only can be called TRANSFORMATIVE CHANGE. As our scientists continue accelerating discoveries in the fight against cancer, The Hormel Institute is undergoing an expansion to double the size of our facilities and overall employment.

Our friends and collaborators know and understand The Hormel Institute's unique story. Together, we know that for a healthier tomorrow, research must be funded today. We deeply thank one and all for sharing our vision "Today's Research, Tomorrow's Cures."

"Research is the only answer to cancer, and that makes community involvement in support of cancer research so vital in the fight against this devastating disease. We are deeply honored and grateful for the generosity and trust shown by all of our supporters."

Gail Dennison, Director of Public Relations & Development

Thank You . . . Partners in Growth

The Hormel Foundation
Hormel Foods Corporation
Mayo Clinic Health System
Minnesota Governor Mark Dayton
U.S. Senator Amy Klobuchar
U.S. Senator Al Franken
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
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Gary & Pat Ray
Mahlon & Karen Schneider
Dr. Harald & Pat Schmid
Adams, Rizzi & Sween, P.A.
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5th District Eagles Cancer Telethon
Lyle Area Cancer
U.S. Bank
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Austin Bruins' "Paint the Rink Pink"
Austin area's "Paint the Town Pink"
Karl R. Potach Foundation
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Austin Area Foundation
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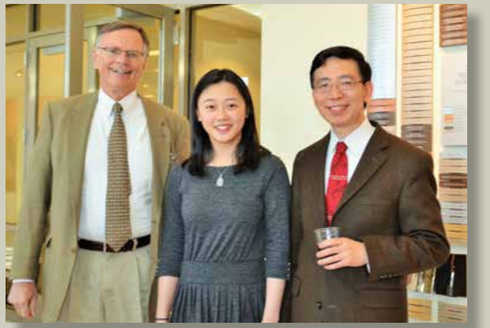
IBM Rochester
University of Minnesota – Rochester
Mower County
Riverland Community College
Austin Public Schools
Pacelli Catholic Schools
Southern Minnesota Initiative Foundation
Dave "Tolly" Tollefson Memorial Golf Tournament
Bowling for the Battle – A Fight Against Prostate Cancer
Deryl Arnold Memorial 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 – "Plunging for Pink" polar plunge
Norma Foster Memorial "Ride for a Reason"
Jim & Vicky King/Spiritually Motivated
Larry Anderson
Sharon Lewis
Paint the Town Pink – Austin, Adams, Brownsdale, Rose Creek
Blooming Prairie Cancer Group
St. Marks Lutheran Home
Hormel Historic Home
Austin ArtWorks Festival

"Today's RESEARCH, Tomorrow's CURES"



The Karl R. Potach Foundation

unite

NORMA FOSTER
RIDE FOR A REASON
2015

hope

believe

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 has been supported by The Hormel Foundation, Austin Port Authority and the State of Minnesota. Construction started in summer 2014 and has progressed significantly over the past year. In spring 2015, we broke ground on the Institute's west side for our future Live Learning Center that will feature 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 once the expansion is completed.

Building Operations and Maintenance

Mark Severtson
Supervisor

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

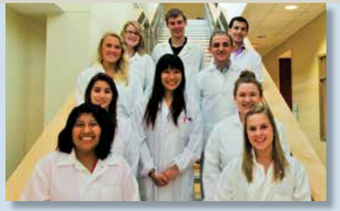
The maintenance support unit's main goal is to provide all personnel with a comfortable and safe working environment. Regular inspection and maintenance of all buildings and equipment is performed to assure continuous, efficient operation and comfort. All safety equipment is routinely checked to assure 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.

Educational Outreach

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 to talk about science and work with students in labs; and hosting all Austin sixth-graders for a full day of tours.

SURE (Summer Undergraduate Research Experience)



(Left to right) Front row: Maetzin Cruz-Reyes, Brenna Nordeng

Second row: Taylor Picha, Sela Fadness

Third row: Tori Simonson, Emily Qin, Mark Mizrachi

Back row: Celeste Underriner, Tommy Dvergsten, David Ciota

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.

"I'll need these skills as a doctor to interpret research published in medical journals and communicate with patients and other healthcare professionals to ensure my patients get the best care possible. This is the perfect opportunity for my career path."

