



THE HORMEL INSTITUTE
UNIVERSITY OF MINNESOTA

2017-18 ANNUAL REPORT



THE HORMEL INSTITUTE
UNIVERSITY
OF MINNESOTA

MAYO CLINIC




TABLE OF CONTENTS

Cellular and Molecular Biology	6
Molecular Bioengineering and Cancer Vaccine	10
Membrane Biochemistry and Molecular Biophysics	12
Cancer Stem Cells and Necroptosis	14
Cell Death and Cancer Genetics	16
Cancer Cell Biology and Translational Research	18
Cellular Dynamics	20
Cancer Biology	22
Tumor Microenvironment and Metastasis	24
Transcription and Gene Regulation	26
Cancer Epigenetics and Experimental Therapeutics	28
Cryo-EM and Molecular Cell Biology	30
Stem Cells and Cancer	32
Cell Signaling and Tumorigenesis	34
Computational Cancer Genomics	36
Partners in Growth	42
Dollars Furthering Research	44



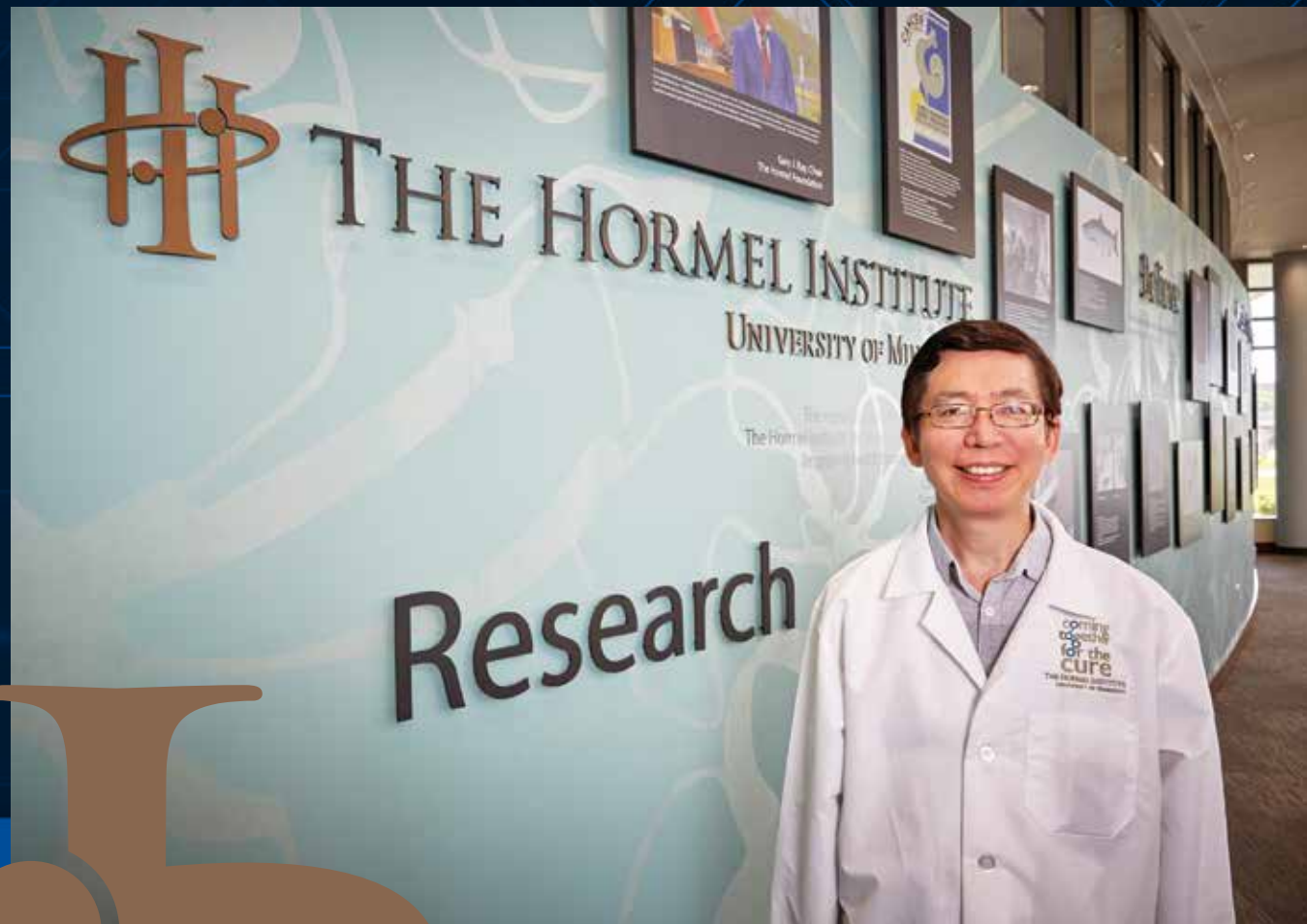
Accelerate to



ating **ANSWERS**
CANCER

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.



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

Dr. Zigang Dong

Message from the Executive Director Dr. Zigang Dong

Dear Friends,

One of the great joys of serving as Executive Director of The Hormel Institute, University of Minnesota is to work with a great and diverse group of wonderful people. Our common quest - to accelerate answers to cancer through ground-breaking research - is inspirational and motivating to one and all.

From within our medical center, I applaud the talented, growing body of faculty, postdoctoral fellows, students, and dedicated staff who make up The Hormel Institute. These employees work together to pave the way for research to flourish and results to be furthered and shared. From securing grants to operating technologies, from performing experiments to gathering data, from writing articles for publication to ensuring the building operates according to strict protocols and processes, each year our teams work together to produce an amazing body of work. I am very proud of and thankful for our hardworking faculty, postdoctoral fellows, students, and staff.

I'm also privileged to work closely with some of the great leaders of academics and industry. University of Minnesota's President Eric Kaler and Vice President for Research Dr. Allen Levine have been key partners in supporting the growth of The Hormel Institute and I look forward to working with newly appointed Vice President for Research Dr. Christopher J. Cramer in the coming years. Their support helped as we doubled in size just two years ago, and are now in the process of adding up to 15 new research sections. Dr. Doug Yee, head of the Masonic Cancer Center and Dr. Jakub Tolar, the new medical school dean of University of Minnesota, are key partners. Their strong support of The Hormel Institute's cancer research helps our progress continue.

The leaders, doctors, researchers and scientists of Mayo Clinic remain among the most valuable research partners we could hope for. For 76 years Mayo Clinic has been part of The Hormel Institute, serving on our advisory board, developing research collaborations and coming together with one mind as together we work for the common goal to improve human health. I am thankful for former CEOs Drs. Hugh Smith and Glenn Forbes who forged

Mayo's growing collaboration with The Hormel Institute, and the current leadership of Dr. John Noseworthy who helped Mayo Clinic again become the top hospital in the United States for the third consecutive year. We look forward to working with Mayo's next CEO, Dr. Gianrico Farrugia, and supporting his vision for Mayo Clinic, a world class health care system.

Without question, The Hormel Foundation indeed is our foundation. The success and hard work of Hormel Foods makes The Hormel Foundation's support possible. The vision, leadership, funding, guidance and encouragement we receive from The Hormel Foundation - and the cancer research made possible - is a gift they give which positively impacts the entire world. One of the major founding purposes of The Hormel Foundation is to benefit the worldwide community through the scientific research of The Hormel Institute. We thank The Hormel Foundation's leaders, including Mr. Richard L. Knowlton, Mr. Gary J. Ray and our new Chair, Mr. Jeffrey M. Ettinger. We thank Mr. Joel W. Johnson for his brilliant service and faithful support to The Hormel Foundation and we welcome Mr. James P. Snee, new to the board. How incredibly fortunate we are to work with such highly skilled leaders.

Thank you for your continued support and we look forward to utilizing the support and resources we receive to further and accelerate answers to cancer so as to help people live longer, healthier lives. Thank you for allowing me the privilege of being executive director and know our work is dedicated to you.

In friendship,



Zigang Dong, M.D., Dr. P.H.
Executive Director



“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.”

Zigang Dong

secretion from peripheral blood mononuclear cells was decreased compared with healthy subjects. The ribosomal S6 kinase (RSK) family of proteins has multiple cellular functions, and we examined their role in decreased IFN γ . Analysis of wild-type (WT) and RSK2 knock-out (KO) *in vivo* models revealed that the level of IFN γ was significantly lower in RSK2 KO *in vivo* models compared to WT *in vivo* models. Because IFN γ is a component of immunity, which can protect against metastatic carcinoma, a CRC liver metastasis experiment was conducted. We found that metastasis was significantly increased in RSK2 KO *in vivo* models compared to WT. Transcription factor T-bet directly activates *IFN γ* gene transcription. *In vitro* kinase assay results showed that RSK2 phosphorylates T-bet at Ser498 and 502. We showed that phosphorylation of T-bet by RSK2 is required for IFN γ expression, because knocking down RSK2 expression or over-expressing T-bet S498A/S502A mutants reduced *IFN γ* mRNA expression.

Inflammation is a complex biological host reaction to tissue damage, infection, or trauma. Studies of the inflammatory response led to the identification of several protein kinases essential for signaling and as potential therapeutic targets, including RSK2. We found that RSK2 mediates

inflammation signaling and interacts with TRAF6. *In vitro* kinase assay results indicated that RSK2 strongly phosphorylates TRAF6 at Ser46, 47, and 48. Overexpression of TRAF6 or knocking down RSK2 confirmed that RSK2 is positively mediates TRAF6 K63 ubiquitination. TRAF6 is also required for RSK2 ubiquitination and for phosphorylated TRAF6-mediated colon inflammation.

Tumor necrosis factor receptor (TNFR)-associated factor 1 (TRAF1) is a unique TRAF protein that interacts with multiple TNFR family members, regulatory proteins, kinases, and adaptors that contribute to its diverse functions in specific tissues. However, the role of TRAF 1 in non-small cell lung cancer (NSCLC) remains unknown. We report that TRAF1 is overexpressed in human lung cancer cells and tissues and its expression level inversely correlates with patient survival. Loss of TRAF1 decreased tumor invasion in a urethane-induced lung cancer *in vivo* model. Furthermore, TRAF1 expression affected TRAF2-mediated BRAF Lys48-linked ubiquitination, which was followed by inhibition of growth and differentiation and induction of death in lung cancer cells. Overall, this suggests that TRAF1 plays a novel role in regulating the BRAF/MEK/ERKs signaling pathway in NSCLC and offers a possible molecular target for lung cancer prevention and therapy.

Summary

Cancer is a leading cause of death worldwide. By focusing on its molecular mechanisms, we continue to discover key molecular events in cancer development and agents for cancer prevention and therapy.

1. Discovery of key molecular events in cancer development and metastasis

Metastasis is the major cause of death for patients with solid malignancies. Approximately 20 and 80% of colorectal cancer (CRC) patients develop lung metastasis and liver metastasis, respectively. We found that at different stages of colon cancer, the patients' interferon (IFN) γ

Solar ultraviolet (sUV) irradiation is a major environmental carcinogen that causes inflammation and skin cancer. The costs and morbidity associated with skin cancer are increasing, and thus identifying molecules that can prevent skin cancer is important. We identified the p53-related protein kinase (PRPK) as a novel oncogenic protein that is phosphorylated by the T-LAK cell-originated protein kinase (TOPK). Knockdown of TOPK inhibited PRPK phosphorylation and conferred resistance to solar-simulated light (SSL)-induced skin cancer in *in vivo* models. Clinically, acute SSL irradiation significantly increased epidermal thickness as well as total protein and phosphorylation levels of TOPK and PRPK in human skin tissues. We identified two PRPK inhibitors that suppressed SSL-induced skin cancer.

The *Wilms' tumor 1 (WT1)* gene is believed to act as a canonical tumor suppressor. However, it has also been reported to be an oncogene. Germline *WT1* deletion is associated with Wilms' tumor, and exogenous *WT1* cDNA introduction into cells induces transcriptional suppression of its oncogenic target genes. In contrast, high *WT1* expression is associated with poor prognosis in patients with various cancers. Why *WT1* acts as a tumor suppressor under certain conditions but as an oncogene under other conditions is unknown. We report that the CUG-translated *WT1* (cugWT1), an N-terminally extended form of the canonical AUG initiation site for *WT1* protein synthesis (augWT1), is overexpressed in most cancer cell lines and cancer tissues and functions as an oncogene, whereas the classical augWT1 acts as a tumor suppressor. cugWT1 induced transformation and increased oncogene expression of *c-myc*, *bcl-2* and *egfr*, whereas

overexpression of augWT1 repressed cancer cell colony formation and inhibited the expression of the same target genes by recruiting histone deacetylase 1. Additionally, we found that protein kinase B (AKT)-phosphorylated cugWT1 on Ser62 and protected cugWT1 from degradation induced by F-box/WD repeat-containing protein 8. These results provide an important breakthrough in cancer biology and contribute to the resolution of the chameleon function of *WT1*.

2. Discovery of novel targets and agents for cancer prevention

SUV irradiation is a major factor in skin cancer development and the mitogen-activated protein kinase (MAPK) cascades are activated by SUV irradiation and are critical for skin carcinogenesis. The RSK and mitogen and stress-activated protein kinase (MSK) proteins, constitute a family of kinases that mediate signal transduction



FROM LEFT TO RIGHT:

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 Sixth Row: Souren Paul, Moeez Ghani Rathore, Humberto De Vitto, Tian Xie

downstream of MAPKs. We observed up-regulated phosphorylation of RSK and MSK1 in human squamous cell carcinoma and sUV-treated *in vivo* model.

An urgent need exists for developing more effective molecular strategies targeting nonmelanoma skin cancer (NMSC), the most common cancer worldwide. Inflammatory signaling downstream of Toll-like receptor 4 (TLR4) is implicated in many cancers, yet its role in sUV-induced skin cancer remains undefined. We previously showed in cultured keratinocytes and SKH-1 *in vivo* models that topical application of a specific TLR4 antagonist resatorvid (TAK-242) blocks acute UV-induced activator protein-1 (AP-1) and NF- κ B signaling, associated with down-regulation of inflammatory mediators and MAPK phosphorylation. We thus explored TLR4 as a novel target for chemoprevention of UV-induced NMSC. We selected resatorvid based upon target specificity, potency, and physicochemical properties. We used *ex vivo* permeability assays to show that topical resatorvid can be effectively delivered to skin, and *in vivo* studies to show that topical resatorvid can block UV-induced AP-1 activation in *in vivo* models. We also report that topical resatorvid displays potent photochemopreventive activity in *in vivo* models, significantly suppressing UV-induced tumor area and multiplicity. Tumors harvested from resatorvid-treated *in vivo* models display reduced activity of UV-associated signaling pathways and increased apoptosis compared with tumors from controls. Further mechanistic insight on resatorvid-based photochemoprevention revealed a significant attenuation of key UV-induced proteomic changes induced by resatorvid in chronically treated high-risk SKH-1 skin prior to tumorigenesis. Taken together, our data identify TLR4 as a novel molecular target for topical photochemoprevention of NMSC.

AP-1 regulates a variety of protein-encoding genes and is a participant in many cellular functions, including proliferation, transformation, epithelial mesenchymal transition (EMT), and apoptosis. Inhibitors targeting AP-1 have potential use in the treatment of cancer and inflammatory diseases. We identified veratramine as a potent natural modulator of AP-1, which selectively binds to a specific site (TRE5'-TGACTCA-3') of the AP-1 target DNA sequence and regulates AP-1-dependent gene transcription without interfering with signaling cascades that might lead to AP-1 activation. Moreover, RNA-seq experiments demonstrate that veratramine does not act on the Hedgehog signaling pathway in contrast to its analogue, cyclopamine, and likely does not harbor the same teratogenicity and toxicity. Also, veratramine effectively suppresses EGF-induced AP-1 transactivation and transformation of JB6 P+ cells. Finally, we demonstrate that veratramine inhibits sUV-induced AP-1 activation in *in vivo* models. The identification of veratramine and new findings in its specific regulation of AP-1 downstream genes will assist in discovering and designing agents to regulate this transcription factor.

3. Discovery of novel targets and agents for cancer therapy

Esophageal cancer is one of the most aggressive malignancies of the upper digestive tract. In spite of advances in surgical techniques and treatment, the prognosis of esophageal cancer has only slightly improved. Thus identifying novel molecular targets and developing therapeutic agents are critical. Aurora kinases play crucial roles in mitosis and selective inhibitors might provide an effective therapeutic cancer treatment. However, the role of Aurora kinases in esophageal cancer is still unclear. We identified a novel compound, referred

to as APIO-EE-9, which inhibits growth and colony formation and induces apoptosis of esophageal cancer cells. We found that APIO-EE-9 interacted with both Aurora A and B in the ATP-binding pocket and inhibited Aurora A and B kinase activities dose-dependently. Treatment with APIO-EE-9 substantially reduced the downstream Aurora kinase phosphorylation of histone H3 (Ser10), resulting in formation of multiple nuclei and centrosomes. Additionally, esophageal cancer cells expressing silenced Aurora A or B kinase exhibited a dramatic reduction in proliferation and transformation. Injection of these cells as xenografts in *in vivo* models reduced tumor formation compared to WT cells. APIO-EE-9 significantly decreased the size of esophageal patient-derived xenograft (PDX) tumors in SCID *in vivo* models. These results demonstrated that APIO-EE-9 is a specific Aurora kinase inhibitor that might be developed as a therapeutic agent against esophageal cancer.

Overexpression or activation of AKT is known to control cell growth, survival, and gene expression in solid tumors. Oridonin, an inflammatory diterpenoid compound, exhibits antitumor, antibacterial, and anti-inflammatory effects. We demonstrated that oridonin inhibits AKT and suppresses proliferation of esophageal squamous cell carcinoma (ESCC) *in vitro* and *in vivo*. The role of AKT in ESCC was studied using a tumor microarray, AKT knockdown, and MK-2206, an AKT inhibitor. Oridonin blocked AKT kinase activity and interacted with the ATP-binding pocket of AKT. It inhibited growth of KYSE70, KYSE410 and KYSE450 esophageal cancer cells time- and dose-dependently. Oridonin induced G2/M cell cycle arrest, stimulated apoptosis, and increased expression of apoptotic biomarkers, including cleaved PARP, caspase-3, caspase-7 and Bims in ESCC cells. Mechanistically, oridonin diminished the phosphorylation and activation of AKT

signaling. Furthermore, a combination of oridonin and 5-fluorouracil or cisplatin (chemotherapeutic agents) enhanced the inhibition of ESCC growth. The effects of oridonin were verified in PDX tumors expressing high levels of AKT. Overall, our results indicate that oridonin acts as an AKT inhibitor to suppress the ESCC growth by attenuating AKT signaling.

Fibroblast growth factor receptor (FGFR) 2 and its downstream signaling cascades, PI3-K/AKT/mTOR, play important roles in cell survival and proliferation. We found that picrasidine Q (PQ), an alkaloid component, has anti-transformation and anticancer activities. PQ targeted FGFR 2, which was verified by FGFR2 kinase assay as well as computational docking. FGFR2 is highly expressed in esophageal cancer tissues and PQ inhibited fibroblast growth factor (FGF)-induced cell transformation. Furthermore, PQ inhibited proliferation and induced cell cycle arrest and apoptosis in KYSE30, KYSE410, and KYSE450 ESCC cells. Results were confirmed by detection of biological markers, such as cyclins D1, D3, and B1 for cell cycle or cleaved caspase-7, caspase-3, and PARP for apoptosis. PQ targeting of FGFR2 kinase activity suppressed downstream target proteins, including phosphorylation of AKT and mTOR but not MEK/ERKs. Overall, our results identified PQ as a chemopreventive and chemotherapeutic agent that directly targets FGFR2 and inhibits proliferation of ESCC cells.

