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.
During the 2014-15 year, we continued our focus on cancer research because cancer already has surpassed heart disease as the No. 1 killer of Americans under age 80. In fact, cancer is the leading cause of death worldwide. Cancer affects all of us: women and men; poor and rich; old and young; and all races. The Hormel Institute is a leading medical research institute making contributions to the identification and discovery of novel targets and agents for cancer prevention and therapy. We experienced continued success during 2014-2015 in obtaining research funding and producing major research breakthroughs, even in a national environment of overall decreased funding for research.

On May 28, 2014, we finished the design of a new building expansion and held a groundbreaking ceremony with numerous local, state, and national leaders. This 20-laboratory expansion is funded in part by $13.5 million in State of Minnesota bonding funds included in a bill supported by State Senator Dan Sparks and State Representative Jeanne Poppe, and signed by Governor Mark Dayton. The Hormel Foundation matched the state’s $13.5 million commitment to construct the laboratory space on our east side and was a major contributor to the $4.5 million Live Learning Center on our west side, featuring a multi-purpose room and 250-seat lecture hall with theater-style seating and state-of-the-art global communications technology. Both additions are scheduled for completion by January 2016.

All of us from The Hormel Institute are very thankful for the generous support from the State of Minnesota, The Hormel Foundation, Hormel Foods Corporation, University of Minnesota, Mayo Clinic, 5th District Eagles Cancer Telethon, Paint the Town Pink, and many other individuals and groups. In particular, I would like to thank Mr. Gary Ray, Mr. Jeff Eitinger, Mr. Richard Knowlton, Mr. Joel Johnson, Mrs. Bonnie Rietz, Mr. Jerry Anfinson, and Mr. Steve Rizzi. We thank Drs. Eric Kaler and Brian Herman (University of Minnesota); and Drs. John Noseworthy, Glenn Forbes, Robert Diasio, and Greg Gores (Mayo Clinic) for their leadership and support. We thank our elected leaders, Minnesota Governor Mark Dayton; U.S. Senators Amy Klobuchar and Al Franken; U.S. Representative Tim Walz; Minnesota State Senator Dan Sparks; Minnesota State Representative Jeanne Poppe; Minnesota State Senator David Senjem; and Austin Mayor Tom Stiehm for their continued support. We remain deeply grateful to our community, our partners, and our collaborators for giving us the gift of being able to work here. Their support and gifts allow today’s research to flourish and pave the way for tomorrow’s progress to continue.

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

Dr. Zigang Dong
Executive Director
Many proteins are overexpressed only in cancer. The epidermal growth factor receptor (EGFR) is overexpressed only in cancer.

1. Discovery of key molecular events in cancer development.

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

2. Discovery of novel targets and agents for skin cancer prevention.

Solar UV (SUV) irradiation is a major factor in skin carcinogenesis, the most common form of cancer in the United States. The mitogen-activated protein kinase (MAPK) cascades are activated by SUV stimulation. We found that p38 signaling is critical for skin carcinogenesis. The 90 kDa ribosomal S6 kinase (RSK) and mitogen and stress-activated protein kinase (MSK) proteins phosphorylate at Ser795 and Ser807/811. Overall results indicated that kaempferol inhibits their respective kinase activities. Mechanistic investigations showed that kaempferol interacts with RSK2 and MSK1 at the ATP-binding pocket and inhibits their kinase activities. The regulation of p38 and MSK1 stability by kaempferol was observed during the etoposide-induced DNA damage response. These results provide a possible mechanism explaining the oncogenic function of RSK2 and, as kaempferol is important for cancer cell survival and proliferation, it might be an ideal target for cancer therapy or prevention.

Caffeic acid (4'-O-diphenylacetyl flavone) is a well-known phenolic phytochemical in coffee that reportedly has anti-cancer activities in vitro. Importantly, we resolved the co-crystal structure of ERK2 with compound 69407, a chrysin derivative, referred to as compound 69407, which inhibits cyclin-dependent kinase 2 (CDK2). Overall results indicated that compound 69407 is an ATP-noncompetitive cyclin-dependent kinase inhibitor that acts by binding inside the CDK2 allosteric pocket. The anti-cancer activity of chrysin observed in vivo studies, however, has been disappointing. A chrysin derivative, referred to as compound 69407, which inhibits cyclin-dependent kinase 2 (CDK2). Overall results indicated that compound 69407 is an ATP-noncompetitive cyclin-dependent kinase inhibitor that acts by binding inside the CDK2 allosteric pocket.

Chrysin (5,7-dihydroxyflavone), a natural flavonoid widely distributed in plants, reportedly has chemopreventive properties against various cancers. Chrysin (5,7-dihydroxyflavone), a natural flavonoid widely distributed in plants, reportedly has chemopreventive properties against various cancers. Chrysin (5,7-dihydroxyflavone), a natural flavonoid widely distributed in plants, reportedly has chemopreventive properties against various cancers.

We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Lastly, 2'-HCA potently suppressed the growth of mouse xenografts representing human leukemia or skin cancer. We also investigated the anti-cancer effect of isoliquiritigenin (ILQ), a chalcone derivative. We first studied the effects of ILQ on the growth of human cancer cells in vitro. ILQ inhibited the catalytic activity of both wild-type and double-mutant EGFR. ILQ also inhibited the activity of Src and attenuated its kinase activity. The compound also was effective as a chemopreventive agent against EGFR-mediated neoplastic transformation. Last
In the MNU rat model, metformin dosing (150 or 50 mg/kg BW/d) by gavage yielded plasma levels (Cmax and AUC) higher than humans taking term metformin (150 mg/kg BW/d) treatment increased levels of osteopontin, integrin αvβ3, and p21, and decreased cell viability by targeting PI3K/Akt, and subsequently decreased Akt signaling in UM-UC-5 and UM-UC-14 urinary bladder cancer cells. Furthermore, naproxen suppressed anchorage-independent cell growth and decreased cell viability by targeting PKB in both cell lines. Naproxen arrested cells in the G1 phase mediated through cyclin-dependent kinase 4, cyclin D1, and p21. Moreover, naproxen-induced significant apoptotic effects, accompanied with increased levels of cleaved caspase-3 and PARP in both cell types. Naproxen-induced cell death was mainly due to apoptosis that involved a prominent downregulation of Bcl-2 and up-regulation of Bax. Naproxen also caused apoptosis and inhibited AKT phosphorylation in rat urinary bladder cancer induced by NO-naproxen. Naproxen [(S)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid] is a potent nonsteroidal anti-inflammatory drug that inhibits both COX-1 and COX-2 and is widely used as an over-the-counter medication. Naproxen exhibits analgesic, anti-inflammatory, and anti-arthritis properties. Naproxen, as well as other nonsteroidal anti-inflammatory drugs, is now recognized to be hormesis in the prevention of urinary bladder cancer in rodents. Potential targets other than the COX-2 pathway, therefore, have not been explored. We examined potential additional targets in urinary bladder cancer cells and rat bladder cancers. Computer kinase profiling results suggested that phosphoinositide 3-kinase (PI3K) is a potential target for naproxen. In vitro kinase assay data revealed that naproxen interacts with PKB and inhibits its kinase activity. Pull-down binding assay data confirmed that PKB directly binds with naproxen in vitro and ex vivo. Western blot data showed that naproxen decreased phosphorylation of Akt, and subsequently decreased Akt signaling in UM-UC-5 and UM-UC-14 urinary bladder cancer cells. Furthermore, naproxen suppressed anchorage-independent cell growth and decreased cell viability by targeting PKB in both cell lines. Naproxen arrested cells in the G1 phase mediated through cyclin-dependent kinase 4, cyclin D1, and p21. Moreover, naproxen-induced significant apoptotic effects, accompanied with increased levels of cleaved caspase-3 and PARP in both cell types. Naproxen-induced cell death was mainly due to apoptosis that involved a prominent downregulation of Bcl-2 and up-regulation of Bax. Naproxen also caused apoptosis and inhibited AKT phosphorylation in rat urinary bladder cancer induced by NO-naproxen. Naproxen [(S)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid] is a potent nonsteroidal anti-inflammatory drug that inhibits both COX-1 and COX-2 and
The Hormel Institute

programs are underway in our laboratory:

The major focus of our laboratory is in the area of translational research. The following outcomes of therapy in African-Americans.

1. Understand the biochemical, cellular and molecular processes crucial for the development of hormone-related (prostate and breast cancer) and lethal (pancreatic and colon) cancers.
2. Identify potential agents that could be used to treat and prevent cancer in humans.
3. Reactivation of Tumor Suppressor Genes

4. Role of S100A4 in the development of prostate cancer

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer are not limited to cancer cells but include (1) abolition of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cellular senescence is an essential defining property of a pluripotent stem cell–like phenotype of human prostate cancer and are known to confer aggressiveness to cancer cells are reported to be essential for tumor progression and metastasis of epithelial malignancies. These are generated from normal prostate epithelial cells and are not destined to be cancerous. We have concluded that the prostate normal epithelial cells (PNT1A) and prostate cancer cells (TRAMP) differ in the activation of specific stem cell signaling pathways.

