MESSAGE FROM THE EXECUTIVE DIRECTOR

Today, The Hormel Institute, University of Minnesota is a prominent cancer and chronic disease research center and high-performing part of the Masonic Cancer Center. After two major expansions in 11 years, The Hormel Institute is home to some of the world’s expert cancer researchers, a stunning design for our cancer center, and labs filled with state of the art technologies. We are focused on accelerating answers to cancer and other chronic diseases so people can live longer, healthier lives. Today, The Hormel Institute is currently comprised of 140 faculty researchers, and staff. We now have 19 research sections with plans to continue to fill the Institute’s labs with expert scientists to further our mission. In fact, two more research sections will be added in the late fall of 2019. After joining The Hormel Institute in 1999, I have had a great and incredible journey with The Hormel Institute faculty and staff to help build The Hormel Institute, University of Minnesota, to where we are today. Strengthened by leadership and support from the University of Minnesota, The Hormel Foundation, and our generous community, we are fully committed to enhancing and maintaining our quest for continued success through discoveries leading to cancer prevention and healthier controls. I’m honored to serve as Interim Executive Director and I thank you on behalf of all of The Hormel Institute, UMN for your continued support.

Sincerely,

Ann M. Bode, Ph.D.
Interim Executive Director

MISSION STATEMENT

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.
Summary

The Alam lab uses a combination of biochemical and structural (Cryo-EM and X-ray crystallography) techniques to primarily study macromolecules and macromolecular complexes involved in membrane transport, homeostasis, and biogenesis, with a particular focus on pinpointing lipid/protein interactions in context of membrane protein function. Maintenance of membrane bilayer integrity and tight control over material transfer across cellular and organellar membranes is central to proper physiological functioning. Dysfunction of these systems lies at the heart of several devastating, often fatal pathologies ranging from rare inherited diseases such as Zellweger’s syndrome and adrenoleukodystrophy (both stemming from peroxisomal dysfunction) to a range of neurodegenerative disorders, diabetes, and cancer.

The Hormel Institute ranks amongst a handful of elite institutions housing a Titan Krios microscope combined with a direct electron detector, a setup designed to obtain near-atomic resolution (routinely achieving better than 0.5 nanometer resolution). This allows for accurate visualization of the molecular details underlying the functioning of macromolecules and has revolutionized structural biology and allowed for targeting of complex biological problems previously considered off-limits to high resolution visualization. Such insight is invaluable in obtaining molecular details of membrane protein interactions with drugs, transport substrates, and inhibitors and can aid in the design of novel therapeutics targeting diseases stemming from membrane protein dysfunction.

Primary Research Areas:

1) Membrane transport processes
2) Peroxisome biogenesis and homeostasis
3) Lipid/protein interactions
4) Lipid and fatty acid metabolism

Research Specialties:

1) Membrane protein biochemistry
2) Cryo electron microscopy
3) X-ray crystallography

Structural Biology of Membrane Transport
Amer Alam, Ph.D.
SECTION LEADER / ASSISTANT PROFESSOR

FROM LEFT TO RIGHT: Mehedi Hasan, Amer Alam, James Thompson

npj PRECISION ONCOLOGY

- Springer Nature launched the journal “npj Precision Oncology” in partnership with The Hormel Institute, University of Minnesota in Austin, Minnesota, United States.
- npj Precision Oncology is a new open access, international, peer-reviewed journal that publishes cutting edge scientific research in all aspects of precision oncology from basic science to translational applications to clinical medicine.
- The journal defines precision oncology as cancer diagnosis, prevention, and/or treatment tailored specifically to the individual patient based on their genetic and/or molecular profile. npj Precision Oncology fills the need of a journal where both preclinical and early clinical studies can be published together to help support this rapidly expanding field.
- According to the Managing Editor at Nature Research, “npj Precision Oncology has been exceptionally successful.” We have passed the first landmark of 25 peer-reviewed published articles, which makes our journal eligible to apply for inclusion in PUBMED, one of the first steps required to obtain an IMPACT FACTOR. We are also looking for 1-2 additional Associate Editors to bring on board.
- Featured topics include cancer development and prevention, therapies that target specific cellular pathways, cancer metabolism and genetic risk factors.
- In addition to publishing original basic science, translational and clinical research articles, npj Precision Oncology also publishes case reports, brief communications, commentaries, perspectives, and review articles.
- The journal also publishes a professionally written Editorial Lay Summary to accompany each research Article, which summarizes the key issues being addressed within the article aimed to keep readership at the vanguard of new discoveries in the field.
- Please visit us at: https://www.nature.com/npjprecisiononcology/
Summary

We currently use our bioengineered capsid-optimized adeno-associated virus (AAV) vectors to develop anti-cancer vaccine. Briefly, tumor specific antigen carried by these novel AAV vectors are injected into animal model of melanoma or prostate cancer using standard needle vaccination procedures. As a result, local antigen presenting cells (APC) upload with the AAV-delivered tumor antigen either directly or by a cross-presentation pathway activate both a cytotoxic CD8+ T-cells and a humoral response against the tumor. We showed that our designed AAV based vaccine has superior cytolytic capacity against encoded antigen. This vaccine prevents metastatic tumor spread, significantly delays tumor development and extend in vivo model survival. Therefore, the path forward that we are planning to implement in our future studies to completely eradicate tumor is multi-target vaccination in concert with other therapies that target tumor microenvironment and re-activate/support immune cells infiltrating tumor.

Our research has demonstrated that a strong antigen-specific immune response is developed after a single injection of AAV-based vaccine in vivo model. We attribute this to our novel capsid-optimized AAV based system, which has overcome many of the shortcomings of past viral cancer vaccine technologies: the precise modifications in the AAV capsid significantly increase transduction efficiency of the APCs and subsequent antigen presentation. In current studies we further optimized AAV expression cassettes by fusing antigen with MHC class I molecule trafficking signals. This modification significantly increased AAV mediated level of both antigen-specific CD8+ T and CD4+ T cells, enhanced the formation of effector memory (CD 62L-/CD127+) cells which ensure long-lasting anti-tumor immune response, as result, demonstrated superior Ag-specific killing capacity in vivo model. We also were able to track down dendritic cell (DC) carrying reporter gene such as GFP in draining lymph nodes after intramuscular injection and confirmed antigen expression by flow and microscopic analysis. More importantly, vaccination changes the immune landscape of the tumor by inducing massive invasion of immune cells, especially with CD8+ T cells and NK cells. Consequently, we showed that tumor-infiltrated lymphocytes displaying increased expression of PD-1 should sensitize tumor to aPD-1 therapy. Indeed, use AAV based vaccination in combination with aPD-1 treatment significantly delayed tumor development and extend in vivo model survival. Therefore, the path forward that we are planning to implement in our future studies to completely eradicate tumor is multi-target vaccination in concert with other therapies that target tumor microenvironment and re-activate/support immune cells infiltrating tumor.

Additionally, we plan to test our anti-cancer vaccination approach in companion dogs with spontaneous melanoma. Importantly, companion dogs are exposed to the same environmental factors, and are developing cancer with clinical pathology very similar to humans. This makes dogs the most adequate preclinical model to evaluate the efficacy of our anti-cancer vaccination. Testing of our vaccine on clinically relevant dog patients will not only help to translate the life of people’s best friends, but provide critical data ensuring progress into clinical application for humans is warranted.
by studying the structural features of sphingolipids and their physical basis for raft microdomain functionality. Early on, we investigated the in membranes, certain sphingolipids form 'raft' anchoring devices for select membranes in cells. (e.g. C2-domains) that act as targeting and membrane lipid-binding domains that shuttle sphingolipids between intracellular proteins including sphingolipid transfer proteins (GL TPs). Our findings revealed how GL TPs recognize and bind glycolipids from different glycolipids by X-ray diffraction. Our findings both in glycolipid-free form and complexed with different glycolipids. We performed the first cloning of GL TPs initially identified as glycolipid transfer proteins in cells. These sphingolipid transfer proteins were shuttling sphingolipid between membranes in mouse) as well as plants and fungi and developed thereby forming and maintaining 'raft' microdomains.