Malignant melanoma is an aggressive skin tumor and lacks effective preventive and therapeutic treatments. In melanoma, both the BRAF/MEK/ERKs and PI3-K/AKT signaling pathways are constitutively activated through multiple mechanisms, resulting in cell cycle progression and prevention of apoptosis. Thus, developing novel strategies for targeting BRAF and PI3-K are

clearly needed. We found that Ashitaba chalcones, 4-hydroxyderricin (4HD) and xanthoangelol (XAG), suppressed melanoma development by directly targeting both BRAFV600E and PI3-K, blocking the activation of downstream signaling. This led to the induction of G1 phase cell cycle arrest and apoptosis in melanoma cells. Importantly, 4HD or XAG dramatically attenuated tumor incidence and volume in the BRAF-activated *Pten*-deficient melanoma *in vivo* model. Our findings suggest that 4HD and XAG are promising chemopreventive or therapeutic agents against melanomagenesis that act by targeting both BRAF and PI3-K, providing hope for rapid clinical translation.

Intake of soy isoflavones is inversely associated with esophageal cancer risk. Experimental results support the anticancer activity of soy isoflavones. We studied the anti-esophageal cancer activity of 6,7,4'-trihydroxyisoflavone (6,7,4'-THIF), a major metabolite of daidzein, which is metabolized in the human body. Notably, 6,7,4'-THIF inhibited proliferation and increased apoptosis of esophageal cancer cells. Pin1 was identified as a target protein of 6,7,4'-THIF and pull-down assay results using 6,7,4'-THIF Sepharose 4B beads showed a direct interaction between 6,7,4'-THIF and Pin1. Pin1 is a critical therapeutic and preventive target in esophageal cancer because of its positive regulation of β -catenin and cyclin D1. 6,7,4'-THIF simultaneously reduced Pin1 isomerase activity and the downstream activation targets of Pin1. The 6,7,4'-THIF compound affected Neu/Pin1 WT MEFs, but not Neu/Pin1 KO MEFs. Furthermore, xenograft assay results using Neu/Pin1 WT and KO MEFs were similar to those obtained from the *in vitro* assay. Overall, we found that 6,7,4'-THIF specifically reduced Pin1 activity in esophageal cancer models. Importantly, 6,7,4'-THIF directly

bound to Pin1 but not FKBP or cyclophilin A, the same protein family. Because *Pin1* acts like an oncogene by modulating various cancer-related proteins, this study might at least partially explain the underlying mechanism(s) of the anti-esophageal cancer effects of soy isoflavones.

The soy isoflavone daidzein is metabolized to 7,8,4'-trihydroxyisoflavone (7,8,4'-THIF) in humans. Here, we found that 7,8,4'-THIF inhibited matrix metalloproteinase (MMP)-1 and UVB-induced transcriptional activity of AP-1, a major activator of MMP-1 expression, in primary human dermal fibroblasts. Additionally, the MAPK pathway, a crucial signaling cascade for MMP-1 expression, was suppressed by 7,8,4'-THIF. Protein kinase C ι (PKC ι) was suspected to be a direct target of 7,8,4'-THIF and the direct interaction between 7,8,4'-THIF and PKC ι was confirmed using various assays. Finally, we observed that 7,8,4'-THIF inhibited UVB-induced MMP-1 expression in a human skin equivalent model. Taken together, these results suggest that 7,8,4'-THIF, a bioconversion product of daidzein, suppresses UVB-induced MMP-1 expression.

Gefitinib is a targeted drug therapy against NSCLC, which initially shows dramatic clinical efficacy. However, most patients eventually develop resistance. Although researchers identified different mechanisms contributing to the drug resistance, developing a single therapy to overcome the drug resistance remains difficult. We found that tetraploidization of cancer cells through YAP-MKK3/6-p38 MAPK signaling could be a common mechanism in developing drug resistance. We used losmapimod to eliminate tetraploidization and overcome gefitinib-resistance in an *in vivo* model, suggesting that this drug might be a clinical agent to overcome gefitinib-resistance in NSCLC.

Molecular Bioengineering and Cancer Vaccine
George Aslanidi, Ph.D.

SECTION LEADER / ASSOCIATE PROFESSOR

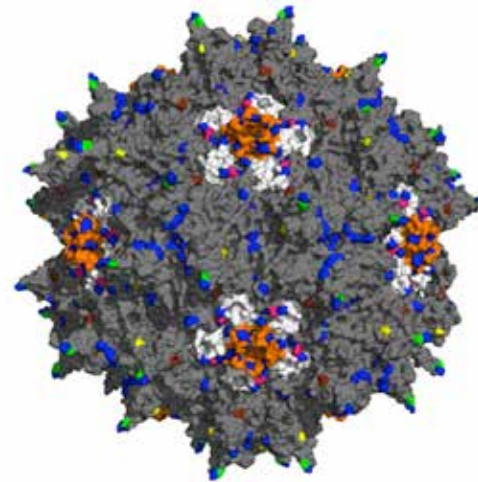


Summary

Our recent studies of the three-dimensional structures of Adeno-Associated Virus (AAV) vectors combined with data from amino acid scanning and mutagenesis experiments on the capsid have identified specific regions of the viral surface which are critical for vector-host interactions, including both viral entry and intracellular trafficking. By modifying these viral surface-exposed regions we developed novel gene delivery platform with superior balance of immunogenicity and safety. We currently trying to employ our capsid-optimized AAV vectors

to develop anti-cancer vaccine. Briefly, tumor specific antigen carried by these novel bioengineered AAV vectors are injected into *in vivo* model using standard needle vaccination procedures. As a result, local antigen presenting cells (APC) uploaded with the AAV-delivered tumor anti-gene either directly or by a cross-presentation pathway activate both a cytotoxic CD8+ T-cells and a humoral response against the tumor.

Our lab is working on understanding of how specifically activate host immune system with rationally design AAV vectors and redirect that immune response to efficiently kill cancer cell.



“Our lab develops a safe and effective antigen-based immunotherapy strategy to activate patient immune system and complement and/or augment conventional cancer treatments.”

George Aslanidi

First, our research has demonstrated that a strong antigen-specific immune response is developed after a single injection of AAV-based vaccine in *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. Second, our AAV-based vaccines are safe: same modification reduces proteasome-mediated degradation of the vector, subsequently reducing a virus-specific immune response. Our bioengineered AAV vectors (unlike other viruses) do not induce cytopathic changes in APCs during infection. Third, our technology is highly compatible with and complementary to current cancer treatments, including other immunotherapies. We currently evaluating dose, route of administration and compatibility/synergetic effect of our anti-cancer vaccine with other clinically relevant stimulators of immune system to maximize effect of cancer treatment.

Other professional activities:

Our lab is initiating pre-clinical test of AAV-based vaccine in collaboration with the largest, standalone specialized Veterinary Cancer Center solely dedicated to diagnosing and treating cancer in animals. Testing of that vaccine on a clinically relevant animal model will provide the necessary data to determine if advancement into human clinical trials is warranted.

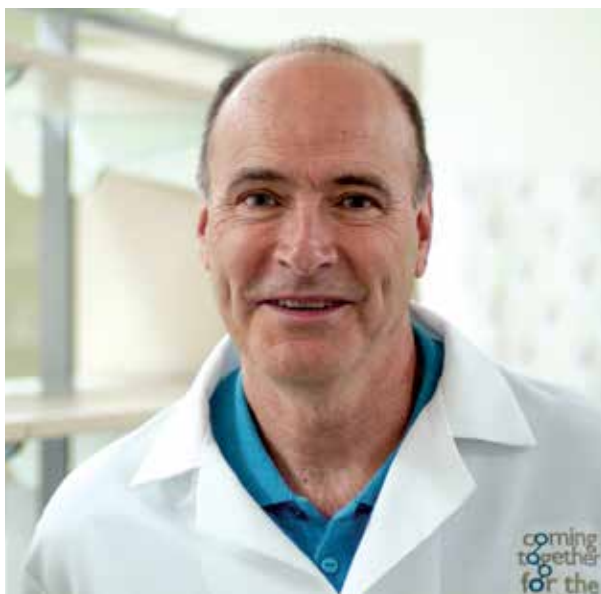


FROM LEFT TO RIGHT:
Becky Berg, Noah Johnson, Karina Krotova,
Andy Day and George Aslanidi

Membrane Biochemistry and
Molecular Biophysics

Rhoderick Brown, Ph.D.

SECTION LEADER / PROFESSOR



Summary

Our research focuses on proteins that interact non-enzymatically 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. Certain sphingolipids form 'raft' microdomains in membranes 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. To define sphingolipid structural features that regulate their lateral and

transbilayer interactions with other lipids in membranes, we used fluorescence spectroscopy, Langmuir surface balance approaches, calorimetry, and NMR. In collaboration with the H.L. Brockman lab (UMN-Hormel Institute), we developed ways to quantitatively measure model membrane lateral elasticity to accurately assess physical variations that occur within the 'raft environment' when the content and structure of sphingolipids and sterols change. Our research identified physical features central to the lateral organizing functionality of sphingolipid-enriched microdomains.

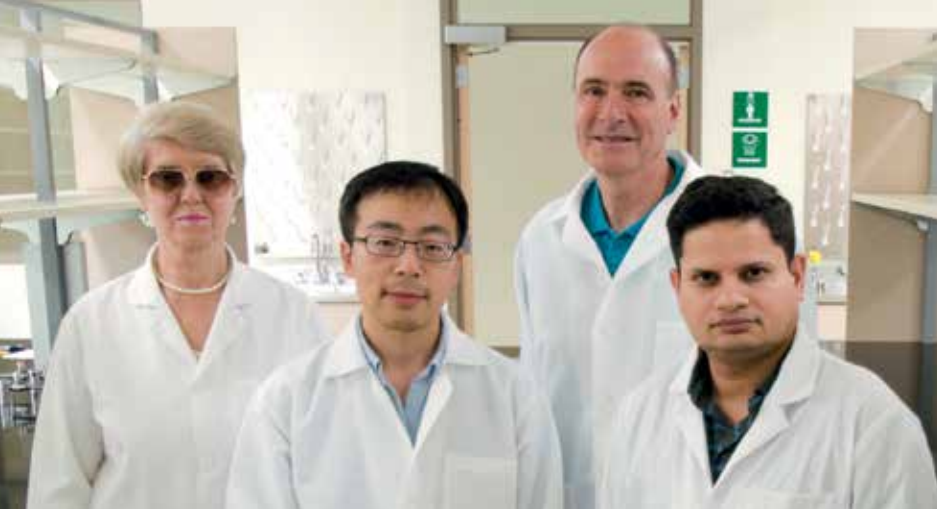
Because our findings are important for understanding how the lipid organization in membranes regulates proteins that must translocate onto membranes to function, we also study sphingolipid transfer proteins that help form and maintain 'raft' microdomains in cells. These sphingolipid transfer proteins were initially identified as glycolipid transfer proteins (GLTPs) due to their ability to specifically transfer glycosphingolipids between membranes. We performed the first cloning of GLTPs from various mammals (humans, bovine, porcine, mouse) as well as plants and fungi. We developed bacterial expression systems to purify and crystallize the proteins and determine their molecular structures both in glycolipid-free form and complexed with different

glycolipids. Our studies revealed how GLTPs recognize and envelope glycolipids to accomplish intermembrane transfer by shedding light on: i) GLTP binding site adaptation to accommodate different glycolipids; ii) the function played by intrinsic tryptophan residues in glycolipid binding and membrane interaction; iii) the structural basis for the more focused glycolipid selectivity of fungal GLTP and the GLTPH domain of human FAPP2. The findings are published in *Nature*, *PLoS Biology*, *Structure*, *The Journal of Biological Chemistry*, *Biophysical Journal*, *Biochemistry*, and *Journal of Lipid Research*. Our work benefited from collaboration with D.J. Patel at Memorial Sloan Kettering Cancer Center (MSKCC), L. Malinina at CIC bioGUNE (Derio/Bilbao, Spain) and J.G. Molotkovsky at the Shemyakin Institute of Bioorganic Chemistry at the Russian Academy of Science.

Recent studies 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), CPTP intracellular location in mammalian cells using state-of-the-art fluorescence microscopy (collaboration with Ted Hinchcliffe, UMN-Hormel Institute), and showed that CPTP depletion in human cells by RNAi leads to C1P over-accumulation in the *trans*-Golgi (collaboration

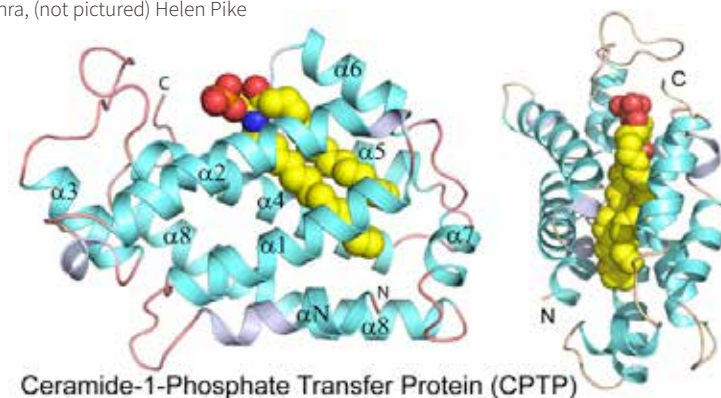
“Unraveling how sphingolipid transfer proteins regulate sphingolipid intracellular levels and locations to control inflammation and programmed cell death is of fundamental importance for developing new therapeutic approaches to treat diseases such as cancer.”

Rhoderick “Rick” Brown



FROM LEFT TO RIGHT:

Lucy Malinina, Yong-guang Gao, Rhoderick (Rick) Brown,
Shrawan Mishra, (not pictured) Helen Pike



Current research projects:

- 1) Structural Characterization and Function of Sphingolipid Transfer Proteins in Eukaryotes
- 2) The Functional Role of the cPLA2 α /C1P Interaction in Sepsis Resolution
- 3) Role of Inflammation in Breast Cancer Initiation and Progression: Intervention Potential by Sphingolipid Transfer Proteins
- 4) Regulation of Ceramide-1-Phosphate Transfer Protein (CPTP): New Strategy for Enhancing Breast Cancer Therapeutics

with Charles Chalfant, Univ. South Florida). The C1P over-accumulation triggers cytoplasmic phospholipase A2 action to generate arachidonic acid and downstream pro inflammatory eicosanoid production. Ongoing studies of human cytoplasmic phospholipase A2 (cPLA2 α) are being pursued to understand how cPLA2 α can initially promote but subsequently help reverse and resolve sepsis-related inflammation. Our discoveries are likely to help develop new treatments for sepsis and other inflammation associated pathologic conditions, i.e. cancer, diabetes and dementia.

In studies of plant CPTP, ACD11, in collaboration with John Mundy (Univ. Copenhagen) and D.J. Patel (MSKCC), we found that disruption of the *acd11* gene accelerates cell death. X ray structures, published in *Cell Reports*, revealed that ACD11 is a GLTP-fold evolved to bind and transfer C1P and phytoC1P. Disruption of *acd11* gene impaired plant development by severely altering C1P and ceramide levels to drive programmed cell death. The findings stimulated recent studies reported in *Autophagy*, showing that human CPTP functions an endogenous regulator of autophagy and inflammasome assembly that drives interleukin release (IL1B and IL18).

Our studies of GLTP and CPTP will likely facilitate their development as nano-devices 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 GLTP, CPTP, and related proteins which has been possible due to financial support from NIH National Institute of General Medical Sciences, NIH National Heart Lung and Blood Institute, NIH National Cancer Institute, Southern Minnesota's Paint-the-Town Pink Initiative, and The Hormel Foundation. For more details regarding our

research activities, expertise and scientific publications, please visit the following web sites:

REB Lab research activities:

<http://www.hi.umn.edu/research/membrane-biochemistry/>

ORCID ID (REB):

<https://orcid.org/0000-0002-7337-3604>

Experts-UMN (REB research expertise and publications):

<http://experts.umn.edu/en/persons/rhoderick-e-brown%28b67653a3-667a-4e50-a17c-202e43bc0884%29.html>

Other professional activities:

- Biophysical Society
- American Society for Biochemistry and Molecular Biology
- Membrane Structure & Assembly Subgroup, Biophysical Society
- Ad hoc NIH Study Section member and consultant
- National Science Foundation reviewer
- Japan Society for Promotion of Science reviewer
- Chemistry & Physics of Lipids, Editorial Board
- Journal of Lipids Editorial Board

Cancer Stem Cells and Necroptosis

Ilana Chefetz Menaker, Ph.D.

SECTION LEADER / ASSISTANT PROFESSOR



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 pathogenesis 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

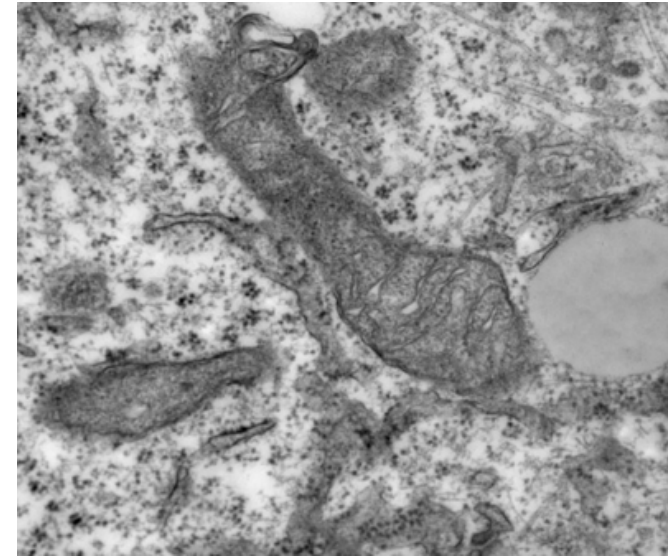


Figure 1: Transmission Electronic Microscopy of mitochondria.

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. Necroptosis execution involves formation of micro-complex (20 MDa) necroptosome followed by disintegration of mitochondrial and plasma membranes. Despite necroptosis importance, many molecular downstream events are unknown or being disputed.

“We used to think that necrosis happens due to injury, ischemia, inflammation, but recently, scientists realized that this process could also happen in a regulated manner—allowing researchers to probe this pathway to identify novel ways to combat cancer. We would like to accelerate necroptosis to kill as many cancer stem cells as possible.”

Ilana Chefetz Menaker

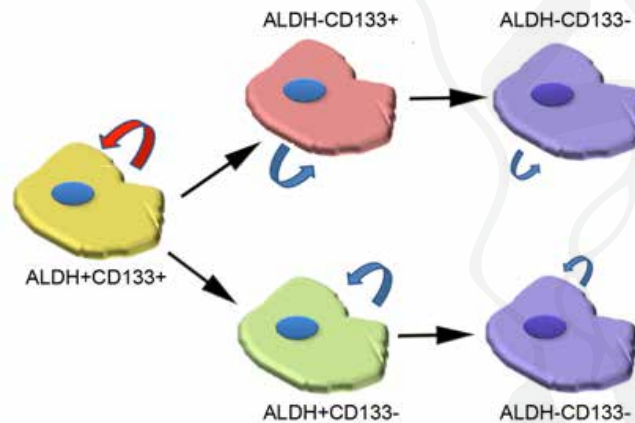


FROM LEFT TO RIGHT:
 Wootae Ha, Anmbreen Jambroze,
 Ilana Chefetz Menaker,
 Mikhail Chesnokov, Naresh Golla,
 Madison Jones

Presentations:

- November, 2018. Gynecological Oncology research symposium, UMN
- October, 2018. Minnesota Chemoprevention Consortium
- September, 2018. Exosome interest group. Mayo clinic.
- July, 2018. University of Chicago, OBGYN department
- December, 2017. The Hormel Institute Seminar Series
- September, 2017. Ovarian cancer spore group, Mayo clinic

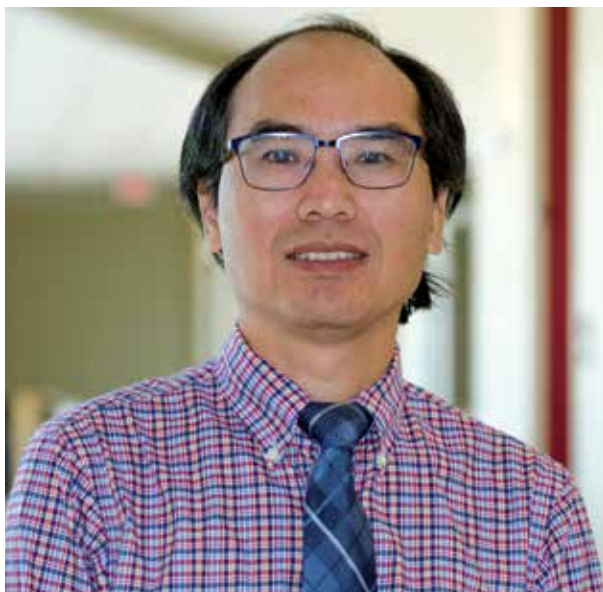
Figure 2: Self renewal and differentiation capacity of Cancer Stem cells.