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer are not limited to cancer cells but include (1) abolition of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cellular senescence is an essential defining property of a pluripotent stem cell–like phenotype of human prostate cancer and are known to confer aggressiveness to cancer cells are reported to be essential for tumor progression and metastasis of epithelial malignancies. These are generated from normal prostate epithelial cells and are not destined to be cancerous. We have concluded that the prostate normal epithelial cells (PNT1A) and prostate cancer cells (TRAMP) differ in the activation of specific stem cell signaling pathways.

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer are not limited to cancer cells but include (1) abolition of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cellular senescence is an essential defining property of a pluripotent stem cell–like phenotype of human prostate cancer and are known to confer aggressiveness to cancer cells are reported to be essential for tumor progression and metastasis of epithelial malignancies. These are generated from normal prostate epithelial cells and are not destined to be cancerous. We have concluded that the prostate normal epithelial cells (PNT1A) and prostate cancer cells (TRAMP) differ in the activation of specific stem cell signaling pathways.

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer are not limited to cancer cells but include (1) abolition of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cellular senescence is an essential defining property of a pluripotent stem cell–like phenotype of human prostate cancer and are known to confer aggressiveness to cancer cells are reported to be essential for tumor progression and metastasis of epithelial malignancies. These are generated from normal prostate epithelial cells and are not destined to be cancerous. We have concluded that the prostate normal epithelial cells (PNT1A) and prostate cancer cells (TRAMP) differ in the activation of specific stem cell signaling pathways.

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.

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

The critical pathological processes that occur during the development and progression of human prostate cancer are not limited to cancer cells but include (1) abolition of senescence of normal prostate epithelial cells; (2) self-renewability of prostate cancer cells even after chemotherapy and radiation; and (3) dysregulated cellular senescence is an essential defining property of a pluripotent stem cell–like phenotype of human prostate cancer and are known to confer aggressiveness to cancer cells are reported to be essential for tumor progression and metastasis of epithelial malignancies. These are generated from normal prostate epithelial cells and are not destined to be cancerous. We have concluded that the prostate normal epithelial cells (PNT1A) and prostate cancer cells (TRAMP) differ in the activation of specific stem cell signaling pathways.

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

The lack of effective therapies for advanced prostate cancer reflects to a large extent, the paucity of knowledge about the mechanisms of transcriptional post-transcriptional cancer development. After undergoing chemotherapy and radiation, several cancer patients come back to the clinics with recurrence of aggressive forms of the disease. Thus, the identification of novel 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 cancer cells (even after chemotherapy) also show excellent candidate targets for staging the disease as well as establishing effectiveness of therapeutic and chemotherapeutic intervention of prostate cancers. We investigate the molecular mechanisms that causes the failure of chemotherapy and radiation in cancer patients. We have identified several molecules (genes and gene-products) responsible for the development and recurrence of aggressive forms of prostate cancer. These include S100A4 (a calcium-binding protein), BMI-1 (a polycomb-group gene and stem cell factor), BHLA (a receptor-8 inhibitor) and matriptase (a serine protease). The main objectives of this studies is to take the benchside research to the bedside use in clinics.
of these therapies, however, is temporary, and after a short remission period, tumors may 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 Flutamide, that are widely used in clinics to treat prostate cancer, showed only modest results. Although numerous AR-targeting therapies have been developed, over-expression of AR is the most-common event associated with emergence of CRPC phenotype, particularly of CRPC phenotype. AR signaling inhibitors, such as Bicalutamide, that are widely used in clinics to treat prostate cancer patients exhibiting CRPC disease. Emergence of CRPC phenotype depends on different mechanisms, such as activation of receptor tyrosine kinase, uncontrolled cell growth, genomic mutation of AR that allows response to nonspecific AR ligands. We are studying whether isoforms or splice variants of androgen receptor play a role in the CRPC. Our 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 splice variants induce its pro-growth activity in tumor cells. Notably, we have identified an inhibitor that activates the AR splice variant in CRPC cells. The validation of the molecular mechanisms-based agent in animal models, is expected to provide an excellent alternative or add-on modality for the treatment of advanced prostate cancer, particularly of CRPC phenotype.

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

Dr. Mohammad Saleem (Bhat)

6. Investigating the causes of racial disparity in prostate cancer

According to American Cancer Society, the higher overall cancer death rate among African American men. We recently showed that BMI1, a stem cell protein, could be developed as a predictive biomarker for prostate cancer in African Americans as well as in Caucasian men. We also recently showed that BMI1, a stem cell protein, could be developed as a predictive biomarker for prostate cancer in African Americans as well as in Caucasian men. The larger aim is to identify novel biomarkers that could be used for prostate cancer progression in Caucasians as well as in African American men. We recently showed that BMI1, a stem cell protein, could be developed as a predictive biomarker for prostate cancer in African Americans as well as in Caucasian men. Another major goal of our laboratory is to identify novel and non-toxic agents that could be developed as chemoprotective and chemotherapeutic agents for other inhibiting cancer development or treating cancer in humans. We have identified a novel-arsenic compound called “Lupel” that inhibits a potential to be developed as a chemoprotective and chemotherapeutic agent against cancer. Lupel, a fruit and vegetable based dietary supplements, is composed of olive, grapes, cucumbers, berries, and mangos as well as herbs, such as soy, green tea, and cloves. Our laboratory has shown that lupel application on skin prevents cancer development in animal models. Further, we have shown that lupel treatment inhibits the growth of various human malignant and pre-malignant prostate and pancreatic cells harboring (human origin) using mouse models. These studies have generated interest in studying lupel for other cancer types. We recently observed that lupel has the potential of improving chemotherapy in colon cancer. Our preclinical studies have shown that lupel is bioavailable in relevant mouse models after consumption (as oral administration).

7. Lupel, a dietary triterpenic 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 chemoprotective and chemotherapeutic agents for other inhibiting cancer development or treating cancer in humans. We have identified a novel-arsenic compound called “Lupel” that inhibits a potential to be developed as a chemoprotective and chemotherapeutic agent against cancer. Lupel, a fruit and vegetable based dietary supplements, is composed of olive, grapes, cucumbers, berries, and mangos as well as herbs, such as soy, green tea, and cloves. Our laboratory has shown that lupel application on skin prevents cancer development in animal models. Further, we have shown that lupel treatment inhibits the growth of various human malignant and pre-malignant prostate and pancreatic cells harboring (human origin) using mouse models. These studies have generated interest in studying lupel for other cancer types. We recently observed that lupel has the potential of improving chemotherapy in colon cancer. Our preclinical studies have shown that lupel is bioavailable in relevant mouse models after consumption (as oral administration).

8. Testing cause-polypol (plant-disc, chocolate-based) food products in the prevention of cancer

Functional food is any healthy food claimed to have a health-promoting or disease-preventing property, such as weight loss, blood pressure, or improved bone health. Functional chocolate consumption has been associated with improvements in delayed oxidation of low-density lipoprotein and improved platelet function in humans. Cocoa-based chocolate consumption has been associated with short-term improvements in delayed oxidation of low-density lipoprotein, improved endothelial function, lowered blood pressure, and improved platelet function. Epicatechin has been a major component of cocoa. We have employed a technique called ATR-FTIR to test epicatechin content in chocolate samples. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells. Our studies show that epicatechin rich cocoa polyphenol selectively inhibits growth of prostate cancer, breast cancer, and colon cancer cells while sparing normal cells.
When people read or hear the word “lipid,” the picture that often comes to mind is the hydrophobic, amphipathic nature of most membrane lipids that surround and divide the cell interior into specialized compartments depending on lipids. These lipids are specially modified at the molecular level so that they are polar at one end and nonpolar at the opposite end. As the polar ends prefer to be in contact with water and the nonpolar ends do not, these special lipids medially form layers only two molecules thick, i.e. bilayers, commonly known as cell membranes. The thin, flexible nature of cell membranes enables them to act as selective permeability barriers to control what gets in and out of cells. Interestingly, there are many more lipids on cell membranes than are found in membranes of certain membrane proteins. The discovery of these new functions for membrane lipids can function as intracellular messenger signals that regulate cell growth, proliferation, and programmed cell death and survival processes, while other membrane lipids, i.e. especially long chain aminophospholipids (CLPs) acquire roles in the intermembrane transfer of glycolipids. To do so, we carried out the first molecular characterization of CLP and showed the existence of integral homologs in mammals, plants, and fungi. Molecular biological approaches involving polymerase chain reaction (PCR)-enabled amplification of mRNA transcript open reading frames and production/purification of Human GLTP and related homologs using bacterial expression systems. The successes established application of X-ray crystallographic approaches that led to molecular structural determination of GLTP and related homologs in glycolipid-free form and complexed with different glycolipids in collaboration with structural biologists in the D.J. Patel lab at Memorial Sloan Kettering Cancer Center in New York and in the L. Malina lab at CK Begg NL in Denia (Spain). Our work showed that human GLTP forms a novel structural fold among known proteins. The Worldwide Protein Data Bank has designated human GLTP as the founding member of a new superfamily of lipid glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2.