We also studied sphingolipid transfer proteins that help form and maintain raft microdomains by shuttling sphingolipids between membranes in cells. These sphingolipid transfer proteins were initially identified as glycolipid transfer proteins (GLTPs) because of their specificity for glycosphingolipids. We performed the first cloning of GLTPs from mouse (Rhoderick Brown). Our findings demonstrated the importance of lipid environment' when the content and structure of physical variations that occur within the 'raft environment' when the content and structure of sphingolipids and sterols change. This research revealed how GLTPs recognize and bind glycolipids to help form and maintain 'raft' microdomains by shuttling sphingolipid between membranes in cells.

Summary
Our research focuses on proteins that interact with membrane lipids known as sphingolipids. Such proteins include sphingolipid transfer proteins that shuttle sphingolipids between intracellular membranes and protein lipid-binding domains (e.g. C2-domains) that act as targeting and anchoring devices for select membranes in cells. These proteins include sphingolipid transfer proteins which have been shown to help form and maintain 'raft' microdomains that function as organizing regions for signaling kinases and target sites for certain viruses and bacteria. Early on, we investigated the physical basis for raft microdomain functionality by studying the structural features of sphingolipids that regulate their lateral and transbilayer interactions with other lipids in membranes. Our investigations relied on fluorescence spectroscopy, cryo-electron microscopy, and Langmuir surface tension balance approaches. The latter approach, carried out in collaboration with the H.L. Brooks lab (UMN-Hormel Institute), enabled measurement of model membrane lateral elasticity which led to development of ways to quantitatively assess physical variations that occur within the 'raft environment' when the content and structure of sphingolipids and sterols change. This research identified physical features central to the lateral organizing function of sphingolipid-enriched microdomains.

Current research projects:
1) Structural Characterization and Function of Sphingolipid Transfer Proteins
2) The Functional Role of the Phosphoinositide 3-kinase (PI3K) Pathway in C2 Domain-Containing Proteins
3) Regulation of Ceramide-1-Phosphate (C1P) Transfer Proteins
4) Regulation of Ceramide-1-Phosphate (C1P) Transfer Proteins

The C1P over-accumulation triggers cytoplasmic phospholipase A2 action to generate arachidonic acid and downstream pro-inflammatory eicosanoids. Recent studies have led to discovery of new GLTP superfamily members, ceramide-1-phosphate (C1P) transfer proteins (CPTPs). In Nature, we reported structural characterization of human CPTP (collaboration with D.J. Patel, MSKCC, J. Molotov, and R. D. Bagley, Michigan State University) and showed that CPTP depletion in human cells by RNAi leads to C1P over-accumulation in the trans-Golgi (collaboration with Charles Chaffant, Univ. South Florida). Our findings stimulated recent studies reported in Autophagy, showing that human CPTPs function as an endogenous regulator of autophagy and inflammation amelioration that drives interleukin release (IL1β and IL18).

Our studies of GLTP superfamily proteins will likely facilitate their development as nanodevices for targeted manipulation of cellular sphingolipid composition. Such strategies could help selectively destroy cancer cells and lead to new therapeutic approaches to treat other diseases. The exciting research progress emphasizes the need for continuing studies of GLTPs and related proteins which has been fueled by financial support from NIH National Institute of General Medical Sciences, Japan Society for Promotion of Science, and the Japan Society for the Promotion of Science. For more details regarding our research activities, expertise and scientific publications, please visit the following websites:
Summary
Our lab studies the molecular and metabolic aspects of cell programmed necrosis (necroptosis) in order to design targeted therapies and prevent recurrent disease. Cell programmed necrosis or necroptosis is a recently identified novel regulated cell death pathway. Cell death with necrotic morphology and features though to be a non-regulated and uncontrollable event associated with cell injury, inflammation or ischemia. However, recent studies now reveal that necrosis can occur in regulated manner. Necroptosis participates in pathogenies of diseases including neurodegeneration, ischemia and heart disorders, and viral infections; thus targeting necroptosis will prevent or mitigate undesirable cell death. On the other hand, drugs, inducing necroptotic cell death in tumors, can potentially overcome drug resistance in cancer cells due to elevated expression of anti-apoptotic proteins. Thus, elucidation of necroptosis/cell proliferation or necroptosis/apoptosis balance is essential to trigger cancer cell death or prevent pathological conditions such as ischemia or inflammation. The most studied kind of necroptosis is initiated by TNF-α while Caspases are inhibited using pan-Caspase inhibitor ZVAD-FMK, requires the kinase activity of Receptor-interacting proteins 1 and 3 (RIPK1 and RIPK3) followed by their downstream target MLKL.

Current research projects:
1) Novel combination therapy in high grade serous ovarian cancer: dual inhibition of ALDH1A and MEK1/2
2) Novel compounds that target Oxidative Phosphorylation as a preferable source of energy of ovarian cancer stem cells
3) Effect of exosomes on ovarian cancer cell, purification and characterization

Invited seminars:
1) A Novel Pan-ALDH1A Inhibitor Induces Necroptosis in Ovarian Cancer Stem-Like cells. September 21st, 2017. Mayo clinic, Ovarian cancer spore group

"We are trying to identify and characterize novel targeted therapies that target specifically Cancer Stem cells taking into consideration that tumor cells are heterogeneous.

Ilana Chefetz Menaker, Ph.D.
Summary

My research interests are focused on investigating the function of repetitive areas of the human genome. I have a special interest in centromere genomics. The centromere is the structural unit responsible for the correct segregation of chromosomes during cell division. Distillation of centromere function results in chromosome mis-segregation and instability, hallmarks of fibrosis, cancers, and teratocarcinoma. This suggests that cancer cells, including breast, ovarian, and teratocarcinoma, exhibit profound centromere instability. Interestingly, some of these cancers, including breast, ovarian, and teratocarcinoma, exhibit profound centromere instability. Interestingly, some of these cancers, including breast, ovarian, and teratocarcinoma, exhibit profound centromere instability. It is known that healthy cells undergo cell division through epigenetic factors HP1 and H3K9me3; factors that ensure the correct deposition of kinetochores towards juxtaposed centromere/pericentromere architecture, and therefore, chromosomal segregation. We predict increased occupancy of centromere marks on ectopic chromosomal arms with the establishment of neo-centromeres as the original centromere mutates and becomes inactive. We will expand these observations in vivo using nude mice, which are transplanted with cells with centromere defects.

Centromeres in Trisomy 21

We have found extraordinary evidence of centromere instability specifically in the centromere core and pericentromere of Chr 21 in individuals with trisomy 21 (Down syndrome) but not other chromosomal trisomies. We have found extraordinary evidence of centromere instability in Down syndrome (trisomy 21) patients. This research is supported by the Scleroderma Foundation. Scleroderma is a disease that affects the skin, muscles, and connective tissue. Some of these findings are shown in the journal Scleroderma.

Research Specialties:
1) Pathogenesis of Sclerodermal Fibrosis and Cancers
2) DNA instability and Repair of Centromeres
3) Deep sequencing of centromeres

Centromeres in Scleroderma

Last but not least, we have a special attention on the pathogenesis of centromere instability. In scleroderma patients with this disease produce antibodies directed to centromeres. These antibodies were fundamental for the discovery of human centromeres and kinetochores. Besides the novel finding of centromere instability in scleroderma, we have characterized other centromere alphoid sequences in healthy cells and how these sequences are reported in a recent manuscript accepted for publication in the journal Genome Research. These technologies will generate unprecedented findings. This research is supported by the Scleroderma Foundation.

Human Centromere Genomics

My research has been focused on investigating human endogenous retroviruses, and the role these elements play in the epigenetic interactions of chromatin factors – of centromere function results in chromosomal instability in cells with trisomy 21. We are creating centromere retroviruses resulted in selection of new mutant centromeres with centromere instability specifically in the centromere core and pericentromere of Chr 21 in individuals with trisomy 21 (Down syndrome) but not other chromosomal trisomies. We have found extraordinary evidence of centromere instability in Down syndrome (trisomy 21) patients. This research is supported by the Scleroderma Foundation. Scleroderma is a disease that affects the skin, muscles, and connective tissue. Some of these findings are shown in the journal Scleroderma.

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"DNA repair plays an active and critical role in cancer development and treatment. Robust and tightly regulated DNA repair systems protect our cells from cellular transformation. In many different cancer types DNA repair processes are highly dysregulated creating a unique opportunity for selective anticancer drugs without harming the normal cells. Our studies will reveal new mechanisms of tumor suppression and identify novel targets in personalized cancer therapy."