Cell Death and Cancer Genetics

Yibin Deng, M.D., Ph.D.

SECTION LEADER / ASSOCIATE PROFESSOR



Summary

My research lab has been utilizing genetic engineered *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 selectively activated *in situ* in tumorigenesis; and utilizing computational drug target screen and design to discover novel small molecular compounds that selectively target human cancer cells while sparing normal cells.

*“Our studies will reveal whether and how the genetic changes identified in cancer patients contribute to tumorigenesis *in vivo* and identify effective strategies targeting cancerous cells while leaving normal cells untouched.”*

Yibin Deng

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

The tumor suppressor *TP53* gene encodes p53 protein that maintains genomic integrity and prevents tumorigenesis in response to a variety of genotoxic stresses. The importance of p53 in tumor suppression is highlighted by mutations identified in more than half of human cancers that lead to the loss of wild-type p53-mediated tumor suppressive function and/or the gain-of-oncogenic-function (GOF) *in vivo*. However, the tumor suppressive mechanisms of p53 remain incompletely understood.

While many studies have focused on the role of apoptosis and/or senescence in p53-mediated tumor suppression, my lab focuses on studying the function of p53-DRAM (Damage-Regulated Autophagy Modulator)-dependent autophagy in tumorigenesis. To determine the role of DRAM-dependent autophagy *in vivo*, we generated conditional *Dram* knockout *in vivo* models. Our findings suggest that *Dram* potentially functions as a tumor suppressor because deletion of *Dram* induces spontaneous tumor development *in vivo*. Currently, we are trying to dissect the molecular basis underlying *Dram*-deficiency-driven tumorigenesis *in vivo*.

2. Discovery of a novel target for currently incurable castration-resistant prostate cancer

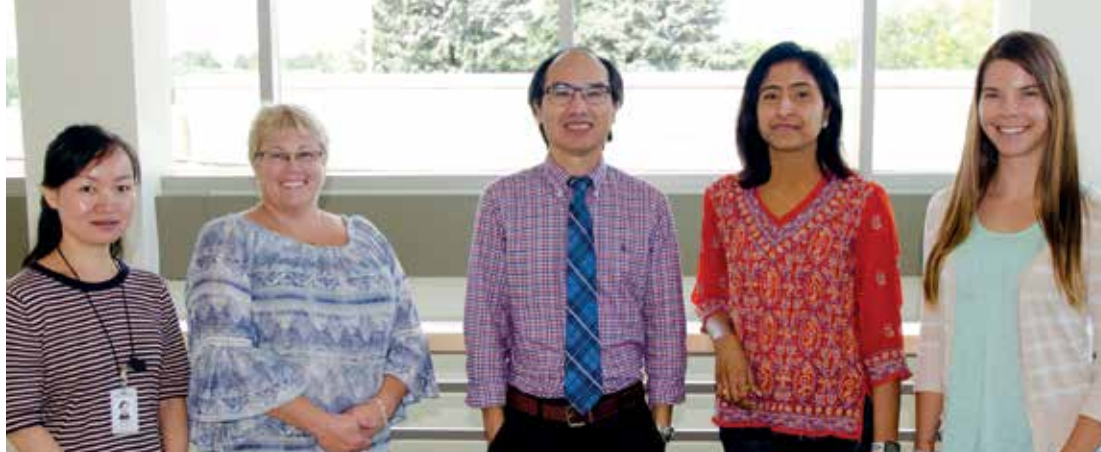
Androgen deprivation therapy (ADT) by surgical and/or chemical castration remains the gold standard-of-care therapy for metastatic prostate cancer. Unfortunately, these prostate cancers invariably develop resistance to ADT and progress to a more aggressive castration-resistant prostate cancer (CRPC) within 18-24 months. Currently, no therapeutic options exist for CRPC patients who have developed resistance to the second generation of anti-androgen receptor (AR) signaling axis therapy.

Clinically, approximately 30% of CRPC patients carrying both *PTEN* mutation and AR amplification while additional 30% of CRPC patients harboring co-deletion or -mutation of *PTEN* and *TP53*. Our latest data show that HK2 (hexokinase 2) protein, which catalyzes the irreversible first step of glycolysis by phosphorylating glucose to glucose-6-phosphate, is highly expressed in CRPC harboring *PTEN* loss/p53 mutation or AR amplification; Mechanistically, we demonstrate that (a) AR amplification increases hexokinase 2 (HK2) mRNA transcription through direct occupation at the AR binding sites (ARBS) within HK2 gene; (b) p53 deficiency increases HK2 mRNA through inhibition of miR143-mediated HK2 mRNA degradation; and (c) *PTEN* loss

selectively enhances HK2 mRNA translation (protein synthesis) through AKT1-mTORC1-eIF4A1-mediated axis; Genetically, we demonstrate that HK2-mediated Warburg effect is required for CRPC tumor growth *in vivo*; Pharmacologically, we demonstrate that co-targeting the HK2-mediated Warburg effect with 2-deoxyglucose (2-DG, a hexokinase inhibitor) and ULK-1-dependent autophagy with FDA-approved chloroquine (CQ) efficiently kills HK2-dependent CRPC cells and remarkably extends host survival in CRPC *in vivo* models. Taken together, our recent findings strongly support that targeting HK2-mediated Warburg effect as a selective and effective strategy for currently incurable CRPC.

3. Dissect the role of dysfunctional telomere-driven chromosomal instability in tumorigenesis

Telomeres are nucleoprotein caps that protect chromosomal ends from being recognized as aberrant damaged DNA and prevent chromosome end-to-end fusions. Telomeres that no longer can exert end-protective functions are said to be dysfunctional, and these telomeres could arise either from progressive telomere attrition (telomere shortening) or when components of the telomeric DNA-binding proteins – termed “shelterin complex” – are perturbed (telomere uncapping). In human cancers, chromosomal instability fueled by dysfunctional telomeres is associated with the transition from normal cells to cancerous cells *in situ*. This strongly supports the notion that telomere dysfunction-induced chromosome instability initiates tumorigenesis. Our laboratory has been engineering a novel *in vivo* breast and prostate cancer models harboring telomere uncapping-induced chromosomal instability without affecting the activity of telomerase. We have been utilizing these novel *in vivo* breast/prostate cancer models to identify the key genetic



FROM LEFT TO RIGHT:
Min Luo, Teri Johnson, Yibin Deng, Puja Singh,
Adrienne Wessel

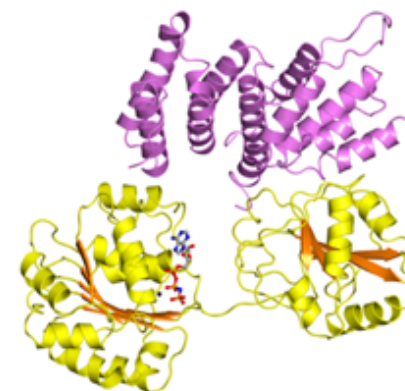
pathways perturbed in chromosomal instability-driven tumorigenesis *in vivo* and target these pathways with novel therapeutics that potentially could inhibit human breast/prostate cancer.

4. Understanding oncogene translation 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 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. Site-mutagenesis studies reveal the crucial residues contributing to the complex formation *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

Crystal structure of eIF4A/eIF4G complex



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 translation, which in turn leads to tumorigenesis.

Our research projects are well supported by the grants from The University of Minnesota, Hormel Foundation and National Cancer Institute of NIH (R21s and R01s).

Other professional activities:

Grant Reviewer, National Cancer Institute

Cancer Cell Biology and Translational Research
Sergio Gradilone, Ph.D.

SECTION LEADER / ASSOCIATE PROFESSOR



Summary

Our section focuses on understanding the basic biological processes involved with a normal cell transforming into a cancerous one. We continue investigating the role of the primary cilium in tumor biology. Primary cilia are multisensory organelles – similar to a cell antenna – that sense and receive signals from the environment surrounding the cells. We've found that these antennae are lost in tumor cells; therefore, we are trying to understand the mechanisms of ciliary loss, and what are the consequences of such a loss.

1 - Mechanisms of Ciliary Loss

Project 1

Cholangiocarcinoma (CCA) or bile duct cancer is a lethal malignancy increasing worldwide. Therefore, it is imperative to identify the cellular networks regulating disease initiation and progression to develop better therapies. Our current overall objective is to explore the importance of cholangiocyte deciliation, a pathologic process recently discovered by us in the pathogenesis and progression of CCA. Our data support the CENTRAL HYPOTHESIS that in CCA, primary cilia resorption resulting from exportin-5/miRNA/HDAC6 dysregulation disrupts the normal, ciliary dependent, tumor-suppressor signals that protect cholangiocytes from malignant transformation.

Project 2

We propose here that autophagy, a physiological process that degrades organelles, is linked to ciliary disassembly by a mechanism dependent on HDAC6, which is a protein overexpressed in tumor cells and induces the resorption of cilia by regulating ciliary stability and the transport of its components to the cellular degradative compartments. We hypothesized 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. The autophagy inhibitor hydroxychloroquine has been extensively used in humans as an antimalarial treatment, therefore it is readily available for use in our research. Our experiments are evaluating the effects of combined HDAC6 and autophagy inhibition *in vitro* and *in vivo*, laying the foundation for a potential clinical trial.

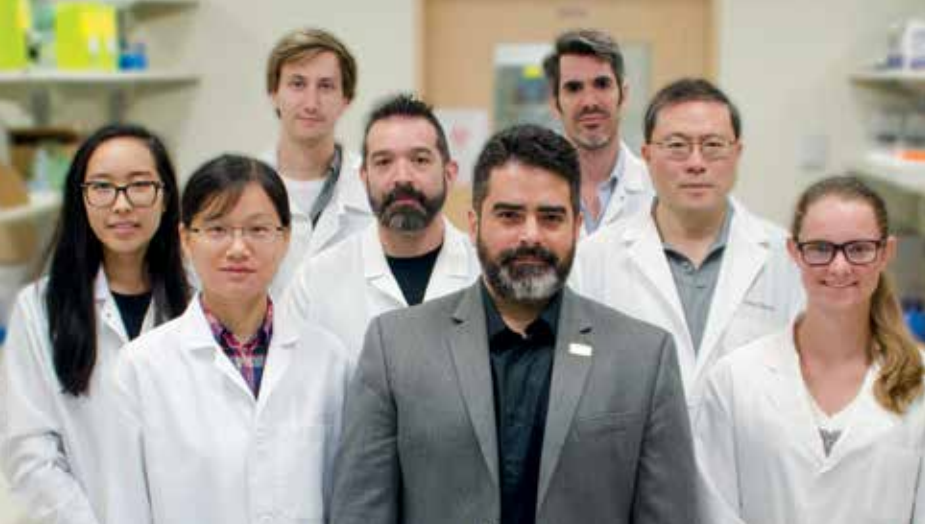
2 - Consequences of Ciliary Lost

Project 3

Here, we tested the hypothesis that the chemosensory function of cholangiocyte primary cilia acts as a mechanism for tumor suppression. We found that in the presence of extracellular nucleotides, ciliary-dependent chemosensation of the nucleotides inhibited migration and invasion in normal ciliated cholangiocytes. In contrast, in normal experimentally deciliated cholangiocytes and tumor cells, the nucleotides induced the opposite effects, i.e. increased migration and invasion. We found the compound hesperidin methyl chalcone (HMC) can mimic ciliary functions, resulting in the inhibition of migration, proliferation, and tumor growth (Figure 1).

“Our research is uncovering novel and generalizable information on fundamental, ciliary-dependent mechanisms controlling the proliferation and migration of malignant cells, and provide the foundation for anti-cancer therapies based on the rescue of primary cilia functions, i.e Ciliotherapy.”

Sergio Gradilone



FROM LEFT TO RIGHT:
 Suji Jin, Wei Cao, Seth Richard, Adrian Mansini, Sergio Gradilone, Estanislao Peixoto,
 Da-Qing Yang, Hannah Hitchcock

3 - New therapies and translational studies.

Project 4

In collaboration with Dr. George Alslanidi, we aimed to develop safe and effective vectors based on a human virus, the adeno-associated virus (AAV), for genetic manipulation of bile duct cells. Our overall objective is to develop new gene therapy tools for specifically targeting CCA tumor cells. This virus causes no known disease and currently being used in a number of clinical trials for the potential treatment of a wide variety of human diseases.

Project 5

Other studies in the Section under the direction of Dr. Da-Qing Yang include the investigation of two important proteins, p53 and ATM, which are critical for multiple physiological processes, including cell cycle progression, DNA damage repair, insulin signal transduction, and glucose metabolism. Our goal is to restore p53 tumor suppressor function in breast cancer cells by

inhibiting HDAC6 activity. Signal transduction of the ATM protein kinase in response to insulin and metformin is known to be linked to both cancer and diabetes. Inhibition of ATM-mediated glucose uptake and aerobic glycolysis has shown great potential in preventing mammary tumor development and in suppressing cancer cell survival. The investigation of the abnormal glucose metabolism in cancer cells using LC-MS-based targeted metabolomics has also led to the discovery of

potential biomarkers for early detection of pre-invasive breast cancer. LC-MS-based targeted metabolomics has also led to the discovery of potential biomarkers for early detection of pre-invasive breast cancer.

Other professional activities:

Invited Talks:

- “Emulating the Sensory Functions of Primary Cilia in Tumor Cells”. Thursday Morning GI Seminar Conference. Mayo Clinic, Rochester, MN, April 26, 2018
- “The Primary Cilium as a Therapeutic Target in Carcinogenesis”. The Telethon Institute of Genetics and Medicine (TIGEM). Pozzuoli, Italy, June 19, 2018
- “Primary Cilia Expression in CCA: from prognostic marker to preventive and therapeutic target”. European Network for the Study of Cholangiocarcinoma (ENS-CCA). Rome, Italy, June 23, 2018

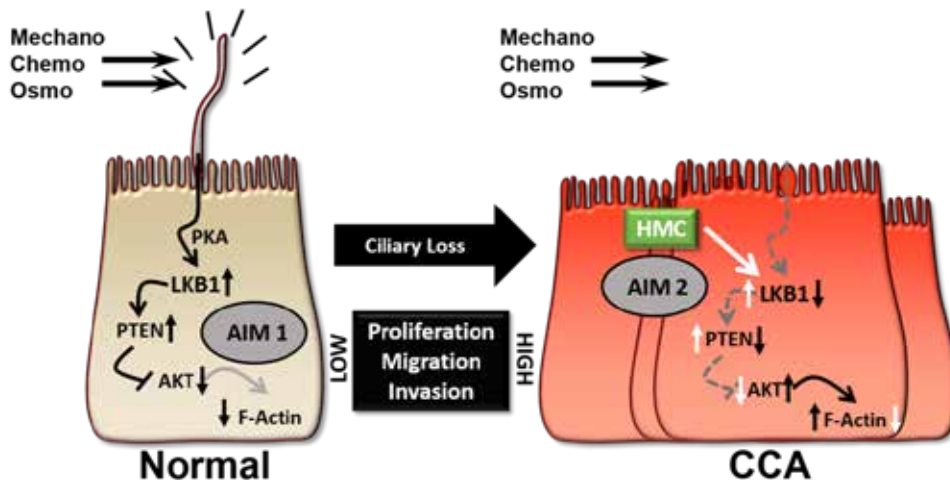


Fig. 1: Aim 1 explores the mechanisms by which the multi-sensory functions of primary cilia regulate cell proliferation, migration, and invasion. Aim 2 determines the outcomes of the emulation of ciliary functions by LKB1 direct activation with hesperidin methyl chalcone (HMC) on CCA progression.

Scientific Meetings:

- American Association for Cancer Research (AACR) Annual Meeting. Chicago, IL, April 14-18, 2018
- Hepatobiliary Cancers: Pathobiology and Translational Advances. Richmond, VA December 7-10, 2017
- Cholangiocarcinoma Foundation Annual Conference. Salt Lake City, UT Jan 31- Feb 2, 2018

Cellular Dynamics

Edward H. Hinchcliffe, Ph.D.

SECTION LEADER / PROFESSOR



Summary

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. Mistakes in mitosis lead to uneven chromosome segregations, which is a hallmark of cancer progression. Specifically, we study how changes to DNA (mutations) lead to chromosome missegregation during mitosis. By understanding the molecular mechanisms underlying these cellular defects, we will provide insight into new methods of diagnosis, prevention and treatment for cancer.

“We focus on the role of mitotic mechanisms in the generation of human disease.”

Edward H. Hinchcliffe

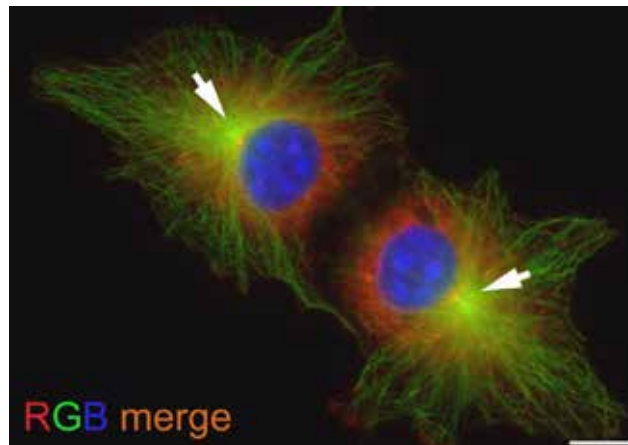
Chromosome missegregation:

Inadvertent chromosome missegregation in anaphase generates aneuploid cells, but the proliferation of these cells is normally blocked, because chromosome missegregation also triggers a p53-dependant failsafe that triggers cell cycle arrest in the ensuing G1. The molecular mechanisms underlying this trigger are not known.

Recently we have identified a conserved feedback mechanism that monitors the relative position of lagging chromosomes during anaphase via the differential phosphorylation of the histone variant H3.3 at Ser31. During normal mitosis H3.3 Ser31 is phosphorylated exclusively at peri-centromeres, which are

rapidly dephosphorylated in anaphase. We induced non-transformed cells to missegregate chromosomes by transiently depolymerizing spindle microtubules with cold. These cells undergo the metaphase-anaphase transition in the presence of one or more misaligned chromosomes that lack BubR1 labeling. These cells transit mitosis with relatively normal timing and lack DNA damage. After re-warming, correlative same cell live and fixed imaging revealed that isolated chromosomes (e.g. lagging in anaphase) have hyper-phosphorylated H3.3 Ser31 (pS31) along their arms that persists into G1 as these chromosomes assemble into a micronucleus. Surprisingly, during telophase Ser31 phosphorylation along individual chromosomes initiates global phosphorylation of H3.3 Ser31 in both

reforming nuclei, suggesting both an amplification step of the aneuploid failsafe, and an explanation for why both daughter cells trigger p53 activation in response to a single chromosome missegregation event. pS31 is mimicked by the hyperlocalization of ATRX to isolated chromosome arms. 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.