In studies of the model plant, Arabidopsis thaliana, carried out in collaboration with Dr. John Mundy at the University of Copenhagen, we showed that a gene originally identified by its ability to induce accelerated cell death, known as acd11, actually encodes a plant GLTP ortholog. X-ray structural determinations showed that ACD11 is a GLTP-fold that has evolved for binding/glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2. In studies of the model plant, Arabidopsis thaliana, carried out in collaboration with Dr. John Mundy at the University of Copenhagen, we showed that a gene originally identified by its ability to induce accelerated cell death, known as acd11, actually encodes a plant GLTP ortholog. X-ray structural determinations showed that ACD11 is a GLTP-fold that has evolved for binding/glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2. In studies of the model plant, Arabidopsis thaliana, carried out in collaboration with Dr. John Mundy at the University of Copenhagen, we showed that a gene originally identified by its ability to induce accelerated cell death, known as acd11, actually encodes a plant GLTP ortholog. X-ray structural determinations showed that ACD11 is a GLTP-fold that has evolved for binding/glycolipid selectivity of a fungal GLTP ortholog as well as the GLTPH domain of human FAPP2.
We anticipate that elucidation of the fundamental structure-function relationships governing GTLP and CPTP action will facilitate the development of pharmacological ways to modulate GLTP and CPTP while enhancing their potential use as biotechnological resources, i.e. nanotools for targeted manipulation of cellular sphingolipid composition. Such strategies could provide new ways to introduce specific sphingolipid antigens to help achieve the targeted destruction of cancer cells via immunotherapeutic means and lead to new therapeutic approaches to treat disease processes involving sphingolipids.

Our exciting progress to date emphasizes the need for continuing studies into the workings of GLTP, CPTP, and other proteins containing GLTP-like motifs using comprehensive strategies involving biophysical, cell, and molecular biological approaches. Our recent investigations of the gene organization and transcriptional status in humans and other mammals now provide a firm foundation for identification and characterization of inherited diseases involving GLTP and CPTP. Our ongoing efforts benefit from collaborations with researchers at Memorial Sloan Kettering Cancer Center in New York; Virginia Commonwealth University in Richmond; The Russian Academy of Sciences in Moscow; The University of Copenhagen in Denmark; CIC bioGUNE in Derio/Bilbao, Spain; and the Mayo Clinic in Rochester, MN. Our research continues because of financial support received from the National Institute of General Medical Sciences; the National Cancer Institute of NIH; the National Heart, Lung, and Blood Institute of NIH; and The Hormel Foundation.

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


“The discovery of these new functions for membrane lipids underscore the reasons why biomembranes come under direct attack during cancer and infectious disease.”

Dr. Rhoderick E. Brown

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

HNF1α (Hereditary Nephrosis Factor α) and HNF4α are the master regulators of pancreatic β-cell development and function, and their mutations are the most common genetic causes of diabetes referred to as MODY. Over the years, we have determined the crystal structures of the functional complexes made by HNF1α and HNF4α. These structures provided valuable information on the molecular basis of target-gene recognition, ligand-mediated activation, and functional disruption by disease-causing mutations. These structures, however, provided partial answers as to how these proteins are involved in additional protein-protein interactions and physiological function. We seek to elucidate the molecular mechanism of HK2 gene regulation by RNA and its implication to β-cells and to perform structural studies of the complexes and virtual screening of compounds for potential functional disruption by disease-causing mutations. These structures, however, provided partial answers as to how these proteins are involved in additional protein-protein interactions and physiological function. We seek to elucidate the molecular mechanism of HK2 gene regulation by RNA and its implication to β-cells and to perform structural studies of the complexes and virtual screening of compounds for potential functional disruption by disease-causing mutations.

FABP, a family of lipid transporters, is expressed exclusively in prostate cancer cells, particularly elevated in lethal castration-resistant prostate cancer (CRPC). Together with Dr. Yibin Deng of The Hormel Institute, we have assembled a multidisciplinary team to tackle this multifaceted project. Our research currently is focused on elucidating the atomic details of key molecular interactions involved in human diseases, especially diabetes and cancer.

Dahil to improve the prognosis of those hard-to-treat breast cancers. Candidate compounds will be tested in vitro and in vivo for their ability to suppress the disease or to interfere with its progression. We also seek to elucidate the molecular mechanism of HK2 gene regulation by RNA and its implication to β-cells and to perform structural studies of the complexes and functional characterization of MODY mutations. Additionally, we have embarked on new cancer research projects. Dub3 is an ubiquitin hydrolase (de-ubiquitinase) and key protein that relays extrinsic signals to the cellular machinery, which includes the complex's crystal structure, will help identify novel, anti-prostate cancer therapeutic compounds.

Additional cancer-related projects with therapeutic values include FABP-inhibitor complexes, novel protein kinases/inhibitor complexes, and small RNA molecules for drug delivery. Our lab will continue this work and expand target molecules to include additional protein-protein interactions in the context from different angles. One easy to inhibit HK2's oncogenic activity is to suppress its gene expression. It recently was reported that HK2 expression is regulated by untranslated RNAs.

“Today’s Research, Tomorrow’s Cures.”

Dr. Young-In Chi
Hormel Institute

“Our research currently is focused on elucidating the atomic details of key molecular interactions involved in human diseases, especially diabetes and cancer.”

Dr. Young-In Chi
Hormel Institute

Crystal structures of a protein/DNA complex used for structure determination in Kir6.1

Structural Biology

Young-In CH. 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. Given that their biological functions are tightly coupled to their molecular structures, elucidating atomic details of their structures is crucial to understanding the molecular mechanisms underlying their physiological functions. Biomolecules are too small to be seen even with the most-advanced electron microscope. Special techniques need to be employed. We particularly harness X-ray crystallography as a main experimental tool to elucidate these dimensional structures. This technique involves various disciplines of modern biomedical research, such as molecular biology, nuclear acid/protein chemistry, bioinformatics, and X-ray crystallography. We also perform cellular or cell-based functional studies to complement the structural studies. Our long-term goal is to elucidate how biomolecules work and identify new avenues for developing therapeutics and an attractive target for diabetes treatment. We finished the Foxo1/DNA complex structure and have submitted the manuscript for publication in which we will identify a new Foxo1 binding site and novel binding modes on G6pase promoter.

We also have embarked on new cancer research projects. Dahil is an ubiquitin hydrolase (de-ubiquitinase) and key protein that relays extrinsic-signal to regulate epithelial-mesenchymal transition (EMT) and metastasis in breast cancer. It can serve as a druggable target for treating triple negative basal-like breast cancers. We started determining the crystal structure of the Dahil catalytic domain alone and/or in complex ubiquitin/substrate. We have made sufficient progress and are improving the crystals as well as finishing the structure determination. Once complete, we will start computer-assisted docking analysis of chemical library compounds to discover design-specific inhibitors of Dahil to improve the prognosis of those hard-to-treat breast cancers. Candidate compounds will be tested in vitro and in vivo for their ability to suppress the disease or to interfere with its progression. We also seek to elucidate the molecular mechanism of HK2 gene regulation by RNA and its implication to β-cells and to perform structural studies of the complexes and virtual screening of compounds for potential functional disruption by disease-causing mutations. These structures, however, provided partial answers as to how these proteins are involved in additional protein-protein interactions and physiological function. We seek to elucidate the molecular mechanism of HK2 gene regulation by RNA and its implication to β-cells and to perform structural studies of the complexes and virtual screening of compounds for potential functional disruption by disease-causing mutations.

Thirdly, hexokinase II (HK2), which catalyzes the first committed step in glucose metabolism, is expressed exclusively in prostate cancer cells, particularly elevated in lethal castration-resistant prostate cancer (CRPC) harboring PTEN/p53 deletions. HK2 has emerged as an attractive target for incurable CRPC. Not pictured: Shu-Ping Tung

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

Dr. Young-In Chi
Hormel Institute

We seek to elucidate the molecular mechanism of HK2 gene regulation by RNA local structures at the untranslated region, in particular its association with the translation initiation factors, eIF4F. These studies' successful outcomes, including the complex's crystal structure, will help identify novel, anti-prostate cancer therapeutic compounds.