Wioletta Czaja

Summary

Nearly all forms of cancer contain significant levels of genomic instability (high frequency of mutations, chromosomal rearrangements), resulting from deficient or dysregulated DNA repair processes. The molecular events leading to genomic instability are not well understood. We investigate the fundamental mechanisms protecting genomic integrity, with a special focus on the epigenetic and chromatin-based regulation of DNA damage repair. We are also working on development of new approaches enabling direct detection, and chromosomal mapping of the accessed regions in damaged and modified DNA bases, with the goal of uncovering novel mechanisms involved in mutagenesis and carcinogenesis.

The long-term objective of our research is to understand how stability of the human genome is maintained and regulated in various cells and tissues, and to apply this new knowledge to promote advances in novel anti-cancer therapy and personalized medicine. We employ complementary approaches in biochemistry, cell and molecular biology, genetics and genomics using fungal model organisms (yeast-Saccharomyces cerevisiae) and human cell lines.

New tools in cancer risk identification and prevention: Development of new methodology ADA-SMRT enabling direct, genome-wide profiling of mutagenic adenine alkyltransferase (ADA) adducts. Alkyltransferase (ADA) adducts are cytotoxic and mutagenic DNA lesions that arise from exposure of cancer cells to numerous environmental carcinogens and cellular metabolites. Some of the most toxic alkyl DNA adducts are commonly used anti-cancer drugs. DNA modifications induced by alkylating agents play significant role in both the development and treatment of cancer.

Identification of new mechanisms of tumor suppression: Epigenetic (chromatin-based) mechanisms of DNA damage repair. DNA repair capacity varies considerably between individuals and between different tissues, highlighting involvement of genetic and epigenetic (chromatin-based) mechanisms in modulation of cellular toxicity to genotoxic agents. One of the major challenges in the DNA repair field is to understand how efficient DNA repair is accomplished in the context of highly compacted chromatin, which is inherently inhibitory to DNA repair processes. Our research in this area focuses on investigating the role of chromatin remodeling and chromatin remodeling factors in modulating the repair of the alkylated DNA damage via Base Excision Repair (BER). The Base Excision Repair (BER) is considered a fundamental tumor suppressor pathway in all cancer cells, and is an attractive target for novel anti-cancer drug discovery. However, unlike other DNA repair pathways, the chromatin-based regulation of BER has been substantially understudied. In human cells, robust and tightly regulated BER is essential for the efficient repair of alkyl DNA adducts and protection of cells from the accumulation of mutations and malignant transformation. Dysregulation of the BER pathway (BER imbalance) is thought to drive carcinogene- sis and contribute to chemoresistance. Previously, we identified a link between the essential SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeler and the BER of alkyl DNA adducts in yeast cells. Currently, we investigate the BER in human cancer cells deficient in the SWI/SNF. The human SWI/SNF remodeler is frequently mutated in 20% of cancers, raising the possibility that loss of SWI/SNF function might lead to impaired BER in SWI/SNF-deficient cancers.

These studies will elucidate new chromatin-based mechanisms that modulate the responses of the human cells to chemotherapy alkylating agents, and will provide new insights for improved therapy of SWI/SNF-deficient cancers.

Funding:

1) Role of chromatin remodeler LSH/HELLS in genome stability and cancer [Investigating new role of LSH/HELLS in repair of heterochromatin domains]
2) Chromatin-based regulation of Base Excision Repair (BER) [BER balance in cancer prevention and treatment]
3) Development of new methodology ADA-SMRT [Genome-wide profiling of the chemotherapy-induced DNA adducts]
Cancer is one of the leading causes of human death worldwide. By focusing on its molecular mechanisms, we continue to discover key molecular events that could significantly inhibit PDX tumor growth. We report that PRPK, a natural compound, is an inhibitor of Aurora A and B. Importantly, APIO-EE-9 significantly decreased the size of esophageal patient-derived xenograft tumors suggesting that APIO-EE-9 could be developed as a therapeutic agent against esophageal cancer. Osteosarcoma is the primary human malignant tumor affecting bone and prognosis is very poor. Aurora B is overexpressed in osteosarcoma cancerous tissue. We identified a novel compound, referred to as HOI-07, as a specific Aurora B kinase inhibitor. Results of a xenograft model study indicated that HOI-07 treatment suppressed the growth of osteosarcoma cell growth.

Third Row:

First Row: Tara Adams, Hanyong Chen, Hisae Yoshitomi, Thi-Thi My-Le Le, Zigang Dong, Eunmiri Roh, Qiushi Wang, Kanamata Reddy, Teri Johnson, Xinli Ma, Jian Li, Faisal Aziz, Yifei Xie, Seung Ho Shin, Tressie Kinney, Ke Yao, Abhijit Chakraborty, Humberto de Vitto

Second Row: Junsheng Zhu, Jinhua Wang, Souren Paul, Joohyun Ryu, Moeez Rathore, Xiaoyu Chang, Tianshun Zhang, Wei-Ya Ma, Raja Dey

Summary

Cancer is one of the leading causes of human death worldwide. By focusing on its molecular mechanisms, we continue to discover key molecular events in cancer development, as well as agents for cancer prevention and therapy.
Our research projects are well supported by The University of Minnesota, Hormel Foundation and National Cancer Institute of NIH (R21s and R01s). Our research activities to decipher how the eukaryotic innate immune response in tumorigenesis will be supported by the grants from The University of Minnesota, Hormel Foundation and National Cancer Institute of NIH (R21s and R01s).

Other professional activities:
Standing Member, National Cancer Institute Study Section, Reviewer for Scientific Journals

Summary
My research lab has been utilizing genetic engineering in vivo models to address whether and how the genetic changes identified in cancer patients contribute to tumor initiation, progression and metastasis in vivo; utilizing multiple approaches including genome editing technology (CRISPR-Cas9), X-ray crystallography and Cryo-EM to functionally and structurally understand how oncogenes are translated in tumorigenesis; and clinical practice aiming to identify the Achilles’ heel of cancers that can serve as a means to selectively and effectively kill cancer cells.

1. Discovering a gene-regulated metabolic target for currently incurable castration-resistant prostate cancer
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. Androgen deprivation therapy (ADT) by surgical or chemical castration remains the gold standard of care therapy for metastatic prostate cancer. Unfortunately, these prostate cancers invariably develop resistance to ADT and progress to a more aggressive castration-resistant prostate cancer (CRPC). Currently, no therapeutic options exist for CRPC patients who have developed resistance to the second generation of anti-androgen receptor (AR) signaling axis therapy. Clinically, approximately 30% of CRPC patients carrying both PTEN mutation and AR amplification while leaving normal cells untouched. “Our studies will reveal whether and how the genetic changes identified in cancer patients lead to tumorigenesis in vivo and identify effective strategies targeting cancerous cells while sparing normal cells untouched.” Yibin Deng

Figure 1. A novel therapeutic strategy for CRPC

Figure 2. Crystal structure of human eIF4A/eIF4G complex

Workshop effect with 2-deoxyglucose (2-DG, a hexokinase inhibitor) and H211-dependent autophagy with FDA-approved chloroquine (CQ) or less toxic quinoline derivative hydroxychloroquine (HCQ) efficiently kills CRPC dependent Cancers and remarkably extends host survival in CRPC in vivo models (Figure 1). Taken together, our recent findings strongly support that targeting H2-mediated Warburg effect as a selective and effective strategy for currently incurable CRPC.

2. Understanding oncogene mRNA translation in tumorigenesis
Dysregulated messenger RNA (mRNA) translation into oncogene protein plays a crucial role in tumorigenesis. mRNA translation regulation occurs at multiple steps of the translation process, but it is largely achieved during translation initiation, which is predominantly mediated by the eukaryotic translation initiation factor 4F (eIF4F) heterotrimeric complex composed of three subunits of eIF4E, eIF4A and eIF4G. Biochemical studies suggested that interaction of eIF4A and eIF4G plays a crucial role in initiating oncogene mRNA translation in cancer cells. We have been utilizing X-ray crystallography to successfully solve the complex structure of human eIF4A/eIF4G (Figure 2). Site-mutagenesis studies reveal the crucial residues contributing to the complex formation and tumorigenesis in vivo. Our studies thus provide a structure-based discovery of small-molecule compounds that disrupt the eIF4A-eIF4G interaction in cancer cells to selectively block oncogene protein synthesis and inhibit tumor development in vivo. Currently, we are combining X-ray crystallography, Cryo-electron microscopy (cryo-EM), and biological studies to decipher how the eukaryotic translation initiation complex involved in selective oncogene mRNA translation, which leads to tumorigenesis.