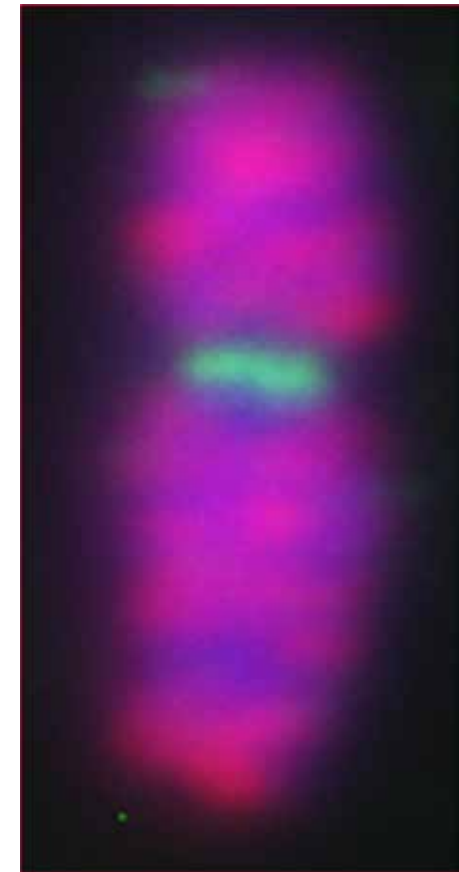


Cultured cells showing position of centrosome (arrows)

Finally, we demonstrate that post-anaphase H3.3 pS31 and ATRX are required to trigger p53 stabilization in the subsequent G1. Microinjection of monospecific 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 normally monitored and suppressed. Furthermore, driver mutations in H3.3 (flanking Ser31) and null mutations in ATRX are both found in pediatric glioblastomas, suggesting that disrupting the aneuploidy failsafe contributes to neoplastic progression.

The role of the centrosome in mitotic spindle assembly: The role of centrosomes/centrioles during mitotic spindle assembly in vertebrates remains controversial. In cell-free extracts and experimentally derived acentrosomal cells, randomly oriented microtubules (MTs) self-organize around mitotic chromosomes and assemble anastral spindles. However, vertebrate somatic cells normally assemble a connected pair of polarized, astral MT arrays – termed an amphiaster (“a star on both sides”) – that is formed by the splitting and separation of the microtubule-organizing center (MTOC) well before nuclear envelope breakdown (NEB). Whether amphiaster formation requires splitting of duplicated centrosomes is not known. We found that when centrosomes were removed from living vertebrate cells early in their cell cycle, an acentriolar MTOC re-assembled, and

prior to NEB, a functional amphiastal spindle formed. Cytoplasmic dynein, dynactin, and pericentrin are all recruited to the interphase aMTOC, and the activity of kinesin-5 is needed for amphiaster formation. Mitosis proceeded on time and these karyoplasts divided in two. However, ~35% of aMTOCs failed to split/separate before NEB, and these entered mitosis with persistent monastral spindles. The chromatin-mediated RAN-GTP path-



Isolated chromosome labeled with anti-modified histone H3.3 (red), anti-CENP A (green), and DAPI (blue)

way 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 in its absence, the fidelity of bipolar spindle assembly is highly compromised.



FROM LEFT TO RIGHT:
Charles Day, Paiton Schwab, Edward Hinchcliffe

Cancer Biology

Luke Hoepfner, Ph.D.

SECTION LEADER / ASSISTANT PROFESSOR



Summary

Discovering new ways to combat lung cancer is a primary focus of our 'Cancer Biology' section. Our National Institutes of Health funded research program integrates molecular, genetic, and biochemical approaches to analyze in vivo models,

“We have discovered that a specific form of DARPP-32 is overexpressed in lung cancer, and it may represent a new target for lung cancer therapy.”

Luke Hoepfner

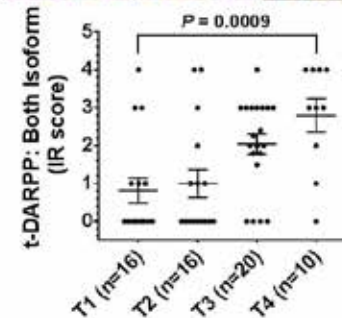
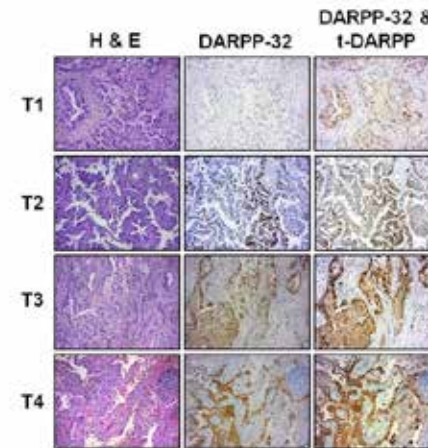
clinical samples, and patient databases to discover novel mechanisms that regulate cancers without clear therapeutic options. Our goal is to rapidly identify potential prognostic indicators, therapeutic targets, and strategies to overcome drug resistance in lung cancer patients. Our laboratory also studies molecular mechanisms and signal transduction pathways involved in vascular permeability, angiogenesis, cancer progression, metastasis, and adverse effects of cancer therapy.

Our talented research team consists of Sk. Kayum Alam, Ph.D. and Li Wang, M.D., Ph.D., two outstanding postdoctoral research fellows. Dr. Alam is primarily focused on accelerating our lung cancer discoveries. Dr. Wang specializes in vascular biology and angiogenesis research, which is applicable to finding new treatments for cardiovascular disease and stroke as well as cancer. This past summer, our research group was pleased to host Christina Hernandez, a summer undergraduate research experience (SURE) intern who learned a variety of laboratory techniques and contributed to several research projects. Together, our group has made excellent progress on numerous research directions this past year.

Highlights include publishing our discovery that DARPP-32 isoforms promote lung cancer growth (*Communications Biology*, 2018), authoring an article describing new in vivo precision oncology models (NPJ Precision Oncology, 2017), and contributing to work showing BMI1 is a potential therapeutic target for treatment of metastatic prostate cancer (*Clinical Cancer Research*, 2018).

1. Triggering the dopamine pathway to inhibit lung cancer progression

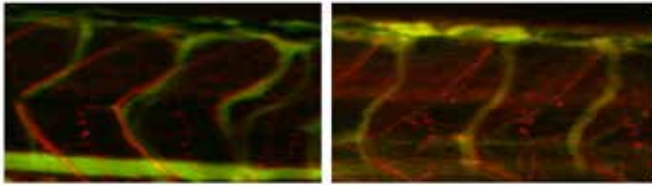
Lung cancer is the leading cause of cancer-related death worldwide. We demonstrate that elevated expression of dopamine and cyclic adenosine monophosphate-regulated phosphoprotein, Mr 32000 (DARPP-32) and its truncated splice variant t-DARPP promote lung tumor growth, while abrogation of DARPP-32 expression in human non-small cell lung cancer (NSCLC) cells reduces tumor growth in orthotopic in vivo models. We observe a novel physical interaction between DARPP-32 and inhibitory kappa B kinase-α (IKKα) 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 protein expression positively correlates with tumor (T) staging score in lung adenocarcinoma patients. A) Immunohistochemistry. B) Immune reactive (IR) scoring.

Control

VEGF

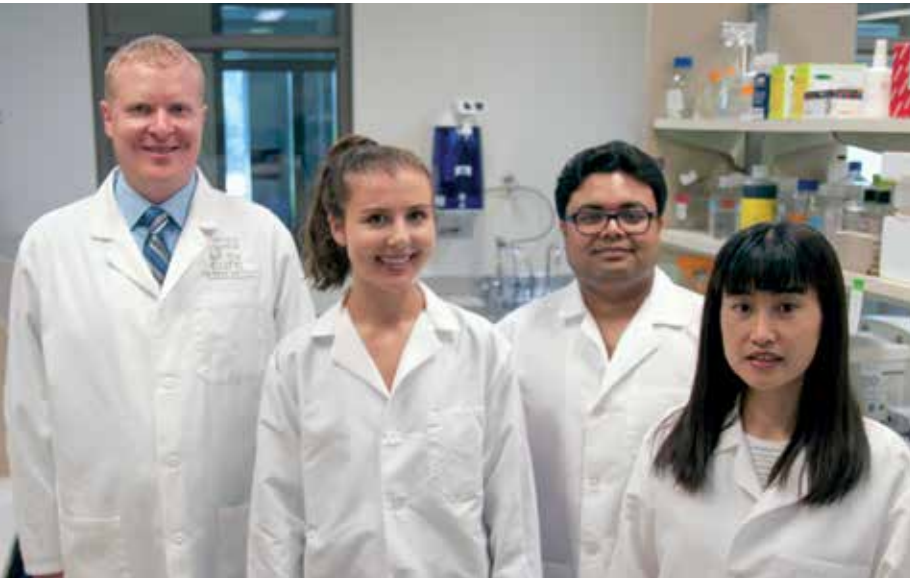


VEGF promotes vascular permeability as evident by increased extravasation of red dextran from green labeled veins.

elevated t-DARPP isoform expression is associated with poor overall survival. Histopathological investigation of 62 human lung adenocarcinoma tissues also shows that t-DARPP expression is elevated with increasing tumor (T) stage (Fig. 1). 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 cell lung cancer. A current area of focus is to understand how DARPP-32 and t-DARPP promote resistance to molecular targeted therapies.

FROM LEFT TO RIGHT:

Luke Hoepfner, Christina Hernandez, Sk. Kayum Alam, Li Wang



2. Development of in vivo models of vascular permeability and cancer metastasis

VEGF induces vascular permeability in stroke, heart attack, and cancer leading to many pathophysiological consequences. Following cerebral or myocardial infarction, VEGF induces gaps between adjacent endothelial cells in ischemic tissue and the resulting vessel leakiness causes deleterious edema formation and tissue damage. In cancer, VEGF-mediated permeability promotes tumor angiogenesis and metastasis. The molecular mechanisms by which VEGF acts to induce hyperpermeability are poorly understood and in vivo models that easily facilitate real-time, genetic studies of permeability do not exist. We developed a heat-inducible VEGF transgenic zebrafish model through which vascular permeability can be monitored in real-time (Fig. 2). Using this approach with protein knockdown, as well as a mammalian knockout model, we described a novel role of phospholipase C β 3 (PLC β 3) as a negative regulator of VEGF-mediated vascular permeability by tightly regulating intracellular calcium release. We have also used this zebrafish model

to elucidate the role of RhoC and other molecules in vascular homeostasis. The zebrafish vascular permeability model represents a straightforward method for identifying genetic regulators of VEGF-mediated vascular as promising targets for cancer, heart disease and stroke therapies. We also developed a zebrafish xenograft model of human cancer cell metastasis (Fig. 3), which has been used in two separate studies to support

our findings from murine cancer models. We are currently using these models to elucidate the molecular regulation of vascular permeability and cancer metastasis.

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

Radiation-induced dermatitis is a common side effect of radiation therapy in cancer patients which negatively impacts quality of life and contributes to radiation treatment delays or premature termination, which puts cancer patients at a higher risk for tumor regrowth. As there is currently no effective prevention or treatment for radiation-induced dermatitis, we seek to comprehensively characterize a unique in vivo model of radiation dermatitis so that we can identify new and innovative therapeutic strategies that reduce the occurrence and severity of radiation skin toxicity. The collective impact of this "Paint the Town Pink" supported research will be broad as it provides the essential foundational building blocks for the development of targeted therapies that prevent or decrease damage to normal skin caused by ionizing radiation. Data we have generated thus far serves as the basis of recently submitted National Institute of Health grant applications.

Other professional activities:

Funding:

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

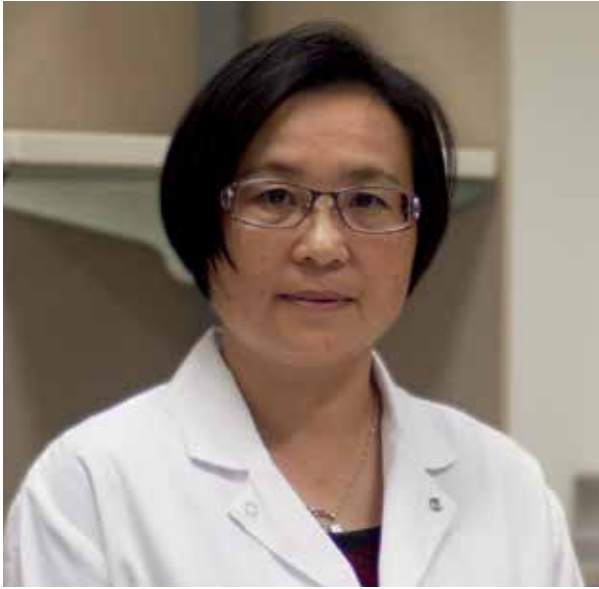
Editorial Board:

Nature Partner Journals: Precision Oncology

Tumor Microenvironment and Metastasis

Ningling Kang, Ph.D.

SECTION LEADER / ASSOCIATE PROFESSOR



Summary

TGF β is one of the most potent cytokines that induce activation of HSCs into tumor-promoting myofibroblasts. So we study (1) novel mechanisms governing intracellular trafficking of TGF β receptors, (2) how SMAD2/3 are transported into the nucleus under TGF β stimulation, and (3) epigenetic regulation of HSC activation in the nucleus. In addition to intracellular biochemical signaling, we also investigate how matrix stiffness-induced mechanosignaling regulates activation of HSCs into tumor-promoting myofibroblasts.

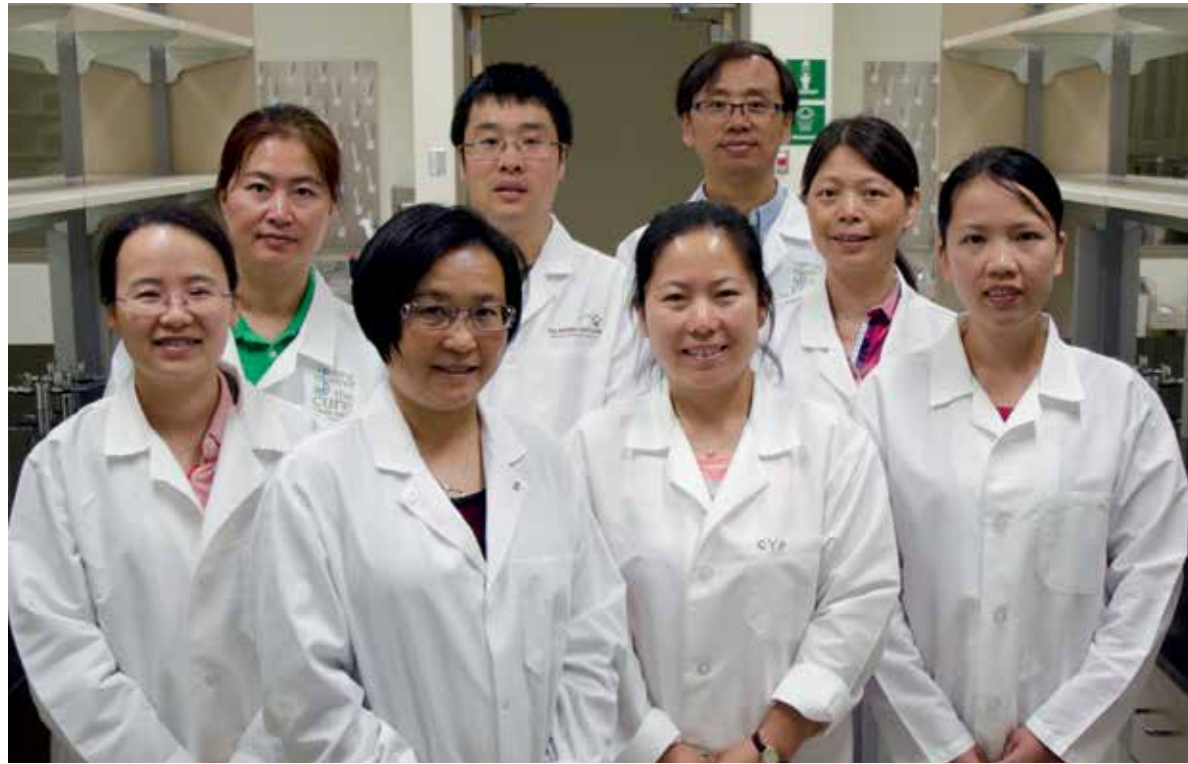
In our prior summary, we reported that a stiffness substrate can induce activation of quiescent hepatic stellate cells (HSCs) into tumor-promoting myofibroblasts through p300 acetyltransferase. On a soft substrate, p300 of HSCs undergoes degradation by cytoplasmic proteasomes whereas on a

stiff substrate, p300 is phosphorylated by a RhoA-AKT signaling pathway and subsequently it translocates to the nucleus to epigenetically promote gene transcription of HSCs. These findings have been published by a high-impact journal *Gastroenterology* (Dou, C. et al. *Gastroenterology*, June 2018) and highlighted by editorial comment (Torok NJ, *Gastroenterology*, June 2018).

Cytokine- and growth factor- induced biochemical signaling pathways are another potent factors for activation of HSCs into myofibroblasts. For example, TGF β promotes HSC activation by initiating intracellular signaling events, including receptor activation, SMAD nuclear translocation, and gene transcription. Understanding how these signaling events are regulated may lead to new targets to inhibit HSCs. Therefore, we tested a novel hypothesis in the last year that TGF β -induced nuclear transport of SMAD2/3 and its coactivator TAZ may be facilitated by p300. Using Western blot and immunofluorescence for HSC activation markers, alpha-smooth muscle actin and fibronectin, we found that TGF β 1-induced HSC activation was inhibited by p300 knockdown or C646 inhibition. Additionally, TGF β 1-induced nuclear accumulation of SMAD2/3 and TAZ was suppressed by p300 knockdown or C646. Our mechanistic studies supported that TGF β 1 induced a p300/SMADs/TAZ protein complex and that a nuclear localization signal of p300 (PSAKRPK) was required for SMAD2/3 and

“Under cancer invasion of the liver, hepatic stellate cells (HSCs) are activated into myofibroblasts by tumor-derived paracrine factors. In return, activated-HSC/myofibroblasts promote cancer implantation and proliferation in the liver by paracrine mechanisms. Thus, the bidirectional interactions between cancer cells and HSCs represent a therapeutic target for liver metastasis.”

Ningling Kang



FROM LEFT TO RIGHT:

Front: Xinghui Fu, Ningling Kang, Yunru Chen, Donglian Liu

Back: Xipu He, Kangsheng Tu, Yuanguo Wang, Yingzi He

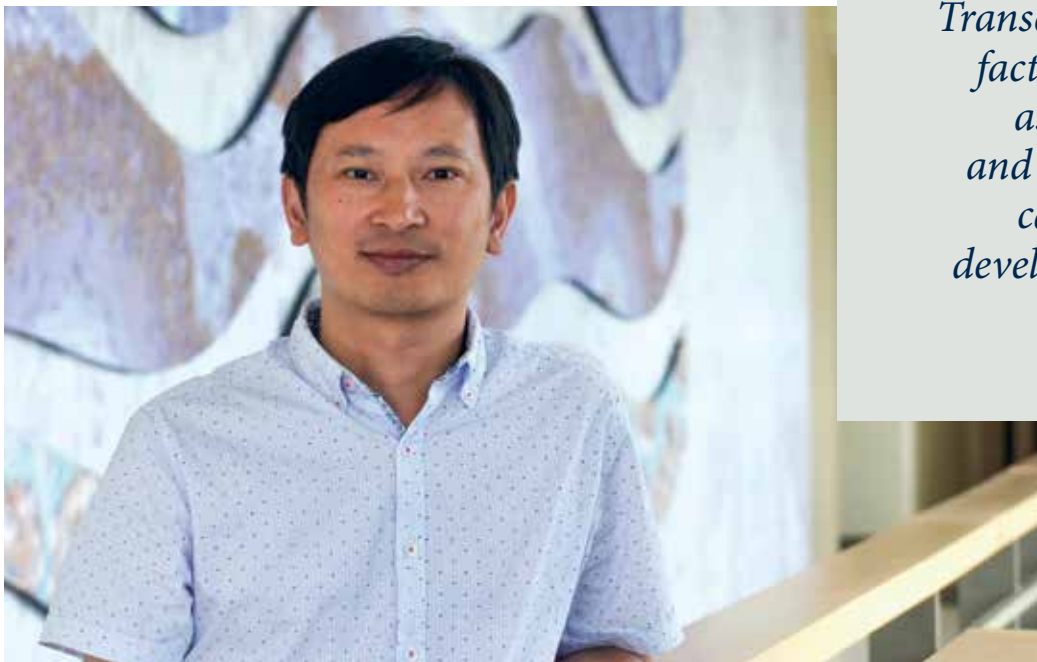
TAZ nuclear transport. Moreover, microarray and CHIP-qPCR showed that nuclear p300 acetylated histones and facilitated HSCs to express TGF β target genes encoding tumor-promoting factors, including CTGF, TNC, POSTN, PDGFC, and FGF2. In agreement with these findings, function assays revealed that p300 knockdown HSCs were less effective than control HSCs on promoting tumor proliferation and growth in a tumor/HSC coculture and tumor/HSC coimplantation *in vivo* model and that therapeutic targeting of activated-HSC/myofibroblasts selectively by C646 suppressed tumor growth in *in vivo* models. In summary, TGF β -mediated

HSC activation process requires orchestration of both the cytoplasmic and nuclear p300. The cytoplasmic p300 regulates nuclear transport of SMAD2/3 and TAZ via its scaffolding function and nuclear localization signal and the nuclear p300 facilitates gene expression via epigenetic mechanisms. P300 acetyltransferase represents a critical target for inhibiting HSC activation and the prometastatic liver microenvironment.