Additional cancer-related projects with therapeutic values include FABP-inhibitor complexes, novel protein kinases/inhibitor complexes, and small RNA molecules for drug delivery. Our lab will continue this work and expand target molecules to include additional protein-protein interactions in the context from different angles. One easy to inhibit HK2's oncogenic activity is to suppress its gene expression. It recently was reported that HK2 expression is regulated by untranslated RNAs.
Primary interests of the Nutrition and Metabolism section are the effects of body weight and food intake on the development of breast cancer using mouse models. Past studies have included effects of genetic and dietary induced obesity on breast/mammary tumor development, particularly with respect to body fat and serum IGF-I, leptin and adiponectin levels. Other studies have assessed the effect of calorie restriction on the prevention of mammary tumors in several mouse models of breast cancer. Of particular interest, we consistently find that periods of moderately severe calorie restriction followed by refeeding – which we term “intermittent calorie restriction” – results in much greater reduction in mammary tumor incidence than the same degree of restriction implemented chronically with both interventions resulting in 20 to 25 percent calorie reduction. Mechanisms of the protective effect of caloric restriction on cancer development include studies of leptin/leptin receptors, adiponectin/adiponectin receptors, and the IGF-axis. Based on results of our studies, we hypothesized that the altered (i.e. reduced) adiponectin/leptin ratio that is characteristic of obesity provides a permissive environment for tumor development. In contrast, the reductions in IGF-I and leptin and increased adiponectin/leptin ratio resulting from intermittent calorie restriction result in decreased mammary tumor incidence in comparison to ad libitum feeding as well as to chronic calorie restriction. These studies have been expanded by Dr. Michael Grossmann of The Hormel Institute to include the interaction of an omega-3 fatty acid in combination with intermittent calorie restriction on the development of mammary tumors. Intermittent calorie restriction might provide an easier approach for individuals to reduce caloric intake for disease prevention. In fact, several recently promoted weight-loss programs utilize this approach. Although calorie restriction has an incredible effect on cancer prevention in many rodent models, the practical aspects of implementing and maintaining this intervention in human populations has not been successful. This has led to interest in identifying compounds that act like calorie restriction, such as calorie-restriction mimetics. One such compound is metformin, a commonly used type 2 diabetic drug. Our most recent study is being conducted in a transgenic mouse model to mimic post-menopausal breast cancer and includes obese- as well as normal-weight subjects. The intervention was started when the mice were middle-age to reflect also what would occur in at-risk women. We also are conducting studies related to metformin’s effects on cancer progression. We have completed this long-term study, following the mice until they were 90 weeks of age. We did not find that metformin had a cancer-preventing effect in either lean or obese mice. NEEDS MORE TEXT/EDITING In contrast 25% calorie restriction resulted in a significant decrease in mammary tumor incidence and delayed age when tumors were detected.

“Today’s Research, Tomorrow’s Cures.”
23

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

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

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

While many studies have focused on the role of apoptosis and/or senescence in p53-mediated tumor suppression, recent findings suggest that p53 induces DRAM (Damage-Regulated Autophagy Modulator)-dependent autophagy. To study the role of DRAM-dependent autophagy in tumorigenesis, we generated conditional (i.e., tissue-specific) knockout mouse models. One important mechanism that can give rise to the dysfunctional DRAM in tumorigenesis is mutations in the p53 protein that maintain genomic integrity and prevent tumorigenesis. We have identified that p53 suppresses tumorigenesis in response to a variety of genotoxic stresses. The importance of p53 in tumor suppression is highlighted by mutations that lead to the loss of wild-type p53 function and/or oncogenic gain of function (GOF) identified in more than half of human cancers. The comprehensive genomic/whole exons sequencing analyses sponsored by The Cancer Genome Atlas (TCGA) consortium confirmed the high frequency of TP53 mutations in all of the sequenced human cancers. TCGA studies, for example, revealed 96 percent of human cancers; 37 percent of breast cancers; 54 percent of colorectal cancers; 35 percent of ovarian cancers; 34 percent of breast cancers; 34 percent of colorectal cancers; and 81 percent of lung squamous cell carcinomas display TP53 mutations. Mouse genetic studies provide compelling evidence that TP53 mutations play a causal role in tumorigenesis. Mouse genetic studies provide compelling evidence that TP53 mutations play a causal role in tumorigenesis.

To answer the critical function of p53-mediated autophagy, apoptosis and senescence in suppressing tumor development in vivo, we have generated "triple" mutant mouse models containing the constitutive mutant p53, engineered mouse models with a positive feedback loop to sustain the mutant p53 protein (p105 shut-off knockout in Puma knockout and sensorless-deficient mice (p21 knockout)). We expect that by utilizing these complex, genetically engineered mouse models, we will be able to address the critical question about how the p53-regulated signaling axis contributes to its tumor suppressive function in vivo.

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

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

Telomeres are nucleoprotein caps that protect chromosome ends from being recognized as damaged DNA and prevent the normal end-to-end fusion of chromosome ends, which can result in the loss of genetic information. Telomeres are dynamic structures that grow and shorten in response to cellular stresses. The importance of p53 in telomere integrity and prevention of tumorigenesis is highlighted by mutations in the wild-type p53 protein found in patients in breast epithelium. We believe that mutant p53 promotes breast tumor development by targeting the telomere dysfunction network in developing breast epithelium. Our long-term goal in this project is to establish "chromosomal instability" mouse breast cancer models and discover the "causal" genomic events driving breast tumorigenesis in vivo. One important mechanism that can give rise to the unstable breast cancer genome is the dysfunction of telomeres.

Our studies currently suggest that endogenous expression of the "hot spot" mutant p53 promotes breast tumor development in comparison with the loss of p53 in breast epithelial cells. To understand the molecular mechanism underlying mutant p53-mediated GOF, we found that "hot spot" mutant p53 protein cooperates with G0 to G1 cyclin-dependent kinase (CDK) transcriptionally downregulate PHLPP2 resulting in activation of AKT1-mTORC1 signaling. To establish the novel murine breast cancer model, we have engineered a novel mouse breast cancer model harboring telomere uncapping-induced chromosomal instability without affecting the activity of other drivers in this mouse model. Importantly, the mouse model harboring telomere uncapping-induced chromosomal instability or mutants p53 protein found in cancer patients in breast epithelium. We believe that this novel murine breast cancer model recapitulates the salient characteristics of human breast carcinomas. We are establishing and using this novel murine breast cancer model to identify the key genomic pathways that lead to the loss of wild-type p53 suppressor function.

"Finding effective and selective means of killing prostate cancer cells carrying PtenX5 deficiency is critical to successfully treat current incurable CRPC."
challenging, our novel findings provide a potential and effective therapeutic strategy for human cancers carrying mutant p53.

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

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

We recently made progress in our study on prostate cancers. Prostate cancer strikes one in six men and is the second-leading cause of cancer-related deaths in men after lung cancer in the United States. Prostate cancer arises mainly from prostate 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, prostate cancers invariably develop resistance to conventional ADT and progress to a more aggressive, castration-resistant prostate cancer (CRPC) within 18 to 24 months.

The discovery that persistent androgen receptor (AR) signaling plays a crucial role in the progression of CRPC leads to “second generation” ADT treatments, such as androgen synthesis blocker abiraterone recently approved by the Food and Drug Administration (2011, FDA); and the second generation of AR signaling inhibitor enzalutamide (formerly MDV3100) (2012, FDA), which has demonstrated efficacy against chemotherapy-resistant CRPC with median increase in survival of four to five months. Nearly all CRPC patients, however, inevitably develop acquired resistance to the “second generation,” anti-AR signaling axis treatments within about six to 12 months. No therapeutic options currently exist for CRPC patients who have developed resistance to the second generation of anti-androgen receptor (AR) signaling axis therapy. We found that co-deletion of Pten and p53 in prostate epithelium—often observed in human lethal CRPC—leads to AR-independent CRPC and, thus, confers de novo resistance to “second generation” androgen deprivation therapy (ADT) in multiple independent, yet complementary, preclinical mouse models. In striking contrast, mechanism-driven, co-targeting hexokinase 2 (HK2)-mediated Warburg effect with 2-deoxyglucose (2-DG) and ULK1-dependent autophagy with chloroquine (CQ) selectively kill cancer cells through intrinsic apoptosis to cause tumor regression in xenograft and lead to near-complete tumor suppression in Pten-/p53-deficiency-driven CRPC mouse model. Mechanistically, 2-DG causes AMPK phosphorylation, which in turn, inhibits mTORC1-S6K1 translation signaling to preferentially block anti-apoptotic protein MCL-1 synthesis to prime mitochondria-dependent apoptosis while simultaneously US6-driven autophagy for cell survival to counteract the apoptotic action of anti-Warburg effect.

Inhibition of autophagy with CQ, accordingly, sensitizes cancer cells to apoptosis upon 2-DG challenge. Given that 2-DG is recommended for phase II clinical trials for prostate cancer and that CQ has been used clinically as an anti-malaria drug for many decades, the preclinical results from our “proof-of-principle” studies in vivo are imminently translatable to clinical trials to evaluate the therapeutic efficacy by the combination modality for a subset of currently incurable CRPC patients. Our laboratory also is utilizing multiple genetic and pharmacological approaches to identify targets that can be targeted selectively in human lung and colon cancers.

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

Ofer Professional Activities

Grant Reviewer, National Cancer Institute

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

Our ongoing projects involve collaborations with researchers from Texas Tech University Health Sciences Center School of Pharmacy in Amarillo, Texas; The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Roswell Park Cancer Institute in Buffalo, N.Y.; and Mayo Clinic College of Medicine in Rochester, Minn. Our research projects are supported by grants from the National Cancer Institute of the National Institutes of Health and The Hormel Foundation.
This shows a cross section of a biliary duct, where the nuclei of cholangiocytes lining the duct are stained in blue and a primary cilium (shown in red) extending into the ductal lumen.

Our section started in November 2014 and we equipped the new laboratory, putting together a small team to start moving our research forward. The “Cancer Cell Biology and Translational Research” section focuses on understanding the basic biological processes involved with a normal cell transforming into a cancerous one. By understanding these mechanisms, potential therapeutic interventions might be envisioned. We currently are investigating the role of the primary cilium – that sense and receive signals from the environment surrounding the cells. We've found that these antennae are lost in tumor cells; therefore, their loss might contribute to the development of new therapeutic strategies based on the rescue of primary cilium integrity.