3. Dissecting the role of dysfunctional telomere-induced DDR-STING innate immune response in tumorigenesis
Telomeres are nucopolitropin caps that protect chromosomal ends from being recognized as adventitious damaged DNA and prevent chromosome end-to-end fusions. Dysfunctional telomeres or short telomeres are associated with telomere attrition (telomere shortening) or when components of the telomeric DNA binding proteins – termed “telomere complex” – are perturbed (telomere uncapping). Our laboratory has been engineering a novel breast and prostate cancer models harboring telomere uncapping, which in turn reduces DNA damage response signaling (DDR)-STING (TOLL/IL1R) innate immune pathway in vivo. We have been utilizing these novel breast/prostate cancer models to dissect the roles of imparting telomere dysfunction-driven tumorigenesis in vivo and stimulate the immune pathways to effectively kill human breast/prostate cancer cells.

FROM LEFT TO RIGHT: Fajie Liang, Hong Deng, Zhengjie Song, Hong Deng, Ping Li

Figure 1. A novel therapeutic strategy for CRPC

Figure 2. Crystal structure of human eIF4A/eIF4G complex
found that these antennae are lost in tumor cells. Primary cilia – that sense and receive signals from the extracellular environment – are multisensory organelles, similar to a cell’s primary cilium in tumor biology. Primary cilia play a role in cellular differentiation and have been implicated in the pathogenesis and progression of CCA. We proposed that by pharmacological inhibition of HDAC6, CCA can undergo ciliary disassembly by a mechanism dependent on HDAC6, which is a protein overexpressed in tumor cells and induces the resorption of cilia and the degradation of the ciliary components by autophagy. Thus, our hypothesis is that by pharmacological inhibition of HDAC6 and/or autophagy, it is possible to restore the expression of cilia on tumor cells and transform them back to a less aggressive and more normal phenotype.

**Project 2**

Primary cilia that can detect several kinds of environmental signals and then transmit this information into the cell. Here, we tested the hypothesis that the chemosensory function of primary cilium acts as a mechanism for tumor suppression. We found that in the presence of extracellular nucleotides, ciliary-dependent chemoreception of the nucleotides induced migration and invasion in normal cholangiocytes via a P2Y11 receptor and a LKB1-PEN2-AMP-dependent mechanism. In contrast, in normal, experimentally deciliated cholangiocytes and tumor cells, the nucleotides induced the opposite effects, i.e. increased migration and inhibition of invasion. As activation of LKB1 via a ciliary dependent mechanism was required for the nucleotide mediated inhibitory effects on migration and invasion, we attempted to activate directly LKB1, independent of ciliary expression, using the compound hesperidin methyl chalcone (HMC). We found that HMC induced activation of LKB1 in both cholangiocytes and deciliated cells in vitro, resulting in the inhibition of migration and proliferation. Furthermore, using an in vivo CCA model, we found that HMC inhibited tumor growth. These findings highlight the importance of the chemosensory function of primary cilium for the control of migration and invasion, and suggest that by directly activating LKB1 and bypassing the need for primary cilium, it is possible to emulate this chemosensory function in cancer cells (Figure 2). These data warrant further studies for evaluating the possibility of using HMC as a novel therapy for CCA.

**3 - New therapies and translational studies**

In collaboration with Dr. George Asal, we aimed to develop a safe and effective vector based on a human virus, the adenovirus-associated virus (AAV), for genetic manipulation of bile duct cells. Our proposal is designed to develop vectors for the manipulation of the viral capsid structures and expression cassettes for specifically targeting CCA tumor cells. Our overall objective is to develop new gene therapy tools for specifically targeting CCA tumor cells and manipulate the expression of important target genes in these cells that were recently identified by us and could help devise novel therapeutics. This virus causes no known disease and currently is being used in a number of clinical trials for therapeutic intervention of a wide variety of human diseases. The study of the translational mechanism by directly activating LKB1 and bypassing the need for primary cilium, it is possible to emulate this chemosensory function in cancer cells.

**4 - Other studies in the Section in collaboration with Dr. Cheuk Loi**

Our research is uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation of both malignant and non-malignant cells, and provide the foundation for anti-cancer therapies based on the rescue of primary cilium functions, i.e. Cilothrapy.

Sergio Gradilone
"We focus on the role of mitotic mechanisms in the generation of human disease." Edward H. Hinchcliffe

Chromosome missegregation:
Inadvertent chromosome missegregation in anaphase generates aneuploidy, but the progression of these cells is normally blocked, because chromosome missegregation also triggers a p53-dependent fail-safe that monitors the relative segregation of chromosomes during mitosis. By understanding the molecular mechanisms underlying this trigger, we will provide insight into new methods for tumorigenesis. Specifically, we study how changes in mitosis H3.3 Ser31 is phosphorylated of the histone variant H3.3 at Ser31. During normal mitosis H3.3 Ser31 is phosphorylated along individual chromosomes initiates the generation of human disease. This work provides insight into how aneuploidy is monitored and suppressed. Further, driver mutations in H3.3 (flanking Ser31) and null mutations in ATRX are both found in pediatric glioblastomas. We will explore the pathway that triggers p53 activation in response to a single chromosome missegregation event. pS31 is required for ATRX recruitment to lagging chromosomes. ATRX – a member of the SWI/SNF family of chromatin binding protein – is known to load histone H3.3 into nucleosomes. Unlike H3.3 S31 phosphorylation during anaphase, the association of ATRX with isolated chromosomes is transient; by nuclear envelope reformation ATRX is absent from the resulting micronucleus. Finally, we demonstrate that post-anaphase H3.3 pS31 and ATRX are required to trigger p53 stabilization in the subsequent G1. Microinjection of monoclonal antibodies against either pS31 or ATRX into anaphase cells containing lagging chromosomes blocks p53 accumulation in G1 nuclei. Here we show that p53 cell-cycle arrest – triggered by chromosome missegregation – is mediated via a novel signaling mechanism dependent upon H3.3 S31 phosphorylation and ATRX recruitment to lagging chromosomes. This work provides insight into how aneuploidy is monitored and suppressed. Further, driver mutations in H3.3 (flanking Ser31) and null mutations in ATRX are both found in pediatric glioblastomas, suggesting that disrupting the aneuploidy fail-safe contributes to neoplastic progression.

Our work seeks to understand the cellular basis for tumorigenesis. We study the process where cells separate duplicated chromosomes into two daughter cells – called cell division or mitosis. Chromosomes are not known. We found that when centrosomes were removed from living vertebrate cells early in their cell cycle, an amphiaster (“a star on both sides”) – that is a functional amphiasteral spindle – rapidly forms, recruiting to the interphase aMTOC, and prior to NEB, a functional amphiasteral spindle forms. Cytoplasmic dynein, dynactin, and pericentrin are all recruited to the interphase aMTOC, and the activity of kinesin-5 is needed for amphiaster formation. Mitosis is proceeded on time and these karyoplasts divided in two. However, ~35% of aMTOCs failed to split/separate before NEB, and these entered mitosis with pericentric monastral spindles. The chromatin mediated Ran-GTP pathway could not restore bipolarity to monastral spindles, and these cells exited mitosis as single daughters. Our data reveal the novel finding that MTOC separation and amphiaster formation does not absolutely require the centrosome, but its absence, the fidelity of bipolar spindle assembly is highly compromised.
Our research team is focused on discovering the molecular basis for new and improved lung cancer therapies.