Other professional activities:

An abstract entitled: *Focal adhesion kinase promotes myofibroblastic activation of hepatic stellate cells by preventing lysosomal targeting and degradation of TGF β receptor II* has been submitted in June 2018 and selected as Oral Presentation for The Liver Meeting, AASLD, 2018.

An abstract entitled: *P300 acetyltransferase scaffolds with SMAD2/3 and TAZ to mediate their nuclear transport in TGF β activation of hepatic stellate cells* has been submitted in June 2018 and accepted as Poster Presentation for The Liver Meeting, AASLD, 2018.



“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

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 σ_{32} , σ_{28} , σ_{24} and σ_{19} .

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.

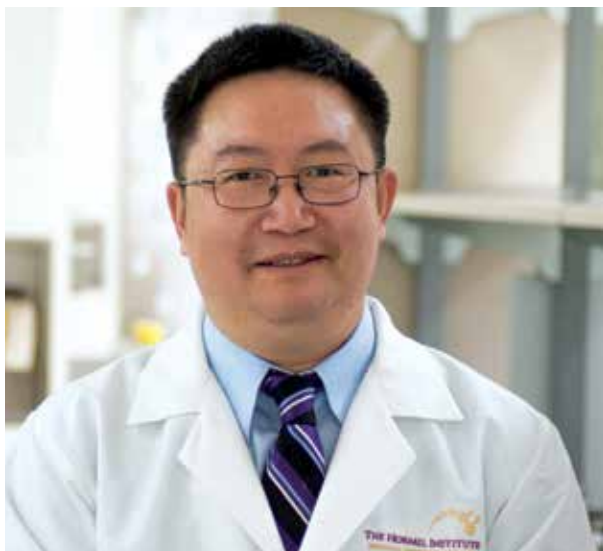
3. To characterize the basis of transcription termination and its regulation by the general transcription factors: NusA and NusG

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.





Summary

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

Receptor tyrosine kinases are epigenetic activators in leukemia

Receptor tyrosine kinases (RTKs) are membrane-spanning proteins that exhibit intrinsic phosphotyrosine kinase activity. RTKs are frequently dysregulated in leukemia, yet the biological consequences of this dysregulation are largely unclear. The mechanisms underlying aberrant methylation, a hallmark of leukemia, are not fully understood. Further, because hyperactive RTKs crucially contribute to leukemia pathogenesis, their inhibitors (TKIs) have been broadly tested against leukemia. However, the molecular mechanisms by which TKIs suppress leukemia growth remain elusive. We found that upregulation of RTKs paralleled DNMT overexpression in leukemia cell lines and patient blasts. Knockdown of RTKs disrupted, whereas enforced expression increased, DNMT expression and DNA methylation. Treatment with the RTK inhibitor, nilotinib, resulted in a reduction of Sp1-dependent DNMT1 expression, the diminution of global DNA methylation and the upregulation of the p15INK4B gene through promoter hypomethylation in AML cell lines and patient blasts. This led to disruption of AML cell clonogenicity and promotion of cellular apoptosis without obvious changes in cell cycle. Importantly, nilotinib administration in *in vivo* models and human patients with AML impaired expression of DNMTs followed by DNA hypomethylation, TSG re-expression, and leukemia regression. Our study provides the first evidence that RTKs are modulators of DNMT1-dependent DNA methylation in leukemia cells. Our study has for the first time documented that TKIs impair DNMT1 expression resulting in global and gene specific DNA hypomethylation. These findings demonstrate RTKs as new types of epigenetic regulators and unravel a signaling interaction between RTKs

and DNMTs in leukemia pathogenesis, shedding light on leukemia molecular biology. Our data identify the DNA hypomethylating activities of TKIs, thus significantly expanding the pool of DNA methylation inhibitors. Our discoveries provide a mechanistic explanation why TKIs show therapeutic efficacy in patients without target mutations, and suggest that altered DNA methylation profile might be alternative predictors of responses in patients without RTK mutations. Altogether, our work provides the preclinical rationale for using TKIs 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 leukemia therapy

Acute myeloid leukemia (AML) is a highly aggressive hematologic malignancy characterized by the swift uncontrolled growth of immature myeloblasts. It is a lethal disease that lacks effective treatment. Although the precise molecular causes that are responsible for AML development and disease progression are unclear, it seems to result from an interplay of genetic and environmental factors that are largely unidentified. Aberrant DNA methylation mediated by dysregulation of DNA methyltransferases (DNMT) is a key hallmark of AML, yet efforts to target DNMT dysregulation for drug development have lagged. We previously demonstrated that upregulation of fatty acid-binding protein 4 (FABP4) promotes AML aggressiveness through enhanced DNMT1-dependent DNA methylation. Here we demonstrate that FABP4 upregulation in AML cells occurs through vascular endothelial growth factor (VEGF) signaling, thus elucidating a crucial FABP4-DNMT1 regulatory feedback loop in AML biology. We show that FABP4 dysfunction by a selective inhibitor BMS309403 leads to downregulation

of DNMT1, decrease of global DNA methylation and re-expression of p15INK4B gene by promoter DNA hypomethylation *in vitro*, *ex vivo* and *in vivo*. Functionally, BMS309403 suppresses cell colony formation, induces cell differentiation, and, importantly, impairs leukemic disease progression in *in vivo* models of leukemia. Our findings highlight AML-promoting properties of the FABP4-DNMT1 vicious loop, and identify an attractive class of therapeutic agents with a high potential for clinical use in AML patients. The results will also assist in establishing the FABP4-DNMT1 loop as a target for therapeutic discovery to enhance the index of current epigenetic therapies.

Crosstalk between epigenome and kinome regulates the aggressiveness of cancers

DNA methylation occurs at the 5-position of cytosine in a CpG dinucleotide context and is a major epigenetic mechanism regulating chromosomal stability and gene expression. DNA methylation is under control of DNA methyltransferases (DNMTs) that are highly expressed in cancers. Our findings suggest that DNMT overexpression is attributed to Sp1/miR29 network, miR101, nucleolin, and

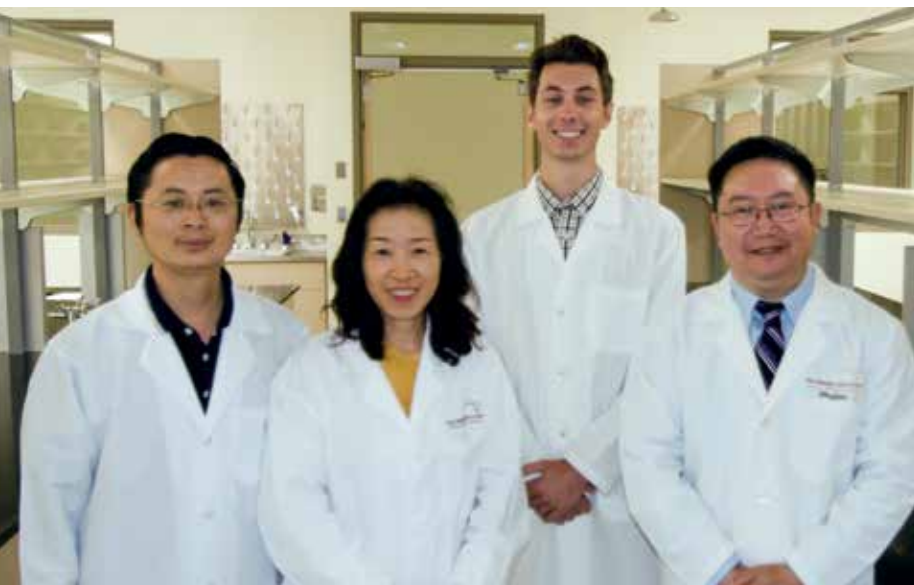
recently, cytokines (e.g., IL-6/IL-15). In addition, abnormal kinase activities are essential in cancer initiation and metastasis. While kinase mutations are crucial, our main focus is shifted to kinase overamplification, which significantly contributes to the development, progression and drug resistance of cancers. Our discoveries support the idea that receptor tyrosine kinases are regulated by the Sp1/miR29 network. Because Sp1/miR29 is also involved in DNMT gene regulation, we proposed that aberrant DNMT activities may control kinase signaling. Indeed, we demonstrated that KIT and DNMT1 form a regulatory circuit, in which KIT regulates DNMT1 expression through STAT3 pathway, whereas DNMT1 modulates KIT expression through the Sp1/miR29 loop. Functionally, KIT and DNMT1 synergistically enhance cancer cell survival and proliferation, implicating the effectiveness of dual inhibition. The crosstalk of KIT and DNMT1 also exists in leukemia, liver cancer and breast cancer. These findings identify the regulatory and functional interactions between kinases and DNA methyltransferases, and highlight the key role of the crosstalk between the dysregulated KIT signaling and DNA hypermethylation in cancer cell survival and proliferation.

ity, high affinity to plasma proteins and poor cellular uptake. Gold nanoparticles (AuNPs) with high-density lipoprotein (HDL) have been utilized to deliver oligonucleotides, yet HDL-AuNPs functionalized with small molecule inhibitors have not been systematically explored. We have constructed an AuNP-based therapeutic system (HDL-AuNPs-BMS), and successfully delivered BMS309403 (BMS), a small molecule that selectively inhibits AML-promoting factor fatty acid binding protein 4 (FABP4), *in vitro* and *in vivo*. Compared to free drug, HDL-AuNPs-BMS conjugates are more readily internalized by AML cells and have more pronounced effects on downregulation of DNA methyltransferase 1 (DNMT1), induction of DNA hypomethylation, and restoration of epigenetically-silenced tumor suppressor p15INK4B coupled with AML growth arrest. Importantly, systemic administration of HDL-AuNPs-BMS conjugates into AML-bearing *in vivo* models inhibits DNMT1-dependent DNA methylation, induces AML cell differentiation and diminishes AML disease progression without obvious side effects. In summary, these data, for the first time, demonstrate HDL-AuNPs as an effective delivery platform with great potential to attach distinct inhibitors, and HDL-AuNPs-BMS conjugates as a promising therapeutic platform to treat leukemia.

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

HDL-AuNPs-BMS conjugates are promising therapeutic platforms to treat leukemia

The current chemotherapeutic drugs (i.e., small molecules, siRNA or miRs), although having potent anti-cancer activity, suffer from a variety of drawbacks when administered particularly *in vivo*, including rapid clearance, lack of tissue selectiv-

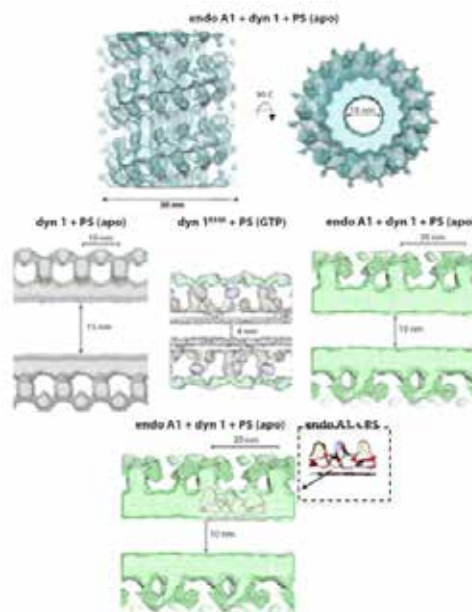


FROM LEFT TO RIGHT:
Xiaochang Liu, Jiuxia Pang, Ryan Kempen, Shujun Liu



“Insight into the functions of a protein start with understanding its structure.”

Anna Sundborger-Lunna



for recruitment and assembly of dynamin 1 at sites of plasma membrane fission (1).

Our preliminary cryo-EM 3D reconstruction of an endophilin A1-dynamin 1 complex assembled on lipid tubes indicate that endophilin A1 assembles into a helical membrane scaffold for dynamin 1 that promotes membrane binding and dynamin organization (Fig. 2).

We propose that endophilin B1 regulates mitochondrial dynamics and cell death events in a similar fashion, via recruitment and organization of Drp1, IRGM, Bax, and other effector proteins at the MOM. We speculate that loss of endophilin B1 has a detrimental effect to mitochondrial health and consequently plays a key role in carcinogenesis. Critical in elucidating the role of endophilin B1 in regulation of mitochondrial dynamics and cell death is defining the molecular mechanisms underlying endophilin B1 function. Our preliminary data shows that Endophilin B1 adopts multiple organizations on lipid membranes (helical scaffolds and small assemblies (Fig. 3). We find that endophilin B1 membrane binding is facilitated by mitochondrial-specific lipid, cardiolipin, which is enriched in the MOM. Endophilin B1 scaffold assembly and membrane remodeling activity is auto-inhibited, and our current efforts are to define the role of Drp, IRGM and Bax in regulation of endophilin B1 function at the MOM.

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); (ii) Immunity-Related GTPase M (IRGM), an 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

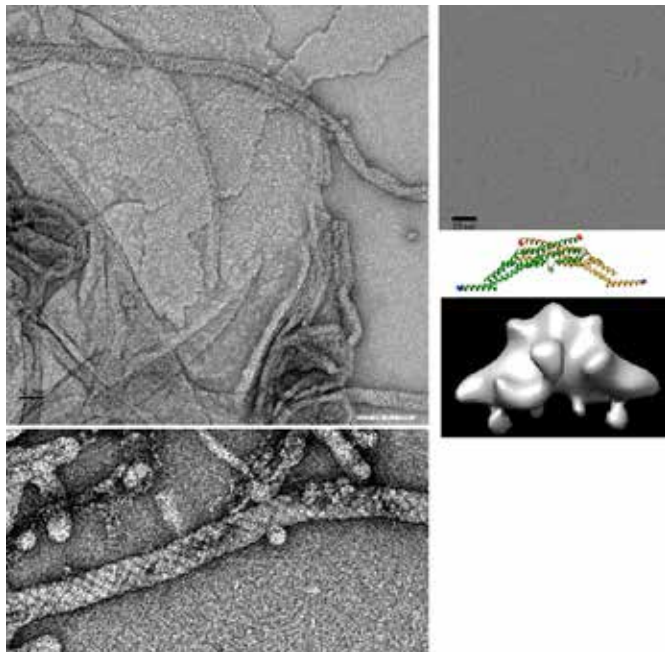
Bob Ashley, Cryo-EM Manager



Bob Ashley is the Electron Microscopy Core Facility manager. He is a graduate of Madison College in Madison Wisconsin, which at the time, was one of two professional schools in the nation with a program focused solely on electron microscopy and electron optics. His first position was at the Penn State College of Medicine in Hershey Pennsylvania and received further training at The University of Pittsburgh as an apprentice in the craft of cryo-EM. After 6 years developing a biological cryo-EM core at Penn State, he came back to the Midwest when the Hormel Institute recruited him to run their premier Electron Microscopy facility and has been here since August of 2016.

Other professional activities:

- *10th Annual Bioinformatics and Computational Biology Research Symposium*
University of Minnesota, Rochester, MN
- *Van Andel Seminar Series*
Van Andel Research Institute, Grand Rapids, MI
- *LCMB Research Seminars*
National Institutes of Diabetes & Digestive & Kidney Diseases, Bethesda, MD

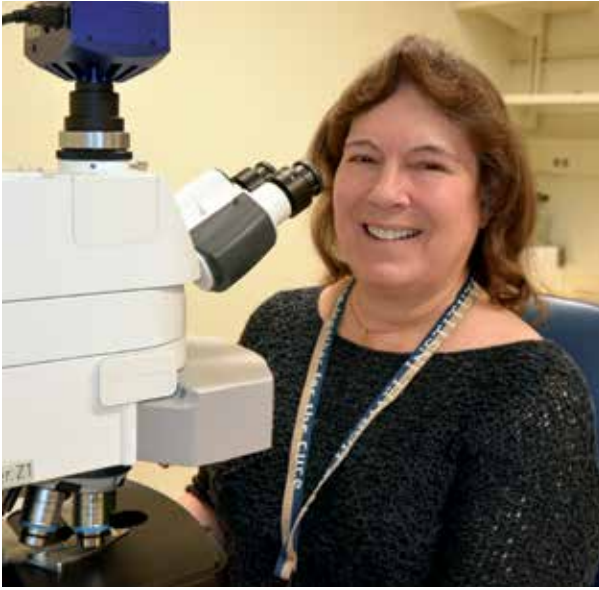


FROM LEFT TO RIGHT:
Veer Bhatt and Anna Sundborger-Lunna

Stem Cells and Cancer

Rebecca J. Morris, Ph.D.

SECTION LEADER / PROFESSOR



Summary

The epidermal layer of the skin is composed largely of cells called keratinocytes. Keratinocytes in the basal layer are organized into subpopulations based on their proliferative nature and include stem cells (relatively rare)

Non-melanoma skin cancer is a significant problem for cancer research because, although rarely a cause of death, it occurs more frequently than any other malignancy, and more than five million new cases are diagnosed in the United States annually with a burden of more than

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

eight billion dollars. An estimated one-third to one-half of all human cancers originate in the skin; skin cancers exceed all others combined; and the lifetime risk of skin cancer the United States is one in five. Solar ultraviolet radiation is the major known cause of non-melanoma skin cancers and is directly relevant to the etiology as demonstrated by epidemiological evidence and the tight correlation between non-melanoma skin cancer in humans, and solar radiation- and chemically-induced skin carcinogenesis in murine models. These cancers progress through an orderly sequence in which genetic, biochemical, and cellular abnormalities accumulate in target cells over time. Mild alterations initially seen within keratinocytes can only be identified histologically. Increased cellular atypia occurs with further sun damage, and hyperkeratotic, pre-malignant actinic keratoses develop.

Current research projects:

- We are investigating the roles of bone marrow derived cells in non-melanoma skin cancer: the mechanisms of recruitment, the nature of the recruiting molecules, the identity of the recruited cells, and the interaction of epithelial cells and their environment in tumor development.
- We are also investigating the roles of bone marrow derived cells and their environment in mammary epithelial cancers.
- We thereby hope to predict malignant conversion and to understand how adult tissue stem cells are regulated.

“We ‘visualize how things might happen’ and determine how stem cells behave, how they move around the body, and how they develop into tumors.”

Rebecca J. Morris

Of these, one to ten percent will progress to squamous cell carcinomas. Therefore, determining the etiology of nonmelanoma skin cancer is a critical problem in cancer research. Because avoiding exposure to sunlight is far more easily said than done, there is considerable interest in increasing knowledge of skin cancer etiology and finding targets for prevention.