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

Loss of primary cilium also has been described in other solid tumors – including pancreatic, prostate, breast and kidney cancers – broadening the spectrum of potential applications of this research. During our time at The Hormel Institute, our section brought a federal grant form NIH/NCI (R21 CA166635) and secured new funding for the coming five years (R01 CA183764), also from the National Cancer Institute, part of the National Institutes of Health.

We established several collaborations, both intra- and extramural, with prestigious investigators and institutions including: Dr. Mohammad Saheb Bhat (The Hormel Institute); Drs. Nicholas LaRusso and Steven Alberts (Mayo Clinic Rochester, MN); Dr. Kaist Medsy and Debabrata Mukhopadhyay (Mayo Clinic, Jacksonville, FL); Dr. Aram Hezel (University of Rochester School of Medicine, Rochester, NY); Dr. Mina Komuta (Cliniques Universitaires Saint-Lu, Brussels, Belgium); Dr. Jesus Banales (Biodonostia Research Institute -Donostia University Hospital, San Sebastian, Spain); and Aystylon Pharmaceuticals Inc. (Boston, MA), among others. The results of our research are uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilium architecture and function. By partnering with collaborators directly engaged in the treatment of patients and with pharmaceutical industries, our ultimate goal is to translate our basic research to the bedside by developing new clinical trials for these diseases. Importantly, in collaboration with collaborators directly engaged in the treatment of patients and with pharmaceutical industries, our ultimate goal is to translate our basic research to the bedside by developing new clinical trials for these diseases. Importantly, in collaboration with 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.

The results of our research are uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of malignant cells and provide the foundation for plausible, novel anti-cancer therapies based on the restoration of primary cilium architecture and function. By partnering with collaborators directly engaged in the treatment of patients and with pharmaceutical industries, our ultimate goal is to translate our basic research to the bedside by developing new clinical trials for these diseases. Importantly, in collaboration with 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.

“Loss of primary cilium also has been described in other solid tumors – including pancreatic, prostate, breast and kidney cancers – broadening the spectrum of potential applications of this research.”

Dr. Sergio Gradilone

Clinical trial that hopefully will start patient recruitment in early 2016. Our section also initiated and organized a new weekly seminar series “Thursdays HI Research Seminar Series” that fosters the interaction, discussion of experimental results and collaboration between the different sections of our Institute.

Publications/Masteries

“Today’s Research, Tomorrow’s Cures.”

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

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

In vitro assembly of a frog nucleus and chromosomes.

Our research is funded by grants from the National Institutes of Health, the Department of Defense CDMRP (Congressionally Directed Medical Research Programs). We study the regulation of cell division – the process by which cells proliferate. We have several ongoing research projects in the lab, including understanding the molecular mechanisms underlying the generation of mitotic spindle bipolarity, and the gain/loss of whole chromosomes during mitotic division, a process which is associated with tumor progression.

Cell division lies at the heart of normal tissue development and maintenance. The division of cells must occur in a strict one-to-two fashion to ensure genomic duplication to once per cell cycle. Therefore, it is important to understand the molecular mechanisms that ensure normal cell division. We have been working to understand the molecular mechanisms behind centrosome separation errors. However, despite an increasing mechanistic understanding of how CIN is generated, we know relatively little about how chromosome missegregation becomes transduced into cell transformation and 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. 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 fail-safe devices to ensure that cell division occurs with absolute fidelity. Unfortunately, DNA mutations – often caused by environmental factors – may lead to aneuploidy in which daughter cells have variable chromosome numbers. This is a major problem for cells because there is a change in the p53 pathway and induce durable cell cycle arrest – a molecular fail-safe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is the first of the two checkpoints. However, it has 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.

Chromosome instability (CIN) is the loss or gain of individual chromosomes during mitosis – generation aneuploidy, and correlates with the aggressive behavior of advanced tumor cells. Recent studies have linked chromosome segregation errors to mitotic kinetochore attachments caused by transient defects in spindle geometry, often mediated by supervisory centrosomes. Yet despite our increasingly mechanistic understanding of the causes of CIN, the important question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood. To this end, we recently have identified a novel biochemical pathway that monitors chromosome missegregation 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 fail-safe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is the first of the two checkpoints. However, it has been identified that monitor chromosome mispositioning - either before or after anaphase - at the single-chromosome level.

To address these fundamental questions in cell biology. Our research has direct relevance to understanding the underlying mechanisms 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 fail-safe devices to ensure that cell division occurs with absolute fidelity.

In our lab, we use cultured mammalian cells and cytogenetic extracts generated from Xenopus frog to examine the basic control mechanisms underlying the synchronization of the cell cycle. We use advanced imaging techniques, such as live-cell confocal fluorescence microscopy, 3-dimensional in vitro microsurgery, and microscopy to address these fundamental questions in cell biology. Our research has direct relevance to understanding the underlying mechanisms that lead to cancer initiation and progression. Our work also is relevant to identifying potential targets for chemotherapy agents.

Experimental research results:

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

Dr. Edward H. Hinchcliffe

1. Chromosome missegregation: Contributing to the onset of tumorigenesis

Our long-term goal is to understand the cell cycle regulation of bipolar mitotic spindle assembly and function. Proper bipolar mitotic spindle assembly ensures that each daughter cell receives an exact set of chromosomes. Chromosome instability (CIN) – the loss or gain of individual chromosomes during mitosis – generation aneuploidy, and correlates with the aggressive behavior of advanced tumor cells. Recent studies have linked chromosome segregation errors to mitotic kinetochore attachments caused by transient defects in spindle geometry, often mediated by supervisory centrosomes. Yet despite our increasingly mechanistic understanding of the causes of CIN, the important question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood. To this end, we recently have identified a novel biochemical pathway that monitors chromosome missegregation 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 fail-safe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is the first of the two checkpoints. However, it has 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.

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 – generation aneuploidy, and correlates with the aggressive behavior of advanced tumor cells. Recent studies have linked chromosome segregation errors to mitotic kinetochore attachments caused by transient defects in spindle geometry, often mediated by supervisory centrosomes. Yet despite our increasingly mechanistic understanding of the causes of CIN, the important question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood. To this end, we recently have identified a novel biochemical pathway that monitors chromosome missegregation 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 fail-safe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is the first of the two checkpoints. However, it has 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.

In our lab, we use cultured mammalian cells and cytogenetic extracts generated from Xenopus frog to examine the basic control mechanisms underlying the synchronization of the cell cycle. We use advanced imaging techniques, such as live-cell confocal fluorescence microscopy, 3-dimensional in vitro microsurgery, and microscopy to address these fundamental questions in cell biology. Our research has direct relevance to understanding the underlying mechanisms that lead to cancer initiation and progression. Our work also is relevant to identifying potential targets for chemotherapy agents.

Experimental research results:

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

Dr. Edward H. Hinchcliffe

1. Chromosome missegregation: Contributing to the onset of tumorigenesis

Our long-term goal is to understand the cell cycle regulation of bipolar mitotic spindle assembly and function. Proper bipolar mitotic spindle assembly ensures that each daughter cell receives an exact set of chromosomes. Chromosome instability (CIN) – the loss or gain of individual chromosomes during mitosis – generation aneuploidy, and correlates with the aggressive behavior of advanced tumor cells. Recent studies have linked chromosome segregation errors to mitotic kinetochore attachments caused by transient defects in spindle geometry, often mediated by supervisory centrosomes. Yet despite our increasingly mechanistic understanding of the causes of CIN, the important question of how both transformed and non-transformed cells respond to chromosome instability remains poorly understood. To this end, we recently have identified a novel biochemical pathway that monitors chromosome missegregation 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 fail-safe device that monitors aneuploidy and prevents the proliferation of aneuploid cells. Current work focused on DNA damage caused by lagging chromosomes is the first of the two checkpoints. However, it has 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.

In our lab, we use cultured mammalian cells and cytogenetic extracts generated from Xenopus frog to examine the basic control mechanisms underlying the synchronization of the cell cycle. We use advanced imaging techniques, such as live-cell confocal fluorescence microscopy, 3-dimensional in vitro microsurgery, and microscopy to address these fundamental questions in cell biology. Our research has direct relevance to understanding the underlying mechanisms that lead to cancer initiation and progression. Our work also is relevant to identifying potential targets for chemotherapy agents.

Experimental research results:

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

Dr. Edward H. Hinchcliffe
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 into an organized array. Interestingly, the acentrosomal microtubule focus can separate into two distinct poles prior to nuclear envelope breakdown. In the spindle midzone function: PRC1 and Kif4, in response to experimental loss of tektin deficiencies. We are interested in uncovering the molecular mechanisms underlying these observations. We currently are examining the role of microtubules, and regulatory microtubules fail to become compacted, and appear to exhibit abnormal plus-end microtubule motility. The result is failure of cytokinesis. In addition to the tektins, we are exploring the role of two highly conserved proteins, Cdc13 and Kif4, as regulators of midbody and midzone microtubules. Our goal is to integrate molecular studies with live-cell physiology to understand the mechanisms underlying cell division.