Luke Hoeppner

“Discovering new ways to combat lung cancer is a primary focus of our “Cancer Biology” section. Our research program integrates molecular, genetic, and biochemical approaches to analyze important contributions to multiple research projects. Together, our group has made excellent progress on numerous research directions this past year. Highlights include discovering that DARPP-32 isoforms promote non-small cell lung cancer growth through IKKα-dependent NF-κB signaling. We observe a novel physical interaction between DARPP-32 and inhibitory estrogen receptor (IκR) that promotes NSCLC cell migration through non-canonical nuclear factor kappa-light-chain-enhancer of activated B cells 2 (NF-κB2) signaling. Bioinformatics analysis of 513 lung adenocarcinoma patients reveals elevated t-DARPP isoform expression is associated with poor overall survival. Hotspot identification of transcription 3 (STAT3) in lung adenocarcinoma tissues also shows that expression of STAT3 is elevated with increasing tumor (T) stage. Our data suggest that DARPP-32 isoforms serve as a negative prognostic marker associated with increasing stages of NSCLC and may represent a novel therapeutic target. We are now beginning to investigate the role of DARPP-32 isoforms in different subtypes of lung cancer, specifically EGFR mutant NSCLC and small lung cell cancer. A current area of focus is to understand how DARPP-32 and t-DARPP promote resistance to molecular targeted therapies.

2. DARPP drives small cell lung cancer growth and neuroendocrine tumor cell survival

Small cell lung cancer (SCLC) is the most aggressive form of lung cancer, and new molecular insights are necessary for prognostic and therapeutic advancements. We demonstrate in orthotopic models that DARPP-32 and its splice variant, DARPP-32, promote SCLC growth through increased proliferation, AKT/Erk-mediated survival and anti-apoptotic signaling. DARPP-32 and t-DARPP proteins are overexpressed in human SCLC cells. Taken together, we hypothesize that DARPP-32 isoforms serve as a negative prognostic indicator for SCLC and serve as a potential target for the development of new therapies.

3. VEGF activates STAT3 to promote vascular permeability

Vascular endothelial growth factor (VEGF) induces vascular permeability in ischemic diseases and cancer, leading to many pathophysiological consequences. For example, in heart attacks, stroke, expression of VEGF leads to vascular permeability, edema, and tissue damage. However, following cardiovascular or cerebrovascular infarction, VEGF promotes repair of ischemic tissue. Consequently, understanding the molecular mechanisms of VEGF-induced vascular permeability will facilitate the development of promising therapies that achieve the delicate balance of inhibiting vascular permeability while preserving ischemic tissue repair mediated by VEGF signaling. VEGF signals through its receptors, VEGFR-1 to 3, to activate signal transducer and activator of transcription (STAT)3. Phosphorylation of STAT3 promotes its nuclear translocation, enabling STAT3 to promote vascular permeability and angiogenesis in ischemic target tissues. We show in human umbilical vein endothelial cells (HUVECs) that VEGF activates STAT3 and promotes VEGF-induced vascular permeability by utilizing a VEGF-inducible baicalin model in conjugation with STAT3 knockdown and baicalin-generated stable gene- and CAR genome editing. We also confirm VEGF promotes VEGF-inhibited vascular permeability in a mammalian model system. Taken together, our results suggest STAT3 plays a critical role in VEGF-induced vascular permeability, which may translate to improved therapies for patients affected by heart disease, stroke, or cancer.
Summary

Tumor-derived factor TGFβ is the most potent cytokine that induces HSC activation. So we focus on (1) intracellular trafficking of TGFβ receptors in HSCs, (2) mechanisms by which SMAD2/3 enter the nucleus in response to TGFβ stimulation, and (3) epigenetic mechanisms and regulation of HSC activation. In addition, we also investigate the role of extracellular matrix-mediated forces in HSC activation.

In the annual report of 2018, we described that knockdown of the transcription coactivator p300 or p300 inhibitor C646 inhibited TGFβ1-stimulated nuclear accumulation of SMAD2/3 and TAZ. Additionally, deleting the nuclear localization signal of p300 (P54KPRK) abolished SMAD2/3 and TAZ nuclear transport induced by TGFβ1. As interrogated with additional mechanistic studies in this year, we further demonstrated that p300 in fact played both non-canonical and canonical roles for HSC activation by functioning as a scaffold for SMAD2/3 and TAZ and by epigenetically promoting gene transcription via histone acetylation and chromatin remodeling. Thus, p300 in fact played both non-canonical and canonical roles for HSC activation by functioning as a cytoplasm-to-nucleus shuttle for SMAD2/3 and TAZ and by epigenetically promoting gene transcription via histone acetylation and chromatin remodeling. Thus, p300 is an attractive target for inhibiting HSC activation and the prometastatic liver microenvironment. These data have been published by a high-impact journal Hepatology (Wang Y. et al. Hepatology, 2019).

In addition, we tested the hypothesis that focal adhesion kinase (FAK) may regulate intracellular trafficking of TGFβ receptor II (TβRII) thereby promoting HSC activation. FAKY397F mutant and FAK inhibitor PF-573,228 were used to test this hypothesis. TβRII protein level was quantified by immunoblotting and HSC differentiation into myofibroblasts was assessed by expression of HSC activation markers, alpha-smooth muscle actin, fibronectin, or CTGF. We found that targeting the kinase activity of FAK indeed suppressed TβRII protein level, TβRII induced SMAD phosphorylation, and myofibroblastic activation of HSCs. At the molecular and cellular level, active FAK (phosphorylated FAK at Y397) bound to TβRII and kept TβRII at the peripheral plasma membrane of HSCs, and it induced TβRII phosphorylation at tyrosine 336. In contrast, targeting FAK or mutating Y336 to F on TβRII led to lysosomal sorting and degradation of TβRII. Additionally, we identified by RNA sequencing that the transcripts of 764 TGFβ targets were influenced by FAK inhibition and that through FAK, TGFβ1 stimulated HSC to produce a panel of tumor-promoting factors, including extracellular matrix remodeling proteins, growth factors and cytokines. Functionally, targeting FAK inhibited the tumor promoting effects of HSCs in vivo and in a tumor implantation in vivo model. Thus, FAK regulates HSC activation by preventing TβRII to the plasma membrane and protecting TβRII from lysosome-mediated degradation. A manuscript about this project is currently under peer review.

"Cancer invasion of the liver induces activation of hepatic stellate cells (HSCs), which are liver resident cells, into myofibroblasts and the activated-HSC/myofibroblasts in turn promote cancer implantation and proliferation in the liver. The bidirectional interactions between cancer and HSCs thus represent a therapeutic target for liver metastasis. My research program, funded by NIH R01 grant, focuses on identification of the molecular and cellular mechanisms governing HSC activation, which may lead to novel targets to inhibit HSC/cancer interactions and liver metastasis."

Ningling Kang
Summary

Our overall goal is to provide a structural basis of the initiation, elongation and termination of transcription and their regulations in bacteria. We shall study the formation of the transcription initiation complexes with various sigma factors, the transition from initiation to elongation and termination phases, the translocation of the RNA polymerase (RNAP) on template DNA, and the regulation of the RNAP by transcription factors at various stages of transcription. This objective will be achieved by determining the structures of the RNAP complexed with functionally associated proteins and appropriate DNA/RNA substrates captured at various steps in the processes, using cryo-electron microscopy and X-ray crystallography, as well as by appropriate biochemical experiments.

1. To elucidate the mechanisms of transcription initiation with alternative sigma factors and its regulation by activators

1.1 Transcription initiation with alternative sigma factors. In order to understand the underlying differences in promoter recognition and open complex formation by alternative sigma factors, we shall try to obtain structures of transcription initiation complexes with alternative sigma factors, including σ32, σ28, σ24 and σ19.

1.2 Regulation of initiation by activators. To enrich and advance our understanding of transcription regulation at initiation, we aim to obtain the structures of initiation complexes that include a bound general transcription factor, FNR protein, as well as other transcription factors (MerR-family proteins). The obtained information from this study would help us to understand how MerR-family members respond to the effector of xenobiotics and activate the transcription of multidrug resistance genes whose products are multidrug efflux pumps, which are one of three evolved antibiotic resistance mechanisms in bacteria.

2. To understand the molecular basis for the regulation of transcription elongation by ATPases

In order to understand how ATPases regulate transcription reactivation, termination and transcription-associated DNA repair, we shall attempt to obtain structures of the RNAP elongation complexes in association with RapA and other ATPases, such as mfd and UvrD. We shall try to assemble and determine the structures of those complexes.

3. To characterize the basis of transcription termination and its regulation by the general transcription factors: NusA and NusG

3.1 In order to understand how intrinsic hairpin terminator induces transcription termination by a hyper-translocation mechanism, we shall try to obtain structures of the RNA hairpin-associated termination complexes. In addition, to understand how the transcription factor NusA enhances intrinsic termination, we shall also try to assemble and determine the structure of the intrinsic termination complex with NusA.

