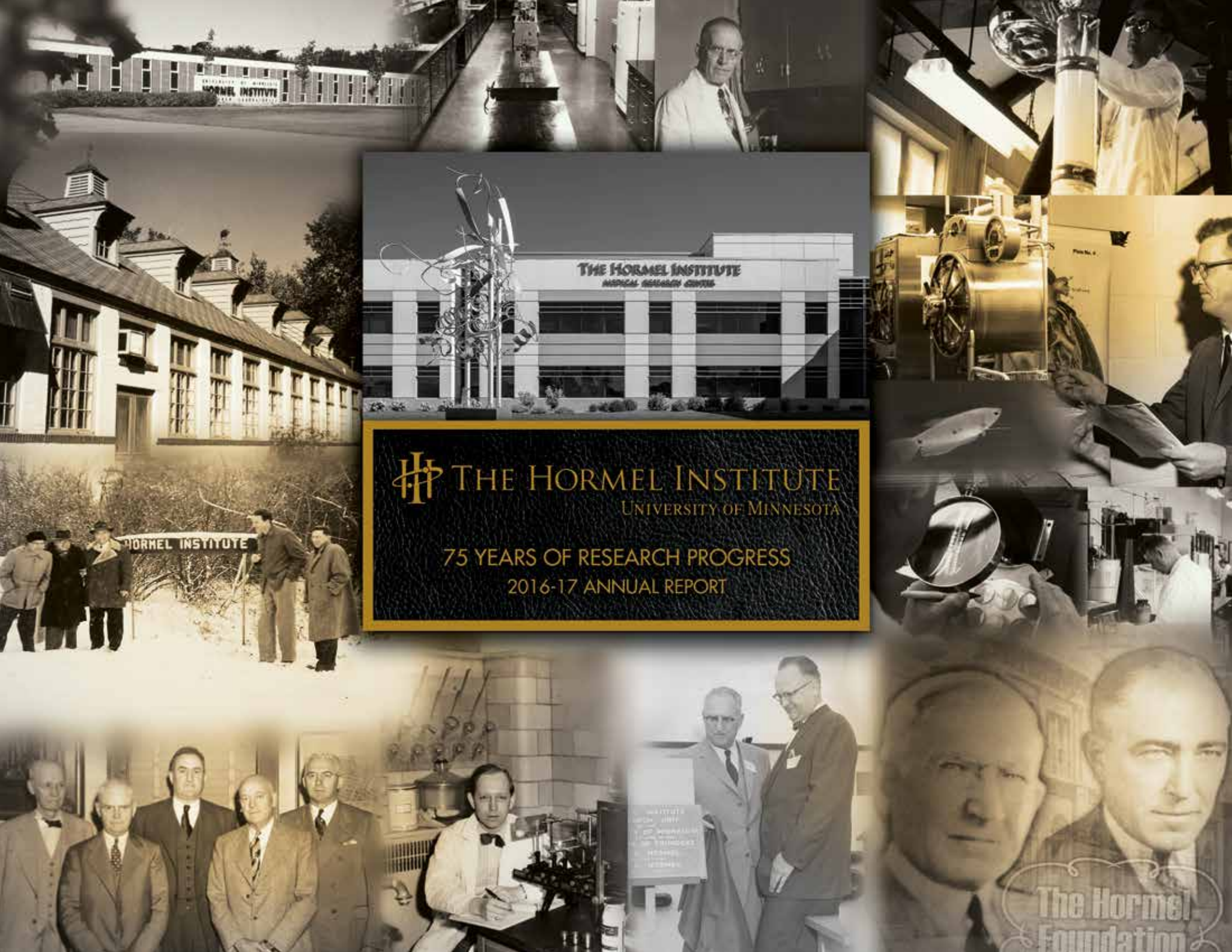


THE HORMEL INSTITUTE

UNIVERSITY OF MINNESOTA

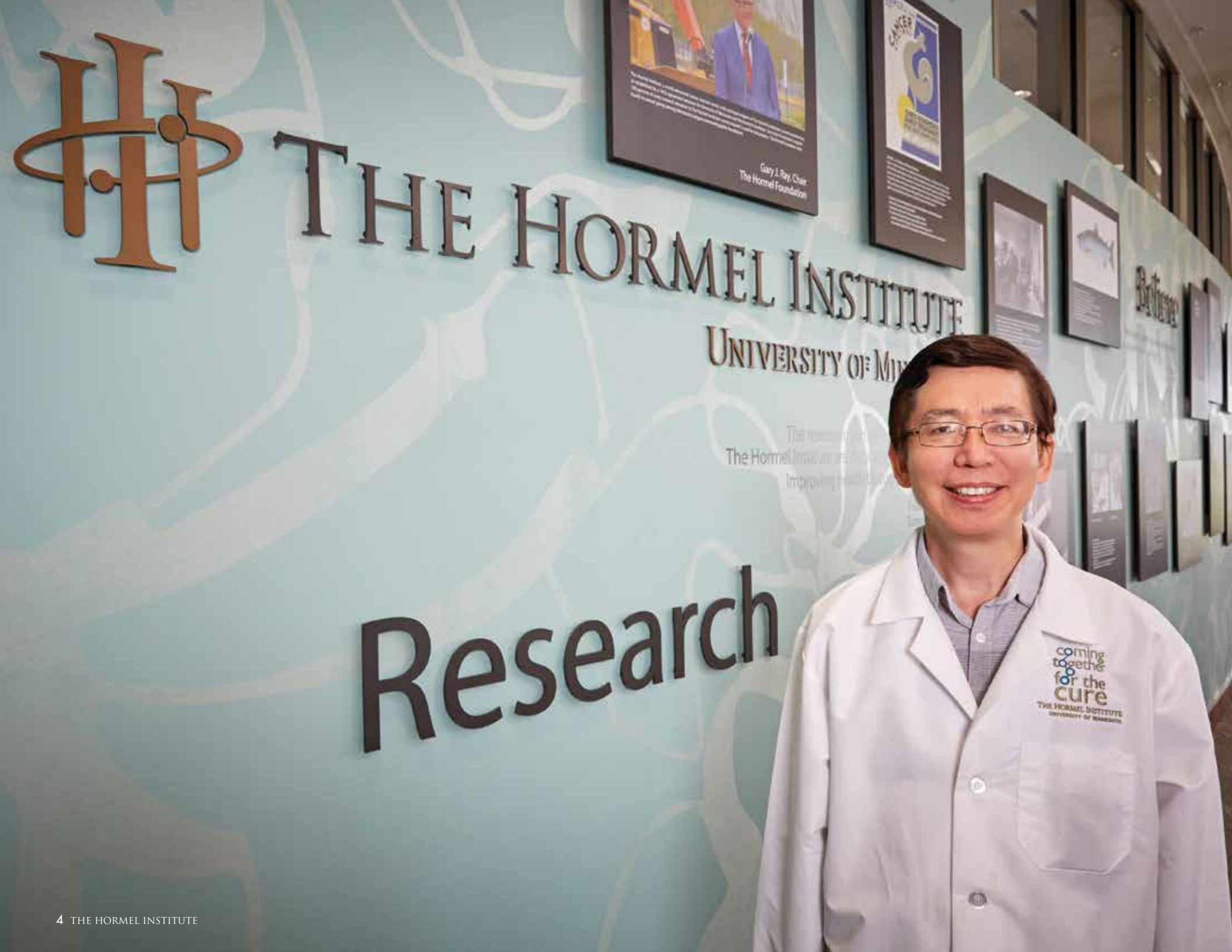
75 YEARS OF RESEARCH PROGRESS

2016-17 ANNUAL REPORT

Today's RESEARCH, Tomorrow's CURES

Historical facts for the special section, Then & Now, were compiled from a number of different sources including past Annual Reports of The Hormel Institute, historical copies of Austin Daily Herald and other historical documents from the Mower County Historical Society, the article "The University of Minnesota's Hormel Institute: The first 66 years of a unique scientific enterprise" by Harald H. O. Schmid, the book In Quest of Quality: Hormel's First 75 Years by Richard Dougherty, and the book The University of Minnesota, 1945-2000 by Stanford Lehmberg and Ann M. Pflaum.

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.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Research
Gary J. Ray, Chair
The Hormel Foundation
CANCER
coming together for the cure
THE HORMEL INSTITUTE

Message from the Executive Director Dr. Zigang Dong

Dear Friends,

This year celebrates the milestone 75th anniversary of The Hormel Institute, University of Minnesota. We thankfully reflect on our beginning in 1942 and the newly formed Hormel Foundation's notable decision to create a research center. Under the leadership of founder Jay C. Hormel, the establishment of a scientific research center here in Austin, Minnesota made history and through the years, has allowed us to make significant contributions to science. With great respect we acknowledge the dedicated scientists and staff who have comprised The Hormel Institute through seven and a half decades. Above all, we thank The Hormel Foundation and Hormel Foods Corp. for their successful achievements and unwavering support. Working together, the research of The Hormel Institute has been made possible.

The Hormel Institute has remained true to its mission for 75 years: To further scientific knowledge and share that knowledge with the world. We have had the opportunity to advance science through research focused first on food safety and preservation, to world recognized lipid research, to today's great contributions in cancer research.

The transformative expansions of 2008 and 2016 provided tremendous new opportunities to advance research and develop worldwide collaborations - and progress truly continues daily. We are deeply thankful these research opportunities are in a field where the work accomplished by our scientists are for the improvement of human health - where advancements and discoveries can be celebrated by one and all, around the world.

Throughout 2016-17, new faculty with exciting new expertise joined The Hormel Institute as we began to fill the newly built labs. The growing body of expertise broadens our scope of cancer research and expands the capabilities of The Hormel Institute, University of Minnesota.

As we celebrate our 75th anniversary, we thank you who support us for the opportunity to contribute to The Hormel Institute, University of Minnesota's great legacy. With your important support, we will continue our quest to advance discoveries and improve the health of our world - for the benefit of people today and future generations to come.

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"As we look forward to the future, we know through The Hormel Institute's research and its discoveries, continued progress will improve human health worldwide."

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

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

1. Discovery of key molecular events in cancer development and metastasis. Approximately 90% of all cancer deaths occur because of the spreading of the primary tumor to other sites in the body, through metastasis. Metastasis occurs in many cancers, and significantly contributes to the lethality of colorectal cancer. A better understanding of the molecular mechanisms that contribute to metastasis, and the cellular signaling pathways involved, is important for improving the prognosis of metastatic cancers, and preventing metastasis in the clinic. We investigated the role of the T-LAK cell-originated protein kinase (TOPK) in colorectal cancer metastasis. TOPK is highly expressed in human metastatic colorectal cancer tissue, as compared with malignant colorectal tissue (which is the stage before metastasis). We found that TOPK interacts with the p53-related protein kinase (PRPK). TOPK binds with and phosphorylates PRPK at Ser250 *in vitro* and *ex vivo*. We found that TOPK promotes metastasis of colorectal cancer by modulating PRPK.

Cyclin dependent kinase 2 (CDK2) is a known regulator in the cell cycle control of the G1/S and S/G2 transitions. CDK2 enhances Ras (G12V)-induced foci formation. Knocking down CDK2 expression dramatically decreases EGF-induced cell transformation mediated through the down-regulation of *c-fos* expression We also observed that the ETS-like transcription factor 4 (ELK4) is over-expressed in melanoma cells. Knocking down ELK4 or CDK2 expression significantly attenuated the malignant phenotype of melanoma cells. Our study reveals a novel function of CDK2 in EGF-induced cell transformation, and the associated signal transduction pathways. These findings indicate that CDK2 could be a useful molecular target for chemoprevention and therapy against skin cancer.

2. Discovery of novel targets and agents for skin cancer prevention and therapy. Solar UV (SUV) irradiation is a major factor in the development of skin cancer, a common form of cancer in the United States. The mitogen-activated protein kinase (MAPK) cascades are activated by SUV irradiation. We found that MAPK signaling is critical for skin carcinogenesis. The 90 kDa ribosomal S6 kinase (RSK) and the mitogen and stress-activated protein kinase (MSK) proteins, constitute a family of protein kinases that mediate signal transduction downstream of the MAPK cascades. We observed that the phosphorylation of RSK and MSK1 was upregulated in human squamous cell carcinoma (SCC), and SUV-treated *in vivo* model skin.

The primary sensor of solar UV-induced cellular signaling has not been identified. Using an experimental system of solar simulated light (SSL) to mimic solar UV, we demonstrated that Fyn is a primary redox sensor for SSL-induced signal transduction. Reactive oxygen species (ROS) generated by SSL exposure directly oxidize Cys488 on Fyn, resulting in increased Fyn kinase activity. We found that Fyn oxidation was increased in *in vivo* model skin after SSL exposure. Also, Fyn knockout (Fyn -/-) *in vivo* models had larger and more numerous tumors, compared to Fyn wild-type *in vivo* models, when exposed to SSL for an extended period of time. Murine embryonic fibroblasts (MEFs) lacking Fyn, as well as cells in which Fyn expression was knocked down were resistant to SSL-induced apoptosis. Furthermore, cells expressing mutant Fyn (C448A) were resistant to SSL-induced apoptosis. These findings suggest that Fyn acts as a regulatory nexus between solar UV, ROS and signal transduction during skin carcinogenesis.

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. Using kinase arrays we observed that kaempferol inhibited RSK2 and MSK1. A combination of 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. An examination of the

mechanism of action of kaempferol revealed that kaempferol suppresses RSK2 and MSK1 kinase activities. Kaempferol also attenuated the SUV-induced phosphorylation of the CAMP-responsive element binding protein (CREB), and histone H3 in *in vivo* model skin cells, which are implicated in skin carcinogenesis. Taken together, these findings show that, kaempferol was a potent inhibitor of SUV-induced *in vivo* model skin carcinogenesis. Further analysis showed that the skin from the kaempferol-treated *in vivo* models 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.

Arsenic exposure has been associated with the development of cancer, and is reported to cause neoplastic transformation of cells through the activation of PcG proteins. We found that the activation of the p38α mitogen-activated protein kinase (MAPK) is required for arsenic-induced neoplastic transformation. Exposure of cells to 0.5 µM arsenic increased CRE and c-Fos promoter activities, that were accompanied by increases in p38α MAPK and CREB phosphorylation and expression levels, along with AP-1 activation. Introduction of short hairpin (sh) RNA-p38α into BALB/c 3T3 cells markedly suppressed arsenic-induced colony formation, as compared with wild-type cells. CREB phosphorylation and AP-1 activation were decreased in p38α MAPK knockdown cells after arsenic treatment. Arsenic-induced AP-1 activation, measured as c-Fos and CRE promoter activities and CREB phosphorylation were attenuated by p38αMAPK inhibition in BALB/c 3T3 cells. Thus, we showed that p38α MAPK activation is required for arsenic-induced neoplastic transformation, which is mediated through CREB phosphorylation and AP-1 activation.

3. Discovery of novel agents for lung cancer prevention and therapy.
Several carcinogens induce EGFR/RAS/MAPK signaling, which is critical in the development of lung cancer. In particular, constitutive activation of the extracellular signal-regulated kinase 2 (ERK2), is observed in many lung cancer patients, therefore developing compounds that target ERK2 in lung carcinogenesis could be beneficial. We examined the therapeutic effect of the compound catechol, in lung cancer treatment. We found that catechol suppressed anchorage-independent growth of murine KP2 and human H460 lung cancer cell lines in a dose-dependent manner. Catechol inhibited ERK2 kinase activity *in vitro*, and we also confirmed its direct binding to the ERK2 active site by X-ray crystallography. Phosphorylation of c-Myc, a substrate of ERK2, was decreased in catechol-treated lung cancer cells, and reduced the protein stability, and subsequent down-regulation of total c-Myc. Treatment with catechol induced G1 phase arrest in lung cancer cells, and decreased protein expression related to G1-S progression. In addition, we showed that catechol inhibited the growth of both allograft and xenograft lung cancer tumors *in vivo*. In summary, catechol inhibited ERK2/c-Myc signaling, which reduced lung cancer tumor growth *in vitro* and *in vivo*, including a preclinical patient-derived xenograft (PDX) model. These findings suggest that catechol, a natural small molecule could be a novel therapeutic agent against lung carcinogenesis for future clinical approaches.

First Row (L to R): Ann M. Bode, Mingjuan Lei, Yaping Han, Le Thi My Le, Zigang Dong
Second Row (L to R): Seug Ho Shin, Qiushi Wang, Eunmiri Roh, Simin Zhao
Third Row (L to R): Tara J. Adams, Ting Wang, Ruihua Bai, Hiroyuki Yamamoto, Margarita Malakhova, Ke Yao
Fourth Row (L to R): Christopher Dong, Joohyun Ryu, Kanamata Reddy, Abhijit Chakraborty, Yanan Jiang, Tatyana Zykova
Fifth Row (L to R): Souren Paul, Moeez Rathore, Jian Li, Ali Calderon, Tia Rai, KiBeom Bae, Weiya Ma
Six Row (L to R): XiaoYu Chang, Tiansun Zhang, Keke Wang, Humberto de Vitto, Jehangir Ahmed

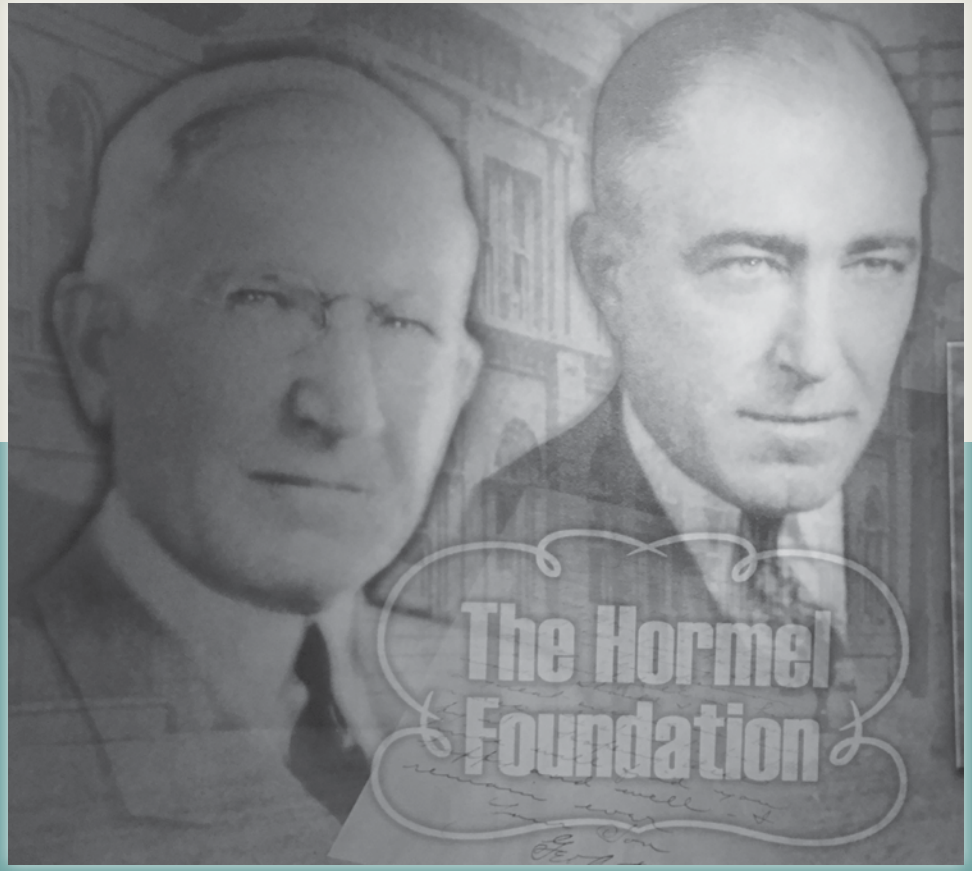
Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. Despite progress in developing chemotherapeutics for the treatment of NSCLC, primary and secondary resistance limits therapeutic success. NSCLC cells exhibit multiple mutations in the epidermal growth factor receptor (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. Utilizing a molecular target-oriented virtual screening we found that that ginger components – including [6]-shogaol, [6]-paradol, and [6]-gingerol, and butein – a USP8 inhibitor, and 3,6,2′,4′,5′-pentahydroxy-flavone could 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*. Importantly, these inhibitors could overcome the resistance to EGFR inhibitors in lung cancer.

4. Discovery of novel targets and agents for inhibition of esophageal cancer and colon cancer.

Aberrant AKT and extracellular signal-regulated kinase (ERK) activation is often observed in many human cancers. Both AKT and ERK are important in the phosphoinositide 3-kinase/AKT and mitogen-activated protein kinase kinase/ERK signaling pathways, which play vital roles in cell proliferation, differentiation and survival. Compounds that block these pathways could therefore be promising candidates for cancer treatment and prevention. The present study revealed that AKT and ERK are activated in esophageal cancer cells. We found that aloe-emodin (an extract from the aloe plant), could suppress the proliferation and anchorage-independent cell growth of esophageal TE1 cells. Aloe-emodin could also modulate the cell cycle, and reduced the number of TE1 cells in the S phase. Protein analysis indicated that aloe-emodin inhibited the phosphorylation of AKT and ERK in a dose-dependent manner. Overall, these finding indicate that aloe -modin could suppress TE1 cell growth by inhibiting AKT and ERK phosphorylation, and suggest its potential use for cancer therapy.

The nuclear factor of activated T cells (NFAT) family proteins are transcription factors that regulate the expression of pro-inflammatory cytokines and other genes during the immune response. Although the NFAT proteins have been extensively investigated in the immune system, their role in cancer progression remains controversial. We found that NFAT3 is highly expressed in several skin cancer cell lines and tumor tissues. Knockdown of endogenous NFAT3 expression by short hairpin RNA (shRNA) significantly inhibited tumor cell proliferation, colony formation and anchorage-independent cell growth. An investigation of potential NFAT3 interaction partners via a mammalian two-hybrid assay, showed that cyclin-dependent kinase 3 (CDK3) directly interacted with NFAT3, and phosphorylated NFAT3 at serine 259 (Ser259). The phosphorylation of NFAT3 at Ser259 by CDK3 enhanced the transactivation, and the transcriptional activity of NFAT3. The phosphorylation of NFAT3 at Ser259 was critical for the transformation of the HaCAT immortalized skin cell line via epidermal growth factor (EGF) stimulation. The mutation of NFAT3 at Ser259 led to a reduction of colony formation in soft agar. We also found that overexpressing wild-type NFAT3, but not mutant NFAT3-S259A, promoted A431 xenograft tumor growth. Importantly, we showed that CDK3, NFAT3 and phosphorylated NFAT3-Ser259 were highly expressed in skin cancer compared with normal skin tissues. These results provide evidence supporting the oncogenic potential of NFAT3, and suggest that CDK3-mediated phosphorylation of NFAT3 has an important role in skin tumorigenesis.