We have found that there is a period following the onset of anaphase where the cell membrane cannot respond to furrow-inducing signals, and thus is insensitive to the loss of microtubules and the activity of Polo-like kinase 1. Once cells progress beyond this point, however, the furrow will form, regardless of whether or not microtubules persist. Polo-like kinase 1 activity also is not required after this “point of no return;” adding kinase inhibitors after this point does not affect the function of the furrow.

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 microtubules during the acentrosomal cell cycle, we have generated primate-like kidney cell line (BSC-1 cells) that constitutively express α-tubulin coupled to GFP. We find that after several hours, acentrosomal cells re-form their microtubule network into an organized array. 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 is possible 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 acentrosomes are absolutely necessary to achieve fidelity during mitotic spindle assembly. This region of the spindle is responsible for initiating cytokinesis and required for the process to continue. Many key regulators of late mitotic events, along with cytokinesis localize to the spindle midzone. When tektin 2 (one of three distinct tektin found in vertebrates) is knocked down using shRNAs, the midzone microtubules fail to become compacted, and appear to exhibit abnormal plus-end microtubule motility. The result is failure of cytokinesis.

In the acentrosomal cells we are exploring the role of the two highly conserved proteins, Cdc13 and Kif4, in response to experimental loss of tektin deficiencies. In addition to the tektins, we are exploring the role of two highly conserved proteins, Cdc13 and Kif4, as regulators of midbody and midzone microtubules. Our goal is to integrate molecular studies with live-cell physiology to understand the mechanisms underlying cell division.

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

Funding
Department of Defense (CDMRP), CA130436
NIH (R01GM107098)

Wellcome Trust, UK
Medical Research Council, UK
European Research Council
European Observatory for Translational Cancer Research
American Society for Cell Biology Minorities Affairs Committee, FRED mentor
Mentor, American Society for Cell Biology Minorities Affairs Committee, FRED mentor

Other professional activities
Review panel, National Science Foundation, USA
Ad hoc reviewer: National Institute for Cell Biology Microtubule Alliance Committee, FRED mentor
Ad hoc reviewer:

Mentor, American Society for Cell Biology Minorities Affairs Committee, FRED mentor
Mentor, American Society for Cell Biology Minorities Affairs Committee, FRED mentor

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

We have identified three critical mechanisms that control TGF-β activation of HSCs and amenable to inhibition by small molecule. 1) We found that vasodilator-stimulated phosphoprotein (VASP) promotes activation of hepatic stellate cells by regulating Rab11-dependent plasma membrane targeting of transforming growth factor beta receptors. 2) PDGF receptor alpha (PDGFRα) promotes HSC activation via regulating TGF-β receptors. HSCs express both PDGFRα and PDGFRβ receptors. PDGFRα but not PDGFRβ, however, is required for TGF-β-mediated activation of HSCs. PDGFRα forms a protein complex with TGF-β receptors, which is required for internalization of TGF-β receptors and TGF-β downstream signaling. PDGFRα of HSCs promotes colorectal cancer cell proliferation and migration in vitro, and it is upregulated when cancer cells invade the liver in a liver metastasis mouse model and colorectal cancer patients. Thus, PDGFRα can cross-talk with TGF-β receptors to promote activation of HSCs. 3) One ongoing study is focused on the role of E1A-binding protein p300 in HSC activation; p300 presents another important target to inhibit HSC activation and the prometastatic liver microenvironment.

publications (7/1/2014 – 6/30/2015)


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

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

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

Dr. Bing Li

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

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

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

Dr. Bing Li
The Hormel Institute
“Today’s Research, Tomorrow’s Cures.”

Primary interests of our research section are to understand the molecular mechanisms and roles of aberrant epigenetics and protein kinase activity in cancer pathogenesis. We also work to translate the discoveries from bench to bedside by means of characterizing novel therapeutic reagents and developing innovative vehicles to efficiently and specifically deliver the drugs to the disease sites. In our laboratory, studies have included the cause of DNA hypermethylation and abnormal protein kinase activity, the mechanism of KIT and DNMT overexpression and leukemia, the dissolution of molecular basis underlying the anti-cancer actions of bioactive compounds and the development of innovative nanoparticulates for drug delivery.

Interplay of epigenome and kinase activity determines cancer cell fate DNA methylation occurs at the 5position 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 DNMTs are drug-resistant to 5-aza-deoxycytidine and modulate drug resistance through Sp1/DNMT1 network (Miller & Miller 2009). Synergistically, DNMT1 and KIT act as positive feedback loops in cancer cells. Functionally, KIT and DNMT1 promote colony-forming ability and enhance wound healing of leukemia cells. Theoretically, our findings shed light on the molecular biology of drug resistance which provides alternative rational in clinics for overcoming drug resistance by kinase inactivation or vice versa and identify an innovative opportunity for early therapeutic intervention against the emergence of drug-resistance.

Mechanistic links between obesity and leukemia Cancer is the representative systemic lesions taking over the first place of lethal diseases throughout the world. Obesity is a “disease” with abnormal body fat accumulation. The World Health Organization estimates that approximately one quarter of population worldwide are obese. Emerging data indicate that obesity is a major risk factor for human cancer. Numerous plant extracts have been tested in vitro and in vivo with huge therapeutic potentials. We have demonstrated that certain types of bioactive compounds [i.e., thymoquinone (TQ), echinomycin or emetine] suppress the expression of DNMT1, DNMT3a and DNMT3b resulting in DNA hypomethylation. Functionally, these compounds block cancer cell proliferation in cell lines, patient primary cells, and metastatic growth in vivo. While the underlying molecular mechanisms remain elusive, these findings suggest that crosstalk between the misregulated KIT signaling and DNA hypomethylation regulates cancer cell fate.

Due to the essential roles of aberrant DNA methylation in cancers, DNA hypomethylating agents have been in clinical use for decades. While some positive response has been achieved, the majority of leukemia patients relapse and eventually die of their disease, arguing for the new type of DNMT inhibitors with different structure and distinct mechanisms.

Clinical trials for overcoming decitabine resistance by kinase inactivation or vice versa and identify an innovative opportunity for early therapeutic intervention against the emergence of drug-resistance.

Not pictured: Lijun Wang

(Left to right) Liping Dou, Shengcai Wei, Shujun Liu, Fei Yan, Jiuxia Pang

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

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

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

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

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

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

Due to the essential roles of aberrant DNA methylation in cancers, DNA hypomethylating agents have been in clinical use for decades. While some positive response has been achieved, the majority of leukemia patients relapse and eventually die of their disease, arguing for the new type of DNMT inhibitors with different structure and distinct mechanisms. Due to their anti-cancer action and lower toxicity to normal cells, numerous plant extracts have been tested in vitro and in vivo with huge therapeutic potentials. We have demonstrated that certain types of bioactive compounds [i.e., thymoquinone (TQ), echinomycin or emetine] suppress the expression of DNMT1, DNMT3a and DNMT3b resulting in DNA hypomethylation. Functionally, these compounds block cancer cell proliferation in cell lines, patient primary cells, and metastatic growth in vivo. While the underlying molecular mechanisms remain elusive, these findings suggest that crosstalk between the misregulated KIT signaling and DNA hypomethylation regulates cancer cell fate. We observed that higher body mass index (BMI) associates with shorter overall survival in leukemia patients.

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 mice. We also evidenced the synergistic effects of combined liposomal bortezomib with nano-miR29b on leukemia cell growth in mice.

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

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

List of Published Work in MyBibliography:

Developing multifunctional drug and gene delivery nanoparticles for cancer therapy
Human non-melanoma skin cancers (NMSCs) occur more frequently than any other malignancy, and approximately 1 million new cases are diagnosed in the United States annually, with a heavy burden on society. An estimated one-third to one-half of all human cancers originate in the skin, and skin cancers exceed all others combined. In the United States, the lifetime risk of skin cancer is 1 in 5. Solar ultraviolet radiation (UV) is the major known cause of NMSCs and is directly relevant to the etiology as demonstrated by epidemiological evidence and the tight correlation between NMSC in humans and UV-induced skin carcinogenesis in murine models.

These cancers progress through an orderly sequence in which genetic, biochemical, and cellular abnormalities accumulate in target cells over time. Mild alterations initially seen within keratinocytes only can be identified histologically. Increased cellular atypia occurs with further sun damage, and then the development of hyperkeratotic, pre-malignant actinic keratoses. Of these, 1 to 10 percent will progress to squamous cell carcinomas (SCCs). Given that avoiding sunlight exposure is more easily said than done, the Morris laboratory is focusing on two specific projects.

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

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

In summary, research in the Morris laboratory continues to highlight the role of hair follicle stem cells in the pathogenesis of non-melanoma skin cancer, and has documented an unexpected contribution of bone marrow-derived cells. Going forward, we will probe the interactions between epidermal stem cells and bone marrow-derived cells as tumor-initiating and -propagating cells.
The Robinson laboratory primarily is interested in the molecular mechanisms by which oncogenic signaling regulates tumorigenesis, with the ultimate goal of developing and improving existing therapeutic approaches to eliminate cancer. Our lab employs two experienced, full-time postdoctoral fellows Basak Celtikci, M.D., Ph.D.; and Hana Yang, Ph.D. This summer we also were joined by Celeste Underriner, an experienced, full-time postdoctoral fellow, Basak Celtikci, M.D. Ph.D.; and Hana Yang, Ph.D. This summer we also were joined by Celeste Underriner, an experienced, full-time postdoctoral fellow.