3.2 In order to understand how the hexameric helicase Rho binds to the rut site in the RNA transcript to terminate transcription, we shall try to obtain structures of the different complexes with or without the transcription factor NusG, which enhances this type of termination.

"Transcription is the central step in the expression of genes, and a major mechanism for controlling the expression of a gene is to regulate its transcription. Transcription is regulated by various transcription factors. Many human diseases and disorders are associated with misregulation of transcription and mutations of transcription factors, including cancer, autoimmunity, neurological disorders, developmental disorders, diabetes, cardiovascular disease, and obesity."

Bin Liu
Research in my lab focuses on the crosstalk between genetic and epigenetic factors that regulates skin homeostasis and carcinogenesis. We integrate epigenomic and functional genomics studies to better understand skin cancer development, and to identify novel actionable molecular targets for developing effective approaches to prevent and treat skin cancer.


Despite decades of extensive research on UV and skin cancer, there remains a significant gap in our knowledge of the critical genes and pathways through which UV promotes skin carcinogenesis. In the past several years, my lab has conducted multi-omics studies to elucidate UV-induced molecular abnormalities in skin cells. Bioinformatics analysis have identified master regulators of skin injury and UV responses as actionable targets for developing mechanism-driven targeted approaches for skin cancer prevention and treatment.

Additionally, we have defined a novel UV gene expression signature (UVGES) panel consisting of conserved UV target genes. This UVGES panel has significant clinical potential because currently there is no sensitive molecular test to quantify skin UV damage for cancer risk assessment. To validate the clinical utility of the UVGES panel, I have collaborated with former dermatologist colleagues at Columbia University Medical Center to collect skin biopsy and tumor tissues for gene expression analysis using the NanoString nCounter platform. We have obtained interesting preliminary results showing that a subset of the UVGES genes are specifically associated with high-risk skin subtypes. The long-term goal of this project is to develop a cost-effective biomarker-based test that can be easily adopted in clinical practice to risk stratify patients for targeted cancer prevention and treatment.

Project 2. Hairless transgenic and knockout mouse models for studying skin homeostasis and immunity, epidermal stem cells and wound healing, and UV-induced tumorigenesis.

Hairless is an epigenetic regulator with histone demethylase activity. Mutational inactivation of hairless alone can dramatically increase tumor incidence and burden in response to chemical induction or UV radiation. In human skin squamous cell carcinomas (SCCs) and other cancer types, we found frequent deletions of the hairless locus. Moreover, hairless expression is frequently down-regulated in human SCCs but not actin- keratotic lesions. Through ChIP-Seq studies, we have identified several hairless target genes that play important roles in cancer development (12). These findings strongly suggest that hairless is a pivotal tumor suppressor gene in skin carcinogenesis. We are now following up these important findings to define the demethylase activity of hairless, its target genes, and the role of histone demethylation in regulating epidermal homeostasis, stem cell activity and skin wound healing.

"Understanding the environmental origin of cancer and its underlying mechanism will facilitate the development of better cancer prevention strategies and targeted therapies." Liang Liu

Summary

Research in my lab focuses on the crosstalk between genetic and epigenetic factors that regulates skin homeostasis and carcinogenesis. We integrate epigenomic and functional genomics studies to better understand skin cancer development, and to identify novel actionable molecular targets for developing effective approaches to prevent and treat skin cancer.

Research Interests:
- Epigenetic mechanisms in development and cancer pathogenesis.
- Role of hairless in epidermal homeostasis, immunity and carcinogenesis.

Patents:
- International Patent Application: “Hairless transgenic and knockout mouse models for studying skin homeostasis, immunity, epidermal stem cells and wound healing”

Memberships:
- 2010 - Society of Investigative Dermatology
- 2012 - New York Academy of Sciences
- 2019 - American Association for Cancer Research

Publications:
innovative nanoparticles for drug delivery.

Schematic model illustrating the DNA hypomethylating potential of nisibin.

Ths, thus significantly expanding the pool of DNA methylation inhibitors. Our discoveries provide a mechanistic explanation why Ths show therapeutic efficacy in patients without target mutations, and suggest that altered DNA methylation profile might be alternative predictors of responses in patients without TKI mutations. Altogether, our work provides the preclinical rationale for using Ths to benefit patient subpopulations characterized by aberrant DNA methylation including those who relapse from current epigenetic therapy.

The FABP4-DNMT1 loop is a new epigenetic target for cancer therapy

Acute myeloid leukemia (AML) is a highly aggressive hematopoietic malignancy with a high mortality rate. Treatment is effective for a subset of patients, but the majority of patients who relapse from current epigenetic therapy.

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Summary

In the Cryo-EM and Molecular Cell Biology Section we are studying how membrane-remodeling proteins assemble into large complexes and regulate fundamental cell events, such as apoptosis, autophagy and mitochondrial dynamics. Our current focus is to determine how dysregulation of mitochondrial dynamics contributes to infectious diseases and cancer (Fig. 1). Several molecular players with membrane-remodeling activity have been implicated in mitochondrial dynamics: (i) a potential tumor suppressor involved in a multitude of intracellular membrane trafficking events; (ii) dynamin family member Drp1, which is required for fission of the mitochondrial outer membrane (MOM); (iii) Immunity-Related GTPase M (IRGM), a GTPase related to the dynamin super family critical for autophagy during the innate response to intracellular pathogens; and (iii) Bax, a pro-apoptotic protein that trans-locates to the mitochondria where it is activated to form pores in the MOM, leading to the release of cytochrome c and subsequently, apoptosis.

Our previous data show that neuronal-specific endophilin isoform, endophilin A1, is critical for recruitment and assembly of dynamin 1 at sites of plasma membrane fission (1).

Figure 1. Mitochondrial dynamics. Mitochondrial membrane-remodeling events, including fission, fusion, mitophagy and apoptosis are controlled by members of the dynamin super family of large atypical GTPases, Drp1, Mitofusin, OPA1 and IRGM (a GTPase related to the dynamin super family critical for autophagy during the innate response to intracellular pathogens). Image modified from original (1).

Other professional activities:

Invited Speakers:

• Department of Pediatrics
  SANFORD Health, Sioux Falls, SD
  2019

• Department of Biological Sciences
  Minnesota State University, Mankato, MN
  2019

• Center for Molecular Medicine and Genetics
  Wayne State University, Detroit, MI
  2018

Current research projects:

1) PROJECT 1: Membrane shape controls neuronal cell death

2) PROJECT 2: Coordinated regulation of Golgi membranes remodeling controls autophagosome formation

3) PROJECT 3: Endophilin B1 mediated membrane remodeling controls Bax-dependent membrane permeabilization and cell death

4) PROJECT 4: ABHD5-mediated membrane remodeling controls PNP-LA2-controlled lipolysis

5) PROJECT 5: Innate immunity protein IRGM controls mitochondrial membrane fragmentation and xenophagy

Figure 2. Cryo-EM three-dimensional (3D) reconstruction of endophilin B1 helical scaffolds assembled on lipid tubes. In Fig. 1b, the 3D density map is colored based on cryo-EM map and homology modeling (3-7). Left panel: Atomic model is colored based on cryo-EM map and homology modeling (3-7). Right panel: Atomic model is colored based on cryo-EM map and homology modeling (3-7).

Figure 3. "Cryo-EM allows us to visualize exactly how critical cellular events, such as membrane remodeling and tubulation are initiated and regulated by BAR proteins." Anna Sundborger Lunda
from the bone marrow with the epidermis. We also perform quantitative histopathology on sections of skin tumors to determine the interaction of cells in epithelial cancers. We determine whether the bone marrow derived epithelial cells behave, how they move around the body, and how they develop into tumors.

Non-melanoma skin cancers such as basal cell and squamous cell carcinomas occur more frequently in the human population than any other type of cancer, and more than one million new cases are diagnosed in the United States annually. It is estimated that one-third to one-half of all human cancers originate in the skin; that skin cancers exceed all others combined, and that the lifetime risk for development of skin cancer in the U.S. population is one in five. Solar ultraviolet radiation is the major cause of non-melanoma skin cancers and is directly relevant to the etiology of skin cancer, as demonstrated by both epidemiological evidence and the tight correlation between non-melanoma skin cancer development and ultraviolet radiation exposure.