Emily Qin, 2015 SURE intern

Gary J. Ray, Chair
The Hormel Foundation

2014 - 16 Expansion

Progress in the fight against cancer took a giant step forward in 2014-15 as construction began on The Hormel Institute's 2014-16 expansion aimed at accelerating answers to this devastating disease.

In summer 2014, work started on The Hormel Institute's east expansion of an additional 20 state-of-the-art laboratories that will house new cancer research sections and more cutting-edge technology for our International Center for Research Technology. The project is expected to be completed by early 2016 along with The Hormel Institute's new Live Learning Center being built on its west side, which began in spring 2015.

Combined, the east and west additions will nearly double the size of The Hormel Institute's facilities and its overall employment, increasing from about 125 to 250 employees over the coming years. A Grand Opening event is planned for June 1, 2016.

The Hormel Foundation committed up to $23 million for the 2014-16 expansion, including a $13.5 million match for the State of Minnesota's bonding funds for The Hormel Institute's east laboratory expansion. That commitment also includes $1.5 million from The Hormel Foundation for the Live Learning Center addition, which is a $4.5 million project. Fundraising is continuing for the remaining $500,000 for acquiring state-of-the-art, global-communications technology in the Live Learning Center.

The Hormel Institute's largest room holds 100, which is not enough for its current faculty and staff. The new auditorium will accommodate the Institute's future 250-person staff and allow for international global research collaborations.

With numerous global collaborations, The Hormel Instute already has scheduled two major international cancer research symposia for 2016 in the future Live Learning Center.

"World-renowned cancer research is being done here at The Hormel Institute, and the 2014-16 Expansion and its Live Learning Center will significantly enhance their global presence and influence even more."

Gary J. Ray, Chair of The Hormel Foundation

transformation

progress

West Expansion - Live Learning Center

The Live Learning Center will feature state-of-the-art technology along with a spacious, multipurpose room and 250-seat, globally interactive lecture hall. Currently, the largest meeting room in The Hormel Institute holds 100, which is not enough for its current faculty and staff. The new auditorium also will accommodate the Institute's future 250-person faculty and staff as well as allow hosting of international cancer research symposiums.

The Hormel Institute, which has numerous global collaborations, already has scheduled two major international cancer research conferences for 2016 in the future Live Learning Center and corporate meeting events requiring the use of its state-of-the-art technologies.

gather
global
collaborations

MAKE A GIFT TO SUPPORT THE EXPANSION

About $500,000 still needs to be raised for acquiring state-of-the-art, global-communications technology for the future Live Learning Center lecture hall at The Hormel Institute, University of Minnesota. Donations are tax-deductible and can be pledged over three years.