Gary and Pat Ray were major benefactors to the 2016 expansion project for The Hormel Institute, UMN reaching an overall lifetime gift to The Hormel Institute of $1 million. The Ray Live Learning Center - used for cancer research conferences, seminars and meetings - includes a 250 person Event Room and Auditorium, equipped with state of the art technology provided in part by Hormel Foods Corporation. Four international cancer research conferences have been held at the Ray Live Learning Center since it opened in 2016.



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"This is the kind of investment that Jay Hormel envisioned when he created the Foundation," said Gary Ray, chair of The Hormel Foundation. "The Institute is engaged in world-class, cutting-edge research in cancer prevention and treatment that benefits all of us. And, because that work is being done right here in Austin, the Institute helps energize our local and state economies, enhances our reputation as an attractive, diverse destination and brings some of the world's leading health researchers to our community."

Gary J. Ray, Chair
The Hormel Foundation

Cancer Biomarkers and Drug Resistance

ANN M. BODE, PH.D.

Associate Director / Section Leader / Professor

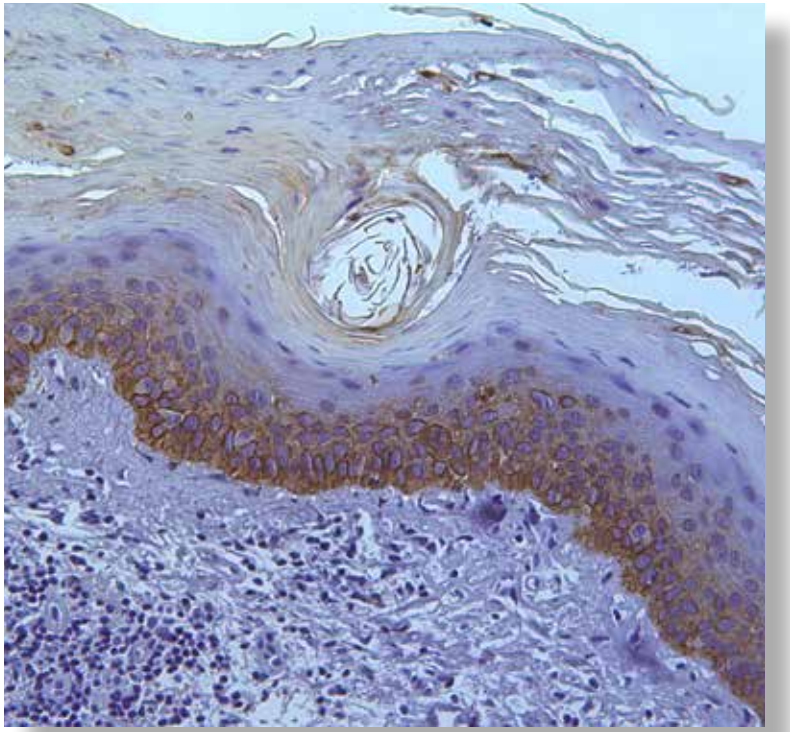
We continue to work with the National Institutes of Health to identify biomarkers important in drug resistance to cancer prevention and treatment. During 2015-2016, we published a number of papers in collaboration with NIH and University of Alabama.

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

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

Epidemiologic studies have shown that diabetics receiving the biguanide metformin, as compared with sulfonylureas or insulin, have a lower incidence of breast cancer. Metformin increases levels of activated AMPK (AMP-activated protein kinase) and decreases circulating IGF-1; encouraging its potential use

in both cancer prevention and therapeutic settings. In anticipation of clinical trials in nondiabetic women, the efficacy of metformin in nondiabetic *in vivo* mammary cancer models was evaluated. Metformin was administered by gavage or in the diet, at a human equivalent dose, in standard mammary cancer models: (i) methylnitrosourea (MNU)-induced estrogen receptor-positive (ER(+)) mammary cancers in *in vivo* models, and (ii) MMTV-Neu/p53KO ER(-) (estrogen receptor-negative) mammary cancers in *in vivo* models. In the MNU *in vivo* 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 *in vivo* models bearing small palpable mammary cancers, short-term metformin (150 mg/kg BW/d) treatment increased levels of phospho-AMPK and phospho-p53 (Ser20), but failed to reduce Ki67 labeling or expression of proliferation-related genes. In the *in vivo* model, dietary metformin (1,500 mg/kg diet) did not alter final cancer incidence, multiplicity, or weight. Metformin did not prevent mammary carcinogenesis in two mammary cancer models, raising questions about metformin efficacy in breast cancer in nondiabetic populations (Kim MS, Lim do Y, Kim JE, Chen H, Lubet RA, Dong Z, Bode AM. Src is a novel potential off-target of RXR agonists, 9-cis-UAB30 and Targretin, in human breast cancer cells. Mol Carcinog. 2015;54(12):1596-604. doi: 10.1002/mc.22232. PubMed PMID: 25328014; PMCID: PMC4402118).



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

Dr. Ann M. Bode
Associate Director

Molecular Therapeutics and Cancer Health Disparity

MOHAMMAD SALEEM (BHAT), PH.D.

Section Leader / Associate Professor

The long term goals of this section are the following:

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

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

RESEARCH PROJECTS UNDERWAY

1. Investigation of mechanisms of chemoresistance in prostate cancer patients

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

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

The critical pathological processes that occur during the development and progression of human prostate cancer and are known to confer aggressiveness to cancer cells are (1) abolishment of senescence of normal prostate epithelial cells, (2) self-renewability of prostate cancer cells even after chemotherapy and radiation, and (3) dysregulated cell cycle resulting in unchecked proliferation of cancer cells. Cellular senescence is physiologically important because it is a potent tumor suppressor mechanism that must be overcome for cells to be immortalized and transformed. Self-renewability of tumor cells is an essential defining property of a pluripotent stem cell–like phenotype of cancer cell which distinguishes it from other cell types. Stem cell–resembling population of cancer cells among the heterogeneous mix of cells constituting a tumor have been reported to

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

Dr. Mohammad Saleem (Bhat)

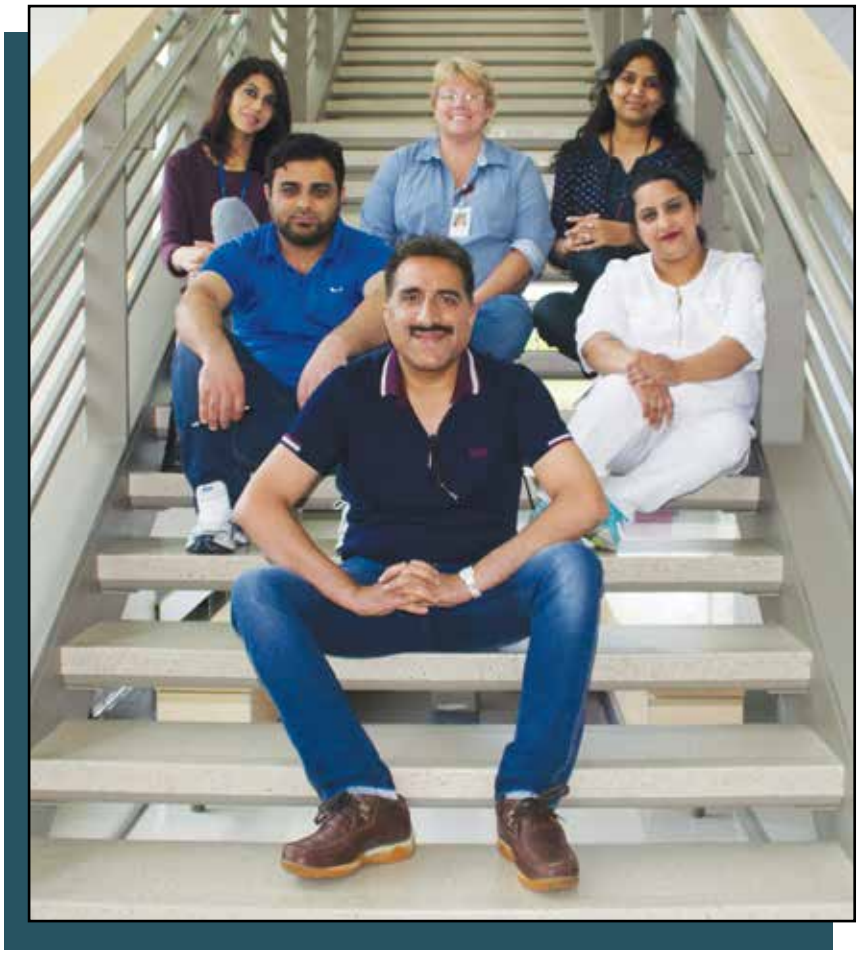
be essential for tumor progression and metastasis of epithelial malignancies. The data generated from our laboratory suggest that several cancer cells which do not respond to chemotherapy or radiotherapy possess the traits of stem cells thus regenerating themselves even after chemo or radiotherapy treatment. Polycomb group (PcG) family of proteins (which form multimeric gene-repressing complexes) has been reported to be involved in self-renewability, cell cycle regulation, and senescence. BMI-1 is a transcription repressor and has emerged as an important member of PcG family. We are investigating the role for Bmi-1 protein in prostate cancer development. We hypothesize that BMI-1 protein could be developed as a diagnostic and prognostic of prostate cancer.

3. Reactivation of tumor supperrosor genes

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

4. Role of S100A4 in the development of prostate cancer

S100A4, also known as mts1, CAPL, p9Ka, and metastasin, belongs to the S100 super-family of calcium-binding proteins and is located in a 2.05 Mbp segment of the genomic DNA of chromosome 1q21 region where most of the S100 family of gene cluster occurs. S100A4 protein has been reported to be associated with invasion and metastasis of cancer cells and has been reported to be frequently over-expressed in metastatic tumors, normal cells with uninhibited movement, such as macrophages, transformed cells and in various cancer types such as breast, ovary, thyroid, lung, esophageal squamous cell carcinoma, gastric, colon, and prostate. Earlier, we reported that S100A4 is overexpressed during progression of prostate cancer in humans and in TRAMP *in vivo* model, an autochnhonous transgenic model that develops prostate cancer in a manner similar to human disease. Recently, we showed that S100A4 regulates the events leading to proliferation and invasion of prostate cancer cells. We showed that S100A4 guides the invasive phenomenon of prostate cancer cells by regulating transcription and function of matrix metalloproteinase (MMP-9) in prostate cancer cells. S100A4 is notably known for its role in metastasis. By creating a transgenic *in vivo* model of prostate cancer lacking S100A4, we, for the first time, provide evidence that S100A4 protein, both in its intracellular and extracellular form plays a tumor promoting role in the development of prostate cancer by regulating the function of Nuclear Factor kappa B/Receptor for Advanced Glycation End products molecular circuitry.



First row: M. Saleem Bhat
Second row: Arsheed Ganaine, Neelofar Bhat
Third Row: Anmbreen Jamroze, Teri Johnson, Tabish Hussain

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

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

6. Investigating the causes of racial disparity in prostate cancer

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

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

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

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

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

Our Research Partner Institutions

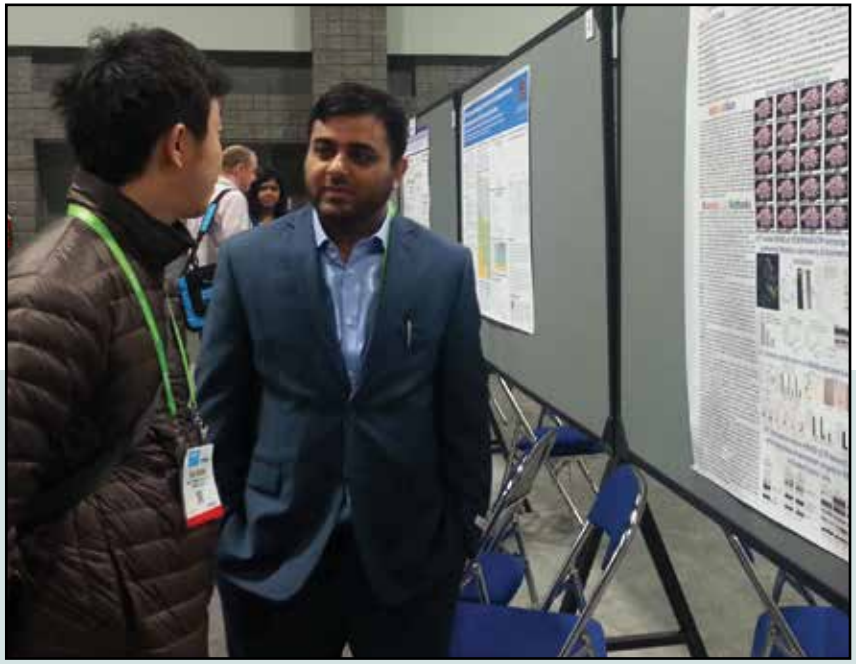
Our section has joined hands with internationally renowned research institutions and investigators in its quest to defeat the lethal disease of cancer in humans.

Studies are underway in partnership with the following research institutions:

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

Sponsors/ Funding Agencies Supporting our Research Activities:

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



Other Professional Activities

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

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

(B) Adhoc-reviewer of Scientific Journals

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

(C) Editorial Board Member of Scientific Journals

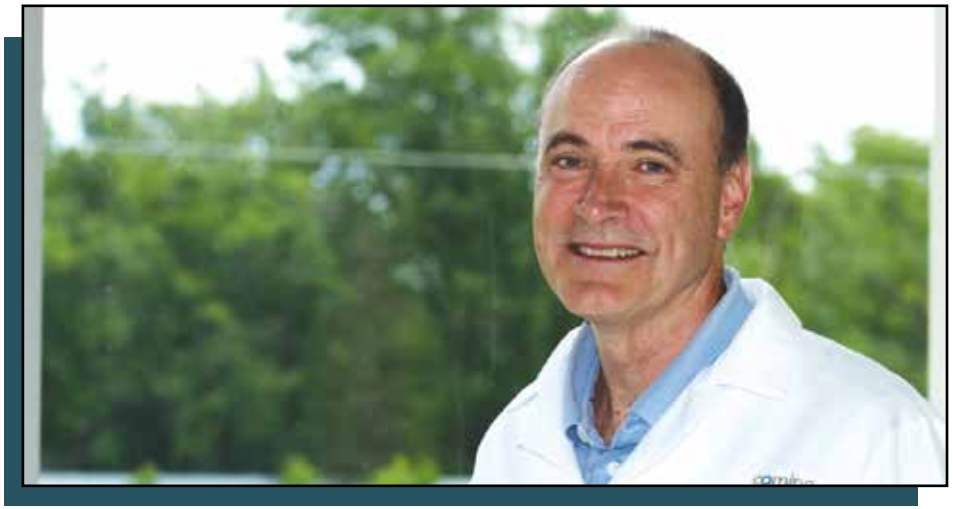
PLOSE ONE;
American Journal of Stem Cell,
Nutrition and Medicine;
American Journal of Clinical Experimental Urology

The Hormel Institute's Dr. Arsheed Ganaie receives Meritorious "Young Investigator" Award

Membrane Biochemistry

RHODERICK E. BROWN, PH.D.

Section Leader / Professor



Eukaryotic cells, including human cells, surround themselves with bilayer membranes, i.e. thin, flexible layers that are only two molecules thick. The molecular building blocks of bilayer membranes are specialized lipids that are polar and nonpolar at their opposite ends. Bilayer membranes also serve as internal partitions to enable formation of functionally-specialized compartments within cells. Interestingly, there are many more varieties of lipids found in membranes than are needed to form bilayers. What is now clear is that certain membrane lipids can function as messenger signals that regulate cell growth, proliferation, inflammation, and programmed cell death processes, while other membrane lipids appear to cluster together in bilayers to form microdomains that regulate the spatial distribution and lateral interactions of membrane proteins. The discovery of these membrane lipid functions underscores why cell membranes so often come under direct attack during cancer and infectious disease.

Our research focuses on membrane lipids known as sphingolipids and on proteins that interact in non-enzymatic fashion with sphingolipids. Such proteins include sphingolipid transfer proteins that function as transporters to shuttle sphingolipids between intracellular membranes as well as lipid-binding domains (e.g. C2-domains) that act as targeting and anchoring devices for certain kinds of sphingolipids embedded in membranes. We began investigating sphingolipids many years ago as findings began to emerge showing that certain sphingolipids form 'raft' microdomains in membranes containing cholesterol. Rafts appear to function as organizing regions for signaling kinases as well as target sites for certain viruses and bacteria. In earlier investigations, we focused on rigorously defining the physical basis for raft microdomain functionality. To gain insights into lipid structural features that control both the lateral and transmembrane distributions of sphingolipids, we have used a combination of biophysical approaches (fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, NMR). We developed ways to quantitatively measure the lateral elasticity within model membranes, to accurately assess the physical changes that occur within the 'raft environment' when the content and structure of sphingolipids and sterols become altered (collaboration with Howard Brockman lab; UMN-Hormel Institute), as well as assess changes in sphingolipid lateral and transbilayer distributions. Our research elucidated sphingolipid structural features that regulate their interactions with other membrane lipids and provided insights into the unique physical features at the heart of the lateral organizing functionality of sphingolipid-enriched microdomains. The findings have proven to be important for current understanding how the spatial organization of lipids in membranes can regulate proteins that translocate onto membranes to function.

We have since focused our efforts on specific proteins that can bind and transfer sphingolipids between membrane surfaces and that may help formation and maintain 'raft' microdomains in cells. These sphingolipid transfer proteins were initially identified as glycolipid transfer proteins (GLTPs) due to their specificity for transferring glycosphingolipids between membranes. We began to elucidate the importance of GLTPs for eukaryotic cells by using PCR approaches to clone GLTPs from various mammals as well as plants and fungi. We also developed ways to use bacterial expression systems to produce sufficient amounts of the various GLTP proteins for enabling us to crystallize the proteins and determine the molecular structures of GLTP and related homologs both in glycolipid-free form and complexed with different glycolipids, in collaboration with the D.J. Patel lab at Memorial Sloan Kettering Cancer Center in New York and the L. Malinina lab at CIC bioGUNE in Derio/Bilbao, Spain. Our studies revealed precisely how GLTPs recognize and envelope glycolipids to accomplish intermembrane transfer and shed light on: i) how GLTP adapts to accommodate different glycolipids within its binding site; ii) the functional role played by intrinsic tryptophan residues in glycolipid binding and membrane interaction; iii) the structural basis for the more focused glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2. Notably, our work revealed that human GLTP forms a novel structural fold among known proteins leading the Protein Data Bank to designate the human GLTP-fold as the founding prototype of the GLTP superfamily. The initial findings were published in *Nature* and *PLoS Biology*, with subsequent studies appearing in *Structure*, *The Journal of Biological Chemistry*, *Biophysical Journal*, *Biochemistry*, and *Journal of Lipid Research*. Nearly all of these studies benefited from collaboration with J. G. Molotkovsky at the Shemyakin Institute of Bioogranic Chemistry at the Russian Academy of Science.

More recently, we reported in *Nature* the discovery and structural characterization of a new GLTP structural homolog in human cells in collaboration with Dinshaw Patel at Memorial Sloan Kettering Cancer Center in New York. Remarkably, the lipid specificity of the new protein has evolved for binding and transfer of ceramide-1-phosphate rather than glycolipids even though the new protein still forms a GLTP-fold but encoded by a completely different gene than GLTP. Thus, the protein is named ceramide-1-phosphate transfer protein (CPTP). In collaboration with Ted Hinchcliffe (UMN-Hormel Institute), we tracked the location of CPTP in mammalian cells using state-of-the-art fluorescence microscopy approaches. In collaboration with Charles Chalfant at Virginia Commonwealth 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, to generate arachidonic acid that then is further metabolized into pro inflammatory eicosanoids. Recently initiated studies of human cytoplasmic phospholipase A2 (cPLA2α) are now being carried out in collaboration with the same talented collaborators. The goal is to determine the molecular basis by which cPLA2αcan initially promote inflammation but then subsequently help reverse and resolve this pathological process. By applying our multipronged cell biological and biophysical approaches, we expect to gain insights that drive new treatments for sepsis and inflammation associated with other pathologic conditions such as cancer, diabetes and dementia.

In related studies involving the model plant, *Arabidopsis thaliana*, published in *Cell Reports*, and carried out in collaboration with John Mundy at the University of Copenhagen and Dinshaw Patel at Memorial Sloan Kettering Cancer Center, we showed that disruption of a gene, known as *acd11*, accelerates cell death via mutation of a plant GLTP ortholog (ACD11). X ray structures revealed that ACD11 is a GLTP-fold evolved to also bind and transfer ceramide-1-phosphate. Disruption of the *acd11* gene impairs plant development by severely altering ceramide-1-phosphate and ceramide levels to drive the programmed cell death response. The involvement of ACD11 in this process stimulated further studies of CPTP in human cells which recently have shown that CPTP functions an endogenous regulator of autophagy and of inflammasome assembly that drives interleukin release (IL1B and IL18). The report describing this work is currently in press in *Autophagy*.

We anticipate that elucidation of the fundamental structure-function relationships governing GTLP and CPTP action will facilitate development of the means to pharmacologically modulate GLTP and enhance their potential use as biotechnological resources, i.e. nanotools, for targeted manipulation of cellular sphingolipid composition. Such strategies could provide new ways to introduce specific sphingolipid antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means, and lead to new therapeutic approaches to treat disease processes involving sphingolipids. The 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 that we have recently reviewed in *Quarterly Reviews of Biophysics and Annual Review of Biochemistry*. Our investigations of the gene organization and transcriptional status in humans and other mammals provide a firm foundation for identification and characterization of inherited diseases involving GLTP and CPTP. Our efforts benefit from continuing collaborations with Memorial Sloan Kettering Cancer Center in New York, The Russian Academy of Sciences in Moscow, Virginia Commonwealth University in Richmond, The University of Copenhagen in Denmark, the Mayo Clinic, and CIC bioGUNE in Derio/Bilbao, Spain. Our research continues because of generous financial support received from the NIH National Institute of General Medical Sciences, the NIH National Heart Lung and Blood Institute, the NIH National Cancer Institute of NIH, the Paint-the-Town Pink Initiative of southern Minnesota, and The Hormel Foundation. For more details regarding the research expertise and scientific publications of our lab, please visit the following web sites:

(from left to right): Rhoderick (Rick) Brown, Yong-Guang Gao, Lucy Malinina, Shrawan Mishra, Helen Pike, Xiuhong Zhai (not pictured)

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

Structural Biology

YOUNG-IN CHI, PH.D.

