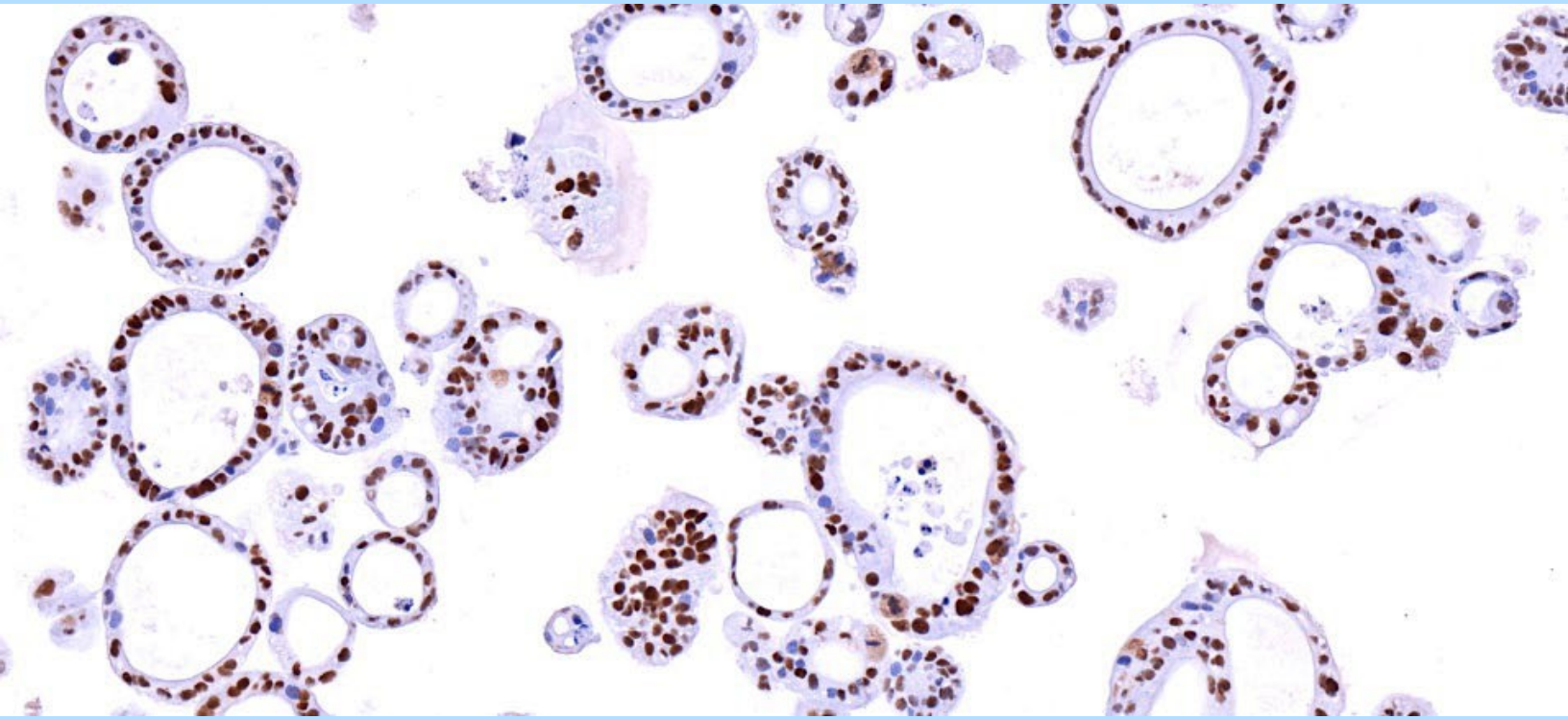
MOLECULAR PHARMACOLOGY
ALBERT EINSTEIN COLLEGE OF MEDICINE



Patient-derived colorectal cancer organoids stained for mutS homolog 6 (Chaoyuan Kuang lab).

Jonathan M. Backer, M.D., Chair

Praveen Agrawal, Ph.D.
Michael Aschner, Ph.D.
Michael D. Brenowitz, Ph.D.
Dongsheng Cai, M.D., Ph.D.
Jiahn Choi, Ph.D.
Edward Chu, M.D., M.M.S.
Kelvin Davies, Ph.D.
Eugen Dhimolea, Ph.D.
Matthew J. Gamble, Ph.D.
Louis Hodgson, Ph.D.
Derek M. Huffman, Ph.D.
Young-Hwan Jo, Ph.D.
Marina Konopleva, M.D., Ph.D.
Chaoyuan Kuang, Ph.D.
Sridhar Mani, Ph.D.
Hayley M. McDaid, Ph.D.
Pabitra K. Parua, Ph.D.
Jeffrey E. Pessin, Ph.D.
Gaetano Santulli, M.D., Ph.D.
Edward L. Schwartz, Ph.D.
David Sharp, Ph.D.
Kosaku Shinoda, Ph.D.
Kamini Singh, Ph.D.
Sylvia O. Suadicani, Ph.D.
Mia M. Thi, Ph.D.