\section*{Anas of investigation}

\subsection*{Colon Cancer}

Our work on colon cancer is funded by a National Institutes of Health (NIH) grant. Colonocellular carcinoma (CRC) is one of the most common cancers worldwide and – after lung and prostate cancer – is the leading cause of cancer death in the United States, with 132,730 new cases and 49,360 deaths anticipated in 2015. About 75 percent of these cases are sporadic, with no obvious evidence of an inherited disorder. The remaining 25 percent of patients have a family history of CRC that suggests a hereditary contribution; common among family members; or combination of both.

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

The study of FAP has led to advances in the understanding of the genetics of colon cancer and human malignancy. Precise elucidation of steps in FAP tumorigenesis, however, remains elusive. Both human and mouse polyps develop with additional genetic alterations other than loss (inactivation of the normal copy of APC). APC loss and mice polyps can be ameliorated greatly by COX-2 inhibition or with anti-inflammatory drugs. Diet, pregnancy, and exercise also might affect polyp numbers and the incidence of sporadic cancer. Our preliminary data has demonstrated that APC loss is insufficient for nuclear accumulation of b-catenin in intestinal epithelial cells. Additional growth signals or mutations also are required for nuclear accumulation of b-catenin and intestinal polyposis. Given that mouse models of FAP develop a multitude of intestinal polyps with additional genetic alterations, these additional signals are likely to arise from adjacent stromal cells. We currently are validating the role of key growth factors HGF and EGF while examining the role of IL17 in colorectal tumorigenesis by assessing if they can promote the nuclear accumulation of b-catenin. Aberrant-stromal signaling following loss or haploinsufficiency of LKB1 or SMAD4 is known to drive polyps in Peutz-Jeghers syndrome and juvenile polyposis syndrome. APC loss of heterozygosity (LOH) is detected in FAP polyposis epithelium, and due to FAP not having a prominent stromal compartment, unlike the other syndromes, a proper assessment of stromal LOH was never attempted. If we can show that stromal signals play a driving role in tumorigenesis following pre-emitting LOH of APC, it should be possible to develop targeted therapeutics to block this signaling.

“"Our studies will contribute to the development of novel therapies and improve the outcome for patients with melanoma."”

Dr. James Robinson

Melanoma

Melanoma incidence is increasing at a greater rate than any other cancer. In 2015, it is estimated that 75,800 Americans will be diagnosed with melanoma and about 9,940 will die of the disease. Melanoma typically can be cured through surgery if detected early; however, the five-year survival rate for patients with metastatic disease is less than 15 percent. The MAPK signaling pathway (RAS>RAF>MEK>ERK) is constitutively activated in more than 85 percent of malignant melanomas. Recent advances in melanoma therapy have involved combinations of drugs that target this pathway. Vemurafenib treatment increases median survival by 6 months, but only 32 percent of patients whose melanomas carry the BRAFV600E mutation. Although the initial response to BRAFV600E inhibition can be dramatic – sometimes causing complete tumor regression – melanomas eventually become resistant and reoccur. Combining MEK and BRAFV600E inhibition improves the response but the majority of patients still eventually experience disease progression (Figure 1). The U.S. Food & Drug Administration (FDA) recently approved humanized anti- PD-1 antibody (nivolumab) as a first line treatment for metastatic melanoma in patients with PD-L1 positivity (28 percent) as a first line treatment for metastatic melanoma in patients with PD-L1 positivity (28 percent) as a first line treatment for metastatic melanoma in patients with PD-L1 positivity (28 percent) as a first line treatment for metastatic melanoma in patients with PD-L1 positivity (28 percent) as a first line treatment for metastatic melanoma in patients with PD-L1 positivity.

Combining BRAF inhibition with PD-1 antibody improves the response rate and overall survival; however, most patients still succumb to the disease. Other approved treatments for melanoma include dabrafenib and trametinib (PTER-TIA-4). These agents, however, produce a response in only a small percentage of patients and their side effects are pronounced. The increased incidence of melanoma, combined with the poor prognosis of patients with advanced disease, makes it imperative that we increase our understanding of the underlying causes of resistance to targeted therapies to enable the development of better therapeutic strategies.

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

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

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

Figure 2. (full page image) Immunohistochemical analysis of a mouse melanoma. Demonstrating BRAFV600E expression and P-Erk activation while ki67 staining demonstrates tumor cells were actively dividing.
Our guiding principle is to support The Hormel Institute’s quest to improve the health of the world through scientific research. Our focused team of expert researchers aims every day to discover the mechanisms of cancer as well as better ways to prevent, detect and control this devastating disease through healthier paths.

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

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

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

Gail Dennison, Director of Public Relations & Development
Research Support Services has had another exciting year as we have continued to provide instrument maintenance along with computer, graphics, telecommunication, network, and Internet support for The Hormel Institute. Maintenance includes a wide variety of scientific instruments, from complex to simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our work load. As always, the network security needs keep us busy.

The Linux cluster CAL42 (Computational Analysis of Life-sciences 42) has been calculating away simulating protein molecules in our supercomputer room, part of The Hormel Institute’s International Center of Research Technology.

As building coordinator, I also have been extremely busy with The Hormel Institute’s 2014-16 Expansion on our east and west sides – an overall $31.5 million project. The east expansion of 20 research laboratories has been supported by The Hormel Foundation, Austin Port Authority and the State of Minnesota. Construction started in summer 2014 and has progressed significantly over the past year. In spring 2015, we broke ground on the Institute’s west side for our future Live Learning Center that will feature innovative, global-communication technology in a 250-seat lecture hall with an adjacent multipurpose room.

This has been another great year for our department, and next year is looking to be even more exciting once the expansion is completed.

Research Support Services
Craig M. Jones
Supervisor

Research Support Services’ 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.

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.

The Building Operations and Maintenance
Mark Severtson
Supervisor

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

Educational Outreach
Sure (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.

Emily Qin, 2015 SURE intern

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

Emily Qin, 2015 SURE intern

Sure (Summer Undergraduate Research Experience)
Progress in the fight against cancer took a giant step forward in 2014-15 as construction began on The Hormel Institute’s 2014-16 expansion aimed at accelerating answers to this devastating disease.

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

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

2014 - 16 Expansion

The Hormel Foundation committed up to $23 million for the 2014-16 expansion, including a $13.5 million match for the State of Minnesota’s bonding funds for The Hormel Institute’s east laboratory expansion. That commitment also includes $1.5 million from The Hormel Foundation for the Live Learning Center addition, which is a $4.5 million project. Fundraising is continuing for the remaining $900,000 for acquiring state-of-the-art, global-communications technology in the Live Learning Center.

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

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

Gary J. Ray, Chair, The Hormel Foundation

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

Gary J. Ray, Chair of The Hormel Foundation
West Expansion - Live Learning Center

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

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

MAKE A GIFT TO SUPPORT THE EXPANSION

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

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

Please make your gift to “The Hormel Institute – Live Learning Center” and send it to:

The Hormel Institute
801 16th Ave. N.E.
Austin, MN 55912.

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

Mahlon & Karen Schneider
East Expansion

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

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

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

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

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

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

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

Jerry Anfinson, Treasurer of The Hormel Foundation
July 11, 2014
John DeGennaro, Ph.D.
Professor, Pharmacology and Toxicology
College of Pharmacy,
The University of Akron
“Aging: Learning-Related Factors and Informal Signaling Pathways as Targets for Cancer Prevention and Treatment”

July 11, 2014 - Broadcast
Reid Rigan, Ph.D.
Professor of Medicine
Stony Brook University
“Neural-Retrograde Anticancer Agents”

July 24, 2014
Sergio Goddline, Ph.D.
Associate Researcher, Department of Internal Medicine,
Mayo Clinic
“The Cholangiocyte Primary Cilium as a Tumor Suppressor Organ”

August 1, 2014
Marina Holz, Ph.D.
Assistant Professor
Department of Molecular Pharmacology
Albert Einstein College of Medicine
“Novel Redox-based Anticancer Agents”

August 1, 2014 - June 30, 2015
Max Wu, Ph.D. & M.D.
Professor of Pathology, Microbiology and Molecular Genetics
Department of Pathology and MCHC Cancer Center
The Ohio State University
“Preclinical validation of NRAS targeting in Melanoma”

August 5, 2014
Dan Dixon, Ph.D.
Director
ITDD (Institute for Therapeutics Discovery and Development)
University of Minnesota Medical School
“Reimagining the Natural Product Balanol as a Potential Therapeutic for Ataxia (SCA1)”

August 5, 2014
Ronald Lubet, Ph.D.
Division of Cancer Prevention
National Institutes of Health
“Calcining a double ended cancer: regulating both cell proliferation and cell death”

May 8, 2014
Vijay Shah, M.D.
Chief, Division of Gastroenterology and Hepatology
Mayo Clinic
“Mechanisms of Hepatorenal and Portal Hypertension: Tales from the Sinusoids”