Section Leader / Assistant Professor

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

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

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

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

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

SCIENCE progress

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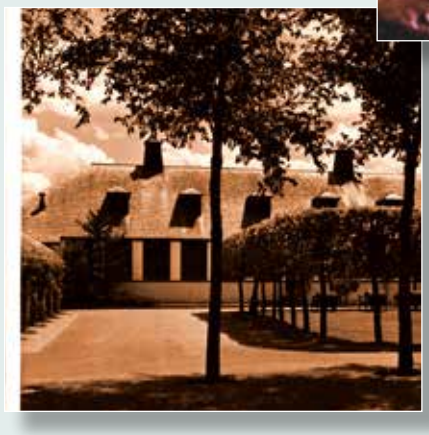

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OF SUPPORTING SCIENCE THAT IMPACTS THE WORLD

Nutrition and Metabolism

MARGOT P. CLEARY, PH.D.

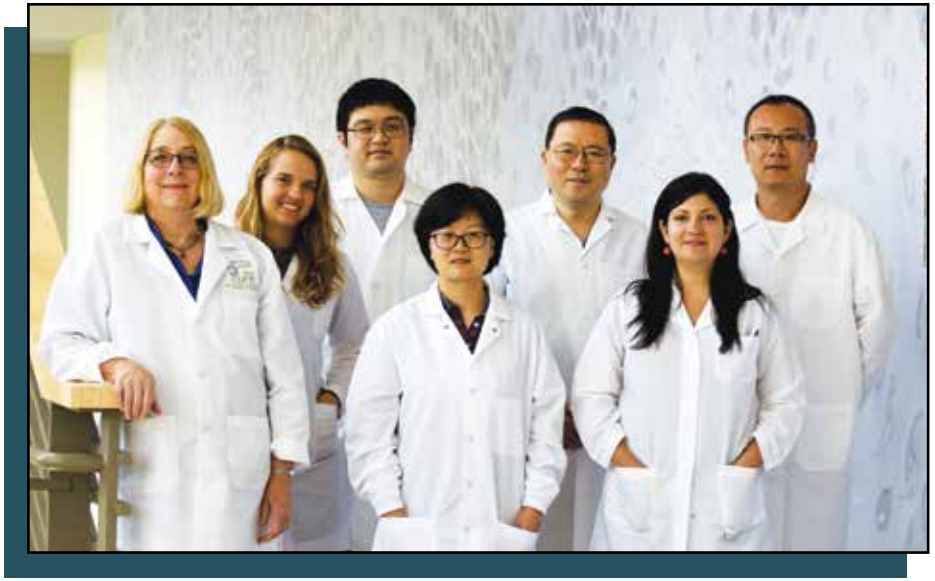
Section Leader / Professor

Our work has focused on the effects of body weight and food intake on the development of breast cancer using *in vivo* models and breast cancer cells in culture. Findings from our lab include identifying that leptin a protein made in adipose tissue is an important growth factor for mammary tumor development. This was accomplished by conducting experiments using genetically obese *in vivo* models that either do not produce leptin or do not have the leptin receptor. When cross-bred with *in vivo* models that normally develop mammary tumors neither of the genetically obese *in vivo* model strains did so. In contrast *in vivo* models with dietary-induced obesity that have elevated serum leptin levels develop mammary tumors at an earlier age than *in vivo* models fed the same high fat diet that stay in the normal body weight range. Cell culture studies using human breast cancer cell lines further provided evidence to the importance of leptin as a growth factor.

Other studies have assessed the impact of calorie restriction on the prevention of mammary tumors in *in vivo* models of breast cancer. Of particular interst, we consistently find that periods of moderately severe calorie restriction followed by ad libitum refeeding, which we term intermittent calorie restriction, results in much greater reduction in mammary tumor incidence than does the same degree of restriction implemented chronically. These two interventions result in the same overall calorie reduction of 20-25%. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors and the insulin-like growth factor (IGF)-axis. Based on results of our studies, we hypothesize that the altered, i.e., reduced adiponectin: leptin ratio which is characteristic of obesity, provides a permissive environment for tumor development. In contrast, the reductions of IGF-I and leptin and increased adiponectin:leptin ratio resulting from intermittent calorie restriction results in decreased mammary tumor incidence in comparison to ad libitum feeding as well as to chronic calorie restriction. These studies have been expanded by Dr. Michael Grossmann to include the interaction of an omega-3 fatty acid in combination with intermittent calorie restriction on the development of mammary tumors. Intermittent calorie restriction may be more tolerable wayfor individuals to reduce caloric intake. In fact several recent weight loss programs utilize this approach.

Although calorie restriction has an incredible effect on cancer prevention in many *in vivo* models, the practical aspects of implementing and maintaining this intervention in human populations has not been very successful. This has led to interest in identifying compounds that act like calorie restriction, i.e., calorie restriction mimetics. One such compound is the commonly used type 2 diabetic drug, metformin. Our most recent work focuses on directly comparing moderate calorie restriction (25% reduction) to metformin treatment on the prevention of mammary tumors. This study has been conducted in a transgenic *in vivo* model to mimic postmenopausal breast cancer and includes obese as well as normal weight subjects. The interventions were started when the *in vivo* models were middle-aged to reflect when this would occur in at risk women. We have completed this long term study where we followed the *in vivo* models until they were 90 weeks of age. We did not find that metformin had a cancer preventing effects in either lean or obese *in vivo* models. In contrast 25% calorie restriction resulted weight maintenance as the *in vivo* models aged as well as in a significant decrease in mammary tumor incidence and delayed age when tumors were detected in lean and obese *in vivo* models. With respect to mechanisms of action of these interventions not only are we assessing alterations in the AMPK pathway but also on aspects of altered glucose metabolism. We anticipate that these ongoing studies will provide valuable insights into ways to prevent mammary tumor development and to slow disease progression.

Other studies in the lab under the direction of Dr. DaQing Yang include the investigation of two important proteins, ATM and p53, which are critical for multiple physiological processes, including cell cycle progression, DNA damage repair, insulin signal transduction, and glucose metabolism. Signal transduction of the ATM protein kinase in response to insulin and metformin



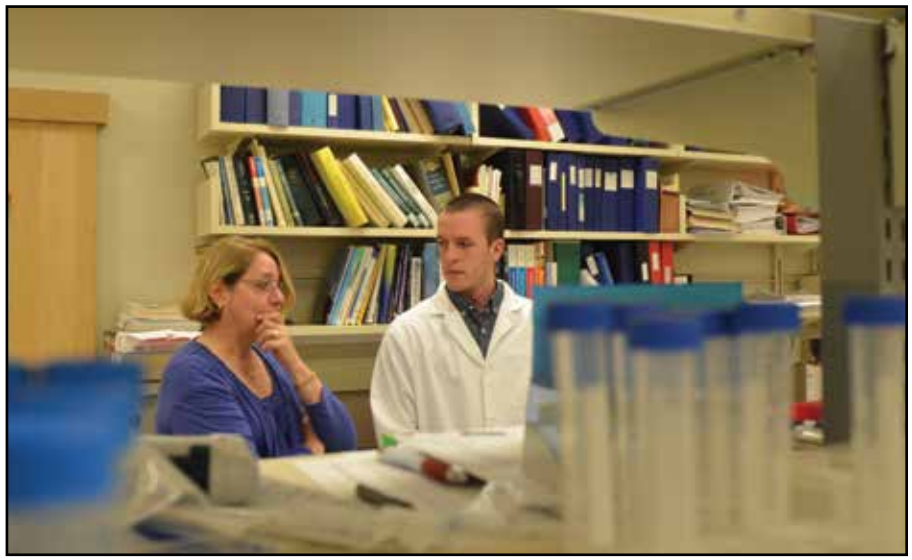
Left to Right: Margot Cleary, Jennyfer Register, Ye Zhang, Hanying Xing, Daqing Yang, Marina Ferrari, Liang Ma

is known to be linked to both cancer and diabetes. The investigation of the abnormal glucose metabolism in cancer cells using LC-MS-based targeted metabolomics has led to the discovery of potential biomarkers for early detection of pre-invasive breast cancer. The study of the translational regulation of p53 induction following DNA damage provides better understanding regarding how defective synthesis of the p53 tumor suppressor is involved in the development of cancer, which may lead to novel diagnosis and treatment strategies for various types of cancer, including breast, prostate, and pediatric cancer.

Other Professional Activities
Margot P. Cleary

Presentations:
Agricultural Utilization Research Institute (AURI) December 2016,
Poster presentation AACR Annual Meeting Washington, DC April 2017

Grant Review Activities:
NIH Study Section September 2016, Italian Association for Cancer Research, Science Foundation of Ireland



"Overweight and obesity were recently reported to be a factor in 40% of all diagnosed cancers (Morbidity and Mortality Weekly Report 66:1052,2017). Thus, our studies on the role of obesity on the development of mammary tumors and ways to prevent to prevent tumor development in preclinical models of breast cancer are very timely."

Dr. Margot P. Cleary

Cell Death and Cancer Genetics

YIBIN DENG, M.D., PH.D.

Section Leader / Associate Professor

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

Our laboratory, therefore, focuses on understanding how the wild-type p53 suppresses tumorigenesis and why the oncogenic "GOF" of mutant p53 found in cancer patients promotes tumor development. To translate our bench work to bedside, we have been utilizing genomic, proteomic, and metabolomics approaches, bioinformatics, computational modeling, structural biology, RNAi- and CRISPR/Cas9 or Cpf1-based screening, and genetically engineered *in vivo* models (GEMMs) that recapitulate the salient characteristics of human cancers to discover the crucial "druggable" targets for cancerous 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 four major areas:

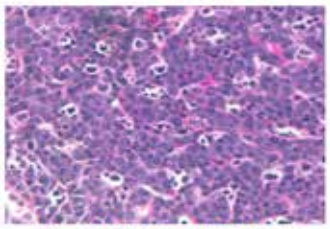


Figure 1. **Dram deficiency causes lung cancer**

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 *in vivo* models. Our findings suggest that *Dram* potentially functions as a tumor suppressor because deletion of *Dram* induces spontaneous tumor development in *in vivo* models (Fig. 1). Currently, we are trying to dissect the molecular basis underlying *Dram*-deficiency-driven tumorigenesis *in vivo*. We are also exploring whether and how the cross-talk 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 *in vivo* models utilizing the conditional Dram knockout *in vivo* models to breed with *in vivo* models deficient in p53-mediated apoptosis (p53R172P knock-in or Puma knockout) and senescence-deficient *in vivo* models (p21 knockout). We expect that by utilizing these complex genetic engineered *in vivo* models, we will be able to address the critical question how the p53-activated 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" *in vivo* breast cancer models and discover the "causal" genomic events driving breast tumorigenesis *in vivo*. One important mechanism that can give rise to the unstable breast cancer

genome is the dysfunction of telomeres. Telomeres are nucleoprotein caps that protect chromosomal ends from being recognized as aberrant damaged DNA and prevent chromosome end-to-end fusions. Telomeres that no longer can exert end-protective functions are said to be dysfunctional, and these telomeres could arise either from progressive telomere attrition (telomere shortening) or when components of the telomeric DNA-binding proteins – termed "shelterin complex" – are perturbed (telomere uncapping). In human breast carcinomas, chromosomal instability fueled by dysfunctional telomeres is associated with the transition from benign ductal hyperplasia to malignant ductal carcinoma *in situ*. This strongly supports the notion that telomere dysfunction-induced chromosome instability initiates the development of breast cancers. Our laboratory has been engineering a novel *in vivo* breast cancer model harboring telomere uncapping-induced chromosomal instability without affecting the activity of telomerase (Fig. 2). Importantly, the *in vivo* model also carries "hot spot" mutant p53 found in breast epithelium of cancer patients. We believe that this *in vivo* model will faithfully recapitulate the genetic abnormality commonly observed in human sporadic breast carcinomas. We have been establishing and utilizing this novel *in vivo* 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 inhibit human breast cancer.

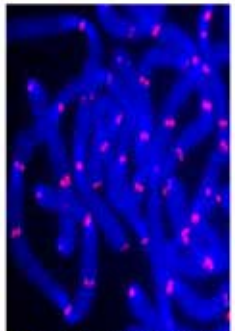


Figure 2. **Uncapped telomeres initiate chromosomal fusion**

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

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

We recently have made progresses in our study on prostate cancers. Prostate cancer strikes one in six men and is the second leading cause of cancer-related deaths in men after lung cancer in the United States. Prostate cancer arises mainly from prostatic intraepithelial neoplasia (PIN), a precursor lesion that ultimately progresses to adenocarcinoma and systemic metastasis. Conventional androgen deprivation therapy (ADT) by surgical and/or chemical castration remains the gold standard-of-care therapy for metastatic prostate cancer. Unfortunately, these prostate cancers invariably develop resistance to conventional ADT and progress to a more aggressive castration-resistant prostate cancer (CRPC) within 18-24 months. The discovery that persistent androgen receptor (AR) signaling plays a crucial role in the

Left to Right: Yibin Deng, Teri Johnson, Puja Singh

progression of CRPC leads to "second generation" ADT treatments, such as the recently Food and Drug Administration-approved androgen synthesis blocker abiraterone (2011, FDA) and the second generation of AR signaling inhibitor enzalutamide (formerly MDV3100) (2012, FDA), which have demonstrated efficacy against chemotherapy-resistant CRPC with median increase in survival of 4-5 months. However, nearly all CRPC patients inevitably develop acquired resistance to the "second generation" anti-AR signaling axis treatments within ~6-12 months. Currently, no therapeutic options exist for CRPC patients who have developed resistance to the second generation of anti-androgen receptor (AR) signaling axis therapy. We found that co-deletion of *Pten* and *p53* in prostate epithelium, often observed in human lethal CRPC, leads to AR-independent CRPC and thus confers *de novo* resistance to "second generation" androgen deprivation therapy (ADT) in multiple independent yet complementary preclinical *in vivo* models. In striking contrast, mechanism-driven co-targeting hexokinase 2 (HK2)-mediated Warburg effect with 2-deoxyglucose (2-DG) and ULK1-dependent autophagy with chloroquine (CQ) selectively kills cancer cells through intrinsic apoptosis to cause tumor regression in xenograft and lead to a near-complete tumor suppression in *Pten*-/*p53*-deficiency-driven CRPC *in vivo* model (Fig. 3).

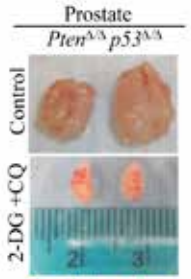


Figure 3. **Targeting cell metabolism**

Given that 2-DG is recommended for phase II clinical trials for prostate cancer and CQ has been clinically used as an anti-malaria drug for many decades, the preclinical results from our "proof-of principle" studies *in vivo* are imminently translatable to clinical trials to evaluate the therapeutic efficacy by the combination modality for a subset of currently

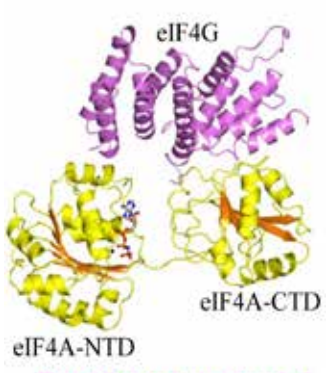


Figure 4. **Crystal structure of complex eIF4A/eIF4G**

incurable CRPC patients. Through collaborations with clinicians, we are translating our experimental studies in CRPC *in vivo* models into clinical trials and hopefully our studies will benefit CRPC patients harboring *PTEN* and *TP53* mutations.

4. Translational control of cancer cells

Our mechanistic studies of AKT-mTOR signaling in prostate cancer lead us to address a novel and challenging question how oncogene mRNA is selectively translated (protein synthesis) in tumorigenesis.

One of the key components involved in translation initiation is the eukaryotic translation initiation factor 4F (eIF4F), a complex consists of the ATP-dependent RNA helicase eIF4A, the adaptor protein eIF4G, and the 5′-cap-binding protein eIF4E. The eIF4A only has low ATPase and helicase activity, however, formation of a complex with eIF4G dramatically increases its activity, which in turn unwinds RNA secondary structures in the 5′-untranslated region (5′-UTR) of mRNA and initiates translation. Thus, interaction of eIF4A and eIF4G plays a crucial role in initiating oncogene mRNA translation in cancer cells. Currently, we utilized x-ray crystallography to successfully solve the complex structure of human eIF4A/eIF4G (Fig. 4). Our studies provide a structure-based discovery of small-molecule compounds that disrupt the eIF4A/eIF4G interaction in cancer cells to selectively block oncogene protein synthesis and inhibit tumor development.

Our laboratory also is combining X-ray crystallography and Cryo-electron microscopy (cryo-EM) to decipher structures of eukaryotic translation complex for our full understanding of their biological mechanisms in tumorigenesis.

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

Other Professional Activities
Yibin Deng
Grant Reviewer, National Cancer Institute

"We are utilizing multiple approaches to understand how the genetic changes identified in cancer patients contribute to tumor initiation, progression and metastasis. We discovered a novel selective and effective therapeutic target for currently incurable castration-resistant prostate cancer (CRPC) and our drug-repurposing studies provide the quickest possible translation from bench to the bedside."

Dr. Yibin Deng

OMEGA-3

Ralph T. Holman (1917 - 2012) was a world recognized biochemist whose research focused on lipids and fatty acids, especially the Omega-3 fatty acid which he named.

He joined The Hormel Institute in the 1950s and served as Executive Director from 1975-1985. The Hormel Institute was considered the world leader in lipid research for his groundbreaking research in essential fatty acids.

In 1981 Dr. Holman became a Member of the National Academy of Sciences, in recognition of his distinguished and continuing achievements in original research. Membership is a widely accepted mark of excellence in science and is considered one of the highest honors a scientist can receive.

Cancer Cell Biology and Translational Research

SERGIO GRADILONE, PH.D.

Section Leader / Assistant Professor

The "Cancer Cell Biology and Translational Research" section focuses on understanding the basic biological processes involved with a normal cell transforming into a cancerous one. By understanding these mechanisms, potential therapeutic interventions may be envisioned.

We continue investigating the role of the primary cilium in tumor biology. Primary cilia are multisensory organelles – similar to a cell antenna – that sense and receive signals from the environment surrounding the cells. We've found that these antennae are lost in tumor cells; therefore, we are trying to understand the mechanisms of ciliary loss, and what are the consequences of such a loss. Furthermore, as we gain knowledge on these mechanisms, we are now able to induce the restoration of primary cilia in tumor cells and bring back the malignant cells to a more normal phenotype, which may contribute to the development of new therapeutic strategies based on the rescue of primary cilia integrity.

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

We continue our collaborations and established new ones, both intra- and extramural, with prestigious investigators and institutions including: Drs. Saleem Bath, Daqing Yang, Ted Hinchcliffe, James Robinson, and Yibin Deng (The Hormel Institute), Drs. Nicholas LaRusso, Lewis Roberts, and Steven Alberts (Mayo Clinic Rochester, MN), Dr. Kabir Mody (Mayo Clinic Jacksonville, FL), Dr. Jesus Banales (Biodonostia Research Institute -Donostia University Hospital, San Sebastian, Spain), Dr. Raul Marinelli (National University of Rosario, Argentina), Dr. Hector Perez (Ability Pharmaceuticals, Barcelona, Spain), Regenacy Pharmaceuticals Inc (Boston, MA), and KARUS Therapeutics (UK).

Our laboratory first federal grant started in July 2015. This research grant from the National Cancer Institute (National Institutes of Health) R01 CA183764 entitled "The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle" supports our main line of research focused on bile duct cancer at The Hormel Institute for five years. Furthermore, during the last year we were honored with three new pilot grants: (i) Mayo Clinic-Jacksonville to explore the role of HDAC6 in pancreatic cancer, and (ii) The Randy Shaver Cancer Research and Community Fund, and (iii) The "Paint the Town Pink" Award to study the new concept of ciliophagy in bile duct and breast cancer, respectively.

Our research has been published in several manuscripts and international meetings, and is uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilia architecture and function. By partnering with collaborators directly engaged in the treatment of patients and with pharmaceutical industries, our ultimate goal is to translate our basic research to the bedside by developing new clinical trials for these diseases.

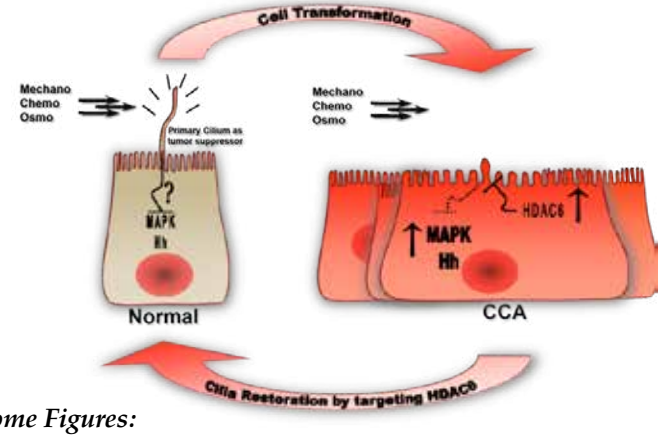
Publications 2017:

1. Mansini AP, Peixoto E, Thelen KM, Gaspari CI, Jin S, Gradilone SA. "The Cholangiocyte Primary Cilium in Health and Disease" Biochim Biophys Acta, in press, 2017. https://doi.org/10.1016/j.bbadis.2017.06.006

2. Peixoto E, Mansini AP, Thelen KM, Gaspari CI, Jin S, Gradilone SA. "The Role of Primary Cilia in Cancer" Physiological Mini Reviews, 10(1), 2017. https://pmr.safisiol.org.ar/archive/vol/10

3. Gradilone SA. "Extracellular vesicles as therapeutic carriers of microRNAs for cholangiocarcinoma". Hepatology, 65(2):404-406, 2017. https://doi.org/10.1002/hep.28925

Front: Sujeong Jin, Ann Weston, Stephanie Holtorf, Adrian Mansini, Sergio Gradilone
Back: Seth Richard, Cesar Gaspari, Estanislao Peixoto; Missing form photo Kristine Thelen as missing



Some Figures:

Figure 1. Working Model. Cholangiocyte primary cilia normally sense the environment and transmit those external cues into intracellular signals that function as suppressor of tumorigenic factors. Upon malignant transformation in cholangiocarcinoma, overexpression of HDAC6 induces the resorption of primary cilia, generating the disengagement between the environment and the cell interior and the derepression of tumorigenic pathways. The restoration of primary cilia through HDAC6 targeting would be a potential approach to decrease cholangiocarcinoma progression.