We have investigated the etiology of squamous cell carcinoma we focus on cytokeratin expressing cells in the blood and bone marrow and their role in cancer development. Cytokeratins are frequently found in the blood and bone marrow of patients with epithelial cancers and are attributed to metastasis. We wondered whether we could find keratin expression in blood and bone marrow in untreated adult *in vivo* models. To address this problem, we have used classical immunoreactivity, Krt1-14;mTmG transgenic *in vivo* models together with fluorescence activated cell sorting, and quantitative reverse transcriptase polymerase chain reaction. We have made several novel findings. First, we discovered, rare but distinctive, keratin-14 and keratin-15 immunoreactive cells the size of small lymphocytes in blood and bone marrow. Second, using Krt1-14;mTmG transgenic *in vivo* models, we found low (8.6 GFP positive cells per 10⁶ cells analyzed), but significant numbers ($p < 0.0005$) of GFP positive cells in bone marrow when compared with negative controls. Third, qRT-PCR demonstrated very low but reproducibly detectable expression of keratin-14 mRNA in blood and bone marrow when compared with epidermal keratinocytes: with blood expressing one thousand times, and bone marrow, one hundred thousand times, less than epidermal keratinocytes.



Moreover, flow cytometric analysis of fresh bone marrow disclosed a subpopulation of keratin-14 immunoreactive cells that was negative for hematopoietic lineage markers. We conclude from these observations that keratin-14 protein and mRNA are expressed at low, but detectable levels in the blood and bone marrow of *in vivo* models. These observations should further our understanding of cutaneous biology, non-melanoma skin cancer, and other epithelia and their cancers.

In summary, research in the Morris laboratory continues to highlight the role of stem cells in the pathogenesis of squamous cell carcinoma, and has documented an unexpected contribution of bone marrow derived cells. Going forward, we will probe the interactions between epidermal stem cells and bone marrow derived cells as tumor initiating- and propagating- cells.

FROM LEFT TO RIGHT:
Stephanie Holtorf, Samantha Skaar, Rebecca Morris,
Sonali Lad, Aalekhya Biswas

Other professional activities:

- **Grants reviews:** for the Veterans' Association, for the National Institutes of Health, and for the State of Nebraska
- **Teaching:** 2017 Summer Short Course on Introduction to Histopathology at the Hormel Institute
- **Educational outreach:** City of Austin School System

Cell Signaling and Tumorigenesis

James Robinson, Ph.D.

SECTION LEADER / ASSISTANT PROFESSOR



Summary

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, Florina Grigore M.D., and Hana Yang, Ph.D, and Nick Hanson a technician whose a former Undergraduate Research Experience (SURE) intern.

Melanoma: Melanoma is the most dangerous form of skin cancer. According to the CDC, Minnesota has the highest incidence of melanoma in Midwest states. Despite advances in melanoma research, the five-year survival rate for patients with advanced Melanoma remains around 16%. Two therapeutic agents, vemurafenib, and dabrafenib, are FDA-approved for the treatment of advanced melanomas that carry BRAFV600E mutations. Although the initial response to these inhibitors can be dramatic, the melanomas nearly always become resistant. Using a novel in vivo model of melanoma we have developed that provides an exceptional experimental system to study this issue. We are determining and validating the mechanisms of melanoma's resistance to these inhibitors. This work is generously funded through an American Cancer Society Research Scholar Grant worth nearly \$800,000.

The American Cancer Society is the largest nonprofit source of grant funding for cancer researchers in the United States, other than the government. Furthermore, in October of 2017 Dr. Otis Brawley, Chief Medical and Scientific Officer for ACS visited The Hormel Institute, UMN, to plan and develop further support for The Hormel Institute's cutting edge cancer research.

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

“We are working toward the ultimate goal of developing and improving existing therapeutic approaches to eliminate cancer.”

James Robinson

Colon Cancer. After lung and prostate cancer, colon cancer the leading cause of cancer deaths in the United States with 132,770 new cases and 49,700 deaths anticipated in 2015. About 75% of cases are sporadic with no obvious evidence of an inherited disorder. The remaining 25% of patients have a family history of CRC that suggests a hereditary contribution, common exposures among family members, or a combination of both. Familial adenomatous polyposis (FAP), is one of the most clearly defined and well understood of the inherited colon cancer syndromes. Our preliminary data has demonstrated that

loss of APC is insufficient for tumorigenesis and additional growth signals or mutations are also required for nuclear accumulation of β -Catenin and intestinal polyposis. Since in vivo models of FAP develop a multitude of intestinal polyps without additional genetic alterations, these additional signals are likely to arise from adjacent stromal cells. If we can show that stromal signaling plays a driving role in tumorigenesis, following or pre-empting epithelial LOH of APC, it should be possible to develop targeted therapeutics to block this signaling. A major preliminary finding is that heterozygous mutation of APC

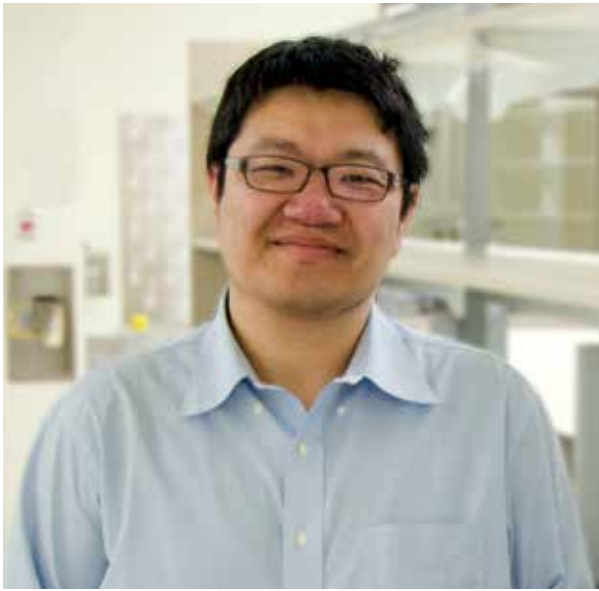
in vivo is not sufficient cause tumor formation. Our sections work on Colon cancer has been funded by the National Institutes of Health (NIH) and our ongoing studies will contribute to the development of novel therapies and improve the outcome for patients with colon cancer.



FROM LEFT TO RIGHT:
Nick Hanson, James Robinson,
Hana Yang, Florina Grigore

Computational Cancer Genomics
Rendong Yang, Ph.D.

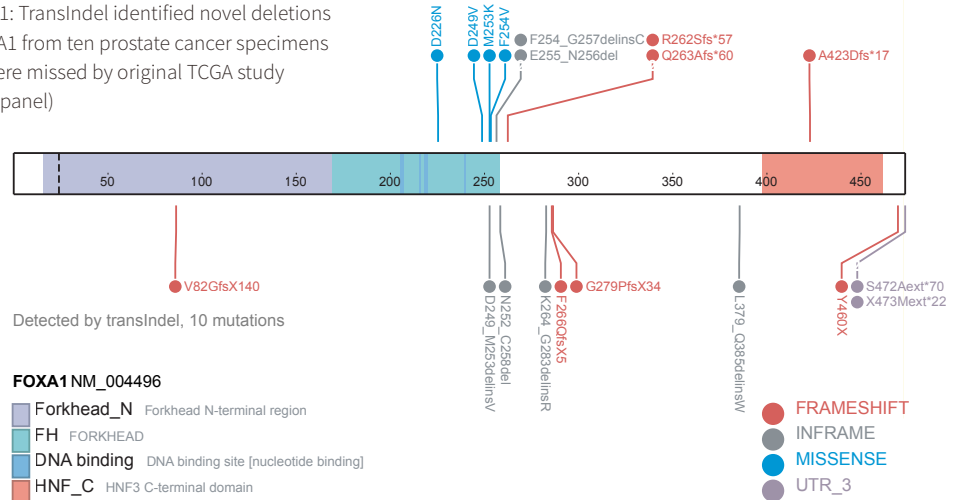
SECTION LEADER / ASSISTANT PROFESSOR



Summary

DNA and RNA alternations detection in cancer genome and transcriptome. Our recent work has been in the development of innovative bioinformatics algorithms for detecting DNA alterations including insertions and deletions (indels) and large-scale structural variations (inversions, tandem duplications and translocations). We developed ScanIndel and transIndel algorithms to detect indel from DNA and RNA sequencing data. With the new algorithms, we discovered recurrent novel indels and exon splicing events in prostate cancer genome.

Figure 1: TransIndel identified novel deletions in FOXA1 from ten prostate cancer specimens that were missed by original TCGA study (lower panel)



Detecting gene rearrangement, splicing and epigenetic regulator of AR in prostate cancer.

We developed an integrated pipeline to detect structural rearrangements in the AR gene, which encodes the androgen receptor. Through this work, we identified diverse genomic-dependent and genomic-independent AR splicing variants expressed prostate cancer. Additionally, our early work focuses on prostate cancer epigenomic studies by analyzing the ChIP-seq data of AR and BRD4 in prostate cancer VCaP cell line. Our study revealed the crosstalk between AR and BRD4 signaling in prostate cancer progression.

1. Detecting novel indels from prostate cancer genome.

We developed transIndel, a splice-aware algorithm that parses the chimeric alignments predicted by a short read aligner and reconstructs the mid-sized insertions and large deletions based on the linear alignments of split reads from DNA-seq or RNA-seq data. TransIndel exhibits competitive or superior performance over eight state-of-the-art indel detection tools on benchmarks using both synthetic and real DNA-seq data. We applied transIndel to DNA-seq and RNA-seq datasets from 333 primary prostate cancer patients from The

“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 treatment.”

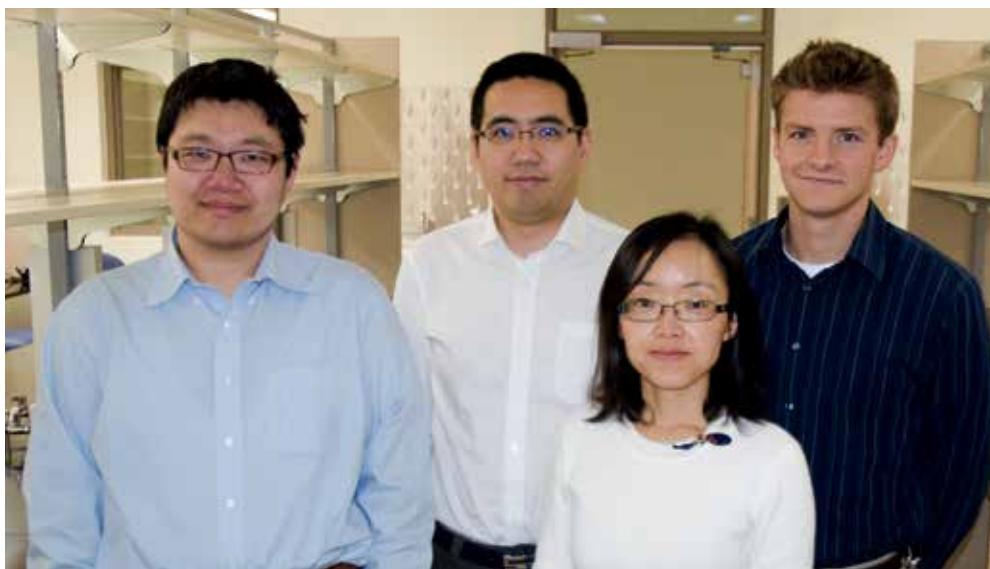
Rendong Yang

Cancer Genome Atlas (TCGA) and 59 metastatic prostate cancer patients from AACR-PCF Stand-Up- To-Cancer (SU2C) studies. TransIndel enhanced the taxonomy of DNA- and RNA-level alterations in prostate cancer by identifying recurrent FOXA1 indels (Figure 1) as well as exon splicing in genes implicated in disease progression.

2. Delineating lncRNA landscape in prostate cancer genome

Prostate cancer (PCa) is the most commonly diagnosed cancer in men in United States, with significant health impact. Clinically, it is complicated with the lack of biomarkers and effective treatments for aggressive disease, particularly castration-resistant prostate cancer (CRPC). We have gained much insight into the biology of PCa through studying protein-coding genes, but they represent only a small fraction of our genome. Long noncoding RNAs (lncRNAs) have increasingly been recognized as playing essential roles in tumor biology, representing a new focus in cancer research.

Many lncRNAs have been shown to be either up- or down-regulated in various cancers, including PCa. Several PCa-specific or PCa-associated lncRNAs have been identified to date, but only a few have been validated in independent patient cohorts or approved for clinical practice. Our current research is developing novel computational methods to achieve the first complete compendia of CRPC-associated lncRNAs and reveal the dynamic interplay between lncRNAs and tumorigenesis, progression and metastasis, which will highlight the importance of lncRNAs in the etiology of PCa.



FROM LEFT TO RIGHT:
Rendong Yang, Tingyou Wang, Yanan Ren, Luke Voneschen

3. Detecting novel biomarkers for cancer immunotherapy

Immune checkpoint blockade therapy has proved to be effective on a number of cancer types such as skin, lung and kidney cancer. However, only part of the patients has response to immunotherapy drugs. We have developed a novel computational algorithm which 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 correlation of 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 identify a list of candidate genomic independent alternative splicing events that play a role underlying the resistance of immunotherapy in the non-responders or the effects in the responders.

Other professional activities:

Award:

PhRMA foundation Research Starter Grant 2018

Publication:

Yang R, Van Etten JL, Dehm SM. Indel detection from DNA and RNA sequencing data with transIndel. *BMC Genomics*. 2018;19:270.

SUPPORTING DEPARTMENTS



FROM LEFT TO RIGHT:
 Front Row, Alisa Wagner, Mark Severtson, Julie Little
 Middle Row, Randy Johnson, Kim Downey, Duane Graff
 Back Row, Nathan Britt, Brandon Hoium

Building Operations and Maintenance

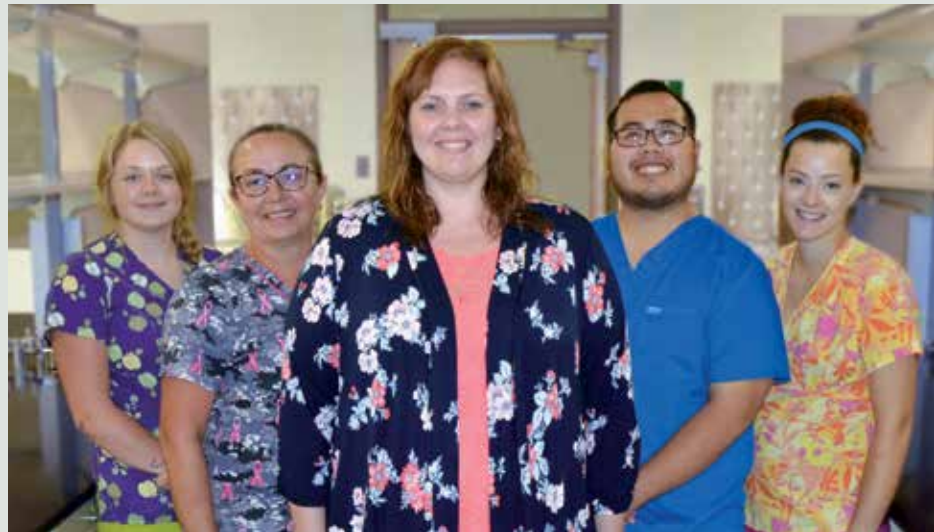
Mark Severtson / Building Systems Manager

My staff and I continue to work 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 are currently working on piggy backing onto the U of M's maintenance program, a software that links our equipment for required maintenance throughout the year.

Research Support Group

Kim Klukas / Supervisor

The Hormel Institute's Research Support Group continues to serve the institute's investigative staff and the research program at large by providing valuable services, training and guidance. This is accomplished through the utilization of trained and dedicated professionals who are committed to biomedical research. In the summer of 2018 an 8 week internship was introduced that will be provided in years to come. Three team members are currently working towards becoming certified within the industry to provide high quality research support that leads to scientific gains that benefit people and animals.



FROM LEFT TO RIGHT:
 Kate Viker, Chelle Jacobson, Kim Klukas, An Le, Chrissa Champbell



Research Support Services

Brian Larson / RSS Manager

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

FROM LEFT TO RIGHT:

Tim Lastine, Mike Conway, Theresa Tucker, Brian Larson

International Center of Research Technology. During the summer of 2017, we installed a large storage solution (DDN) for the Cryo-EM microscope. This was an integral part to process the huge amounts of data produced by the Cryo-EM microscope. This has been another wonderful year for the RSS team, and next year is looking to be just as exciting as the use of the microscope and HI Staff continues to increase.

Library

Andy Lucus / 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 through the MINITEX delivery service and are available for pickup in The Hormel Institute Library. Articles that are not available in electronic form are obtained through interlibrary loan.



FROM LEFT TO RIGHT:

Becky Earl, Loree Anderson, Julie Gerstner, Ann Bode, Jessica Swanson, Nicki Van Erkel Brickman, Betsy Mentel



light with internal grids. Additionally, laser capture users can enjoy hands-free, laser microdissection for isolating high-purity tissue from cryosections and FFPE materials. This feature utilizes a focused laser beam to cut and isolate the region of interest, and the laser catapult transfers the specimen into a small tube for DNA, RNA, or protein analysis. Additional microscopes include a Zeiss stereo, Nikon confocal, and a Leica fluorescent microscope.

Other shared instruments include a Becton Dickinson FACS ARIA II cell sorter and FACSCalibur flow cytometer, ABSCIEX 5600 Triple TOF mass spectrometer with an Eksigent Nano LC system, and a Rigaku X-Ray diffraction system for protein crystallography. Real time qPCR instruments, chemiluminescence imagers, spectrophotometers, and centrifuges are also available for use. Histology equipment consists of a Leica tissue processor, embedder, microtome and cryostat.

Ultimately, we look forward to employing these and other core facility equipment to assist research at the Hormel Institute.

FROM LEFT TO RIGHT:

Todd Schuster, Core Facility Manager
Josh Monts, Core Technician

Office

Ann Bode, Ph.D. / Associate Director

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

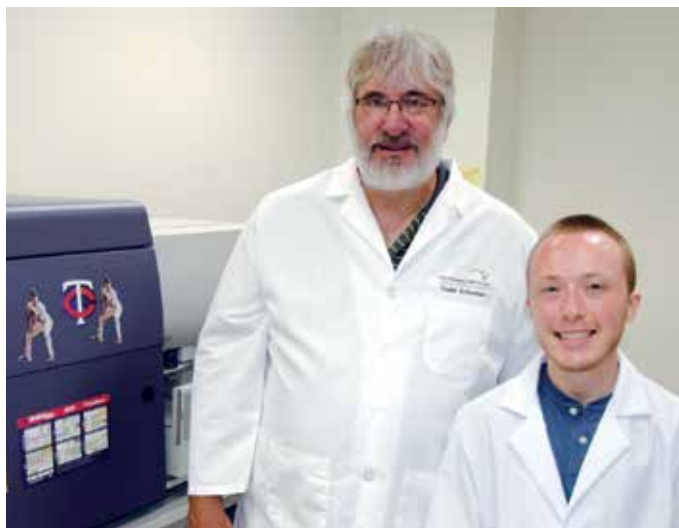
The Bio-Tek Synergy Neo 2 multimode plate reader is another addition that provides sample luminescence, fluorescence, and absorbance information.