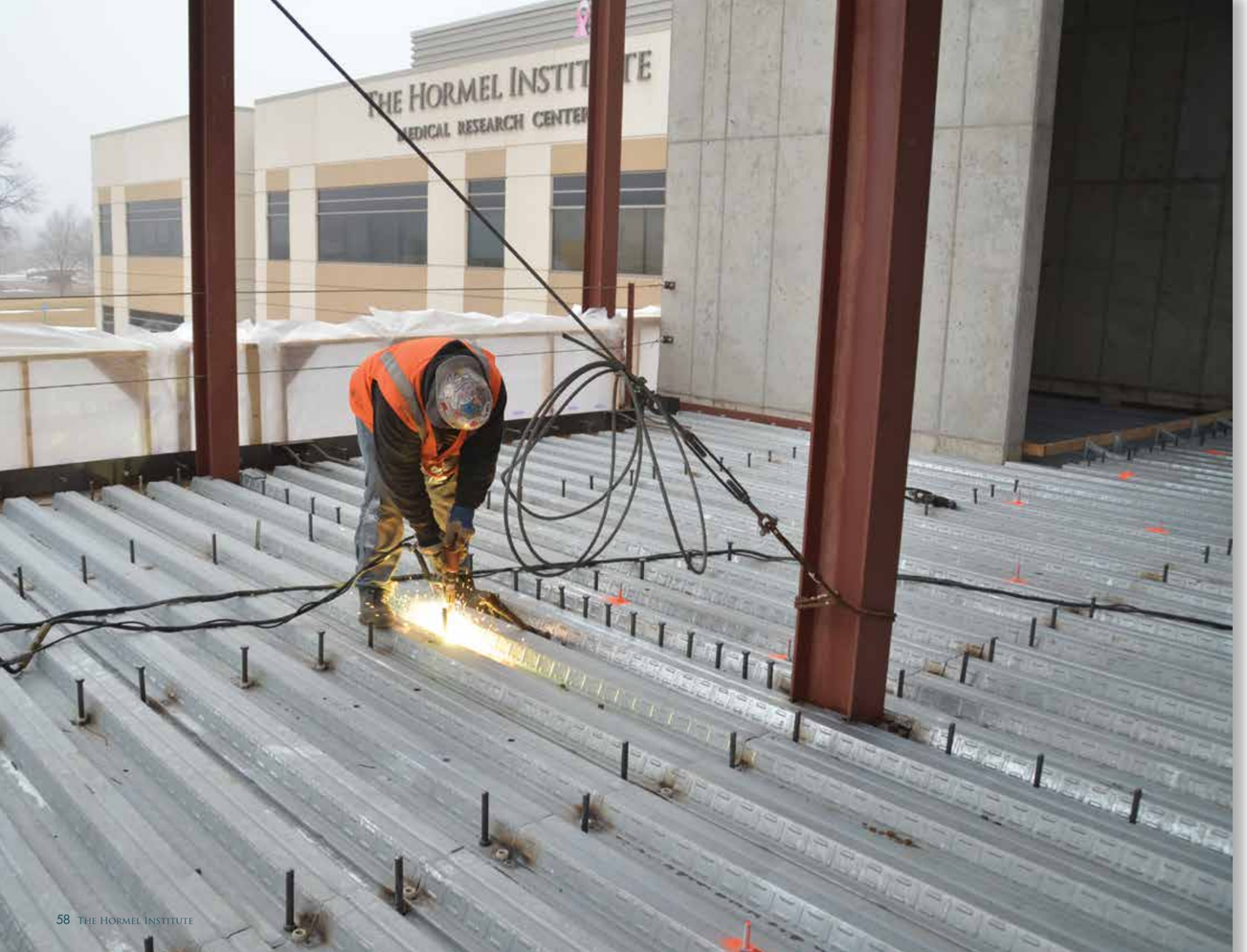
Gifts of $500 or more will be honored on a new donor wall in the Live Learning Center's multipurpose room. Those who donate $1,000 or more also will be invited to attend the historic evening reception June 1, 2016, for the first international cancer research conference hosted in the Live Learning Center.

Please make your gift out to "The Hormel Institute – Live Learning Center" and send it to : The Hormel Institute, 801 16th Ave. N.E., Austin, MN, 55912.

"We strongly believe in The Hormel Institute's research and Live Learning Center with its innovative technology that will accelerate discoveries by connecting top scientists from all over the world to work together in the fight against cancer. It is a privilege to support this work that is making great strides in improving the health of the world through collaborative research."

Mahlon & Karen Schneider

accelarate
answers
donate



East Expansion

Construction started in summer 2014 on The Hormel Institute's east expansion of an additional 20 state-of-the-art cancer research laboratories. Fifteen labs will be for new research section, with the other five for core facilities available to all Institute scientists.

Funding for The Hormel Institute's $27 million east addition – which is expected to add about 125 jobs over the coming years – came half from the State of Minnesota and half from The Hormel Foundation. In 2012, State Sen. Dan Sparks and Rep. Jeanne Poppe, both from Austin, led legislative efforts that enabled the Institute to receive $13.5 million in state bonding funds for the expansion. The project received strong bipartisan support in the legislature, and great support from State Sen. David Senjem.

Work is expected to be completed on the east addition in late 2015.

Dan Sparks
State Senator

Jeanne Poppe
State Representative

David Senjem
State Senator

Science Park Housing

Just across the street from The Hormel Institute's new east addition, a three-story, 42-unit apartment complex is being built to meet the growing demand for quality, rental housing, especially for the Institute's current and future scientists.

Construction started in spring 2015 on the Science Park Housing complex, with occupancy expected to begin in spring 2016. The apartment housing is being led by Science Park Housing LLC, a wholly owned subsidiary of The Hormel Foundation. With about 90 percent of The Hormel Institute's current faculty and staff living and working in Austin, adding another 125 jobs over the coming years due to the Institute's new expansion only will add to the housing demand.

Cancer researchers have non-traditional work hours, making the Science Park complex advantageous due to its close proximity to The Hormel Institute. A reception area, common residential lounge space and outdoor plaza for tenants will be part of the complex.

"With the expansion of The Hormel Institute and the growing number of faculty and staff, the Science Park Housing complex provides quality rental housing and is convenient to the Institute's growing campus. We look forward to further developments in the science park."