4. Ji B, Harris BR, Liu Y, Deng Y, Gradilone SA, Cleary MP, Liu J, Yang DQ. "Targeting IRES-Mediated p53 Synthesis for Cancer Diagnosis and Therapeutics". Int J Mol Sci, 18(1), 2017. https://doi.org/10.3390/ijms18010093

5. Merino-Azpitarte M, Lozano E, Perugorria MJ, Esparza-Baquer A, Erice O, Santos-Laso Á, O'Rourke CJ, Andersen JB, Jiménez-Agüero R, Lacasta A, D'Amato M, Briz Ó, Jalan-Sakrikar N, Huebert RC, Thelen KM, Gradilone SA, Aransay AM, Lavín JL, Fernández-Barrena MG, Matheu A, Marzioni M, Gores GJ, Bujanda L, Marin JJ, Banales JM. "SOX17 regulates cholangiocyte differentiation and acts as a tumor suppressor in cholangiocarcinoma". J Hepatol, 67(1):72-83, 2017. https://doi.org/10.1016/j.jhep.2017.02.017

6. Gradilone SA, Lorenzo Pisarello MJ, LaRusso NF. "Primary Cilia in Tumor Biology: The Primary Cilium as a Therapeutic Target in Cholangiocarcinoma". Current Drug Targets, 18:958-963, 2017. https://doi.org/10.2174/1389450116666150223162737

7. Mansini AP, Thelen KM, Gradilone SA. "Loss of cholangiocyte primary cilia induces LKB1 downregulation and defective AMPK signaling". Proceedings: AACR Annual Meeting 2017; April 1-5, 2017; Washington, DC https://doi.org/10.1158/1538-7445.AM2017-361

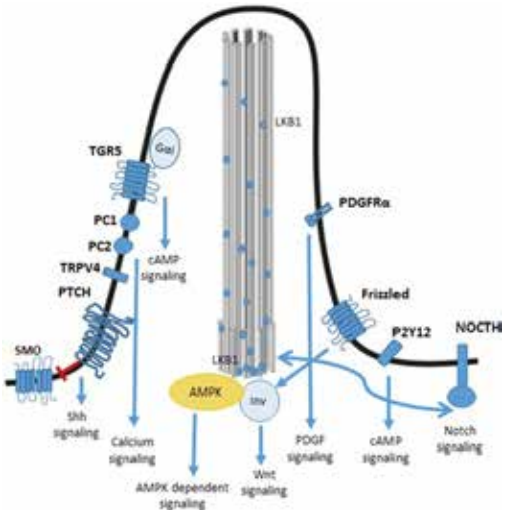


Figure 2. Cholangiocyte primary cilium regulates several signaling pathways. The ability of primary cilia to detect different signals is a consequence of the expression of specific ciliary proteins and ciliary associated receptors. The activation of these receptors results in activation or inhibition of different signaling pathways. TGR5: G-protein-coupled bile acid receptor 1; PC-1: polycystin-1; PC-2: polycystin-2; TRPV4: Transient Receptor Potential Vanilloid 4; PTCH: patched receptor; SMO: Smoothened receptor; PDGFRα: Platelet-derived growth factor receptor α; P2Y12: Purinergic receptor 12; Inv: inversin; AMPK: AMP-activated protein kinase; LKB1: liver kinase B1.

Cellular Dynamics

EDWARD H. HINCHCLIFFE, PH.D.

Section Leader / Professor

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

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

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

Chromosome instability (CIN) is a hallmark of solid tumors, and contributes to the genomic heterogeneity of tumor cells. There are multiple mechanisms believed to underlie the generation of CIN, including cell cycle defects, abnormal centrosome duplication and function, premature chromatid disjunction, and centrosome separation errors. However, despite an increasingly mechanistic understanding of how CIN is generated, we know relatively little about how chromosome missegregation becomes transduced into cell transformation and tumorigenesis. A major unresolved question is the role of cell cycle checkpoints and failsafe devices in preventing chromosome missegregation in the first place. The question of how a single missegregated chromosome can trigger the p53/p21 pathway and induce durable cell cycle arrest – a molecular failsafe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is part of the answer. However, to date, no mechanisms have been identified that monitor chromosome mispositioning – either before or after anaphase – at the single chromosome level.

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

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

Experimental research results

1. Chromosome missegregation: Contributing to the onset of tumorigenesis

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

(from left to right): Edward Hinchcliffe, Sela Fadness, Alyssa Langfald, Charles Day

question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood.

To this end we have recently identified a novel biochemical pathway that monitors chromosome missegregation. We find that misaligned chromosomes (i.e. those well away from the metaphase plate) activate a dynamic positional "sensor", involving phosphorylation of the highly conserved histone variant H3.3. H3.3 differs from the canonical H3.1 by 5 AA substitutions; one of which, Ser 31 is phosphorylated only during mitosis (Ser31-P). Whereas all congressed chromosomes have Ser31-P confined to their peri-centromeric regions, we find that misaligned chromosomes accumulate Ser31-P along their arms. H3.3 Ser31 hyper-phosphorylation persists after anaphase, and is found on both lagging chromosomes in the bridge, and disjoined pairs of chromatids syntelicly-attached to one pole. Thus, Ser31-P serves as a dynamic mark for CIN in both mitotic and post-mitotic cells. We are characterizing the Ser31 phosphorylation pathway used to recognize misaligned chromosomes. We are determining the mechanism used to generate the Ser31-P proximity sensor on misaligned chromosomes, and identify both the kinase and the phosphatase responsible for generating this dynamic mark. We are using live-cell imaging assays to determine the fate of cells that exit mitosis with missegregated chromosomes, while simultaneously using biochemical/genetic methods to inactivate Ser31 phosphorylation in these cells. We are testing whether H3.3 Ser31P affects cell fate or proliferation in CIN cells. Recent work has shown that single nucleotide somatic mutations in the tail of the H3.3 gene (K27M and G34R) are associated with human cancers. Both mutations flank Ser31. We will test the role of these flanking AA substitutions in modulating H3.3 Ser31-P, and in the ability of H3.3 to bind potential regulatory elements. Our work is innovative, because is capitalizes on a novel pathway to identify chromosome missegregation in individual cells. It is also important, because for the first time, it allows for the biochemical manipulation of basic cellular responses to chromosome missegregation and aneuploidy.

2. Building a bipolar spindle

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

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

3. Coordinating cytokinetic furrow formation with anaphase onset

The cell division furrow – created by the recruitment of actin filaments and the motor protein myosin II – is formed between the separating sister chromatids at anaphase. This furrow constricts the dividing cell into two daughters. In order to ensure that cytokinesis occurs in the right place and at the right time, the positioning of the cleavage furrow must be coupled to the segregation of the chromosomes. This occurs through signaling via the microtubule network, specifically the dynamic astral microtubules and the stable overlapping midzone microtubules. Both of these classes of microtubules are important for signaling the formation of the cytokinetic furrow, and for ensuring that the furrow remains restricted to the cell center. We are investigating the regulation of furrow formation using live-cell imaging and single cell manipulation. We are taking

advantage of the fact that microtubules are extremely sensitive to temperature, and can be disassembled by cold treatment, without causing harm to the cell. When the cells are warmed up, the microtubule re-assemble, and the cell cycle proceeds on its way. Using this system, and spinning disk confocal microscopy, we are able to examine the roles of candidate regulatory mechanisms, including Aurora B kinase, Polo-like kinase 1, and the relative contributions of the astral and midzone microtubules. Our goal is to integrate molecular studies with live-cell physiology, in order to understand the mechanisms underlying cell division.

We have found that there is a period following the onset of anaphase where the cell cortex can respond to furrow-inducing signals, and this period is sensitive to the loss of microtubules, and the activity of Polo-like kinase 1. However, once cells progress beyond this point, the furrow will form, regardless of whether or not microtubules persist. Polo-like kinase 1 activity is also not required after this "point of no return"; adding kinase inhibitors after this point does not affect the ability of a furrow to assemble.

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

Our work will provide for a mechanistic understanding of key cell cycle events that may contribute to cancer progression. Together, these studies will also provide a source of potential targets for future anti-cancer drugs.

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

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

"Basic research lies at the heart of our quest to end cancer."

Dr. Edward H. Hinchcliffe

Dr. Harald H.O. Schmid

Dr. Harald H.O. Schmid was executive director of The Hormel Institute from 1987 to 2001, following over twenty years as a faculty member leading the Physiological Chemistry research section.

Dr. Schmid began at the Institute in 1962 and from 1978-1992 was a co-investigator of the Mayo Peripheral Neuropathy Clinical Research Center, the first long-range, funded collaboration between Mayo Clinic and The Hormel Institute, University of Minnesota.

According to Dr. Schmid's historical notes, throughout the first fifty years the Institute's research theme was wide open, although generally related to lipids. Due to financial pressures it had to become more directly related to human health, and finally to the cancer issue. All this was made possible by the rapid development of molecular biology over the past few decades. This transition started during Dr. Schmid's tenure as executive director. Dr. Schmid and his wife Pat, a former Scientist at the Institute, have started an endowment to support continued cancer related lipid research at The Hormel Institute.

"The Hormel Institute owes its existence to the curiousity and foresight of one man - Jay C. Hormel. Hormel's vision and The Hormel Foundation's vision was to realize that mankind's progress is largely based on scientific discoveries."

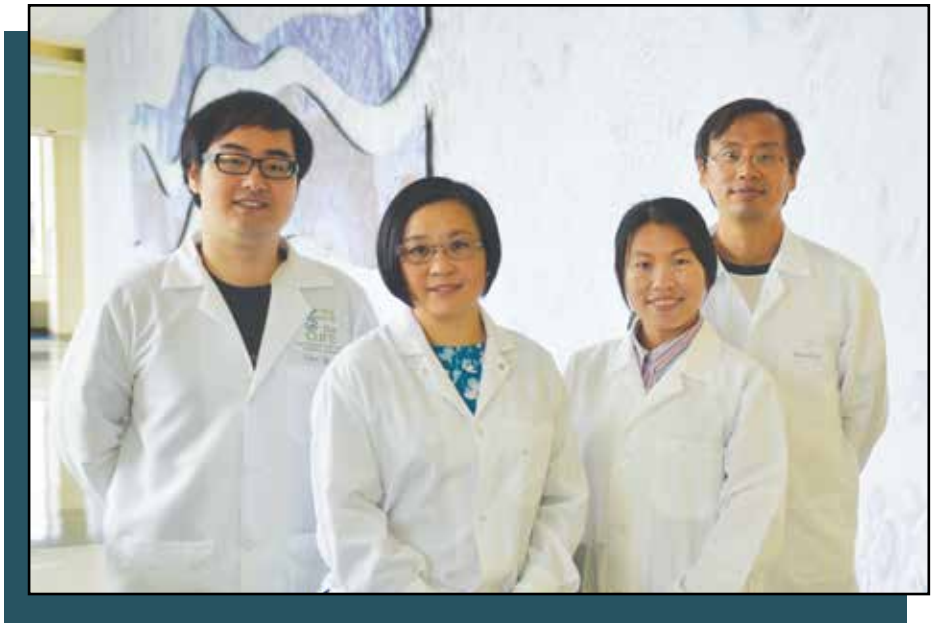
Dr. Harald H.O. Schmid
former Executive Director

NINGLING KANG, PH.D.
Section Leader / Associate Professor

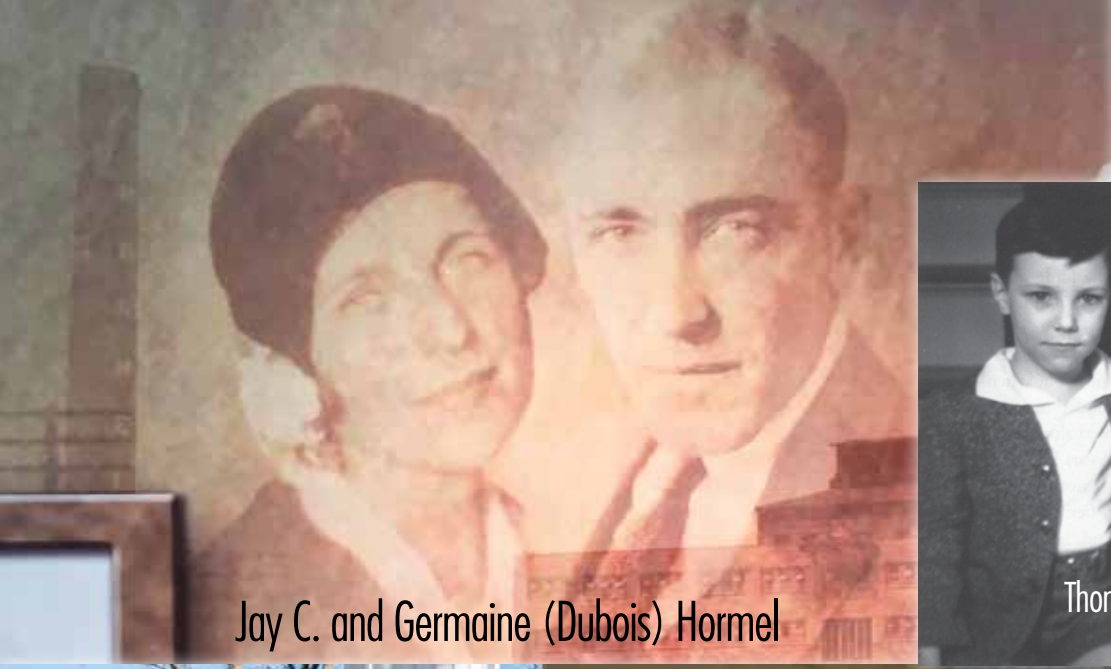
Through the support of NIH grant, *Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver* (R01CA160069), we explored a novel role of p300 acetyltransferase in hepatic stellate cell (HSC) activation in the last year. Liver is a common site for metastatic cancer cells, such as gastrointestinal cancer cells, to colonize and grow. In response to cancer invasion of the liver, cancer cells and other components of the liver microenvironment produce growth factors and cytokines to induce transdifferentiation of quiescent HSCs into myofibroblasts (MFs). In turn, activated-HSC/MFs promote liver metastasis by releasing growth factors, cytokines, extracellular matrix (ECM) proteins, and matrix metalloproteinases. Because the activated-HSC/MFs generate and deposit excessive ECM, they are considered a major contributor to desmoplasia and stiffness of liver metastases.

Although the role of stiffness on the biology of cancer cells has received intensive investigations, it is unknown if stiffness can in return regulate the biology of the activated-HSC/MFs. To address this question, we employed polyacrylamide gels with incremental stiffness as cell culture substrates for HSCs to investigate whether and how stiffness influences myofibroblastic activation of HSCs. Our data indeed show that a stiff substrate induces HSCs to express alpha-smooth muscle actin (α-SMA) and CTGF, markers of HSC activation, and concurrently nuclear accumulation of p300 acetyltransferase in HSCs. Perturbation of p300 by cre-loxP-mediated gene deletion, shRNA-based knockdown, or pharmacological inhibition abrogates stiffness-induced HSC activation. Mechanistically, stiffness activates a RhoA-Akt mechanosignaling to promote p300 phosphorylation at serine 1834 and subsequently targets it to the nucleus to epigenetically regulate gene transcription. RNA sequencing reveals that stiffness promotes HSCs to transcribe a panel of tumor-promoting paracrine factors, including CXCL12, IL11, IL6, VEGFA, PDGFA and B. In agreement with these data, conditioned medium of HSCs on a stiff substrate promotes colorectal tumor growth *in vitro* and in a subcutaneous tumor implantation *in vivo* model as compared to that of HSCs on a soft substrate. Additionally, portal vein injection of colorectal cancer cells into p300 conditional knockout *in vivo* models (p300F/F|collagen1A1-cre) leads to reduced liver metastatic growth as compared to control *in vivo* models.

Our study uncovers "an amplification loop" for liver metastatic growth whereby stromal stiffness, built by activated-HSC/MFs, in return acts on the activated-HSC/MFs to further enhance their activation and tumor-promoting effects via a HSC p300-dependent mechanism. The RhoA-Akt-p300 mechanosignaling of HSCs thus represents as a novel target for anti-liver metastasis therapy. A manuscript about this study has been submitted and it is currently under peer-review.



(from left to right):
Chen Chen, Ningling Kang, Jialing Wen, Yuanguo Wang



Jay C. and Germaine (Dubois) Hormel

The Hormel Institute 1942

Thomas, James and Geordie Hormel

Photo supplied by John Duren
johndurenphotography.com

Then & Now

HORMEL FAMILY

Visited Austin and The Hormel Institute - April 2017

Cryo-EM and Molecular Cell Biology

ANNA SUNDBORGER, PH.D

Section Leader / Assistant Professor

Membrane remodeling and cell fate

In the Cryo-EM and Molecular Cell Biology Section we are studying how membrane-bending proteins assemble into large complexes and regulate fundamental membrane remodeling events, such as apoptosis, autophagy and mitochondrial dynamics. Our primary focus is to determine how dysregulation of these pathways contributes to infectious diseases and cancer. Equipped with a Titan Krios electron microscope (FEI) fitted with phase plates and a Falcon 3 direct electron detector, we are able to solve the 3D structure of key proteins and protein complexes at atomic resolution in the ultimate effort to identify key players that contribute to regulation of cell death and to identify novel drug targets.

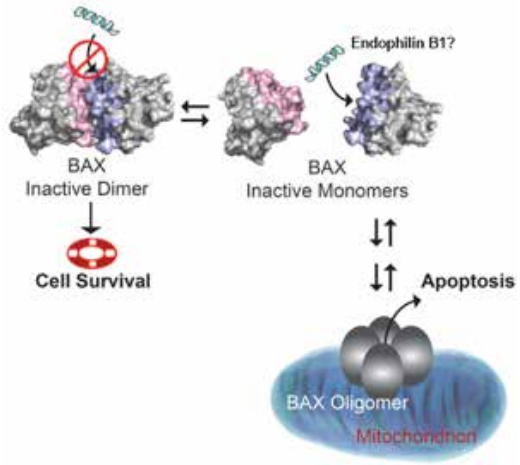


Figure 1. Bax-mediated apoptosis. Inactive Bax dimers are dissociated by interactions with activator proteins, one of which my be endophilin B1. Bax monomers may subsequently oligomerize and form pore in the OMM.

There is a strong link between intracellular pathways that regulate cell death and cancer. Remodeling of cellular membranes is a key feature during these processes and there is emerging evidence that membrane remodeling BAR domain-containing proteins (BAR proteins) serve important tumor suppressor functions in the cell, though their exact mechanisms are unknown. BAR protein endophilin B1 is involved in the regulation of apoptosis, though the exact mechanisms are unclear.

Previous studies show that endophilin B1 promotes oligomerization of pro-apoptotic protein Bax. Bax is recruited to the outer mitochondrial membrane (OMM) where oligomerizes to form a pore, a process critical for apoptosis (figure 1). Knockdown of endophilin B1 in cells inhibits Bax-mediated apoptosis. Bax activity is regulated by BH3-only domain protein from the Bcl-2 family. Our hypothesis is that endophilin B1 promotes apoptosis by facilitating recruitment and activation of Bax at the OMM in a similar manner. Endophilin B1 also interacts with key regulators of autophagy, a pro-survival process, which suggests that endophilin B1 plays an important role in determining cell fate.

Our preliminary data shows that endophilin B1 preferentially binds to lipid membrane vesicles containing cardiolipin, a lipids enriched in the OMM required for Bax activation (figure 2).

We are currently collecting data of these endophilin B1-decorated lipid tubules in the Titan Krios and our goal is to generate a 3D reconstruction at atonic resolution that will shed insight into how endophilin B1 assembles

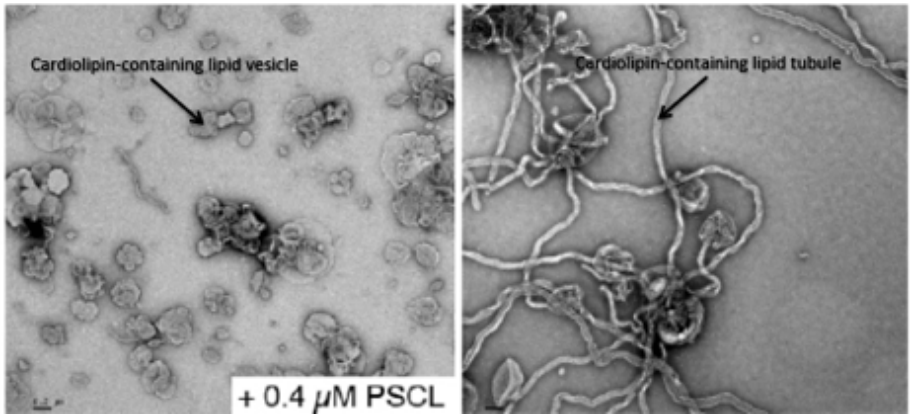
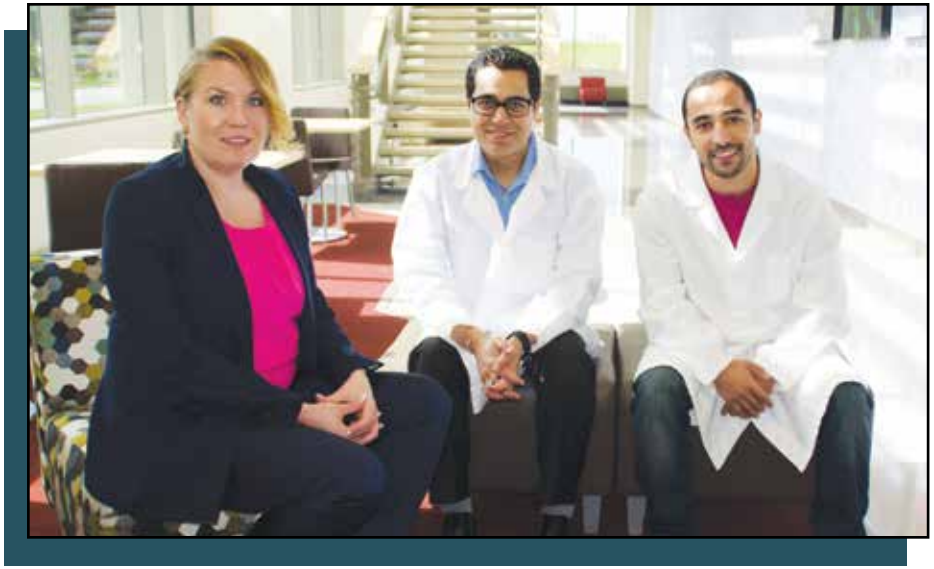


Figure 2. Endophilin B1 binds and tubulates cardiolipin-containing lipid vesicles. Electron micrographs showing lipid vesicles (left) and lipid tubules formed in the presence of endophilin B1 (right) visualized by negative stain and imaged using a Biotwin Spirit electron microscope.