We visualize how cancer happens by determining how stem cells behave, how they move around the body, and how they develop into tumors. We use the GFP to visualize, isolate, and culture these cells in order to study their stem cell epithelial origin. Non-melanoma skin cancers such as basal cell and squamous cell carcinomas are considered “undesirable background” in the “liquid biopsy” that seeks to measure circulating epidermal cells in blood and bone marrow of “normal, healthy human subjects”; however, the proliferative and differentiative properties of these cells are to be considered “undesirable background” in the “liquid biopsy” that seeks to measure circulating epidermal cells from the laboratory of T.C. Wang who reported that bone marrow derived epithelial cells can initiate benign and malignant healing ulcers. For sure, carcinogen-exposed bone marrow contains cells capable of becoming tumor-initiating cells. A critical unanswered question from this work is: what is the nature of non-melanoma skin cancer, and may provide a new source of proliferative diseases of the colon. Moreover, Tamai and colleagues demonstrated that some bone marrow derived epithelial cells might be recruited to cutaneous papillomas and non-healing ulcers. For sure, they are considered “undesirable background” in the “liquid biopsy” that seeks to measure circulating epidermal cells.

Skin cancers as seen in the clinic are actually the results of a long history of which only the later stages are easily observed. The progression from normal skin to neoplastic growth involves multiple changes in cellular phenotype and patterns of gene expression. Cells covering surfaces such as the epidermis or lining spaces like the gastrointestinal and respiratory tracts are epithelial cells, and can be identified by their genetic expression of certain epithelial markers or keratin expression (APF). These observations taken together with the progeny of the hair follicle progenitors can be considered “undesirable background” in the “liquid biopsy” that seeks to measure circulating epidermal cells in blood and bone marrow of “normal, healthy human subjects”; however, the proliferative and differentiative properties of these cells are to be considered “undesirable background” in the “liquid biopsy” that seeks to measure circulating epidermal cells.

The principles we use are: 1) advanced light microscopy of cells and tissues, 2) flow cytometry, and 3) fluorescence activated cell sorting of epithelial cells, cells from skin tumors, and blood and bone marrow cells. These methods enable us to determine the roles of bone marrow cells in epithelial cancers. We perform quantitative histopathology on sections of skin tumors to determine the interaction of cells from the bone marrow with the epidermis. We also determine whether the bone marrow derived epithelial cells contribute to development of chronic cutaneous and hemorrhagic ulcers.

Other professional activities:

We conclude that surprisingly large numbers of bone marrow cells are recruited to a subset of cutaneous papillomas and non-healing ulcers. We have previously unrecognized systemic contribution to these lesions. We also conclude that carcinogen-exposed bone marrow cells originating in the bone marrow can initiate skin tumors in the presence of a skin tumor promoter that by itself does not cause cancer in the U.S. By these findings we may aid discovery of new methods of prevention, diagnosing, or treating non-melanoma skin cancer, and may provide a new source of proliferative cells for use in regenerative medicine. This research is significant because it will have far reaching consequences for fields of hematology and epithelial biology. First, we will document and quantify bone marrow derived epithelial cells in healthy subjects to determine the phenotypes in the humans the phenotypes expressed. Second, we will determine whether the bone marrow derived epithelial cells have functional characteristics of epithelial stem/progenitors in culture and in vivo models. The experiments we have performed will open up a new field of research in epithelial biology and may provide motivation for development of new disease models. The implications of our findings toward understanding the etiology of epithelial cancers in general as well as their diagnosis and treatment have not escaped our notice.
comparative pathology and genetics. We continue to collaborate with worldwide experts at the Masonic Cancer Center (MCC), have and will develop and improve existing therapeutic approaches to eliminate cancer. As part of the largest nonprofit source of grant funding for cancer researchers in the United States, other than the government. Pediatric GBM is defined by mutations in the gene encoding Histone H3.3. We are developing an animal model (Figure 1) to study this disease. In collaboration with the Hinchcliff lab at the Hormel Institute, we seek to bring about a better understanding of the role of this mutation in these tumors in order to develop new therapies to improve survival for children with this devastating disease.

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

Our section is concerned with the molecular mechanisms by which oncogenic signaling regulates Tumorigenesis, with the ultimate goal of developing and improving existing therapeutic approaches to eliminate cancer. As part of the University of Minnesota and a member of the Masonic Cancer Center (MCC), have and will continue to collaborate with worldwide experts in the fields of cell signaling, cancer research, comparative pathology and genetics. We employ two experienced postdoctoral fellows, Flora Grigore M.D., and Hana Yang, Ph.D., and Nick Hanson a technician and Caoimhe Farrell an Undergraduate Researcher. Flora Grigore received her Ph.D. in Cell Signaling and Tumorigenesis from the University of Minnesota in 2015. Nick Hanson has successfully completed his postdoctoral training at the Hormel Institute and started a new phase of his training at the Mayo Clinic in Rochester Minnesota this fall.
Developing novel algorithms for indel detection.

Our most recent work has been in the development of clinical genomic variant detection pipelines for our customized oncology gene panels at University of Minnesota Molecular Diagnostic Lab. Briefly, we developed a new algorithm named ScanIndel, an indel detection algorithm by integrating gene expression microarray data and protein interaction networks to determine their involvement in immunotherapy-resistant prostate cancer patients. We have developed a novel computational algorithm that can sensitively detect previously missed novel splicing events in human transcriptome from RNA-seq data. We utilize whole-exome sequencing and RNA-seq from renal cell carcinoma, lung cancer and melanoma to correlate the expression of our detected splicing event with immune checkpoint therapy response or resistance. This study aims to improve the computational methodology to detect and quantify novel alternative splicing events and to determine their involvement in immunotherapy-associated phenotypes. Integrative analysis of DNA mutations and RNA splicing events in the responders and non-responder patients is able to list a first batch of candidate common alternative splicing events that play a role by underlining the resistance of immunotherapy in the non-responders or the effects in the responders.

Identifying specific subtypes of prostate cancer and the distinct pattern of mutations associated with them will enhance development of precise diagnostic tools that detect specific genetic aberrations, allowing doctors to reliably predict a patient’s outcome and prescribe personalized treatments.

Rendong Yang
Building Operations and Maintenance
Mark Severtson / Building Systems Manager
The Maintenance, Buildings and Grounds team works with all the current departments and new staff coming in to keep the facilities and research running smoothly, keeping the building running as safe, efficient, and as beautiful as possible. We work with new researchers to set up labs as needed, along with any new equipment that arrives. This department continually makes improvements to keep the facility running as efficiently as possible. We are also part of the Energy Hero program with the Austin Utilities to help reduce power usage when there is a peak alert day.

Instrument Core Facility
Todd Schuster / Core Facility Manager
The Shared Instrument Core operates and maintains the shared instruments at the Hormel Institute. We also instruct scientists in the use of these instruments and ensure that they receive the proper maintenance. New instruments added to the Core this year include the BD Fortessa X-20 flow cytometer. With more excitation lasers and more detectors, the Fortessa offers greater fluorophore flexibility and higher resolution than our previous analyzer. Other additions include a Leica TP 1020 Tissue Processor and a Leica HistoCore Arcadia embedder. These devices allow users to prepare tissue samples for mounting on slides. Our Core also includes several microscopes, a Zeiss Apotome which allows for a wide variety of fluorophore options and the ability to eliminate out of focus light with internal grids. Other microscopes include a Zeiss Palm Microbeam laser dissection microscope which can be used to isolate high purity tissue from cryosections and FFPE samples, and a Nikon C1 confocal system. Recent additions include a Bio-Rad iQ500 which uses surface plasmon resonance technology to measure interactions between proteins, lipids, and small molecules, and the IncuCyte S3 Imager which allows researchers to perform real time live cell analysis. Other shared instruments include a Beckton Dickinson FACS ARIA II cell sorter, ABI SCX 3000 Triple TOP mass spectrometer with an Exactive Nano LC system, and a Rigaku X-Ray diffraction system for protein crystallography. A BioTek Synergy plate reader, real time qPCR instruments, chemiluminescence imagers, spectrophotometers, and centrifuges are also available for use. Histology equipment consists of a microtome and cryostat in addition to the newly added equipment listed above. Ultimately, we look forward to employing these and other core facility equipment to assist research at The Hormel Institute.