Jerry Anfinson,
Treasurer of The Hormel Foundation

The Hormel Institute Publications

July 1, 2014 - June 30, 2015

HH.I. No. 1999
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Kim, S. H., Kim, M. O., Cho, Y. Y., Yao, K., Kim, D. J., Jeong, C. H., Yu, D. H., Bae, K. B., Cho, E. J., Jung, S. K., Lee, M. H., Chen, H., Kim, J. Y., Bode, A. M., Dong, Z.
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"Establishment and characterization of a highly tumorigenic African American prostate cancer cell line, E006AA-hT."
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Int J Biol Sci 10(8): 834-845.

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Bernard, J. J., Lou, Y. R., Peng, Q. Y., Li, T., Vakil, P. R., Ding, N., Laskin, J. D., Dong, Z., Conney, A. H., Lu, Y. P. J Carcinog Mutagen 5(183): 2157-2518.

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Wang, L., Xiong, H., Wu, F., Zhang, Y., Wang, J., Zhao, L., Guo, X., Chang, L. J., Zhang, Y., You, M. J., Koochekpour, S., Saleem, M., Huang, H., Lu, J., Deng, Y.
Cell Rep 8(5): 1461-1474.

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"Src is a novel potential off-target of RXR agonists, 9-cis-UAB30 and Targretin, in human breast cancer cells."
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Immunity 42(5): 953-964.

H.I. No. 2043
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Oncotarget 6(15): 13201-13215.

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"Cyclin-dependent kinase 2 (CDK2) is a key mediator for EGF-induced cell transformation mediated through the ELK4/c-Fos signaling pathway."
Peng, C., Zeng, W., Su, J., Kuang, Y., He, Y., Zhao, S., Zhang, J., Ma, W., Bode, A. M., Dong, Z., Chen, X. Oncogene.

H.I. No. 2050
"Multifunctional effects of honokiol as an anti-inflammatory and anti-cancer drug in human oral squamous cancer cells and xenograft."
Cho, J. H., Jeon, Y. J., Park, S. M., Shin, J. C., Lee, T. H., Jung, S., Park, H., Ryu, J., Chen, H., Dong, Z., Shim, J. H., Chae, J. I.
Biomaterials 53: 274-284.

H.I. No. 2051
"Computational and Biochemical Discovery of RSK2 as a Novel Target for Epigallocatechin Gallate (EGCG)."
Chen, H., Yao, K., Chang, X., Shim, J. H., Kim, H. G., Malakhova, M., Kim, D. J., Bode, A. M., Dong, Z.
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H.I. No. 2054
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Zhao, L., Tang, M., Hu, Z., Yan, B., Pi, W., Li, Z., Zhang, J., Zhang, L., Jiang, W., Li, G., Qiu, Y., Hu, F., Liu, F., Lu, J., Chen, X., Xiao, L., Xu, Z., Tao, Y., Yang, L., Bode, A. M., Dong, Z., Zhou, J., Fan, J., Sun, L., Cao, Y.
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Oi, N., Yuan, J., Malakhova, M., Luo, K., Li, Y., Ryu, J., Zhang, L., Bode, A. M., Xu, Z., Li, Y., Lou, Z., Dong, Z.
Oncogene 34(20): 2660-2671.

H.I. No. 2057
"Microtubule motors power plasma membrane tubulation in clathrin-independent endocytosis."
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H.I. No. 2058
"Translational Control Protein 80 Stimulates IRES-Mediated Translation of p53 mRNA in Response to DNA Damage."
Halaby, M. J., Li, Y., Harris, B. R., Jiang, S., Miskimins, W. K., Cleary, M. P., Yang, D. Q. Biomed Res Int 2015: 708158.

H.I. No. 2032
"EBV-LMP1 targeted DNAzyme enhances radiosensitivity by inhibiting tumor angiogenesis via the JNKs/HIF-1 pathway in nasopharyngeal carcinoma."
Yang, L., Liu, L., Xu, Z., Liao, W., Feng, D., Dong, X., Xu, S., Xiao, L., Lu, J., Luo, X., Tang, M., Bode, A. M., Dong, Z., Sun, L., Cao, Y.
Oncotarget 6(8): 5804-5817.