(from left to right): Dr. Anna Sundborger, PI, Dr. Veer Bhat, Hormel Fellow, Nodir Boymatov, SURE student

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

Dr. Anna Sundborger

on cardiolipin-enriched lipid membrane and further how it may regulate Bax assembly. We are also in the process purifying recombinant Bax from E.Coli. Upon completion, we will initiate experiments to determine the structural relationship between endophilin B1 endophilin B1 and Bax on cardiolipin-containing lipid vesicles. Endophilin B1-Bax assembles will be further characterized using cryo-EM.

Presentations
Gordon Conference "Three-Dimensional Electron Microscopy"
Les Diablerets, Switzerland

Department of Gastroenterology and Hepatology *Mayo Clinic, Rochester*

Institute for Medical Virology
University of Minnesota, Minneapolis

Masonic Cancer Center
University of Minnesota, Minneapolis

Biophysical Society 58th Annual Meeting
New Orleans, LA

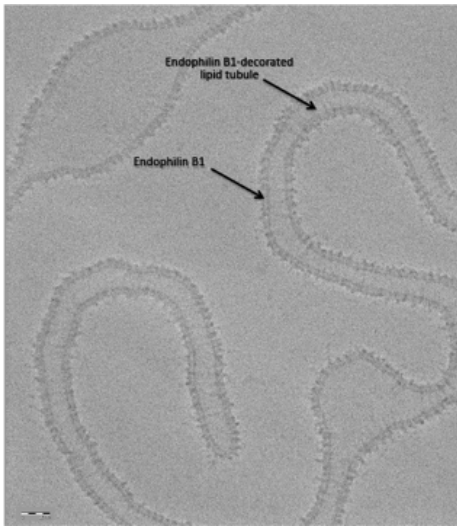


Figure 3. Cryo-electron micrograph of endophilin B1- decorated lipid tubules. Vitrified sample of endophilin B1 scaffolds were imaged with a Titan Krios electron microscope equipped with a Falcon 3 direct electron detector. Scale bar 20 nm.

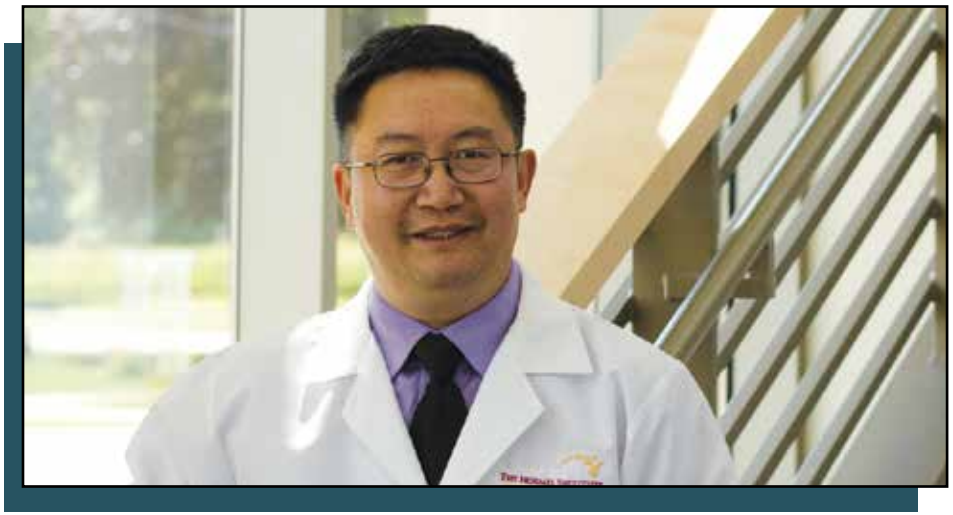
Bob Ashley, CryoEM Manager

Bob Ashley and Joshua Lobo

Cancer Epigenetics & Experimental Therapeutics

SHUJUN LIU, PH.D.

Section Leader / Associate Professor



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

Epigenome and kinome crosstalk regulates lung cancer aggressiveness

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

Protein kinases and DNA methyltransferases cooperatively regulate cancer cell fate decision under drug selections

Because aberrant DNA methylation and abnormal KIT function critically contribute to cancer pathogenesis, as independent practice, KIT and DNMT1 have been extensively used for therapeutic targets and their inhibitors have been tested in various pre- and clinical models. However, resistance of tumor cells to kinase inhibitors or DNA hypomethylating agents poses huge limitations to their use in treatment. Our findings suggest that resistance to decitabine and PKC412 eventually results from simultaneously re-methylated DNA and re-activated kinase cascades, as evidenced by the upregulation of DNMT1, DNMT3a, DNMT3b and tyrosine-protein kinase KIT, the enhanced phosphorylation of KIT and its downstream effectors as well as the increased global and gene-specific DNA methylation with the downregulation of tumor suppressor genes. Interestingly, the resistant cells had higher capability of colony-formation and wound-healing than parental cells *in vitro*, with

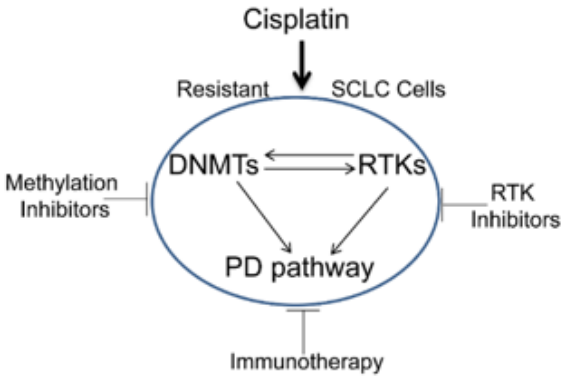
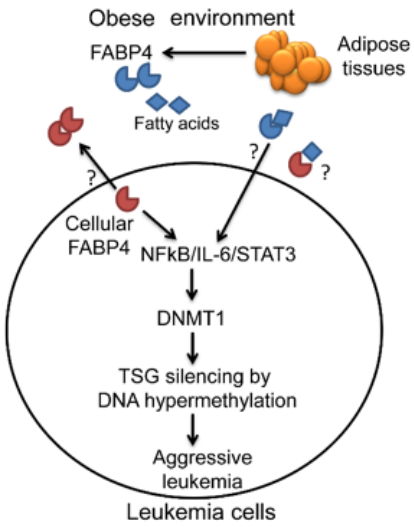


Diagram of interactions among DNMTs, RTKs and PD pathway in cisplatin resistance

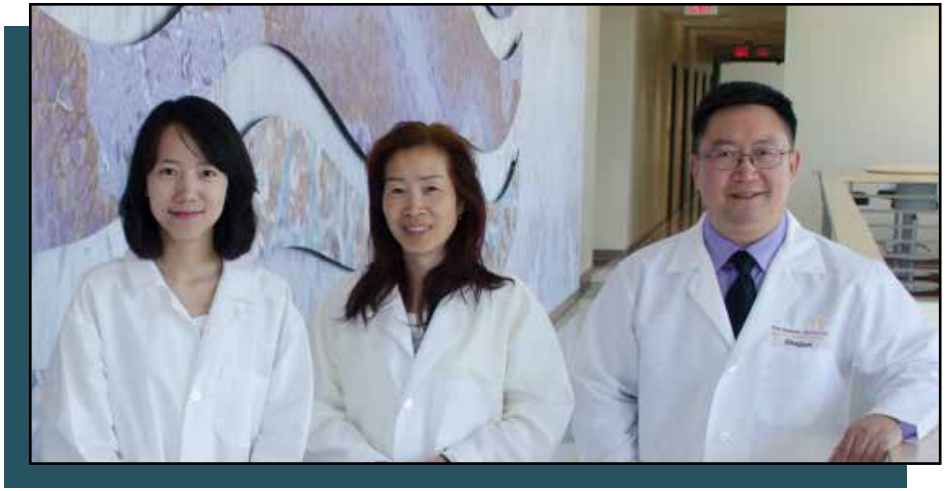
stronger tumorigenicity *in vivo*. Reciprocal inactivation of DNMT1 and KIT eradicates drug-resistant cells. In addition to the molecular targeted therapy, we recently showed that resistance to cisplatin in small cell lung cancer takes place through a new signaling network, DNMT1-KIT-PD1. Theoretically, our findings shed light on the molecular biology of drug resistance; practicably, our studies provide a sound rationale in clinical trials for using inhibitors of new signaling network to override drug resistant phenotypes, and also identify new opportunities for early therapeutic intervention against the emergence of drug-resistance. Our studies have been selected to be included in the PLOS Editor's Picks collection on Cancer Immunotherapy.

Aberrant epigenetic links obesity to leukemia

Cancer is the representatively systemic lesions taking over the first place of lethal diseases throughout the world. Obesity is a "disease" with abnormal body fat accumulation. The World Health Organization estimates that approximately one quarter of population worldwide are obese. While it is a well-established concept that obesity is a major risk factor for breast cancer, colon cancer and prostate cancer etc., whether and how obesity contributes to leukemia remain unexplored. Our findings showed that dietary-induced obesity mediates aggressive leukemia growth *in vitro* and *in vivo* thus, for the first time, experimentally demonstrating obesity-leukemia association. Mechanistic investigations showed that a family of fatty acid binding protein (FABPs) could be responsible for obesity-associated aggressive leukemic phenotypes, because a single change of FABP4 in obese host or in leukemia cells is sufficient to alter leukemia cell fate. Importantly, the deregulated FABP4 in obese host or leukemia cells abnormally modifies the epigenetic landscape in leukemia cells, leading to further silencing of tumor suppressor genes followed by uncontrollable leukemia growth. Mechanistically, we are the first to demonstrate lipid chaperone FABP4 as an epigenetic modulator, and to identify the FABP4/DNMT1 regulatory circuit as a hitherto unknown molecular link behind obesity-cancer association; in terms of practical use, our findings open a novel window of targeting the FABP4/DNMT1 axis for treating leukemia, and potentially, other types of cancers. This work was published in Leukemia, a top journal in hematology.



Schematic of FABP4/DNMT1 axis linking obesity to AML leukemia


(from left to right): Na Zhao, Jiuxa Pang, Shujun Liu

"Theoretically, our findings shed light on the molecular biology of drug resistance; practicably, our studies provide a sound rationale in clinical trials for using inhibitors of new signaling network to override drug resistant phenotypes, and also identify new opportunities for early therapeutic intervention against the emergence of drug-resistance."

Dr. Shujun Liu

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 *in vivo* models. We also evidenced the synergistic effects of combined liposomal bortezomib with nano-*miR29b* on leukemia cell growth in *in vivo* models. Recently, we synthesized HDL/AuNP nanoparticle and successfully delivered small molecule compounds into leukemia cell lines, patient primary cells and in leukemic *in vivo* models, which was demonstrated by the inhibition of leukemia cell colony formation, the reduction of DNA methylation and the blockage of leukemia growth in *in vivo* models. These results revealed that nano-drug delivery displays huge potential to improve therapeutic efficacy while reducing its side effects, including decreased drug toxicity, altered pharmacokinetics, improved drug solubility and more specific target binding.

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

Publications (June 2016-June 2017)

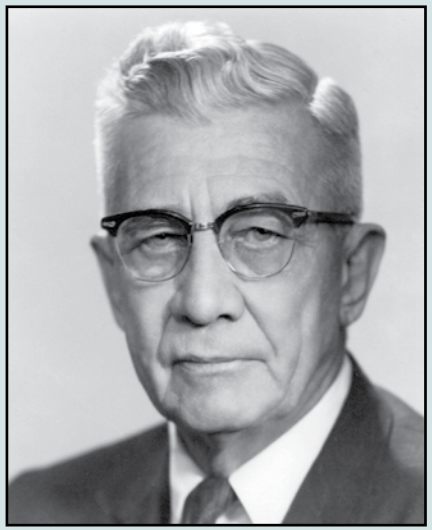
1. Yan F, Pang J, Peng Y, Molina JR, Yang P, Liu S. Elevated Cellular PD1/PD-L1 Expression Confers Acquired Resistance to Cisplatin in Small Cell Lung Cancer Cells. PLoS One. 2016 Sep 9;11(9):e0162925

2. Yan F, Shen N, Pang JX, Zhang YW, Rao EY, Bode AM, Al-Kali A, Zhang DE, Litzow MR, Li B, Liu SJ. Fatty acid-binding protein FABP4 mechanistically links obesity with aggressive AML by enhancing aberrant DNA methylation in AML cells. Leukemia. 2017 Jun;31(6):1434-1442

3. Zhang Y, Rao E, Zeng J, Hao J, Sun Y, Liu S, Sauter ER, Bernlohr DA, Cleary MP, Suttles J, Li B. Adipose Fatty Acid Binding Protein Promotes Saturated Fatty Acid-Induced Macrophage Cell Death through Enhancing Ceramide Production. J Immunol. 2017 Jan 15;198(2):798-807

4. Pang J, Shen N, Yan F, Zhao N, Dou L, Wu LC, Seiler CL, Yu L, Yang K, Bachanova V, Weaver E, Tretyakova NY, Liu S. Thymoquinone exerts potent growth-suppressive activity on leukemia through DNA hypermethylation reversal in leukemia cells. Oncotarget. 2017 May 23;8(21):34453-34467

5. Sun D, Zhou JK, Zhao L, Zheng ZY, Li J, Pu W, Liu S, Liu XS, Liu SJ, Zheng Y, Zhao Y, Peng Y. Novel Curcumin Liposome Modified with Hyaluronan Targeting CD44 Plays an Anti-Leukemic Role in Acute Myeloid Leukemia in Vitro and in Vivo. ACS Appl Mater Interfaces. 2017 May 24;9(20):16857-16868

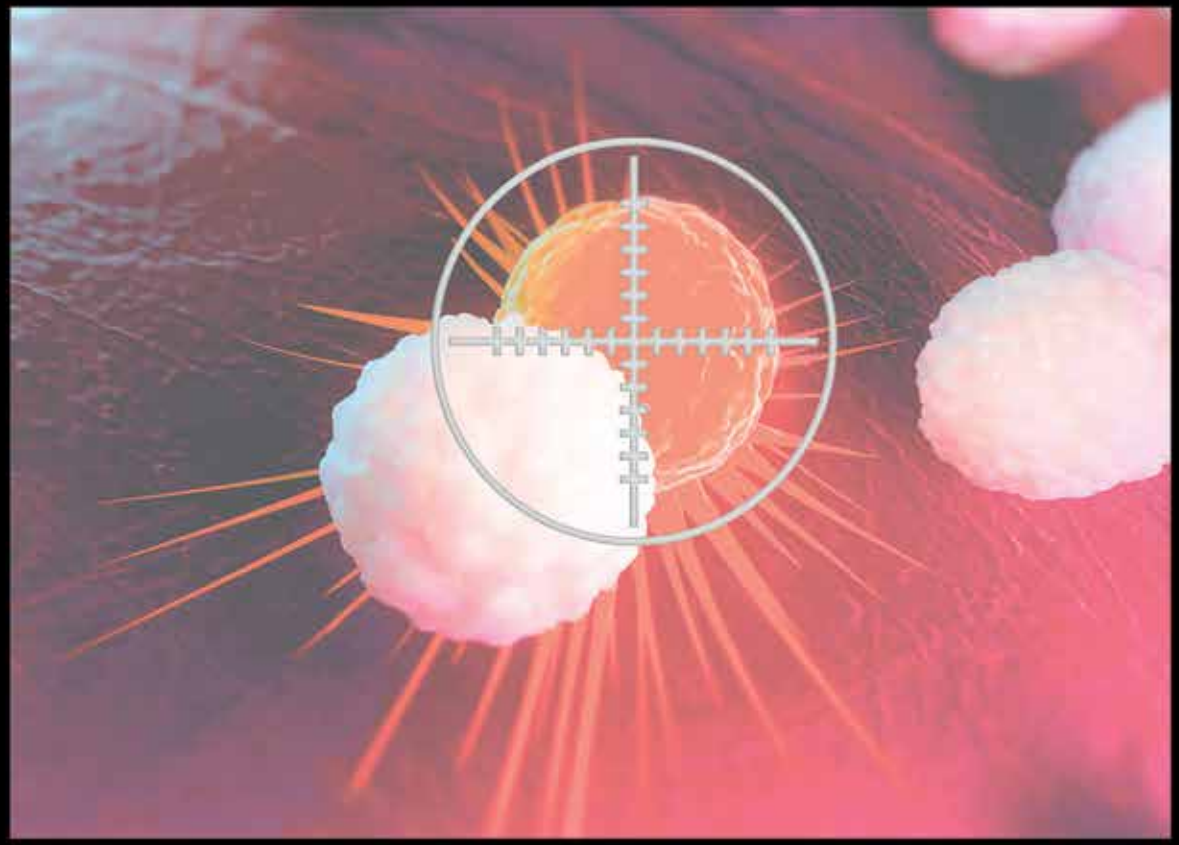


THEODORE BLEGEN, 1957

"The year 1957 marks the fifteenth anniversary of the establishment of this dynamic Institute. A single research project, a study of the nutritive value of soybeans, done in the University of Minnesota's Department of Physiological Chemistry, modestly initiated the Institute's work. In 1944 the Hormel Foundation provided a building which, from humble beginnings, has gradually been converted into an impressive array of well-equipped and well-staffed chemical and biological laboratories where researches are being carried forward day by day. The support and fruitful ideas that emanated from the late Jay C. Hormel helped immensely in the growth of the Institute, and the Foundation through its Board of Directors has continued generously to sustain and advance its activities.

The first project undertaken in the Austin laboratories had to do with rancidity in food fats. In the years that have followed, the Institute has won recognition nationally and internationally for its researches on fats and other lipid materials."

Dr. Theodore Blegen
Dean of Graduate School
University of Minnesota



npj PRECISION ONCOLOGY

-Springer Nature launched the journal *"npj Precision Oncology"* in partnership with The Hormel Institute, University of Minnesota in Austin, Minnesota, United States.

- *npj Precision Oncology*, is a new open access, international, peer-reviewed journal that publishes cutting edge scientific research in all aspects of precision oncology, from basic science to translational applications to clinical medicine.

- The journal defines precision oncology as cancer diagnosis, prevention, and/or treatment tailored specifically to the individual patient based on their genetic and/or molecular profile.

- *npj Precision Oncology* fills the need of a journal where both preclinical and early clinical studies can be published together to help support this rapidly advancing field.

-According to the Managing Editor at Nature Research *"Npj Precision Oncology* has been exceptionally successful". We have passed the first landmark of 25 peer-reviewed published articles, which makes our journal eligible to apply for inclusion in PUBMED, one of the first steps required to obtain an IMPACT FACTOR. We are also looking for 1-2 additional Associate Editors to bring on board.

- Featured topics include cancer development and prevention, therapies that target specific cellular pathways, cancer metabolism and genetic risk factors

-In addition to publishing original basic science, translational and clinical research articles, *npj Precision Oncology* -also publishes case reports, brief communications, commentaries, perspectives, and review articles.

- The journal also publishes a professionally written Editorial Lay Summary to accompany each research Article, which summarizes the key issues being addressed within the article aimed to keep readership at the vanguard of new discoveries in the field.

Please visit us at: https://www.nature.com/npjprecisiononcology/

Stem Cells and Cancer

REBECCA MORRIS, PH.D.

Section Leader / Professor

The epidermal layer of the skin is composed largely of cells called keratinocytes. Keratinocytes in the basal layer are organized into subpopulations based on their proliferative nature and include stem cells (relatively rare) and transit amplifying cells (comprise most of the proliferating cells). When a stem cell divides, one daughter usually remains a stem cell while the other daughter gives rise to transit amplifying cells with limited proliferative potential. Upon completion of their divisions, transit amplifying cells undergo an orderly maturation process called terminal differentiation that includes their outward displacement through the suprabasal layers, production of high molecular weight keratins, loss of their nuclei, and formation of an impervious outer structure called the cornified envelope. This process is exceptionally orderly and maintains the normal thickness and cellularity, and the normal functions of the epidermis throughout life. Our work focuses on the stem cells of the hair follicles because they not only serve as a reservoir of epidermal cells, they also possess remarkable regenerative potential and are known to be able to reconstitute a graft, to heal wounds, and even to give rise to non-melanoma skin cancer.

Non-melanoma skin cancer is a significant problem for cancer research because, although rarely a cause of death, it occurs more frequently than any other malignancy, and more than five million new cases are diagnosed in the United States annually with a burden of more than eight billion dollars. An estimated one-third to one-half of all human cancers originate in the skin; skin cancers exceed all others combined; and the lifetime risk of skin cancer the United States is one in five. Solar ultraviolet radiation is the major known cause of non-melanoma skin cancers and is directly relevant to the etiology as demonstrated by epidemiological evidence and the tight correlation between non-melanoma skin cancer in humans, and solar radiation- and chemically-induced skin carcinogenesis in murine models. These cancers progress through an orderly sequence in which genetic, biochemical, and cellular abnormalities accumulate in target cells over time. Mild alterations initially seen within keratinocytes can only be identified histologically. Increased cellular atypia occurs with further sun damage, and hyperkeratotic, pre-malignant actinic keratoses develop. Of these, one to ten percent will progress to squamous cell carcinomas. Therefore, determining the etiology of non-melanoma skin cancer is a critical problem in cancer research. Because avoiding exposure to sunlight is far more easily said than done, there is considerable interest in increasing knowledge of skin cancer etiology and finding targets for prevention.