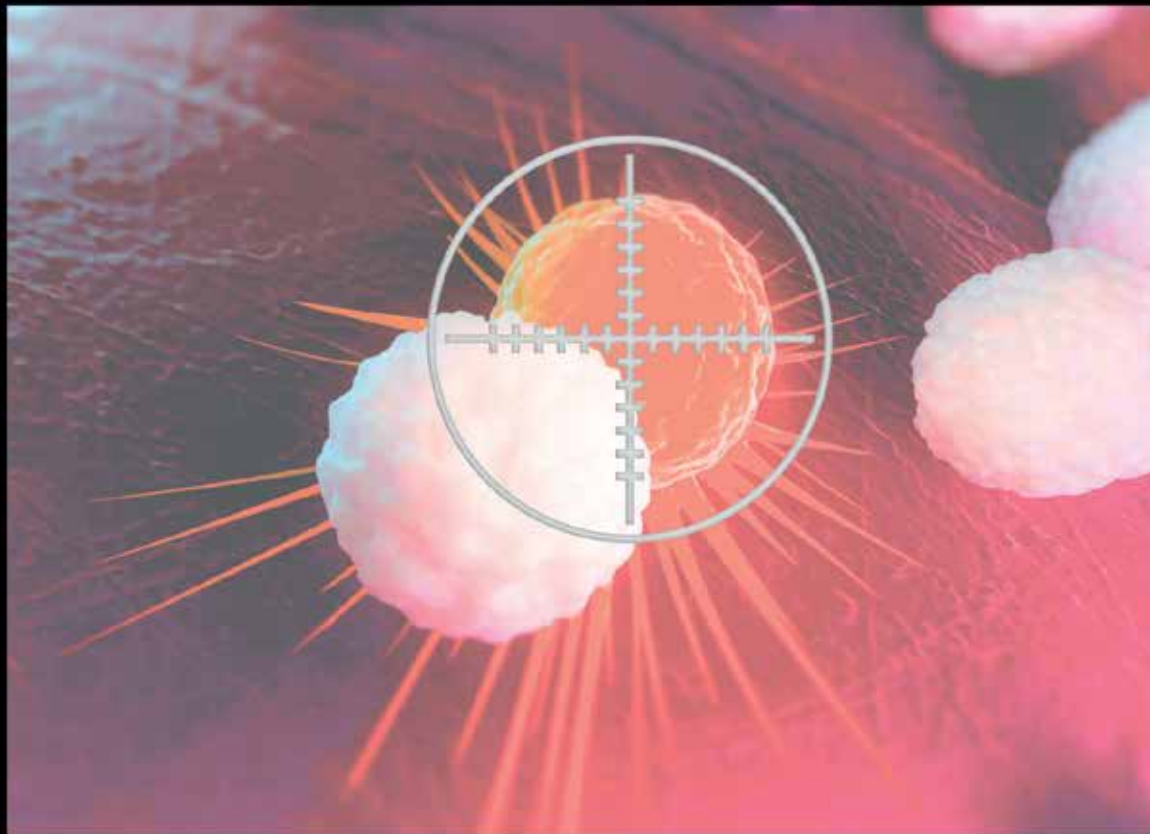
The Shared Instruments Core also acquired two new Zeiss microscopes, an Apotome and laser capture microdissection microscope. The Apotome has many useful capabilities, including 3D rendering with Z stacking and a wide variety of fluorophore options, plus it eliminates scattered out-of-focus

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. Several new instruments were added to the Core this year. The Biacore T200 uses surface plasmon resonance technology to measure interactions between proteins, lipids, and small molecules, and the new IncuCyte S3 Imager allows researchers to perform real time live cell analysis.





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npj PRECISION ONCOLOGY

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

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

DEVELOPMENT AND PUBLIC RELATIONS

Gail Dennison, M.A., CFRE

DIRECTOR / DEVELOPEMENT AND PUBLIC RELATIONS



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

We extend a huge thank you to all who helped to support the innovative cancer research of The Hormel Institute this year through donations, volunteering your time, or spreading the word about The Hormel Institute's world-class research to your friends and family.

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

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

Our guiding principle is to gain support for The Hormel Institute's quest to improve the health of the world through scientific research, so people can live longer, healthier lives - uninterrupted by cancer. Together, we know that for a healthier tomorrow, research must be funded today - thank you for your continued support and joining us on the front lines.

THANK YOU for furthering *The Hormel Institute's* cancer research:

- The Hormel Foundation
- University of Minnesota
- Hormel Foods Corporation
- Mayo Clinic
- Vice President Joseph Biden
- U.S. Ambassador Terry Branstad (China)
- Governor Mark Dayton
- U.S. Senator Amy Klobuchar
- U.S. Senator Tina Smith
- Former U.S. Senator Norm Coleman
- U.S. Representative Tim Walz
- State Senator Dan Sparks
- State Senator David Senjem
- State Representative Jeanne Poppe
- Mayor of Austin – Tom Stiehm
- Mayor of Rochester – Ardell Brede
- Absolute Energy LLC
- Accentra Credit Union
- Adams, Rizzi & Sween
- Clair F. Allen
- American Coalition for Ethanol
- Carol Asleson Estate
- Corrine Astrup
- Austin Area Foundation
- Austin Area Chamber of Commerce
- Austin Bruins "Paint the Rink Pink"
- Austin Community Growth Ventures
- Austin Eagles Club – Aerie 703
- Austin Park & Rec
- Austin Public Schools
- Austin Vision 2020
- Blooming Prairie Cancer Group
- Bowling for the Battle
- City of Austin – Austin Port Authority
- Compeer Financial Fund for Rural America
- Tom and Lori Day
- Deryl Arnold Memorial Golf Tournament
- Development Corporation of Austin (DCA)
- Discover Austin
- Fifth District Eagles Cancer Telethon
- Fishing for a Cure
- GRAUC – Greater Rochester Advocates of Universities and Colleges
- Greater Mower County Paint the Town Pink
- Growth Energy
- Ollie & Shar Hagen
- Home Federal Savings Bank
- Hoot & Ole's and Dutchtown Jumpers
- Hormel Historic Home
- Iowa Renewable Fuels Association
- Joel & Beth Johnson
- Kansas Corn
- Karl R. Potach Foundation
- Richard & Nancy Knowlton
- Randy & Wendy Kramer
- Larry Anderson
- Mike LaValle
- Lyle Area Cancer Auction
- McGough Construction Company
- Dr. Phillip & Gail Minerich
- Minnesota AgriGrowth Council
- Minnesota Chamber of Commerce
- Minnesota VFW Ladies Auxiliary
- Mower County
- Mower County Fair Board
- Mower County USBC Association's "Bowl for a Cure"
- Norma Foster Memorial "Ride for a Reason"
- Pacelli Catholic Schools
- Paint the Town Pink
- Pink Pumpkin Patch Foundation
- Plunging for Pink Polar Plunge
- Dr. Kurt and Brenda Potach
- Gretchen and Mark Ramlo
- Gary & Pat Ray
- Reichel Foods
- Renewable Fuels Foundation
- RSP Architects
- Ryan Gordon Memorial Golf Tournament
- Belita Schindler
- Dr. Harald & Pat Schmid
- Mahlon & Karen Schneider
- Jim & Tammy Snee
- SKB Environmental
- Southern Minnesota Initiative Foundation
- St. Marks Lutheran Home
- Sterling Drug/Astrup Drug/Astrup Family Foundation
- University of Minnesota – Rochester
- U.S. Bank
- U.S. Grains Council
- Thomas & Patricia Wiechmann
- YMCA of Austin

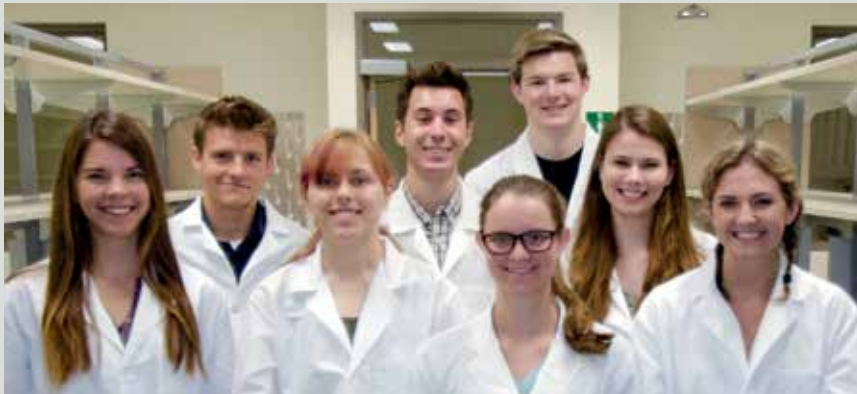
Connections to further cancer research,

Education

The Hormel Institute's faculty and staff conduct extensive educational outreach that reaches children from elementary age to graduate students including scientist judges at local science fairs, scientists visiting Austin's Ellis Middle School and IJ Holton Intermediate School to talk about science and work with students in labs and hosting all Austin sixth-graders for a full day of tours.



SURE Internship (Summer Undergraduate Research Experience)



Undergraduate students selected to work in the annual Summer Undergraduate Research Experience (SURE) program work with 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.

FROM LEFT TO RIGHT:
Front: Adrienne Wessel, Sydney Hastings, Hannah Hitchcock, Madison Jones
Back: Luke Von Eschen, Ryan Kempen, Noah Johnson, Samantha Skaar
Not pictured: Christina Hernandez, Zehua Shao

Mentor Connect

This group brings together Austin area community members and Hormel Institute scientists to develop friendships and help scientists connect with the Austin community.

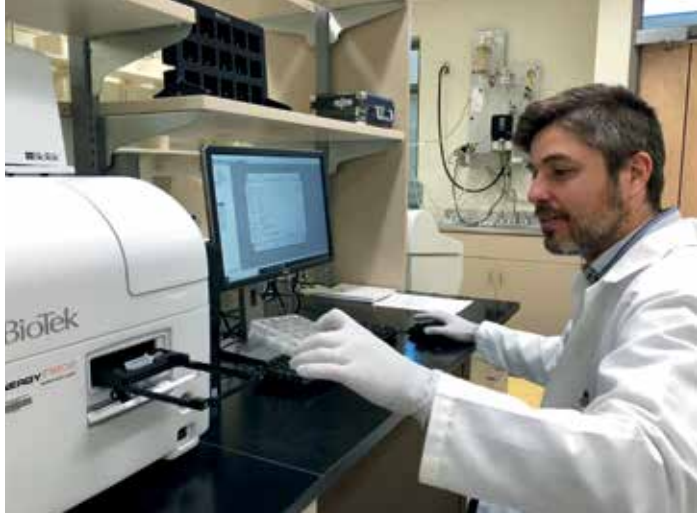


so people live longer, healthier lives

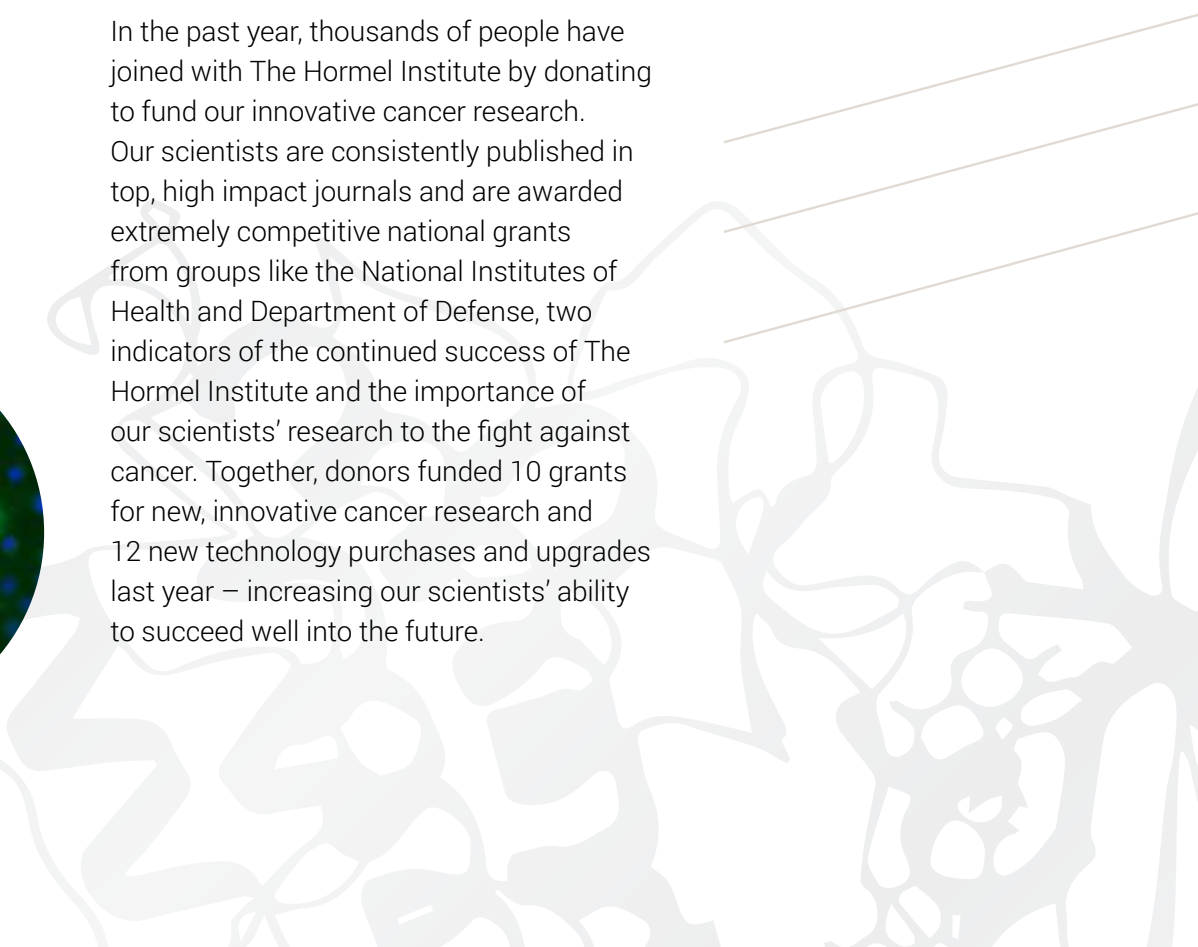
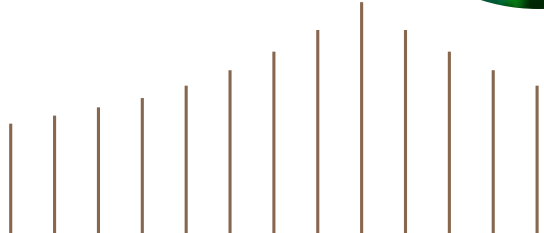
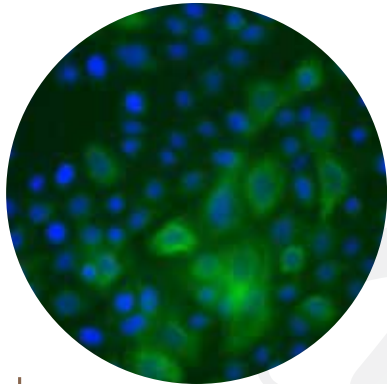


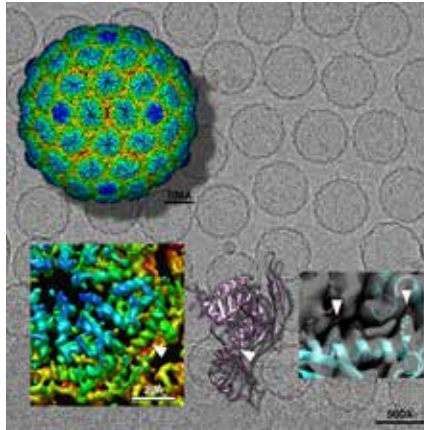
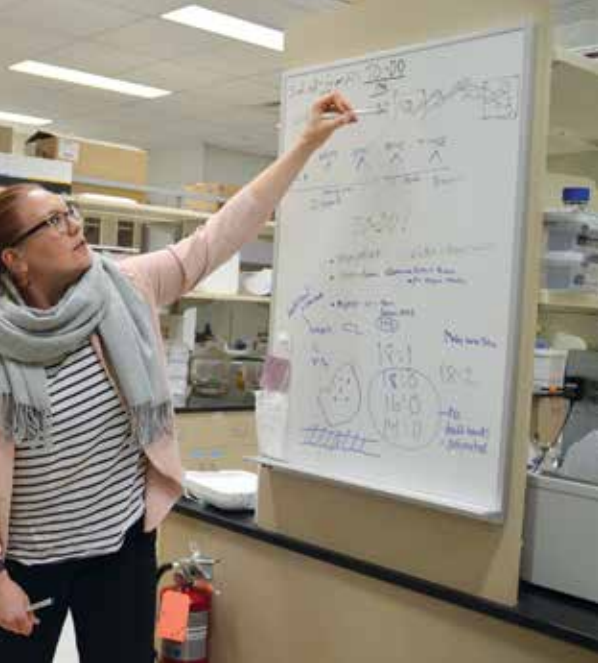
Every

Dollar



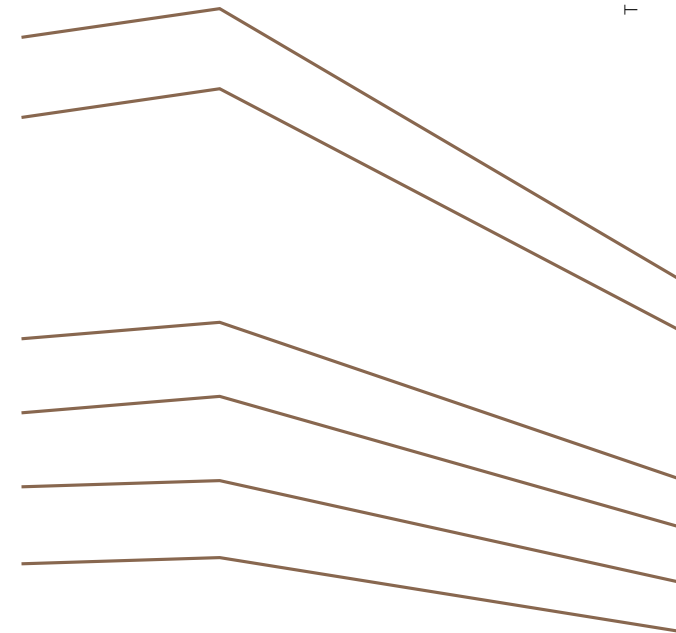
In the past year, thousands of people have joined with The Hormel Institute by donating to fund our innovative cancer research. Our scientists are consistently published in top, high impact journals and are awarded extremely competitive national grants from groups like the National Institutes of Health and Department of Defense, two indicators of the continued success of The Hormel Institute and the importance of our scientists' research to the fight against cancer. Together, donors funded 10 grants for new, innovative cancer research and 12 new technology purchases and upgrades last year – increasing our scientists' ability to succeed well into the future.





We are proud to say that 100% of every donation to The Hormel Institute goes directly to fund research thanks to our generous benefactor, The Hormel Foundation. The Hormel Institute received nearly \$1 million from individual donors last year along with millions in research grants from outside sources. Every dollar drives discoveries, every penny means more research. Know that when you give to The Hormel Institute, your gift joins others to create a major impact that moves us closer to answers to cancer.

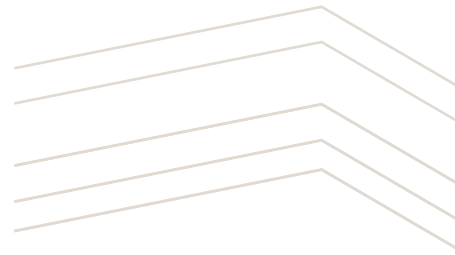
Furtherers Answers





Research

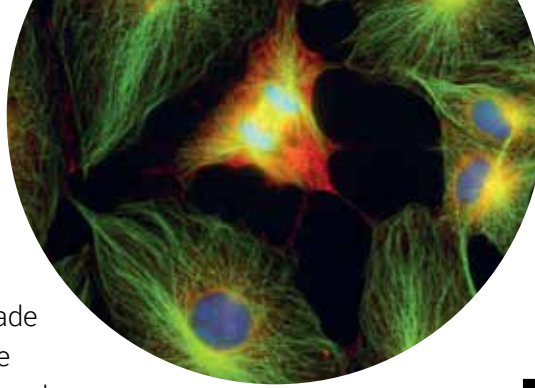
Discoveries



Science and technology walk hand in hand in the race to find new and better ways to prevent and control cancer. Over \$10 million in the latest technology has been added to The Hormel Institute in the last decade to keep our scientists at the forefront of cancer research and to ensure they have the latest tools they need to continue to make breakthroughs that lead to new treatments and new ways to prevent cancer before it ever emerges. Hormel Foods and The Hormel Foundation have been important partners in providing this technology to our scientists.