H.I. No. 2033
"ZBRK1, a novel tumor suppressor, activates VHL gene transcription through formation of a complex with VHL and p300 in renal cancer."
Chen, K., Yu, G., Gumireddy, K., Li, A., Yao, W., Gao, L., Chen, S., Hao, J., Wang, J., Huang, Q., Xu, H., Ye, Z. Oncotarget 6(9): 6959-6976.

H.I. No. 2034
"Membrane-to-Nucleus Signals and Epigenetic Mechanisms for Myofibroblastic Activation and Desmoplastic Stroma: Potential Therapeutic Targets for Liver Metastasis?"
Kang, N., Shah, V. H., Urrutia, R.
Mol Cancer Res 13(4): 604-612.

H.I. No. 2035
"Metformin Treatment for the Prevention and/or Treatment of Breast/Mammary Tumorigenesis."
Grossmann, M. E., Yang, D. Q., Guo, Z., Potter, D. A., Cleary, M. P.
Curr Pharmacol Rep 1(5): 312-323.

H.I. No. 2036
"Prevention of chemically induced urinary bladder cancers by naproxen: protocols to reduce gastric toxicity in humans do not alter preventive efficacy."
Lubet, R. A., Scheiman, J. M., Bode, A., White, J., Minasian, L., Juliana, M. M., Boring, D. L., Steele, V. E., Grubbs, C. J. Cancer Prev Res (Phila) 8(4): 296-302.

H.I. No. 2037
"AID expression increased by TNF-alpha is associated with class switch recombination of Igalpha gene in cancers."
Duan, Z., Zheng, H., Liu, H., Li, M., Tang, M., Weng, X., Yi, W., Bode, A. M., Cao, Y., Cell Mol Immunol.

H.I. No. 2038
"Clinical significance of topoisomerase 2A expression and gene change in operable invasive breast cancer."
Qiao, J. H., Jiao, D. C., Lu, Z. D., Yang, S., Liu, Z. Z. Tumour Biol.

H.I. No. 2039
"Deficiency of AMPK in CD8+ T cells suppresses their anti-tumor function by inducing protein phosphatase-mediated cell death."
Rao, E., Zhang, Y., Zhu, G., Hao, J.,Persson, X. M., Egilmez, N. K., Suttles, J., Li, B. Oncotarget 6(10): 7944-7958.

H.I. No. 2040
"Inhibition of tumor growth by a newly-identified activator for epidermal fatty acid binding protein."
Rao, E., Singh, P., Zhai, X., Li, Y., Zhu, G., Zhang, Y., Hao, J., Chi, Y. I., Brown, R. E., Cleary, M. P., Li, B. Oncotarget 6(10): 7815-7827.

H.I. No. 2041
"Targeting hexokinase 2 in castration-resistant prostate cancer"
Deng, Y and Lu, J.
Molecular & Cellular Oncology (invited commentary). e974465, Vol. 2, Iss. 3, 2015

H.I. No. 2042
"Epidermal Fatty Acid binding protein promotes skin inflammation induced by high-fat diet."
Zhang, Y., Li, Q., Rao, E., Sun, Y., Grossmann, M. E., Morris, R. J., Cleary, M. P., Li, B. Immunity 42(5): 953-964.

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The Hormel Institute Seminars

July 1, 2014 - June 30, 2015

July 11, 2014
John DiGiovanni, P.h.D.
Professor, Pharmacology and Toxicology
College of Pharmacy
The University of Texas at Austin
"Identifying Growth Factor and Inflammatory Signaling Pathways as Targets for Cancer Prevention and Treatment"

July 18, 2014 - Broadcast
Basil Rigas, Ph.D.
Professor of Medicine
Stony Brook University
"Novel Redox-based Anticancer Agents"

July 24, 2014
Sergio Gradilone, Ph.D.
Associate Consultant Researcher
Department of Internal Medicine,
Mayo Clinic
"The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle "

August 1, 2014
Marina Holz, Ph.D.
Assistant Professor
Department of Molecular Pharmacology
Associate Professor of Biology
Albert Einstein College of Medicine
Yeshiva University
Stern College
"Targeting mTOR signaling in breast cancer and lymphangioleiomyomatosis"

August 5, 2014
Mamta Gupta, Ph.D.
Assistant Professor of Medicine
Division of Hemtology
Department of Internal Medicine
Mayo Clinic
"The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle"