Towards this end, we chose the molecule high mobility group A2, (Hmga2), a transcription factor involved in chromatin architecture, and expressed chiefly during development, where it has many key biological functions. When expressed in adult tissues from in various organs, Hmga2 is always related to cancer development. The role of Hmga2 in skin tumorigenesis is, however, not yet understood. We demonstrated that Hmga2 is found in non-transformed epidermis, specifically located to the membrane of keratinocytes in epidermis. Ex vivo culture of keratinocytes and *in vivo* development of skin carcinomas was associated with translocation of the Hmga2 protein from the membrane into the nucleus, where Hmga2 induced its own expression by binding to the Hmga2 promoter. Panobinostat, a histone deacetylase inhibitor, down-regulated Hmga2 expression by preventing Hmga2 from binding its own promoter, and thus inhibiting Hmga2 promoter activity. Hmga2 translocation to the nucleus could in part be prevented by an inhibitor for ROCK1. Our findings demonstrate that upon programing of benign papilloma to malignant squamous cell carcinomas, Hmga2 translocates in a ROCK-dependent manner from the membrane to the nucleus, where it serves as an auto-regulatory transcription factor, causing cellular transformation.

In a second project on the etiology of squamous cell carcinoma we focus on cytokeratin expressing cells in the blood and bone marrow and their role in cancer development. Cytokeratins are frequently found in the blood and bone marrow of patients with epithelial cancers and are attributed to metastasis. We wondered whether we could find keratin expression in blood

From left to right: Sonali Lad, B.S. (Researcher 2 and BICB Master's Student), Rebecca J. Morris, Ph.D. (Principal Investigator), Mara Overby (Sure Intern). Missing, Yong Li, Ph.D. (Research Associate), and Nishitha Paidimukkla, M,S, (BICB Ph.D. Student).

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

In summary, research in the Morris laboratory continues to highlight the role of stem cells in the pathogenesis of squamous cell carcinoma, 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.

"Because avoiding exposure to sunlight is far more easily said than done, there is considerable interest in increasing knowledge of skin cancer etiology and finding targets for prevention."

Dr. Rebecca Morris

Cell Signaling and Tumorigenesis

James Robinson, P.H.D.

ASSISTANT PROFESSOR & SECTION LEADER

Our section is concerned with the molecular mechanisms by which oncogenic signaling regulates Tumorigenesis, with the ultimate goal of developing and improving existing therapeutic approaches to eliminate cancer. As part of the University of Minnesota and a member of the Masonic Cancer Center (MCC), have and will continue to collaborate with worldwide experts in the fields of cell signaling, cancer research comparative pathology and genetics. We employ two experienced postdoctoral fellows, Kwan Hyun Kim, Ph.D. and Hana Yang, Ph.D, and this summer we are joined by Nick Hanson whose Undergraduate Research Experience (SURE) internship was generously funded with an Orville S. Privett Scholarship.

Publications 2017

1. H Yang, D Kircher, KH Kim, AH Grossmann, MW VanBrocklin, SL Holmen, and JP Robinson. Activated MEK cooperates with Cdkn2a and Pten loss to promote the development and maintenance of melanoma. Oncogene. 2017 Jul 6;36(27):3842-3851.

Glioma: Gliomas are the most common primary brain tumor. Glioblastoma (GBM), the highest grade of glioma (most lethal), is highly infiltrative, and is resistant to all conventional therapies. Patients with this cancer rarely survive longer than 12-14 months from the time the tumor is diagnosed. Pediatric GBM is clinically and biologically distinct from the adult disease. It typically develops in the midline or pons. While even the lowest grade of glioma in children Pilocytic astrocytoma is associated with significant morbidity diffuse intrinsic pontine glioma (DIPG), a GBM of the brain stem confers the worst prognosis of any pediatric cancer. It has a 5-year survival rate of <1%, a 1-year survival of <30% and 2 -year survival of <10 %; median survival is < 9 months (15, 16). Pediatric GBM is defined by mutations in the gene encoding Histone H3.3. We are developing an animal model (Figure 1) to study this disease. In collaboration with the Hinchcliffe lab at the Hormel Institute, we seek to bring about a better understanding of the role of this mutation in these tumors in order to develop new therapies to improve survival for children with this devastating disease.

Melanoma: Melanomas develop from melanocytes, the pigment-making cells of the skin (Figure 2).The incidence of melanoma increased 690% from 1950 to 2001, and it continues to increase at a greater rate than any other cancer. Most melanoma patients are under 60; it is the most common form of cancer for ages 25-29 and the second for ages 15-29. Five-year survival for patients with metastatic disease is less than 16%. The rapidly rising incidence coupled with the high rate of mortality associated with advanced disease is particularly troubling. The increased incidence of melanoma, combined with the poor prognosis of patients with advanced disease, make it imperative that we increase our understanding of the underlying causes of resistance to targeted therapies so that better therapeutic strategies can be developed. The mitogen-activated protein kinase pathway is constitutively activated in the majority of cutaneous melanomas, predominantly due to NRAS and $BRAF^{V600E}$ mutations. We have developed a novel retroviral gene delivery *in vivo* model of melanoma that allows for targeted delivery to melanocytes *in vivo*. *In vivo* models are immune-competent and tumors evolve from developmentally normal somatic cells in an unaltered microenvironment. Multiple genetic alterations can be introduced into the same cell without the time and cost associated with crossing multiple strains of transgenic *in vivo* models. Vemurafenib and dabrafenib are FDA-approved drugs for the treatment of advanced metastatic melanomas with BRAFV600E mutations. Although the initial response to these inhibitors can be dramatic, sometimes causing complete tumor regression, the majority of these melanomas eventually become resistant and reoccur. Resistance to $BRAF^{V600E}$ kinase inhibitors is frequently associated with reactivation of MAPK pathway. For this reason, BRAF inhibitors are combined with MEK inhibitors; however, after a period of response and dormancy the tumors still reoccur. We recently demonstrated that gain of function MEK mutants found in drug resistant BRAF

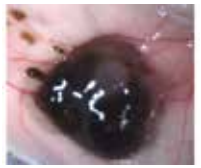
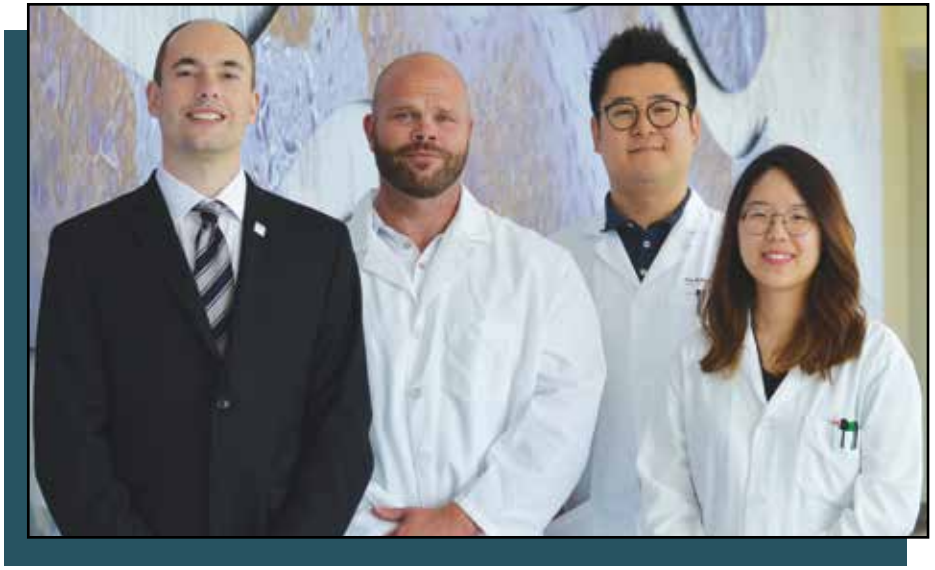


Figure 2: A pigmented melanoma metastasis.



From left to right: James Robinson, Nick Hanson, Kwan Hyun Kim, Hana Yang

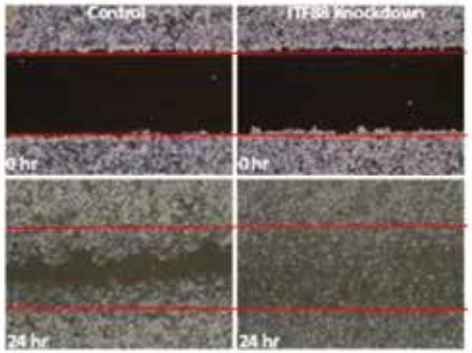


Figure 3: Reduced expression of ITF88 expression in B16 melanoma cells leads to increased migration and proliferation.

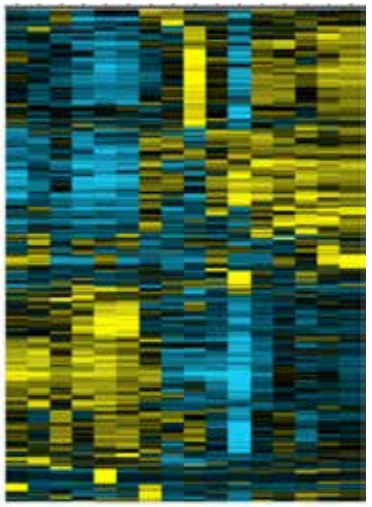


Figure 4: Differential mRNA expression in BRAF melanomas prior to and following resistance to BRAF inhibition.

melanoma drive the de-novo development of malignant melanoma with high penetrance. We are now using next generation RNA sequencing to identify the mechanisms of tumor dormancy and recurrence following BRAF and MEK inhibition in our novel *in vivo* model and in human melanoma samples (Figure 2-4) Colon

Cancer: After lung and prostate cancer, colon 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% of cases are sporadic with no obvious evidence of an inherited disorder. The remaining 25% of patients have a family history of CRC that suggests a hereditary contribution, common exposures among family members, or a combination of both. Familial adenomatous polyposis (FAP), is one of the most clearly defined and well understood of the inherited colon cancer syndromes. Our preliminary data has demonstrated that loss of APC is insufficient for tumorignesis and additional growth signals or mutations are also required for nuclear accumulation of β-Catenin and intestinal polyposis. Since *in vivo* models of FAP develop a multitude of intestinal polyps without additional genetic alterations, these additional signals are likely to arise from adjacent stromal cells. 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. A major preliminary finding is that heterozygous mutation of APC in adult *in vivo* models is not sufficient cause tumor formation. Our sections work on Colon cancer is funded by the National Institutes of Health (NIH) and our ongoing studies will contribute to the development of novel therapies and improve the outcome for patients with colon cancer.

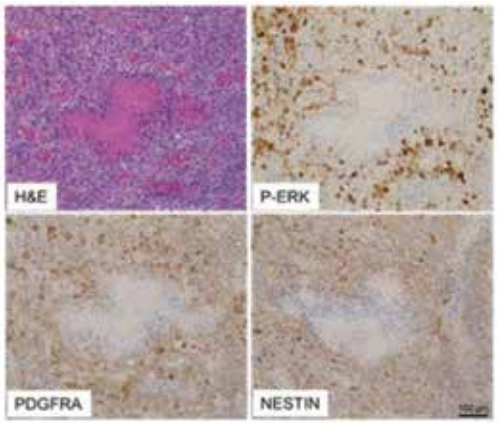


Figure 1: Analysis of GBM an *in vivo* model brain.

Molecular Biology and Translational Cancer Research

LUKE HOEPPNER, PH.D.

Section Leader / Assistant Professor

Our "Molecular Biology and Translational Cancer Research" section studies the molecular mechanisms and signal transduction pathways involved in vascular permeability, cancer progression/metastasis, cancer drug resistance, and adverse effects of cancer therapy. We employ two talented postdoctoral fellows, Sk. Kayum Alam, Ph.D. and Matteo Astone, Ph.D. This summer, Abbygail Coyle, a summer undergraduate research experience (SURE) intern, has been eagerly learning a variety of technical laboratory skills and contributing to aspects of numerous research projects. Our National Institutes of Health funded laboratory was established in the fall of 2015.

Lung cancer is the leading cancer related cause of death in the United States and worldwide. Non-small cell lung cancer (NSCLC) represents 85% of all lung cancer and carries a very poor survival rate: less than 15% of patients survive more than five years. Despite administration of front-line chemotherapeutic agents with molecular targeted systemic therapies, the survival rate of NSCLC patients remains dismal due to the large number of individuals diagnosed with advanced stage disease and the primary and secondary resistance to current therapies. Elucidation of new biomarkers and novel precision therapies will help overcome these challenges and make significant strides in improving lung cancer patient therapies.

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

Vascular endothelial growth factor (VEGF) is required for blood vessel formation and promotes permeability in veins. Tumors produce VEGF because they require their own vasculature to grow, obtain nutrients and oxygen, and eliminate waste products. The permeability induced by VEGF enables cancer cells to escape their primary site, enter the bloodstream, and metastasize to other tissues. Dopamine (DA) and dopamine D2 receptor (D_2R) agonists inhibit VEGF-mediated blood vessel development (angiogenesis) and vascular permeability by inhibiting VEGF binding, VEGF receptor phosphorylation and subsequent downstream signaling. Our recent studies demonstrated D_2R agonists, including FDA approved cabergoline, inhibit lung cancer growth in *in vivo* models by reducing angiogenesis and tumor infiltrating immune suppressor cells. Pathological examination of human lung cancer tissue revealed a positive correlation between endothelial D_2R expression levels and tumor stage as well as patient smoking history.

1. Triggering the dopamine pathway to inhibit lung cancer progression

Currently, we are focused on understanding how a signaling molecule downstream of the dopamine D2 receptor, called DARPP-32 (dopamine and cyclic-AMP-regulated phosphoprotein), can be modulated to inhibit lung cancer growth. Recent studies have demonstrated that elevated expression of DARPP-32 and its truncated splice-variant, t-DARPP, are associated with breast and gastric tumorigenesis. Thus, we hypothesized DARPP-32 and t-DARPP proteins may activate oncogenic signaling that contributes to progression of NSCLC. We demonstrate that overexpression of DARPP-32 and t-DARPP promotes lung tumor growth in human xenograft orthotopic murine models through activation of AKT and ERK signaling. Correspondingly, abrogation of DARPP-32 in human NSCLC cells reduces lung tumor growth in preclinical *in vivo* models. We identify migration as a cellular mechanism by which DARPP-32 proteins stimulate NSCLC. Our studies suggest a novel physical interaction between DARPP-32 and inhibitory kappa B kinase-α (IKKα) promotes NSCLC cell migration through nuclear factor kappa-light-chain-

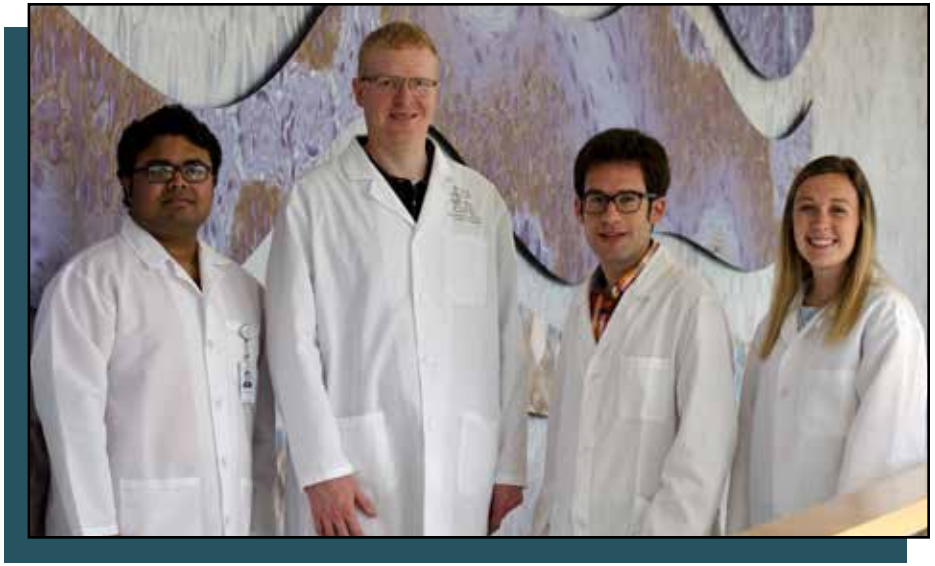
enhancer of activated B cells 2 (NF-κB2) signaling via the non-canonical p52 pathway. Histopathological analysis of over 60 lung adenocarcinoma patient-derived tissues reveals t-DARPP protein overexpression positively correlates with tumor grade, suggesting upregulation of t-DARPP promotes lung adenocarcinoma progression. Evaluation of bioinformatics data corresponding to over 500 lung adenocarcinoma patients confirms elevated t-DARPP expression is associated with worsening tumor grade as well as demonstrates correlation between high t-DARPP levels and poor overall NSCLC patient survival. Taken together, we describe aberrant DARPP-32 isoform expression promotes NSCLC growth and association of DARPP-32 with IKKα stimulates lung cancer cell migration via non-canonical NF-κB2 signaling. Identification of DARPP-32 signaling as a new potential molecular target for NSCLC therapy offers promise to improve the clinical outcome of patients afflicted with lung cancer.

2. Development of zebrafish models of vascular permeability and cancer metastasis

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

3. Topical treatment of radiotherapy-induced skin damage in breast cancer patients

Over three million women living in the United States have a history of invasive breast cancer. In 2017, an estimated 252,710 new cases of invasive breast cancer will be diagnosed and over 40,000 American women will unfortunately



From left to right: L to R: Sk. Kayum Alam, Luke Hoeppner, Matteo Astone, Abbygail Coyle
Kayum and Matteo are postdocs and Abbygail is a SURE intern.

die due to this dismal disease. About half of all breast cancer patients in the United States receive radiation therapy. Radiotherapy uses targeted, high energy X-rays to effectively destroy cancer cells, but healthy skin tissue is also damaged in the process. Radiation-induced skin damage typically manifests as radiation dermatitis, a prevalent side effect affecting approximately 95% of radiotherapy recipients. The effects of radiation dermatitis include pain, itching, poor aesthetic appearance, and chronic reappearance of skin wounds due to pathological changes during the healing process, such as excessive fibrosis. Severe radiation dermatitis occurs in 5-10% of breast cancer patients receiving whole-breast radiotherapy, which leads to delays or stoppage of radiotherapy and increases the risk for cancer recurrence. Common approaches to prevent and reduce radiation-induced dermatitis of the irradiated skin area involve basic moisturizing, cleansing with mild soap, applying topical cortisone creams, and avoiding irritants like scratching or rough clothing. However, reports from a multitude of clinical trials conclude all current radiation dermatitis treatment strategies lack clinical efficacy. Therefore, new treatments that promote recovery from radiation dermatitis are necessary to improve the quality of life and clinical outcome of breast cancer patients by alleviating painful short- and long-term radiation side effects to ensure completion of radiation therapy regimens. The goal of our "Paint the Town Pink" supported work is to define the molecular mechanisms through which

radiation causes skin injury and develop a topical treatment for radiation dermatitis. To achieve this aim, we are conducting ongoing studies using a *in vivo* model of radiotherapy-induced skin injury we developed in collaboration with UMN colleagues.

Funding
National Institutes of Health, National Cancer Institute, R00 CA187035
Paint the Town Pink Funds

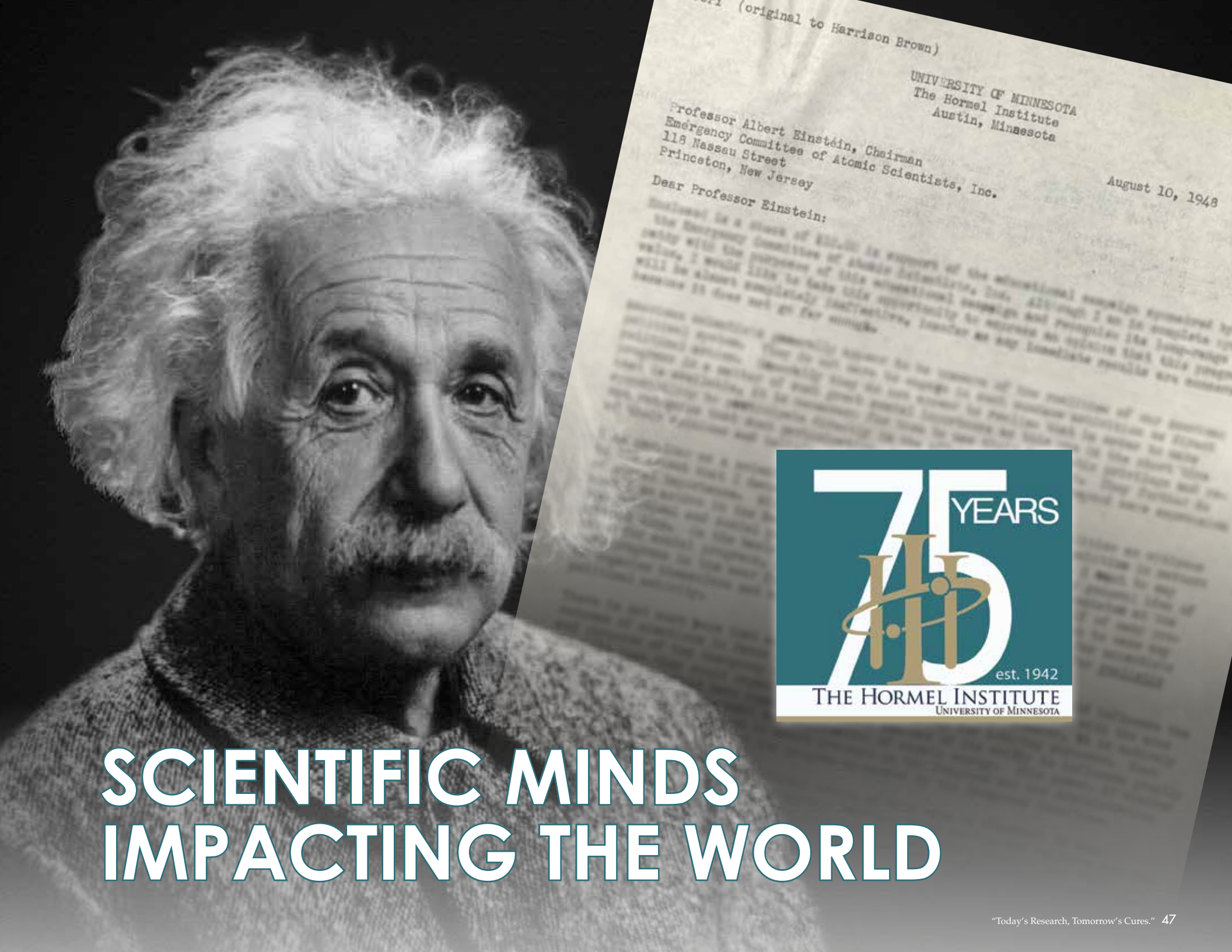
Publications
https://www.ncbi.nlm.nih.gov/pubmed/?term=hoeppner+l

Editorial Board
Nature Partner Journals: Precision Oncology

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

Dr. Luke Hoeppner

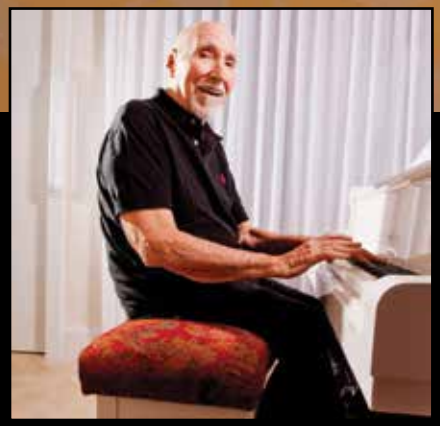
research progress



SCIENTIFIC MINDS IMPACTING THE WORLD

JAY C. HORMEL....FAMILY LEGACY CONTINUES

Tom Hormel Art Work



It is always a special experience at The Hormel Institute, University of Minnesota when members of the Hormel family visit or connect with the research center started by Jay C. Hormel. This past year, The Hormel Institute, in support of the Austin Area Commission for the Arts, was part of a traveling Thomas DuBuois Hormel art exhibit and acquired two pieces: "DNA#2" and "Sunrise," now on permanent display. The Hormel Institute researches DNA in the quest to prevent and control cancer, and the piece named "Sunrise" symbolizes hope and a new beginning, truly the mission behind the work of The Hormel Institute scientists, in the quest to improve human health worldwide.