Library
Andy Lucas / Librarian
The library serves as the information resource center for The Hormel Institute. It provides print and online materials to support faculty and staff research as well as special projects. The collection consists of approximately 10,250 volumes of bound journals and 2,900 volumes of books and serials. The subjects covered include chemistry, biology, biophysics, medicine, and electronics. Researchers also have access to the services and resources of the University of Minnesota Twin Cities Libraries, the 15th largest in North America by collection size. Books are delivered from the Twin Cities campus and are available for pickup at The Hormel Institute library. Articles that are not available in electronic form are obtained through interlibrary loan.

Administration
Ann M. Bode, Ph.D. / Interim Executive Director
The administrative team continues to expand as we strive to provide the highest level of clerical, account management, acquisition, compliance and human resource assistance to our research and support sections. Additionally, Administration works closely with the University’s central adminstration departments, serving as liaison between the two entities.
Research Support Services
Jeffrey McDonald / PSS Manager

Research Support Services continues to provide instrument maintenance along with computer, telecommunication, network, and internet support for The Hormel Institute. Maintenance includes a wide variety of scientific instruments, from complex to simple and large to small. Computers and network connectivity are an extremely important resource for researchers and a major portion of our work load. As always, the network security needs keep us busy. The Linux cluster CAL42 (Computational Analysis of Life-sciences 42) has been calculating away simulating protein molecules in our supercomputer room, part of The Hormel Institute’s International Center of Research Technology.

FROM LEFT TO RIGHT: Mike Connery, Jeffrey McDonald, Theresa Tucker, Tim Lastine

FROM LEFT TO RIGHT: Brenna Gerhart, Kathi Finley, Gail Dennison, Gretchen Ramlo, Michelle Hjelmen

Development and Public Relations
Gail Dennison, M.A., CFRE
Director of Development and Public Relations

Our department’s guiding mission is to gain support for the cancer research of The Hormel Institute, University of Minnesota. As the Institute’s scientists seek meaningful discoveries in the quest to prevent and control cancer, our goal is to shine the light on their research and find support so even more research can be achieved and more answers accelerated. We consider it a privilege to work with these expert researchers from around the world – they have dedicated their lives to research with the broad goal of furthering knowledge so people can live longer, healthier lives, uninterrupted by cancer. To all who contribute so generously and support the research of The Hormel Institute, thank you. Your faith and support indeed makes an important difference.

This year, over one thousand individuals and businesses gave to The Hormel Institute University of Minnesota through monetary donations. Thanks to The Hormel Foundation, every penny of each donation to The Hormel Institute directly funds research – none to administrative costs.

In the past year, donations have funded new technology, 17 seed grants, and projects in new cancer research areas. Donations allow our scientists to pursue research that wouldn’t otherwise be possible and can lead to new discoveries and increased funding.

Thank you from one and all at The Hormel Institute, University of Minnesota.
Our donors make a difference. Nearly 17 innovative research projects are underway that would not be possible without your donations. The studies may be targeted for specific cancers - such as breast, prostate or Wilms’ Tumor cancers - but the knowledge gained about the initiation and progression of cancer can impact understanding of many cancers.

Thank you for joining our mission with your donations - together we will accelerate answers to cancer so people live longer, healthier lives.
Today’s EDUCATION, Tomorrow’s DISCOVERIES

The annual Summer Undergraduate Research Experience (SURE) internship program gives college undergraduate students the opportunity to work with The Hormel Institute scientists 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.

K-12

Scientists from The Hormel Institute participate in area science fairs to promote learning the scientific method and to award “The Hormel Institute OUTSTANDING Science Research Award” to students at various grade levels. Researchers also mentor young students by volunteering their time in the Science Fair Mentoring Project and working with students in the classroom to demonstrate techniques and talk about possible career paths. Every sixth grader in Austin gets an opportunity to tour The Hormel Institute, and as students advance in their studies, taking courses like honors biology, they have additional, increasingly impactful interactions with Institute researchers.

MISSION STATEMENT

The Hormel Institute has been part of University of Minnesota since its inception in 1942. Our mission is to conduct research and provide education in the biological sciences and share our knowledge with the world. The Hormel Institute serves as an education hub and center of technical and educational expertise for the benefit of the Austin community, surrounding region, and State of Minnesota. Education is a core function and we strive to inspire interest in science and prepare people for successful biomedical careers.

POST-DOCS

The Hormel Institute is a hub for postdoctoral training and nearly every lab has a team that includes new PhDs. Postdoc is the de facto next step on the academic career path after earning a doctorate degree (Ph.D.). A postdoc is a temporary position that allows a PhD to continue his or her training as a researcher and gain necessary skills and experience to prepare them for the next steps in their research careers.

COMMUNITY

Educating students has been and remains an important part of the community outreach of The Hormel Institute, University of Minnesota. Our scientists and staff help inspire interest in science education throughout leadership in programs for both individuals and organizations, including:

- Advise/serve on dissertation committee for doctoral students
- BiCo - graduate training for Biomedical Informatics and Computational Biology students at UMN-Rochester
- GRAWC (Greater Rochester Advocates for Universities and Colleges board) - advocate for education in southern Minnesota
- Austin Aspires
- Riverland Community College - support “Be Your Best”
- Austin Science Fair Mentoring Project - mentor students

RESEARCH-FOCUSED

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EDUCATION

Today’s EDUCATION, Tomorrow’s DISCOVERIES

The annual Summer Undergraduate Research Experience (SURE) internship program gives college undergraduate students the opportunity to work with The Hormel Institute scientists 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.
beta-Stimulated Hepatic Stellate Cells
Nuclear Transport in Transforming Growth Factor
panchalcone is mediated by directly targeting the TOPK
interaction
lung carcinoma growth by inhibiting the PREX2-PTEN
hypermethylation of the RIP3 promoter
Y. T., Fan, S., Lu, B., Yin, S., Yang, D., & Kim, D. J. Phytother
ed-Multidrug Resistant Leukemia
3-Iodothyronamine Acting through an
Critical for hepatic stellate cell activation
variant alpha1-antitrypsin disposal
inhibits patient-
The Hormel Institute // JULY 1, 2018 – JUNE 30, 2019

SEMINARS

Income from Grants, Contracts and Development

National Institutes of Health

Chromophore-assisted Liner Transfer (individual project, Wardell, 2019, 2017, 2018)

Delineating coding and regulatory indels in prostate cancer (R. Yang) $75,000

Fine-Tuning the immune system to fight disease and improve health outcomes (R. Yang)

Mechanism of high-efficiency transduction of hepatocytes by optimized AAV vectors (Z. Dong) $123,157

National Cancer Institute

Necroptosis in ovarian cancer cells with gain of function of p53 mutations (J. Robinson) $156,157

National Science Foundation

Optimizing the immune system to fight disease and improve health outcomes (R. Yang)

Optimizing the immune system to fight disease and improve health outcomes (R. Yang)

PhRMA Foundation

Necroptosis: molecular and metabolic aspects (I. Chefetz-Menaker) $54,534

University of Minnesota

Skin Cancer (Z. Dong) $93,375

Glioblastoma (I. Chefetz-Menaker) $258,750

Micro Cells Inc.

Mechanism of high-efficiency transduction of hepatocytes by optimized AAV vectors (Z. Dong) $118,186

Other Resources

The Hormel Foundation

University of Florida/NIH

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University of Minnesota Medicine/NIH

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University of South Florida/NIH

The Functional Role of the IL-6/IL-6R Complex in Septic Shock (L. Hooper) $123,047

WINneapolis/MINneapolis

The Functional Role of the IL-6/IL-6R Complex in Septic Shock (L. Hooper) $142,033

Depts.

Developmental Cell Signaling: mechanisms underlying pediatric glioblastoma – Dr. Hines and Z. Dong and others

University of Minnesota Medicine

Mechanism of high-efficiency transduction of hepatocytes by optimized AAV vectors (Z. Dong) $123,157

Mayo Clinic Rochester

American Cancer Society

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Robert A. Eckstein Research Center

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Arthritis Research Center

Development of a novel anti-inflammatory inhibitor that shows potent therapeutic effects against colitis (S. Liu) $56,157

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

Accelerating **ANSWERS**

to **CANCER**