August 7, 2014
Robert Huber, Dr. Dr.h.c.
Max-Planck-Institut fuer Biochemie
Emeritusgruppe Strukturforschung, Germany
"Protease Control in Health and Disease and my Experience with its Translation into Practice and Business"

August 13, 2014
Liang Wang, Ph.D. & M.D.
Associate Professor of Pathology, Microbiology and Molecular Genetics
Department of Pathology and MCW Cancer Center
Medical College of Wisconsin
"Blood-based biomarkers for cancer diagnosis and prognosis "

August 21, 2014
Oscar Millet, Ph.D.
Structural Biology Unit, CIC bioGUN
Bizkaia Technology Park
Derio, Spain
"Molecular basis and therapeutical approaches against congenital erythropoietic porphyria"

August 26, 2014
James Robinson, Ph.D.
Instructor at Huntsman Cancer Institute
University of Utah
"Preclinical validation of NRAS targeting in Melanoma"

August 28, 2014
Min Wu, Ph.D. & M.D.
Associate Professor
Departments of Basic Biomedical Sciences
School of Medicine & Health Sciences
University of North Dakota
"microRNAs are important regulators in biological function in flammation and immunity"

September 3, 2014
Zheng-Gang Liu
Senior Investigator
Center for Cancer Research
National Cancer Institute
NIH
"ROS, tumor associated macrophages, and cancer"

September 10-12, 2014
Bethany Kerr, Ph.D.
Adjunct Assistant Professor/Associate Member
Department of Molecular Cardiology
Lerner Research Institute
Cleveland Clinic
"Intercepting Cancer's Circulating Communications: Platelets and Progenitor cells in Metastasis"

September 19, 2014
Michael Karin, Ph.D.
Professor of Pharmacology
Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases
American Cancer Society Research Professor
"Liver Inflammation, Obesity and Cancer"

October 21, 2014
Kevin Vaughan, Ph.D.
Associate Professor of Biological Sciences
Harper Cancer Research Institute
University of Notre Dame
"Deciphering How Mitotic Kinases Monitor Chromosome Alignment During Mitosis"

November 6 - 7, 2014
Ronald Lubet, Ph.D.
National Institutes of Health
National Cancer Institute
Division of Cancer Prevention
Chemopreventative Agent Development Research Group
"Chemoprevention Studies: Rationale, Results And Role Of Animal Models In Determining Efficacy And Biomarkers For Human Trials"
"Preclinical Studies in Rat Mammary Cancer Model"

November 13 - 14, 2014
Teresa Rose-Hellekant
Associate Professor
Department of Biomedical Sciences
University of Minnesota Medical School
"Molecular and Cellular Targets of Tamoxifen Chemoprevention in Murine Models of Breast Cancer"

November 19-21, 2014
Carlo Croce, M.D.
Distinguished University Professor
The John W. Wolfe Chair in Human Cancer Genetics
The Ohio State University
"Causes and consequences of microRNA dysregulation in cancer"

November 24-26, 2014
Webster Cavenee, Ph.D.
Director
Ludwig Institute for Cancer Research, San Diego
Distinguished Professor
University of California at San Diego
"Tumor Heterogeneity: An Active Process"

February 2, 2015
Michael Walters, Ph.D.
Director, Lead and Probe Discovery
ITDD (Institute for Therapeutics Discovery and Development)
Research Associate Professor, Department of Medicinal Chemistry
College of Pharmacy
University of Minnesota
"Reimagining the Natural Product Balanol as a Potential Therapeutic for Ataxia (SCA1)"

March 12, 2015
Dan Dixon, Ph.D.
Associate Professor
Co-Leader Cancer Prevention Program
University of Kansas Cancer Center
"The Impact of Altered RNA Decay in Colorectal Cancer"

April 7, 2015
Harry Orr, Ph.D.
Professor
Department of Laboratory Medicine and Pathology
University of Minnesota School of Medicine
"Spinocerebellar Ataxia Type 1 (SCA1): Therapeutic Targets"

May 8, 2015
Vijay Shah, M.D.
Chair, Division of Gastroenterology and Hepatology
Mayo Clinic
"Mechanisms of Fibrogenesis and Portal Hypertension: Tales from the Sinusoids"

May 14, 2015
Luke Hoeppner, Ph.D.
Assistant Professor, Biochemistry/Molecular Biology
Mayo Clinic
"Vascular Endothelial Growth Factor (VEGF) Biology: Novel Zebrafish and Murine Preclinical Models of Disease"