Gary Ray, Chair of The Hormel Foundation

Greetings from Sen. Amy Klobuchar

Mayor Tom Stiehm, City of Austin

Dr. Doug Yee, Dr. Al Levine, Dr. Zigang Dong, Jeff Ettinger, Gary Ray

CELEBRATING 75 YEARS
of Scientific Research & Progress

Leaders and supporters from The Hormel Foundation, Hormel Foods Corporation, University of Minnesota, Mayo Clinic, region and community gathered at the new Ray Live Learning Center on June 19 at The Hormel Institute in celebration of its 75th Anniversary.

Speakers included The Hormel Foundation chair Gary Ray, UMN Vice President Dr. Al Levine, Drs. Zigang Dong and Ann Bode. Mayor Tom Stiehm proclaimed June 19, 2017 to be "The Hormel Institute, University of Minnesota Day" in Austin. Greetings were shared by Governor Mark Dayton, U.S. Senators Amy Klobuchar and Al Franken and U.S. Representative Tim Walz.

Governor Mark Dayton also proclaimed June 19, 2017 to be The Hormel Institute 75th Anniversary Day in the State of Minnesota and his proclamation was read during the celebration.

Supporting Departments

Research Support Group

KIM KLUKAS
Supervisor

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

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

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
CORE Manager

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, Ilsa Burke, Betsy Mentel, Dr. Ann Bode, Nicki Brickman, Julie Gerstner

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

Research Support Services

BRIAN LARSON
Supervisor

(Left to right) Theresa Tucker, Brian Larson, Tim Lastine, Mike Conway

Research Support Services has had another exciting year as we have continued to provide instrument maintenance along with computer, 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.

During the summer of 2017, we installed a large storage solution (DDN) for the Cryo-EM microscope. This was an integral part to process the huge amounts of data produced by the Cryo-EM microscope.

This has been another wonderful year for the RSS team, and next year is looking to be just as exciting as the use of the microscope and HI Staff continues to increase.

Building Operations and Maintenance

MARK SEVERTSON
Supervisor

Front Row: Julie Little, Alisa Wagner; Middle Row: Duane Graff, Brandon Hoium; Back Row: Randy Johnson, Nathan Britt, and Kim Downey

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.

Development and Public Relations Departments

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

(Left to right) Brenna Gerhart, Kathi Finnley, Gail Dennison, Gretchen Ramlo, Michelle Hjelmen

On behalf of the faculty and staff of The Hormel Institute, University of Minnesota, we thank all who helped to support our cancer research this year through your generous gifts of time, effort and money, and your strong faith in what's possible through collaboration.

The Hormel Institute continues to grow in research capabilities, in achieving grants and high impact publications, and in discoveries that move us forward toward new ways to prevent and control cancer. This is only possible because of each of you. We thank the dedicated faculty and staff of The Hormel Institute for their research achievements - representing them is indeed a privilege and an honor.

This year we celebrate the 75th Anniversary of The Hormel Institute, University of Minnesota. In our first year, The Hormel Foundation was the only source of funding for The Hormel Institute. The Hormel Foundation remains our most important and significant partner and through the leadership of Mr. Gary Ray and the board, we have been guided to even greater achievements and potential.

We deeply appreciate the hundreds of people who support The Hormel Institute's dedicated cancer research and we can thankfully say your donations are used only for research - thanks to The Hormel Foundation, none is used to cover administrative costs.

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

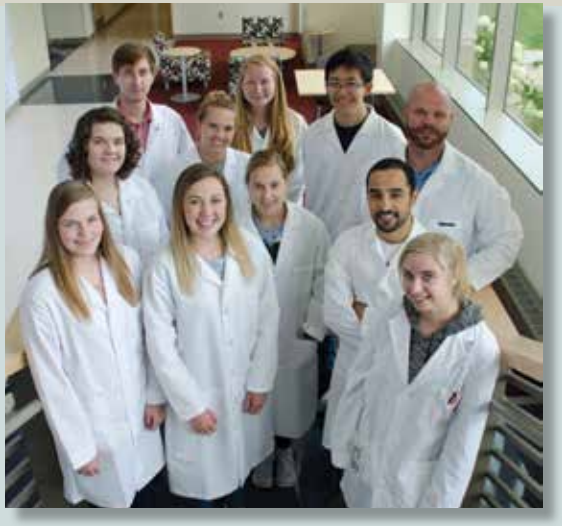
Thank you to our friends... furthering the vision of a cancer-free world.

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

Education . . . Changing lives through research progress

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

SURE INTERNSHIP (Summer Undergraduate Research Experience)



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.

Front row (left to right) Mara Overby, Abbygail Coyle, Kjersten Monson

Middle row (left to right) Anne Weston, Sela Fadness, Nodir Boymatov

Back row (left to right) Seth Richard, Jennyfer Register, Dianna Huisman, Christopher Dong, Nick Hanson

BOWLING FOR THE BATTLE

ABSOLUTE ENERGY

FIFTH DISTRICT EAGLES CANCER TELETHON

AGSTAR

KARL'S TOURNEY GOLF TOURNAMENT

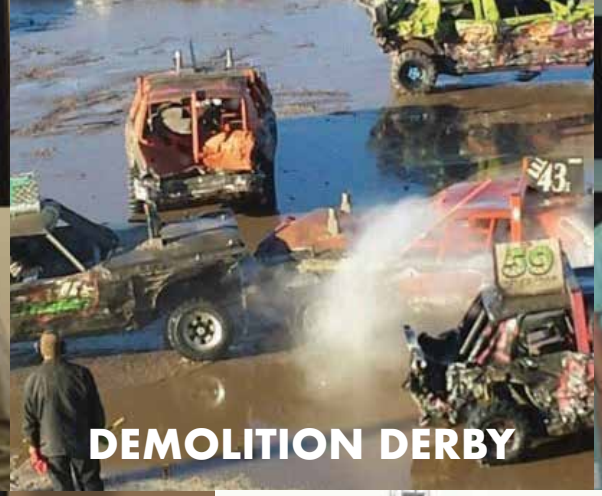
RYAN GORDON MEMORIAL GOLF TOURNAMENT

Thank You… to our Donors

DERYL ARNOLD MEMORIAL GOLF TOURNAMENT

2017 PAINT THE TOWN PINK

Paint the Town Pink
The Hormel Institute Breast Cancer Research



DEMOLITION DERBY

PTTP STEERING COMMITTEE

2017 PAINT THE TOWN PINK

Paint the Town Pink
The Hormel Institute Breast Cancer Research

Then & Now

THE HORMEL INSTITUTE
UNIVERSITY OF MINNESOTA

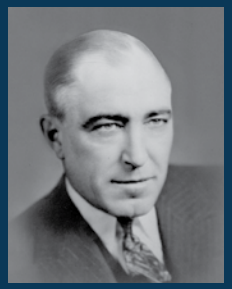
THE BUILDING

THEN Jay C. Hormel and the newly established Hormel Foundation officially developed The Hormel Institute and gifted it to the University of Minnesota on November 30, 1942. Scientists worked on early projects at the University of Minnesota campus and in 1944 moved to the Jay C. Hormel estate grounds, in a converted horse barn. A new state of the art lab was built, with an official dedication taking place on May 27, 1949. More than 100 scientists from throughout the United States joined The Hormel Foundation, Hormel Foods, University of Minnesota, elected officials and Mayo Clinic leadership for the celebration.

It moved to the present building site in 1960, with a new building that held 10 labs, a small library and break room and a maintenance / operations room. In 2001, The Hormel Institute introduced central air conditioning and an indoor smoking ban.

NOW Today The Hormel Institute is a state of the art cancer research center, with 42 labs equipped with some of the world's best technologies. Thanks to support from The Hormel Foundation, State of Minnesota and our community, the Institute experienced a transformational expansion which tripled its size in 2008 and doubled its size in 2016. The Ray Live Learning Center was also added in 2016, a state of the art global communications center with a 250 person Event Room and 250 seat auditorium, for seminars, meetings and community events.

LEADERSHIP

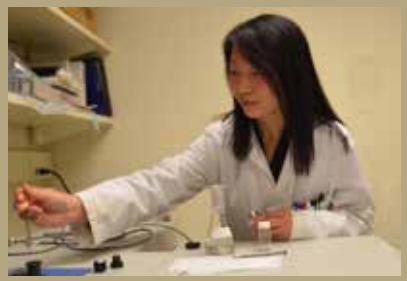


THEN The Hormel Institute was the inspired idea of Jay C. Hormel, longtime president and chairman of Geo. A. Hormel & Co. Recognizing the progress of mankind is built on scientific discovery, he and his father George A. Hormel established through The Hormel Foundation that the major portion of the Foundation's income/distributions should benefit humanity through scientific research. The Institute's first work was done on the main campus of the University of Minnesota under Dr. H. O. Halvorson, a prominent professor in the University's Department of Bacteriology. Halvorson had served as an advisor to Jay Hormel on food stability and became The Hormel Institute's first Executive Director. Another "founding father" was Dr. Theodore C. Blegen, Dean of the University's Graduate School, who served as the chairman of The Hormel Institute's Board of Directors at the time it was founded. Blegen remained chairman for 17 years and had a major influence on the Institute's early development. Other members of the original Institute Board included Dr. C. H. Bailey, Dean and Director of the University's Department of Agriculture; R. P. Crane of The Hormel Foundation; Dr. F.C. Mann, Professor of Experimental Surgery at the Mayo Foundation; and Dr. Walter M. Lauer, Professor of Organic Chemistry at University of Minnesota.

NOW For 75 years, The Hormel Foundation has supported scientific research at The Hormel Institute, truly living up to the foundation's mission to "Support Austin and Impact the World." As directed by the original trust, The Hormel Institute is the main recipient of support given by The Hormel Foundation and today's board of directors continues the legacy started by Jay C. Hormel - to improve the world through scientific discovery. The Hormel Foundation, chaired today by Gary J. Ray, funded major expansions in both 2008 and 2016, virtually transforming The Hormel Institute into a state of the art cancer research center. The vision started by Jay C. Hormel continues through today's Hormel Foundation, leadership at the University of Minnesota and collaborative partnerships, and from leaders throughout our community - that investments in scientific research today will impact and improve the health of the world tomorrow.

RESEARCH

THEN The first research projects of The Hormel Institute took place at the University of Minnesota, College of Agriculture. Early research started in Austin in 1944, on the Jay C. Hormel estate with one lab growing to five well-equipped labs operating by 1946. Research included food technology, biochemistry, bacteriology, nutrition and general utility. Achievements include development of the Swiss Swine, a small pig used for cardiovascular research. The Hormel Institute became a world leader in lipid research and the study of essential fatty acids. Dr. Ralph Holman researched and named omega 3 and omega 6, and was named to the National Academy of Sciences for his groundbreaking research. For more history related to the research achievements of The Hormel Institute, read former director Dr. Harald Schmid's historic notes at www.hi.umn.edu.



NOW Today The Hormel Institute is considered a world leader in cancer prevention research. With 17 research sections, each dedicated exclusively to cancer research, The Hormel Institute is growing in capacity for discoveries leading to the prevention and control of cancer. With the indicators of publishing in top scientific journals and major grant funding, expanding facilities, worldwide collaborations and growing faculty and staff, The Hormel Institute is poised to continue to accelerate discoveries in the quest to improve human health worldwide.

TECHNOLOGY

THEN Technology has always been an important part of pushing research forward at The Hormel Institute. In the early 1950s The Hormel Institute developed new lipid techniques using thin-layer chromatography (TLC) equipment which became the standard method of lipid fractionation and analysis. During the late 1950s and early 1960s The Hormel Institute obtained many new technologies such as early versions of infrared spectrophotometers, some of the first gas-chromatographs, and a number of gas-liquid chromatography units as it continued to accelerate lipid research. In 1964, a new mass spectrometer was added to The Hormel Institute to assist Dr. Holman with lipid studies. In 1987 a joint instrument grant with Mayo Clinic brought a new 300 MHz NMR instrument to the Institute.

NOW In 2008 the International Center for Research Technology (ICRT) was created as part of the expansion and renovation of The Hormel Institute. The ICRT is currently home to some of the world's most innovative technologies to advance research including a confocal microscope, cell sorter, 3D technology, mass spectrometer, protein crystallography, and CAL42; a supercomputing Linux GPU cluster system. In 2016 The Hormel Foundation supported the addition of the Titan Krios G2 cryo-electron microscope and Cryo-EM was added to the ICRT. Cryo-EM is a cutting-edge microscopy technique that captures high-resolution 2D images thereby enabling the 3D reconstruction of proteins at near-atomic level of detail. The Hormel Institute is one of a few organizations in the world to have this type of microscope available to researchers. In 2017 The Hormel Institute upgraded to a) the throughput of the microscope network to fiber (to provide faster data transfer and processing), b) software, and c) the GPU workstations in both the lab and server rooms. Also in 2017 a mass (500TB) storage system was implemented to provide the ability to store the extremely large amount of data that is processed.

DIVERSITY

THEN While diversity in Austin was limited in the 1940s, Dr. Halvorson began recruiting scientists from the international community. The first international scientist to broaden Austin's cultural experience was a young French PhD student, Jacques R. Chipault, the nephew of Jay C. Hormel's wife, Germaine Dubois Hormel.

When lipids became the focus at The Hormel Institute in the late 1950s, postdocs from Germany, France, Denmark, England, Switzerland and Spain began to arrive, and this trend was greatly accelerated with the 1960 building that housed 10 labs. In addition to the United States and Canada, postdocs came from Austria, Israel, Norway, Sweden, Scotland, Italy, Mexico, New Zealand, Argentina, Brazil, Egypt, India, Japan, and later from Korea, Poland, Hungary, Finland, Russia and China. In 1965, there were 17 postdoctoral fellows from 9 different countries working at the Institute.

NOW Today The Hormel Institute's international atmosphere continues and is comprised of expert scientists from around the world. Current scientists are originally from Argentina, Australia, Brazil, China, England, Republic of Georgia, India, Israel, Italy, Pakistan, Russia, South Korea, Sweden, United States, Venezuela and Vietnam. The Hormel Institute also has affiliated labs under HI management in Zhengzhou, China and Seoul, South Korea. The Scientific Advisory Board is also internationally diverse, made up of some of the world's leading scientists from China, Czechoslovakia, Germany, Italy, Japan and South Korea.

Then & Now

The Hormel Foundation

Gary J. Ray, Chair

Then & Now

75 YEARS
The Hormel Foundation

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H.I. No. 2110
How alpha-helical motifs form functionally diverse lipid-binding compartments. Malinina, L, Patel, DJ, & Brown, RE. Annu.Rev. Biochem., 86, 609-636. (2017).

H.I. No. 2111
Extracellular vesicles as therapeutic carriers of MicroRNAs for cholangiocarcinoma. Gradilone, SA. Hepatology, 65(2), 404-406. (2017).

H.I. No. 2112
SOX17 regulates cholangiocyte differentiation and acts as a tumor suppressor in cholangiocarcinoma. Merino-Azpitarte, M, Lozano, E, Perugorria, MJ, Esparza-Baquer, A, Erice, O, Santos-Laso, A, O'Rourke, CJ, Andersen, JB, Jimenez-Aguero, R, Lacasta, A, D'Amato, M, Briz, O, Jalan-Sakrikar, N, Huebert, RC, Thelen, KM, Gradilone, SA, Aransay, AM, Lavin, JL, Fernandez-Barrena, MG, Matheu, A, Marzioni, M, Gores, GJ, Bujanda, L, Marin, JJG, & Banales, JM. J.Hepatol., 67(1), 72-83. (2017).

H.I. No. 2113
Dub3 inhibition suppresses breast cancer invasion and metastasis by promoting Snail1 degradation. Wu, Y, Wang, Y, Lin, Y, Liu, Y, Wang, Y, Jia, J, Singh, P, Chi, Y, Wang, C, Dong, C, Li, W, Tao, M, Napier, D, Shi, Q, Deng, J, Evers, BM, & Zhou, BP. Nat.Commun., 8, 14228-14228. (2017).

H.I. No. 2114
Fatty acid-binding protein FABP4 mechanistically links obesity with aggressive AML by enhancing aberrant DNA methylation in AML cells. Yan, F, Shen, N, Pang, JX, Zhang, YW, Rao, EY, Bode, AM, Al-Kali, A, Zhang, DE, Litzow, MR, Li, B, & Liu, SJ. Leukemia, 31(6), 1434-1442. (2017).

H.I. No. 2115
Circulating tumor cells: Moving biological insights into detection. Chen, L, Bode, AM, & Dong, Z. Theranostics, 7(10), 2606-2619. (2017).

H.I. No. 2116
Phosphorylation of NFAT3 by CDK3 induces cell transformation and promotes tumor growth in skin cancer. Xiao, T, Zhu, JJ, Huang, S, Peng, C, He, S, Du, J, Hong, R, Chen, X, Bode, AM, Jiang, W, Dong, Z, & Zheng, D. Oncogene, 36(20), 2835-2845. (2017).

H.I. No. 2117
Activated MEK cooperates with Cdkn2a and pten loss to promote the development and maintenance of melanoma. Yang, H, Kircher, DA, Kim, KH, Grossmann, AH, VanBrocklin, MW, Holmen, SL, & Robinson, JP. Oncogene, 36(27), 3842-3851. (2017).

H.I. No. 2118
Novel curcumin liposome modified with hyaluronan targeting CD44 plays an anti-leukemic role in acute myeloid leukemia in vitro and in vivo. Sun, D, Zhou, J, Zhao, L, Zheng, Z, Li, J, Pu, W, Liu, S, Liu, X, Liu, S, Zheng, Y, Zhao, Y, & Peng, Y. Acs.Appl.Mater. Interfaces., 9(20), 16858-16869. (2017).

H.I. No. 2119
The role of oxidative stress in EBV lytic reactivation, radioresistance and the potential preventive and therapeutic implications. Hu, J, Li, H, Luo, X, Li, Y, Bode, A, & Cao, Y. Int.J.Cancer, (2017).

H.I. No. 2120
EBV-LMP1 suppresses the DNA damage response through DNA-PK/AMPK signaling to promote radioresistance in nasopharyngeal carcinoma. Lu, J, Tang, M, Li, H, Xu, Z, Weng, X, Li, J, Yu, X, Zhao, L, Liu, H, Hu, Y, Tan, Z, Yang, L, Zhong, M, Zhou, J, Fan, J, Bode, AM, Yi, W, Gao, J, Sun, L, & Cao, Y. Cancer Lett., 380(1), 191-200. (2016).

H.I. No. 2121
A novel strategy for topical photochemoprevention: Pharmacological TLR4 antagonism blocks non-melanoma skin cancer. Dickinson, S, Blohm-Mangone, K, Burkett, N, Tahsin, S, Myrdal, P, Aodah, A, Janda, J, Saboda, K, Dong, Z, Bode, A, Petricoin, E, Calvert, V, Curiel-Lewandrowski, C, & Wondrak, G. J.Invest. Dermatol., 137(5), S131-S131. (2017).

H.I. No. 2122
TRAF1 is critical for DMBA/Solar UVR-induced skin carcinogenesis. Yamamoto, H, Ryu, J, Min, E, Oi, N, Bai, R, Zykova, TA, Yu, DH, Moriyama, K, Bode, AM, & Dong, Z. J.Invest.Dermatol., 137(6), 1322-1332. (2017).

H.I. No. 2123
Molecular mechanisms of green tea polyphenols with protective effects against skin photoaging. Roh, E, Kim, JE, Kwon, JY, Park, JS, Bode, AM, Dong, Z, & Lee, KW. Crit. Rev.Food Sci.Nutr., 57(8), 1631-1637. (2017).

H.I. No. 2124
The protein level and transcription activity of activating transcription factor 1 is regulated by prolyl isomerase Pin1 in nasopharyngeal carcinoma progression. Huang, G, Liao, D, Chen, H, Lu, Y, Chen, L, Li, H, Li, B, Liu, W, Ye, C, Li, T, Zhu, Z, Wang, J, Uchida, T, Zou, Y, Dong, Z, & He, Z. Cell Death Dis., 7, e2571-e2571. (2016).

H.I. No. 2125
AID expression increased by TNF-alpha is associated with class switch recombination of ig alpha gene in cancers. Duan, Z, Zheng, H, Liu, H, Li, M, Tang, M, Weng, X, Yi, W, Bode, AM, & Cao, Y. Cell.Mol. Immunol., 13(4), 484-491. (2016).

H.I. No. 2126
ADA-07 suppresses solar ultraviolet-induced skin carcinogenesis by directly inhibiting TOPK. Gao, G, Zhang, T, Wang, Q, Reddy, K, Chen, H, Yao, K, Wang, K, Roh, E, Zykova, T, Ma, W, Ryu, J, Curiel-Lewandrowski, C, Alberts, D, Dickinson, SE, Bode, AM, Xing, Y, & Dong, Z. Mol.Cancer.Ther., (2017).