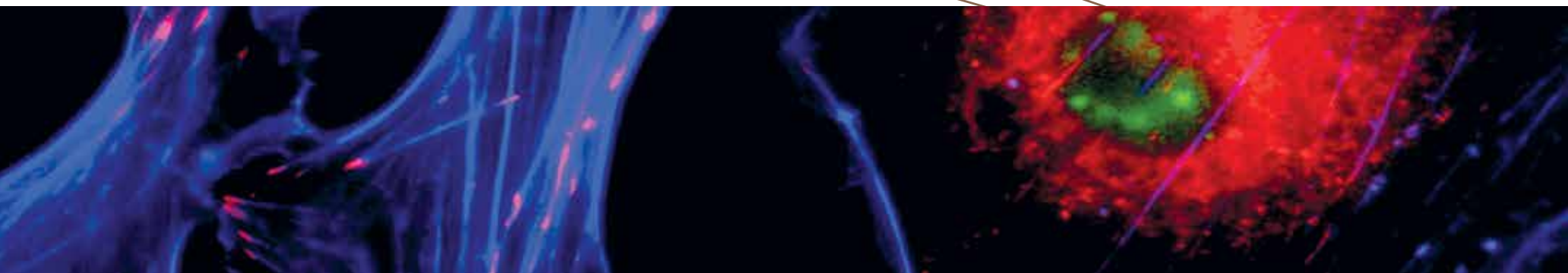
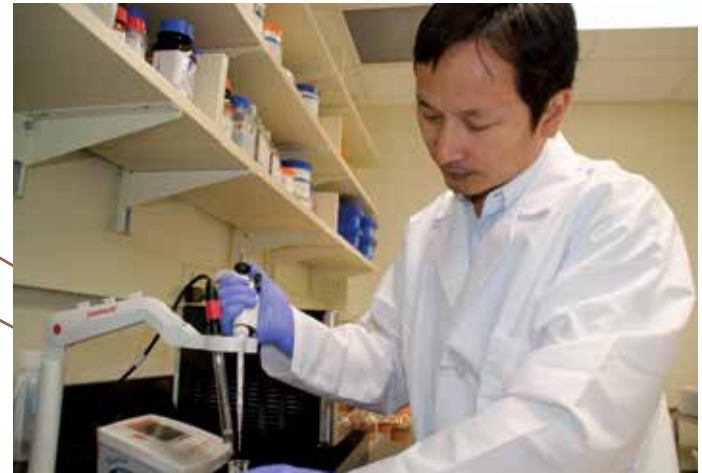
Discoveries in the lab lead to extended lives – because of research done worldwide, 25% fewer lives are lost to cancer each year in the U.S. now than in the 1990s. One example of research in action at The Hormel Institute is the study of Wilms Tumor, a childhood kidney cancer. Our scientists made a significant discovery in understanding this disease thanks to support from the Karl Potach Foundation and “Karl’s Tourney”. The Hormel Institute is also part of the Minnesota Cancer Clinical Trials Network which currently includes two clinical trials using our research, including one based on our research on the effects of ginger on the gut microbiome. Minnesota Chemoprevention Consortium (MC²) - another of The Hormel Institute’s collaborative initiatives - focuses on exploring new ideas and research to prevent and control cancer.

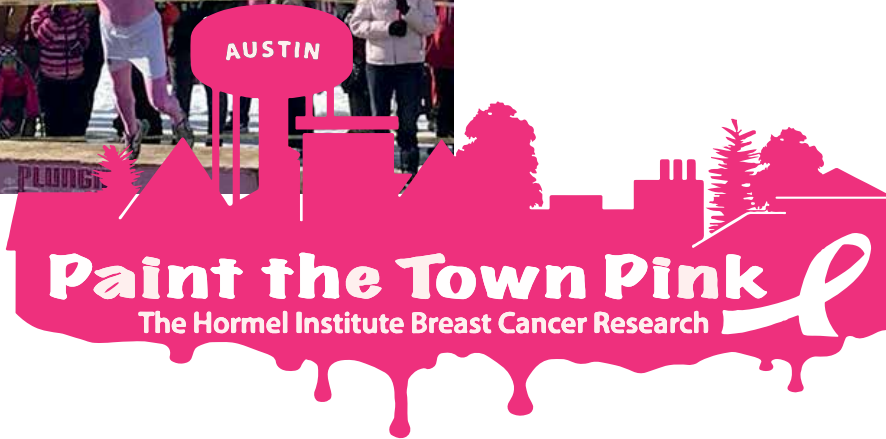
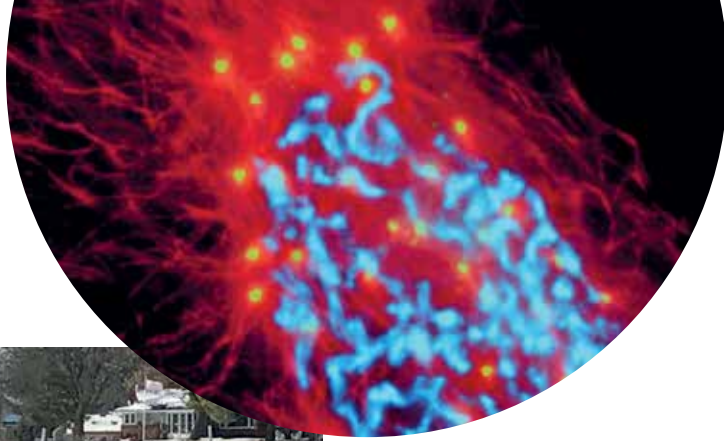


Extending Lives



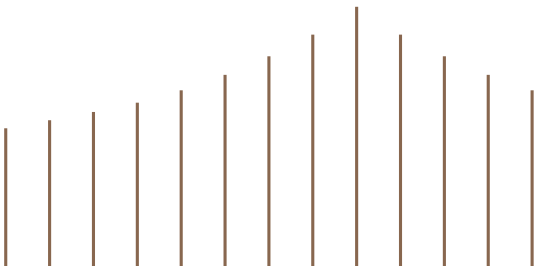
MC²





Your DONATIONS at Work Your Donations IMPACT Science

Our donors make a difference. This year Paint the Town Pink funded eight grants for innovative breast cancer research and two newly funded prostate cancer projects are in process because of Bowling for the Battle. Each of these research projects would not be possible without your donations and impacts not just breast or prostate cancers, but all cancers.



Support from you and organizations like the Fifth District Eagles Cancer Telethon provides not only grant funding and new technology, but also daily encouragement to our scientists who know their community is behind them as they work to find answers to cancer so people can live longer, healthier lives.



Our goal at The Hormel Institute is to intervene and prevent or control cancer at its earliest possible detection. Our community of donors provides the support that keeps our research moving forward toward that goal. Individuals and families, community groups, sports teams, and corporate donors like Compeer Financial, Absolute Energy, and Hormel Foods are all part of our success.



Accelerating **ANSWERS** to **CANCER**

EVERY DOLLAR, EVERY CANCER, EVERY PERSON MATTERS.

- H.I. No. 2163** *L3MBTL2 orchestrates ubiquitin signalling by dictating the sequential recruitment of RNF8 and RNF168 after DNA damage.* Newshean, S. A., K.; Aziz, A.; Deng, M.; Qin, B.; Luo, K. T.; Jegannathan, K. B.; Zhang, H. N.; Liu, T. Z.; Yu, J.; Deng, Y. B.; Yuan, J.; Ding, W.; van Deursen, J. M.; Lou, Z. K. *Nature Cell Biology*, 20(4), 455-464. (2018).
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- H.I. No. 2198** *Jazf1 promotes prostate cancer progression by activating JNK/Slug.* Sung, Y. P., S.; Park, S. J.; Jeong, J.; Choi, M.; Lee, J.; Kwon, W.; Jang, S.; Lee, M. H.; Kim, D. J.; Liu, K.; Kim, S. H.; Lee, J. H.; Ha, Y. S.; Kwon, T. G.; Lee, S.; Dong, Z.; Ryoo, Z. Y.; Kim, M. O. *Oncotarget*, 9(1), 755-765. (2018).
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- H.I. No. 2201** *APIO-EE-9 is a novel Aurora A and B antagonist that suppresses esophageal cancer growth in a PDX mouse model.* Jin, G. G. Y., K.; Guo, Z. P.; Zhao, Z. J.; Liu, K. D.; Liu, F. F.; Chen, H. Y.; Gorja, D. R.; Reddy, K.; Bode, A. M.; Dong, Z. M.; Dong, Z. G. *Oncotarget*, 8(32), 53387-53404. (2017).

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H.I. No. 2243 *Optimization of a microfluidics-based next generation sequencing assay for clinical oncology diagnostics.* Henzler, C. S., M.; Yang, R.; Lambert, A. P.; LaRue, R.; Kincaid, R.; Beckman, K.; Kemmer, T.; Wilson, J.; Yohe, S.; Thyagarajan, B.; Nelson, A. C. *Ann Transl Med*, 6(9), 162. (2018).

H.I. No. 2244 *Protein activation mapping of human sun-protected epidermis after an acute dose of erythemal solar simulated light.* Einspahr, J. G. C.-L., C.; Calvert, V. S.; Stratton, S. P.; Alberts, D. S.; Warneke, J.; Hu, C.; Saboda, K.; Wagener, E. L.; Dickinson, S.; Dong, Z.; Bode, A. M.; Petricoin, E. F. *Npj Precision Oncology*, 1, 10. (2017).

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June 14, 2017

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

August 4, 2017

Doug Kellogg, Ph.D.
 Professor
 MCD
 University of California, Santa Cruz
"Control of cell growth and size"

August 28, 2017

Ronald Lubet, Ph.D.
 Division of Cancer Prevention
 NIH
"Altered Dosing Schedules To Reduce Toxicity And Potentially Enhance Efficacy With Tyrosine Kinase Inhibitors and NSAIDs"
"Chemoprevention Studies In Ras Mutated Tumors In Various In Situ Developing Models: Organ Specificity Of Agents"

October 18, 2017

Dr. Jesus Bañales, Ph.D.
 Head, Liver Diseases Group. Biodonostia Research Institute Donostia University Hospital. Sebastian, Spain
"Role of serum extracellular vesicles for the diagnosis of primary sclerosing cholangitis and cholangiocarcinoma"

Dr. Pablo Ortiz, MD, Ph.D.

CEO One Way Liver, Metabolomics Products & Services.
 Bilbao, Spain.
"Lipidomics as a tool for non-alcoholic steatohepatitis (NASH) diagnosis and staging"

November 2, 2017

Yuanzheng He, Ph.D.
 Research Assistant Professor
 Van Andel Institute
"Structural Basis of GPCR Desensitization"

November 6, 2017

Avner Schlessinger, Ph.D.
 Assistant Professor, Pharmacological Sciences
 Tisch Cancer Institute
 Icahn School of Medicine at Mount Sinai
"Solute Carrier (SLC) Transporters: Structure, Function, and Drug Discovery"

November 15, 2017

Perry Hackett, Ph.D.
 Professor
 Center for Genome Engineering
 Department of Genetics, Cell Biology & Development
 University of Minnesota
"Application of Precision Genome Editing in Large Animals to Biomedical Science and Regenerative Medicine"

November 28, 2017

David Bernlohr, Ph.D.
 UMN
"Uncoupling Lipid Metabolism from Inflammation in Type 2 Diabetes"

December 8, 2017

Joseph Murray, M.D.
 Consultant, Division of Gastroenterology & Hepatology, Department of Internal Medicine
 Consultant, Department of Immunology
 Professor of Medicine
 Mayo Clinic
"Celiac Disease: a model of host-environment tolerance"

December 11, 2017

Daniel Rotroff, Ph.D.
 2nd Interview
 Research Scholar
 Bioinformatics Research Center
 North Carolina State University
"The Search for Signal: Data Driven Approaches to Precision Medicine"

December 14, 2017

Boris Winterhoff, M.D.
 Assistant Professor, OBGYN Department
 University of Minnesota (guest of Ilana Chefetz)
"On the road to precision medicine in gynecological oncology"

January 18, 2018

Jean-Paul Armache, Ph.D.
 2nd Interview
 Postdoctoral Researcher
 Department of Biochemistry and Biophysics
 University of California, San Francisco
"Structural Studies of Macromolecules Using Electron Cryo-Microscopy"

January 29, 2018

Yaping Liu, Ph.D.
 2nd Interview
 Postdoctoral Associate
 Molecular & Cellular Biology
 University of Southern California
"Understanding the interactions between genetic and epigenetic variations: recombination rate valley, Menthyl-HiC and cell-free DNA"

February 27, 2018

Bin Liu, Ph.D.
 2nd Interview
 Associate Research Scientist
 Dr. Thomas A. Steitz's Lab
 Yale University
"Structural Insights into Bacterial Transcription and Its Regulation"

March 6, 2018

Michael Kearse, Ph.D.
 2nd Interview
 Postdoctoral Fellow
 University of Pennsylvania
"Running with RAN Translation: Mechanisms of atypical protein synthesis that causes multiple human diseases"

March 12, 2018

Seung Joong Kim, Ph.D.
 2nd Interview
 Postdoctoral Fellow
 California Institute of Quantitative Biomedical Research
"Integrative Structure and Functional Anatomy of a Nuclear Pore Complex"

March 15, 2018

Eugenia Trushina, Ph.D.
 Associate Professor of Neurology
 Department of Neurology
 Mayo Clinic, Rochester, MN
"Tracking energy failure and its restitution in CNS disorders: from animal models to clinical biomarkers"

March 22, 2018

Kaylee Schwertfeger, Ph.D.
 Associate Professor
 Department of Laboratory Medicine and Pathology
 University of Minnesota
"Defining the impact of JAK/STAT inhibition on the tumor microenvironment"

April 11, 2018

Ivan Liachko, Ph.D.
 Founder & CEO
 Phase Genomics, Inc.
"From Contigs to Chromosomes: How Hi-C is transforming Genome Assembly & Structural Variant Analysis"

April 23, 2018

Mike Anderson
 NanoString Technologies
 Seattle, WA
"Faster than qPCR, Simpler than NGS. An introduction into NanoString Technologies"

April 24, 2018

Kenneth Lee, Ph.D.
 2nd Interview
 Postdoctoral Research Associate
 The Rockefeller University
"Molecular Choreography of KATP Visualized by Cryo-EM"

May 1, 2018

Christoph Lepper, Ph.D.
 2nd Interview
 Staff Associate – Independent Fellow
 Carnegie Institute of Science
"Resizing the Muscle Stem Cell Pool via Signaling from the Myofiber"

May 8, 2018

Shan Yan, Ph.D.
 2nd Interview
 Associate Professor
 University of North Carolina
"Molecular mechanisms of genome integrity and cancer etiology"

May 16, 2018

Kenneth Beckman, Ph.D.
 Director
 University of Minnesota Genomics Center
"The University of Minnesota Genomics Center: Resources for Cancer Research"

May 17, 2018

Carol Lange, Ph.D.
 Professor of Medicine
 University of Minnesota
"Context-Dependent Progesterone Receptor (PR) Actions in Breast Cancer Progression: Jekyll and Hyde"

May 22, 2018

Ying Liang, MD/Ph.D.
 Assistant Professor
 University of Kentucky College of Medicine
"Latexin in Normal & Stress Hematopoiesis"

May 31, 2018

Branden Moriarity, Ph.D.
 Assistant Professor, Department of Pediatrics
 Co-director, Genome Engineering Shared Resource
 University of Minnesota
"Genome Engineering of Lymphohematopoietic Cells for Gene & Cancer Immunotherapy"

June 7, 2018

Saravut (John) J. Weroha, MD/PhD
 Assistant Professor of Medicine
 Assistant Professor of Oncology
 Assistant Professor of Pharmacology
 Mayo Clinic
"Ovarian Cancer PDX Models to Advance Therapeutic Options"

June 12, 2018

Dr. Moon-Shong Tang
 Professor, Department of Environmental Medicine
 Professor, Department of Medicine
 Professor, Department of Pathology
 NYU School of Medicine
"E-cigarettes and multi-organ DNA Damage and Carcinogenesis"

June 19, 2018

Alessandro Carrer, Ph.D.
 Research Associate
 University of Pennsylvania
"Oncogenic Kras engages acetyl-CoA metabolism to initiate pancreatic carcinogenesis"

Income from Grants, Contracts and Development

National Institutes of Health

National Cancer Institute

Chemoprevention of Colon Cancer by Targeting the Wnt/beta Catenin Pathway (Z. Dong)	\$228,750
Chemoprevention of solar UV-induced Skin Cancer by Targeting LTZ4H (Z. Dong)	\$228,750
Developing New Ornithine Decarboxylase Inhibitors to Prevent Skin Cancer (Z. Dong)	\$186,750
Hepatic Stellate Cell Regulation of Metastatic Growth in the Liver (N. Kang)	\$213,750
Novel Targeted Chemo/Immunotherapy Approach for Localized and metastatic CaP (M.S. Bhat)	\$192,251
Targeting High Fat Diet-Driven DNA hypermethylation for AML chemoprevention (S. Liu)	\$50,000
The Cholangiocyte Primary Cilium as a Tumor Suppressor Organelle (S. Gradilone)	\$228,750
Triggering the Dopamine Pathway to Inhibit Lung Cancer Progression (L. Hoepfner)	\$163,279

American Cancer Society

Determination & validation of resistance mechanisms in melanoma (J. Robinson)	\$156,322
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Bob Allison Ataxia Research Center

Function of ATM in Neuronal Survival in Response to Growth Factor Signaling (D. Yang)	\$15,000
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Compeer Financial

AgStar Fund for Rural America (Z. Dong)	
Compeer Fund for Rural America (Z. Dong)	\$10,000

Foundation for Women's Cancer

Necroptosis in ovarian cancer cells with gain of function of p53 mutations (I. Chefetz-Menaker)	\$39,534
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Life Science Research Foundation

Identification and Characterization of Cancer Stem cells in ovarian cancer (I. Chefetz-Menaker)	\$12,936
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Marsha Rivkin Center for Ovarian Cancer Research

Deciphering molecular mechanism of ALDH-inhibition driven necroptosis (I. Chefetz-Menaker)	\$40,961
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MN-REACH

Study to treat AKs in solar UV (A. Bode)	\$2,000
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Ovarian center Research Fund

Drugs Inducing Necroptotic Cell Death as a New Strategy (I. Chefetz-Menaker)	\$150,000
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Pardee Foundation

Necroptosis: Molecular and metabolic aspects (I. Chefetz-Menaker)	\$104,003
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Pennsylvania State University

Prevention of Prostate Carcinogenesis by Next-generation Selenium (Y. Deng)	\$50,298
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Prairie Pharms

The thymoquinone oil in lung cancer therapy (S. Liu)	\$10,468
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Prostate Cancer Foundation

Delineating coding and regulatory indels in prostate cancer (R. Yang)	\$75,000
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University of Florida/NIH

Mechanism of high-efficiency transduction of hepatocytes by optimized AAV vectors (G. Aslanidi)	\$118,186
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University of Louisville/NIH

Prevention of Breast Cancer by Epidermal Fatty Acid Binding Protein (M. Cleary)	\$26,245
The Role of Adipocyte/Macrophage Fatty Acid Binding Protein in Breast Cancer Development (M. Cleary)	\$13,317
The Role of Adipocyte/Macrophage Fatty Acid Binding Protein in Breast Cancer Development (S. Liu)	\$7,526

University of Minnesota Medicinal Chemistry/NIH

Smoking-induced epigenetic changes in the lung: Role of DNA demethylation (S. Liu)	\$21,588
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University of South Florida/NIH

The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (E. Hinchcliffe)	\$86,183
The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (R. Brown)	\$81,354

Virginia Commonwealth University/NIH

The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (E. Hinchcliffe)	\$66,317
The Functional Role of the cPLA2alpha/C1P Interaction in Sepsis Resolution (R. Brown)	\$94,021

Other Resources

The Hormel Foundation	\$9,291,311
University of Minnesota	\$960,729
Indirect Cost Return	\$1,146,935
Fundraising/Development	\$977,926

Total

\$15,050,440

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Changes as of 8/15/2018

Additions to the board:
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James P. Snee

Exiting the board:
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Improving health through medical research.

Accelerating **ANSWERS**
to **CANCER**