May 28, 2015
Anna Sundborger, Ph.D.
Visiting Postdoctoral Fellow
National Institutes of Health
"Dynamin dynamics revealed by cryo-electron microscopy"

June 2, 2015
Pengda Liu, Ph.D.
Pathology Instructor
Beth Israel Deaconess Medical Center
Harvard Medical School
"Deciphering the regulatory mechanisms of the mTOR/Akt pathway in tumorigenesis"

June 3, 2015
Brij Singh, Ph.D.
Professor and Interim Associate Dean for Research
Department of Basic Biomedical Science
University of North Dakota
"Calcium signaling a double edged sword: regulates both cell proliferation (cancer) and cell death"

June 4, 2015
Li Wang, Ph.D.
Postdoctoral Fellow
National Institute of Environmental Health Sciences
"Targeting Chromatin Remodeling Complex to Regulate Pluripotent Stem Cell Fate Decisions and Tumor Progression"

June 17, 2015
Robert J. Lee, Ph.D.
Professor of Pharmaceutics
Division of Pharmaceutics, College of Pharmacy
"Targeted Nanoparticles for Oligonucleotide Therapeutic Delivery"

National Institutes of Health

National Cancer Institute

Chemoprevention of Skin Cancer (Z. Dong)	*92,942*
Prevention of Mammary Tumors by Metformin in Comparison to Calorie Restriction (M. Cleary)	*147,580*
Gain of Function Mutant p53 Telomere Uncapping-driven Breast Tumorigenesis (Y. Deng)	*207,376*
Targeting Aberrant Epigenetics by Nanomedicine (S. Liu)	*182,414*
Molecular Mechanisms and Targets of Soy Compounds in Colon Cancer (Z. Dong)	*81,670*
Developing New Ornithine Decarboxylase Inhibitors to Prevent Skin Cancer (Z. Dong)	*237,032*
Prevention of Prostate Carcinogenesis by Next-generation Selenium (Y. Deng)	*14,531*
Modulation of p53 Induction by Targeting Cap-dependent Translation in Cancer (D. Yang)	*50,579*
Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver (N. Kang)	*219,229*
The Role of A-FABP in Breast Cancer Development (B. Li)	*66,225*
Prevention of Breast Cancer by Epidermal Fatty Acid Binding Protein (B. Li)	*54,553*
The Role of Stromal APC Haploinsufficiency in Colorectal Tumorigenesis (J. Robinson)	*109,065*
Primary Cilia and Malignant Transformation (S. Gradilone)	*72,064*

National Institute of General Medical Sciences

Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown)	*171,651*

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Identification of a Keratinocyte Stem Cell Regulatory Gene (R. Morris)	*260,552*

Department of Defense – U.S. Army

RNA Chimeras as a Gene Signature of Breast Cancer (D.J. Liao)	*64,078*
A Novel Mechanism for the Pathogenesis of Non-melanoma Skin Cancer (R. Morris)	*58,236*
Defects in Histone H3.3 phosphorylation, and ATRX Recruitment to Misaligned Chromosomes During Mitosis Contribute to the Development of Pediatric Glioblastomas (E. Hinchcliffe)	*53,635*

AgStar Fund for Rural America

AgStar Research Project (A. Bode)	*4,986*

Mayo Clinic *(S. Liu)* *5,078*

University of Alabama at Birmingham

Preclinical in vitro and in vivo Agent Development Assays (A. Bode)	*36,785*

University of Louisville/NIH *(S. Liu)* *1,808*

Virginia Commonwealth University/NIH

The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (E. Hinchcliffe)	*60,749*
The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (R. Brown)	*82,221*

Other Resources

The Hormel Foundation	*4,371,000*
University of Minnesota	*440,000*
Indirect Cost Return	*1,179,721*
Fundraising/Development	*255,000*
Expansion/Live Learning Center	*2,138,985*
Other	*660,080*

Total	**$11,124,825**

"We recognize that The Hormel Institute is on the leading edge of cancer research, and we are proud to support them in their work and continued fight against cancer."

-- Teresa Chapman, Director of the
5th District Eagles Cancer Telethon

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Assistant Scientist
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Hormel Fellow
Adrian Mansini
Junior Scientist
Kristen Thelen

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Fei Yan
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Yibin Deng, Assistant Professor

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Ji Wang
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Yingjie Zhang
Research Associate
Lei Wang
Visiting Scholar
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