H.I. No. 2127
The epithelial-mesenchymal transition (EMT) is regulated by oncoviruses in cancer. Chen, X, Bode, AM, Dong, Z, & Cao, Y. FASEB J., 30(9), 3001-3010. (2016).

H.I. No. 2128
hMAGEA2 promotes progression of breast cancer by regulating akt and Erk1/2 pathways. Park, S, Sung, Y, Jeong, J, Choi, M, Lee, J, Kwon, W, Jang, S, Park, SJ, Kim, H, Lee, M, Kim, DJ, Liu, K, Kim, S, Dong, Z, Ryoo, ZY, & Kim, MO. Oncotarget, 8(23), 37115-37127. (2017).

H.I. No. 2129
Thymoquinone exerts potent growth-suppressive activity on leukemia through DNA hypermethylation reversal in leukemia cells. Pang, J, Shen, N, Yan, F, Zhao, N, Dou, L, Wu, L, Seiler, CL, Yu, L, Yang, K, Bachanova, V, Weaver, E, Tretyakova, NY, & Liu, S. Oncotarget, 8(21), 34453-34467. (2017).

H.I. No. 2130
Hmga2 translocation induced in skin tumorigenesis. Li, Y, Pi, X, Boland, K, Lad, S, Johnson, K, Verfaillie, C, & Morris, RJ. Oncotarget, 8(18), 30019-30029. (2017).

H.I. No. 2131
LTA4H regulates cell cycle and skin carcinogenesis. Oi, N, Yamamoto, H, Langfald, A, Bai, R, Lee, MH, Bode, AM, & Dong, Z. Carcinogenesis, 38(7), 728-737. (2017).

H.I. No. 2132
Adipose fatty acid binding protein promotes saturated fatty acid-induced macrophage cell death through enhancing ceramide production. Zhang, Y, Rao, E, Zeng, J, Hao, J, Sun, Y, Liu, S, Sauter, ER, Bernlohr, DA, Cleary, MP, Suttles, J, & Li, B. J.Immunology, 198(2), 798-807. (2017).

H.I. No. 2133
The cholangiocyte primary cilium in health and disease. Mansini, AP, Peixoto, E, Thelen, KM, Gaspari, C, Jin, S, & Gradilone, SA. Biochim.Biophys.Acta, (2017).

H.I. No. 2134
A new functional IDH2 genetic variant is associated with the risk of lung cancer. Li, J, Lu, J, He, Y, Wu, Y, Wu, Y, Song, X, Jiang, Y, Tang, M, Weng, X, Yi, W, Luo, X, Sun, L, Bode, AM, & Cao, Y. Mol.Carcinog., 56(3), 1082-1087. (2017).

H.I. No. 2135
Neoalbaconol inhibits angiogenesis and tumor growth by suppressing EGFR-mediated VEGF production. Yu, X, Li, W, Deng, Q, You, S, Liu, H, Peng, S, Liu, X, Lu, J, Luo, X, Yang, L, Tang, M, Weng, X, Yi, W, Liu, W, Wu, S, Ding, Z, Feng, T, Zhou, J, Fan, J, Bode, AM, Dong, Z, Liu, J, & Cao, Y. Mol.Carcinog., 56(5), 1414-1426. (2017).

H.I. No. 2136
Phosphatidylserine stimulates ceramide 1-phosphate (C1P) intermembrane transfer by C1P transfer proteins. Zhai, X, Gao, Y, Mishra, SK, Simanshu, DK, Boldyrev, IA, Benson, LM, Bergen,H.Robert,,III, Malinina, L, Mundy, J, Molotkovsky, JG, Patel, DJ, & Brown, RE. J.Biol.Chem., 292(6), 2531-2541. (2017).

H.I. No. 2137
The prolyl isomerase Pin1 is a novel target of 6,7,4 '-trihydroxyisoflavone for suppressing esophageal cancer growth. Lim, T, Lee, S, Duan, Z, Lee, M, Chen, H, Liu, F, Liu, K, Jung, SK, Kim, DJ, Bode, AM, Lee, KW, & Dong, Z. Cancer.Prev. Res., 10(5), 308-318. (2017).

H.I. No. 2138
Epstein-barr virus lytic reactivation regulation and its pathogenic role in carcinogenesis. Li, H, Liu, S, Hu, J, Luo, X, Li, N, Bode, AM, & Cao, Y. Int.J.Biol.Sci., 12(11), 1309-1318. (2016).

H.I. No. 2139
Breast cancers from black women exhibit higher numbers of immunosuppressive macrophages with proliferative activity and of crown-like structures associated with lower survival compared to non-black latinas and caucasians. Koru-Sengul, T, Santander, AM, Miao, F, Sanchez, LG, Jorda, M, Gluck, S, Ince, TA, Nadji, M, Chen, Z, Penichet, ML, Cleary, MP, & Torroella-Kouri, M. Breast Cancer Res.Treat., 158(1), 113-126. (2016).

H.I. No. 2140
Measuring relative utilization of aerobic glycolysis in breast cancer cells by positional isotopic discrimination. Yang, D, Freund, DM, Harris, BRE, Wang, D, Cleary, MP, & Hegeman, AD. FEBS Lett., 590(18), 3179-3187. (2016).

H.I. No. 2141
Primary cilia in tumor biology: The primary cilium as a therapeutic target in cholangiocarcinoma. Gradilone, SA, Pisarello, MJL, & LaRusso, NF. Curr.Drug Targets, 18(8), 958-963. (2017).

H.I. No. 2142
Targeting IRES-mediated p53 synthesis for cancer diagnosis and therapeutics. Ji, B, Harris, BRE, Liu, Y, Deng, Y, Gradilone, SA, Cleary, MP, Liu, J, & Yang, D. Int.J.Mol.Sci., 18(1), 93-93. (2017).

H.I. No. 2143
15-deoxy-delta(12,14)-prostaglandin J(2) stabilizes hypoxia inducible factor-1 alpha through induction of heme oxygenase-1 and direct modification ofprolyl-4-hydroxylase 2. Choi, J, Kim, J, Song, N, Suh, J, Kim, D, Kim, S, Na, H, Nadas, J, Dong, Z, Cha, Y, & Surh, Y. Free Radic.Res., 50(10), 1140-1152. (2016).

H.I. No. 2144
Chemoprevention of colorectal cancer by artocarpin, a dietary phytochemical from artocarpus heterophyllus. Sun, G, Zheng, Z, Lee, MH, Xu, Y, Kang, S, Dong, Z, Wang, M, Gu, Z, Li, H, & Chen, W. J.Agric.Food Chem., 65(17), 3474-3480. (2017).

H.I. No. 2145
ERK1 directly interacts with JNK1 leading to regulation of JNK1/c-jun activity and cell transformation. Kang, BS, Hwang, YJ, & Dong, Z. J.Cell.Biochem., 118(8), 2357-2370. (2017).

H.I. No. 2146
Receptor tyrosine kinase (c-kit) inhibitors: A potential therapeutic target in cancer cells. Abbaspour Babaei, M, Kamalidehghan, B, Saleem, M, Huri, HZ, & Ahmadipour, F. Drug Des.Devel. Ther., 10, 2443-2459. (2016).

H.I. No. 2147
Small molecule inhibitors of mesotrypsin from a structure-based docking screen. Kayode, O, Huang, Z, Soares, AS, Caulfield, TR, Dong, Z, Bode, AM, & Radisky, ES. PLoS One, 12(5), e0176694-e0176694. (2017).

H.I. No. 2148
Elevated cellular PD1/PD-L1 expression confers acquired resistance to cisplatin in small cell lung cancer cells. Yan, F, Pang, J, Peng, Y, Molina, JR, Yang, P, & Liu, S. PLoS One, 11(9), e0162925-e0162925. (2016).

H.I. No. 2149
Crystal structures reveal a new and novel FoxO1 binding site within the human glucose-6-phosphatase catalytic subunit 1 gene promoter. Singh, P, Han, EH, Endrizzi, JA, O'Brien, RM, & Chi, Y. J.Struct. Biol., 198(1), 54-64. (2017).

H.I. No. 2150
PKCiota is a target of 7,8,4'-trihydroxyisoflavone for the suppression of UVB-induced MMP-1 expression. Lim, TG, Kim, YA, Kim, JE, Baek, S, Lee, SY, Lee, CC, Chen, H, Kim, JR, Kwon, JY, Bode, AM, Lee, CY, Dong, Z, Oh, DK, Park, JS, & Lee, KW. Exp. Dermatol., (2017).

H.I. No. 2151
Synergistic antitumor effect of sorafenib in combination with ATM inhibitor in hepatocellular carcinoma cells. Liu, J, Liu, Y, Meng, L, Ji, B, & Yang, D. Int.J.Mol.Sci., 14(6), 523-529. (2017).

H.I. No. 2152
Resatorvid-based pharmacological antagonism of cutaneous TLR4 blocks UV-induced NF-B and AP-1 signaling in keratinocytes and mouse skin. Janda, J, Burkett, NB, Blohm-Mangone, K, Huang, V, Curiel-Lewandrowski, C, Alberts, DS, Petricoin,Emanuel F.,,III, Calvert, VS, Einspahr, J, Dong, Z, Bode, AM, Wondrak, GT, & Dickinson, SE. Photochem. Photobiol., 92(6), 816-825. (2016).

H.I. No. 2153
Four is better than 1-strength in numbers! Bode, AM, & Dong, Z. Ebiomedicine, 11, 17-18. (2016).

H.I. No. 2154
The T-LAK cell-originated protein kinase signal pathway promotes colorectal cancer metastasis. Zykova, TA, Zhu, F, Wang, L, Li, H, Bai, R, Lim, DY, Yao, K, Bode, AM, & Dong, Z. Ebiomedicine, 18, 73-82. (2017).

H.I. No. 2155
The influence of different calorie restriction protocols on serum pro-inflammatory cytokines, adipokines and IGF-I levels in female C57BL6 mice: Short term and long term diet effects. Dogan, S, Ray, A, & Cleary, MP. Meta Gene, 12, 22-32. (2017).

H.I. No. 2156
Aloe-emodin suppresses esophageal cancer cell TE1 proliferation by inhibiting AKT and ERK phosphorylation. Chang, X, Zhao, J, Tian, F, Jiang, Y, Lu, J, Ma, J, Zhang, X, Jin, G, Huang, Y, Dong, Z, Liu, K, & Dong, Z. Oncol.Lett., 12(3), 2232-2238. (2016).

H.I. No. 2157
In vitro anticancer activities of some triterpene glycosides from holothurians of cucumariidae, stichopodidae, psolidae, holothuriidae and synaptidae families. Fedorov, SN, Dyshlovoy, SA, Kuzmich, AS, Shubina, LK, Avilov, SA, Silchenko, AS, Bode, AM, Dong, Z, & Stonik, VA. Nat.Prod. Commun., 11(9), 1239-1242. (2016).

H.I. No. 2158
Leptin in cancer: Epidemiology and mechanisms. Cleary, M. P., & Torroella-Kouri, M. (2017). In Reizes O. B.,NA (Ed.), Adipocytokines, Energy Balance, and Cancer.

H.I. No. 2159
Body fatness and cancer--viewpoint of the IARC working group. Lauby-Secretan, B, Scoccianti, C, Loomis, D, Grosse, Y, Bianchini, F, Straif, K, & International Agency for Research on Cancer Handbook Working Group (Cleary, MP, member of working group). N.Engl.J.Med., 375(8), 794-798. (2016).

H.I. No. 2160
Chemoprevention of breast cancer by targeting thromboxane A2 pathway. Li, H, Zhu, F, Grossman, M, Yao, K, Xie, H, Oi, N, Liu, K, Cleary, MP, Bode, AM, & Dong, Z. Npg Precision Oncology, 1(8)(2017).

H.I. No. 2161
Circulating tumor cells: Quintessential precision oncology presenting challenges for biology. Morris, RJ. Npg Precision Oncology, 1(16)(2017).

H.I. No. 2162
The role of primary cilia in cancer. Peixoto, E, Mansini, AP, Thelen, KM, Gaspari, CI, Jin, S, & Gradilone, SA. Physiological Mini Reviews 10(1), 1-11. (2017).

The Hormel Institute Seminars

JULY 1, 2016 - JUNE 30, 2017

July 11, 2016
Matt VanBrocklin, Ph.D. - Assistant Professor
Department of Surgery
Huntsman Cancer Institute
"Development of a novel Nf-1 mouse model of melanoma"

July 20, 2016
Gökhan Tolun, Ph.D. - Postdoctoral CRTA
National Cancer Institute at Fredrick
"Combining Biochemistry and (Cryo-)Electron Microscopy to Study Machines on Genes"

July 22, 2016
Magda Grabowska, Ph.D. - Research Assistant Professor
Urologic Surgery
Vanderbilt University Medical Center
"Regulation of Androgen Receptor Action in Prostatic Diseases"

July 28, 2016
Jernej Murn, Ph.D. - Postdoctoral Fellow in the Shi Lab
Harvard Medical School
Boston Children's Hospital
"RNA-binding proteins as regulators of cell fate in development and disease"

August 2, 2016
Jun Ninomiya-Tsuji, Ph.D. - Professor
Coordinator of the Molecular and Cellular Toxicology program
North Carolina State University
"Protein kinase TAK1, a key regulator of inflammation and cell death"

August 4, 2016
Erhard Bieberich, Ph.D. - Professor
Department of Neuroscience and Regenerative Medicine
Augusta University
"Ceramide-enriched exosomes and cilia in development, cancer, and neurodegenerative disease"

August 9, 2016
Susumu Kobayashi, Ph.D. - Assistant Professor of Medicine
Hematology/Oncology
Beth Israel Deaconess Medical Center
"Primary and acquired resistance to EGFR tyrosine kinase inhibitors in lung cancer"

August 16, 2016
Mickey C. Hu, Ph.D. - Associate Professor
Department of Obstetrics and Gynecology
Division of Gynecologic Oncology
Stanford University School of Medicine
"Out-FOXing Cancer: Tumor Suppression, Reprogramming, and Immunity"

August 18, 2106
Luis Carvajal-Carmona, Ph.D. - Assistant Professor
Genome Center & Department of Biochemistry
& Molecular Medicine
University of California, Davis.
"Opportunities for cancer genetics and epidemiology in Latino populations."

August 26, 2016
Wei Li, Ph.D. - Professor & Faculty Director of Instrument Facility
University of Tennessee Health Science Center
"Discovery of New Tubulin Inhibitors and Selective Surviving Inhibitors for Cancer Therapy"

October 5, 2016
Rui Kuang, Ph.D. - Associate Professor of Computer Science and Engineering
University of Minnesota
"Network-based Learning Algorithms for RNA-seq Transcript Quantification and Survival Analysis of Cancer Transcriptomes"

October 12, 2016
Sihem Cheloufi, Ph.D. - Postdoctoral Fellow
Massachusetts General Hospital
"Epigenetic plasticity during cell fate transitions"

October 14, 2016
Leifu Chang, Ph.D. - Investigator Scientist
Cambridge Biomedical Campus
"Cryo-EM structures and mechanisms of human anaphase-promoting complex"

November 15, 2016
Geoff Johnson, M.D., Ph.D. - Radiologist
Mayo Clinic
"PET/MRI: A Powerful Solution in Search of a Problem"

December 6, 2016
Hui-Ting Chou, Ph.D. - Postdoctoral Fellow
Department of Cell Biology
Harvard Medical School
"Molecular Architecture of Membrane Trafficking Machineries Revealed by Single-particle Electron Microscopy"

December 13, 2016
Kuang-Lei Tsai, Ph.D. - Postdoctoral Fellow
Department of Integrative Structural and Computational Biology
The Scripps Research Institute
"Molecular Visualization of the Transcriptional Mediator Complex by Cryo-EM"

December 16, 2016
Liang Tang, Ph.D. - Associate Professor
Department of Molecular Biosciences
University of Kansas
"Virus Assembly and DNA Packaging: Molecular Gymnastics Viewed at Atomic Resolution"

February 28, 2017
Joey Davis, Ph.D. - Postdoctoral Fellow
Department of Integrative Structural and Computational Biology
The Scripps Research Institute
"Biological Assembly of Macromolecular Machines: Insights into Ribosome Biogenesis"

March 28, 2017
Ilana Chefetz-Menaker, Ph.D. - Research Assistant Professor
Department of Hematology and Oncology
University of Michigan, School of Medicine
"A Novel Pan-ALDH1A Inhibitor Induces Necroptosis in Ovarian Cancer Stem-Like cells and Reverses Chemotherapy Resistance"

March 31, 2017
Rendong Yang, Ph.D. - RISS-LM&P Bioinformatics Analyst
Minnesota Supercomputing Institute
University of Minnesota
"Computational approaches for advancing cancer genomics: from basic research to clinical diagnostics"

April 10, 2017
Hui-Wen Lo, Ph.D. - Associate Professor of Cancer Biology
Department of Cancer Biology
Wake Forest University School of Medicine
"Truncated Gliomaassociated Oncogene Homolog 1 (tGLI1) in GBM Progression, Breast Cancer Metastasis and Cancer Stem Cells"

April 13, 2017
Edward Yu, Ph.D. - John D. Corbett Professor of Chemistry
Professor of Physics
Department of Chemistry
Department of Physics and Astronomy
Iowa State University
"Microbial Efflux Pumps"

April 18, 2017
George Aslanidi, Ph.D. - Assistant Professor
Department of Pediatrics
College of Medicine
University of Florida
"Bioengineering Next Generation of Viral Vectors for Cancer Gene Therapy"

April 18, 2017
Jianhua Yu, Ph.D. - Associate Professor
College of Medicine - Internal Medicine
The Ohio State University
"Understanding and Modulating Innate Immune Cells for Cancer Immunotherapy and Virotherapy"

April 21, 2017
Qing Yang, Ph.D. - Assistant Professor
Department of Integrative Biology and Pharmacology
University of Texas McGovern Medical School
"Decreasing neuronal excitability to prevent chronic pain"

April 24, 2017
Thomas Tomasiak, Ph.D. - NIH Pathway to Independence Fellow
Department of Biochemistry and Biophysics
University of California, San Francisco
"Greasy gatekeepers - drug and lipid transporters and enzymes"

April 27, 2017
Barb Nikolajczyk, Ph.D. - Associate Professor
Department of Microbiology
Boston University School of Medicine
"Defining Inflammation in Human Obesity and Type 2 Diabetes"

May 18, 2017
Stephen Ekker, Ph.D. - Department of Biochemistry
& Molecular Biology
Mayo Clinic
"How to Join the Genome Writers Guild"

May 25, 2017
Peter Palese, Ph.D. - Horace W. Goldsmith Professor and Chair
Department of Microbiology
Professor, Department of Medicine
Icahn School of Medicine at Mount Sinai
"Towards a Universal Influenza Virus Vaccine"

June 6, 2017
S. Saif Hasan, Ph.D. - Postdoctoral Research Associate
Department of Biological Sciences
Purdue University
"A human antibody against Zika virus crosslinks the E protein to prevent infection"

June 12, 2017
Jialiang Wang, Ph.D. - Assistant Professor
Department of Neurological Surgery, Cancer Biology
Vanderbilt University Medical Center
"Epigenetics in drug resistance"

June 14, 2017
Scott Lippman, M.D. - Director, Moores Cancer Center
UC San Diego Health
"Precancer Atlas to Drive Precision Prevention and Immune Interception"

National Institutes of Health

National Cancer Institute

Prevention of Mammary Tumors by Metformin in Comparison to Calorie Restriction (M. Cleary)	*116,566*
Gain of Function Mutant p53 Telomere Uncapping-driven Breast Tumorigenesis (Y. Deng)	*39,807*
Targeting High Fat Diet-driven DNA Hypermethylation for AML Chemoprevention (S. Liu)	*39,569*
Developing New Ornithine Decarboxylase Inhibitors to Prevent Skin Cancer (Z. Dong)	*143,985*
Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver (N. Kang)	*131,091*
The Role of Stromal APC Haploinsufficiency in Colorectal Tumorigenesis (J. Robinson)	*195,132*
Novel Gene That Determines Metastasis in African-American Men (M. Bhat)	*81,000*
Novel Targeted Chemo/immunotherapy Approach for Localized and Metastatic CaP (M. Bhat)	*310,318*
Chemoprevention of Colon Cancer by Targeting the Wnt/beta Catenin Pathway (Z. Dong)	*199,919*
Prevention of solar UV-induced Skin Cancer by Targeting LTZ4H (Z. Dong)	*229,354*
The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle (S. Gradilone)	*300,845*
Triggering the Dopamine Pathway to Inhibit Lung Cancer Progression (L. Hoeppner)	*199,715*

National Institute of General Medical Sciences

Glycolipid Transfer-Regulation by Membrane Interfaces (R. Brown)	*46,503*

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Identification of a Keratinocyte Stem Cell Regulatory Gene (R. Morris)	*205,695*

Department of Defense – U.S. Army

Defects in Histone H3.3 phosphorylation, and ATRX Recruitment to Misaligned Chromosomes During Mitosis Contribute to the Development of Pediatric Glioblastomas (E. Hinchcliffe)	*80,544*

AgStar Fund for Rural America

AgStar Research Project (A. Bode)	*6,010*
AgStar Research Project (Z. Dong)	*19,953*

Mayo Clinic

S. Gradilone	*10,648*

Pediatric Pharmaceuticals

Ginger as an Anti-cancer Agent (A. Bode)	*3,614*

Pennsylvania State University

Prevention of Prostate Carcinogenesis by Next Generation Selenium (Y. Deng)	*104,909*

Prairie Pharms, LLC

Thymoquine Oil in Lung Cancer Therapy (S. Liu)	*80,386*

University of Alabama at Birmingham

Preclinical in vitro and in vivo Agent Development Assays (A. Bode)	*15,574*

University of Arizona/NIH (Z. Dong)

Chemoprevention of Skin Cancer	*41,119*

University of Louisville/NIH

M. Cleary	*27,360*
S. Liu	*15,664*

Virginia Commonwealth University/NIH

The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (E. Hinchcliffe)	*125,573*
The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (R. Brown)	*113,436*

Zhejiang Ausun Pharmaceutical Co.

Ausun Research Project (Z. Dong)	*6,850*

Other Resources

The Hormel Foundation	*5,550,773*
University of Minnesota	*438,791*
Indirect Cost Return	*1,466,540*
Fundraising/Development	*1,145,830*

Total	**11,493,073**

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Abbygail Coyle, Molecular Biology and Translational Cancer Research
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801 16th Avenue N.E.
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Improving health through medical research.

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