May 14, 2014
Luke Hoppner, Ph.D.
Director
Biology and Molecular Biology Laboratory
Mayo Clinic
“CysCysteine Oxidative Stress Therapies: Small Molecules and Mammalian Models of Disease”

September 3, 2014
Zhenzheng Liu
Senior Investigator
Center for Cancer Research
National Cancer Institute
“mTOR signaling: an established and emerging target”

September 10-12, 2014
Bethany Katz, Ph.D.
Assistant Professor
Department of Molecular Cardiology
Lerner Research Institute
“Integrating Cancer in Correlative Communication: Models and Approaches”

September 19, 2014
Michael Karin, Ph.D.
Professor of Pharmacology
University of California at San Diego
“Tumor Heterogeneity: An Active Process”

October 21, 2014
Kevin Vaughan, Ph.D.
Associate Professor of Biological Sciences
Harvard Medical School
“Causes and consequences of microRNA dysregulation in cancer”

February 2, 2015
Michael Welches, Ph.D.
Director, Clinical and Public Discovery
JDIID (Institute for Therapeutics Discovery and Development)
Research Associate Professor, Department of Medicinal Chemistry
College of Pharmacy
University of Minnesota
“Reengineering the Natural Product Balance as a Potential Therapeutic for ATHIA (SCA1)”

February 28, 2015
Amy Sandmayer, Ph.D.
Feinberg Postdoctoral Fellow
National Institute of Diabetes and Digestive and Kidney Diseases
“Dynamics dynamics revealed by cryo-electron microscopy”

June 2, 2015
Pengda Liu, Ph.D.
Pathology Instructor
Beth Israel Deaconess Medical Center
Harvard Medical School
“Dissecting the regulatory mechanisms of the eNOS/cGMP pathway in transformation”

June 3, 2015
Brij Singh, Ph.D.
Professor and Interim Associate Dean for Research
National Institute of Occupational Environmental Health Sciences
“Targering Chronic Nonspecific Rheumatoid Polyarthritis Stem Cell Fate Determinants and Tumor Progression”

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

June 2014 - 2015
Beth Israel Deaconess Medical Center
Robert J. Lee, Ph.D.
Professor of Pharmaceutics
Division of Pharmaceutics, College of Pharmacy
University of Colorado
“Targeted Nanoparticles for Oligonucleotide Therapeutic Delivery”

The Hormel Institute Seminars
July 1, 2014 - June 30, 2015

“The Cholangiocyte Primary Cilium as a Tumor Suppressor Organ”

“Novel Redox-based Anticancer Agents”

“Calcining a double ended cancer: regulating both cell proliferation and cell death”

“Mechanisms of Hepatorenal and Portal Hypertension: Tales from the Sinusoids”

“CysCysteine Oxidative Stress Therapies: Small Molecules and Mammalian Models of Disease”

“Causes and consequences of microRNA dysregulation in cancer”

“Reengineering the Natural Product Balance as a Potential Therapeutic for ATHIA (SCA1)”

“Dynamics dynamics revealed by cryo-electron microscopy”

“Dissecting the regulatory mechanisms of the eNOS/cGMP pathway in transformation”

July 1, 2014
John DeGennaro, Ph.D.
Professor, Pharmacology and Toxicology
College of Pharmacy,
The University of Akron
“Aging: Learning-Related Factors and Informal Signaling Pathways as Targets for Cancer Prevention and Treatment”

July 11, 2014 - Broadcast
Reid Rigan, Ph.D.
Professor of Medicine
Stony Brook University
“Neural-Retrograde Anticancer Agents”

July 24, 2014
Sergio Goddline, Ph.D.
Associate Researcher, Department of Internal Medicine,
Mayo Clinic
“The Cholangiocyte Primary Cilium as a Tumor Suppressor Organ”

August 1, 2014
Marina Holz, Ph.D.
Assistant Professor
Department of Molecular Pharmacology
Albert Einstein College of Medicine
“Novel Redox-based Anticancer Agents”

August 1, 2014 - June 30, 2015
Max Wu, Ph.D. & M.D.
Professor of Pathology, Microbiology and Molecular Genetics
Department of Pathology and MCHC Cancer Center
The Ohio State University
“Preclinical validation of NRAS targeting in Melanoma”

August 5, 2014
Ronald Lubet, Ph.D.
Division of Cancer Prevention
National Institutes of Health
“Calcining a double ended cancer: regulating both cell proliferation and cell death”

May 8, 2014
Vijay Shah, M.D.
Chief, Division of Gastroenterology and Hepatology
Mayo Clinic
“Mechanisms of Hepatorenal and Portal Hypertension: Tales from the Sinusoids”

May 14, 2014
Luke Hoppner, Ph.D.
Director
Biology and Molecular Biology Laboratory
Mayo Clinic
“CysCysteine Oxidative Stress Therapies: Small Molecules and Mammalian Models of Disease”

September 3, 2014
Zhenzheng Liu
Senior Investigator
Center for Cancer Research
National Cancer Institute
“mTOR signaling: an established and emerging target”

September 10-12, 2014
Bethany Katz, Ph.D.
Assistant Professor
Department of Molecular Cardiology
Lerner Research Institute
“Integrating Cancer in Correlative Communication: Models and Approaches”

September 19, 2014
Michael Karin, Ph.D.
Professor of Pharmacology
University of California at San Diego
“Tumor Heterogeneity: An Active Process”

October 21, 2014
Kevin Vaughan, Ph.D.
Associate Professor of Biological Sciences
Harvard Medical School
“Causes and consequences of microRNA dysregulation in cancer”

February 2, 2015
Michael Welches, Ph.D.
Director, Clinical and Public Discovery
JDIID (Institute for Therapeutics Discovery and Development)
Research Associate Professor, Department of Medicinal Chemistry
College of Pharmacy
University of Minnesota
“Reengineering the Natural Product Balance as a Potential Therapeutic for ATHIA (SCA1)”

February 28, 2015
Amy Sandmayer, Ph.D.
Feinberg Postdoctoral Fellow
National Institute of Diabetes and Digestive and Kidney Diseases
“Dynamics dynamics revealed by cryo-electron microscopy”

June 2, 2015
Pengda Liu, Ph.D.
Pathology Instructor
Beth Israel Deaconess Medical Center
Harvard Medical School
“Dissecting the regulatory mechanisms of the eNOS/cGMP pathway in transformation”

June 3, 2015
Brij Singh, Ph.D.
Professor and Interim Associate Dean for Research
National Institute of Occupational Environmental Health Sciences
“Targering Chronic Nonspecific Rheumatoid Polyarthritis Stem Cell Fate Determinants and Tumor Progression”

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

The Hormel Institute Seminars
July 1, 2014 - June 30, 2015

“The Cholangiocyte Primary Cilium as a Tumor Suppressor Organ”

“Novel Redox-based Anticancer Agents”

“Calcining a double ended cancer: regulating both cell proliferation and cell death”

“Mechanisms of Hepatorenal and Portal Hypertension: Tales from the Sinusoids”

“CysCysteine Oxidative Stress Therapies: Small Molecules and Mammalian Models of Disease”

“Causes and consequences of microRNA dysregulation in cancer”

“Reengineering the Natural Product Balance as a Potential Therapeutic for ATHIA (SCA1)”

“Dynamics dynamics revealed by cryo-electron microscopy”

“Dissecting the regulatory mechanisms of the eNOS/cGMP pathway in transformation”
### National Institutes of Health

#### National Cancer Institute
- Chemoprevention of Skin Cancer (Z. Dong) 92,942
- Prevention of Metastasis through Use of Metformin in Comparison to Calorie Restriction (M. Clary) 147,580
- Gene of Function Mapped to 5p (Thyroid Oncogene-driven Breast Tumorigenesis) (Y. Dong) 207,376
- Targeting Abnormal Epigenetics by Nanomedicine (S. Liu) 182,814
- Molecular mechanisms and targets of drug compounds in Colon Cancer (Z. Dong) 81,670
- Developing NovelDirectory Nanoparticles Inhibitors to Prevent Skin Cancer (Z. Dong) 257,032
- Prevention of Breast Cancer by Next-generation Selenium (Y. Dong) 34,351
- Modulation of AXIN Induction by Targeting Cap-dependent Translation in Cancer (D. Yang) 50,579
- Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver (N. Kang) 215,229
- The Role of A-VASP in Breast Cancer Development (S. Li) 66,225
- Prevention of Breast Cancer by Epithelial Fatiguing Acid Breaking Protein (S. Li) 54,535
- The Role of Stressed APO in Hypothalamic Growth (N. Zhang) 109,655
- Primacy Cilia and Malignant Transformation (S. Gradilone) 72,664

#### National Institute of Arthritis and Musculoskeletal and Skin Diseases
- Identification of a Keratinocyte Stem Cell Regulatory Gene (R. Morris) 260,552

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

### Other Resources
- The Hormel Foundation 4,371,000
- University of Minnesota 440,000
- Indirect Cost Return 1,179,721
- Fundraising/Development 2,138,985
- Other 660,080

**Total** $11,124,825

---

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

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