2025-26

The Department of Molecular Pharmacology

Pharmacology is the study of drugs and the signaling pathways that they target. Research in Molecular Pharmacology at Einstein has a strong emphasis on signal transduction and hormone action at the nuclear, cellular and organismic level; the mechanisms of drug action and the development of new therapeutics; and the disruption of normal physiology by toxicants. Work in our department targets important diseases such as cancer, diabetes and obesity, aging, as well as neurodevelopmental and neurodegenerative disorders. We have strong ties to the Cancer and Diabetes Centers as well as the Institute for Aging Research.

Graduate training in Molecular Pharmacology exposes student to state of the art methodologies that cover a wide range of approaches, including genetic studies in flies, worms and mice, genome-wide studies of chromatin organization, mRNA transcription, splicing and translation, glycobiology, advanced quantitative imaging, and biochemical studies on purified enzymes. Studies with animal models and human-derived specimens ensure that our research is at the forefront of translational science.

The Department has 26 primary and secondary faculty members as well as 40 graduate students and postdoctoral fellows. The highly collaborative nature of investigators within the department creates a broad-based and dynamic scientific environment. The Department sponsors a seminar series for visiting scientists from other institutions, as well as journal clubs and weekly work-in-progress research meetings. Monthly afternoon "happy hours" and annual departmental outings promote scientific and social interactions among the students, fellows and faculty.

Graduate students in the Department of Molecular Pharmacology have earned postdoctoral positions in outstanding laboratories and received prestigious fellowships. Our postdoctoral trainees have found positions in academia, biotechnology and pharmaceutical companies, and at the National Institutes of Health and the Food and Drug Administration. We are proud of the accomplishments of our students and postdocs and we welcome new students to join us in this exciting age of scientific advances.

MOLECULAR PHARMACOLOGY - PRIMARY FACULTY

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Praveen Agrawal	Assistant Professor	Forchheimer 231	2604
Michael Aschner	Professor	Forchheimer 209	2317
Jonathan M. Backer	Professor / Chair	Forchheimer 230	2153
Dongsheng Cai	Professor	Forchheimer 216	2426
Eugen Dhimolea	Assistant Professor	Forchheimer 248	4121
Matthew J. Gamble	Professor	Golding 202	2942
Louis Hodgson	Professor	Price Center 217	1027
Derek M. Huffman	Professor	Golding 201	4278
Pabitra Parua	Assistant Professor	Forchheimer 236	4284
David Sharp	Professor	Ullmann 223	3463
Kamini Singh	Assistant Professor	Golding 203	2466

MOLECULAR PHARMACOLOGY - SECONDARY FACULTY

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Kelvin Davies	Professor	Forchheimer 742	3201
Young-Hwan Jo	Professor	Forchheimer 511	2987
Marina Konopleva	Professor	Ullmann 915	4068
Chaoyuan Kuang	Assistant Professor	Channin 628	2594
Sridhar Mani	Professor	Channin 302-D1	2871
Hayley McDaid	Associate Professor	Forchheimer 223	8829
Jeffrey E. Pessin	Professor	Price Center 375	1029
Gaetano Santulli	Associate Professor	Forchheimer 529	3637
Edward L. Schwartz	Professor	Block 614	8864
Kosaku Shinoda	Assistant Professor	Price Center 355	1189
Sylvia O. Suadicani	Professor	Forchheimer 744	3225
Mia M. Thi	Associate Professor	Golding 101	3460

MOLECULAR PHARMACOLOGY - INSTRUCTORS / STAFF SCIENTISTS

Name	Title	Location	Phone
Monica Bastos Paoliello	Staff Scientist	Forchheimer 209	4047
Pan Chen	Research Associate Professor	Forchheimer 209	4047
Airton Da Cunha Martins Junior	Staff Scientist	Forchheimer 209	4047
Beatriz Ferrer Villahoz	Staff Scientist	Forchheimer 206	7920
Kai Mao	Research Assistant Professor	Golding 201	7964

MOLECULAR PHARMACOLOGY - POSTDOCTORAL FELLOWS

Name	Mentor	Location	Phone
Olusiji Akinrinmade	Dhimolea	Forchheimer 248	4121
Slawomir Andrzewski	Dhimolea	Forchheimer 248	4121
Tirthankar Bandyopadhyay	Parua	Forchheimer 236	4556
Baidehi Basu	Parua	Forchheimer 236	4556
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Yuna Choi	Cai	Forchheimer 216	2427
Leandro Encarnacao Garcia	Dhimolea	Forchheimer 248	4121
Gyeongyun Go	Cai	Forchheimer 216	2427
Hyungug Jung	Cai	Forchheimer 216	2427
Swarnali Kar	Agrawal	Forchheimer 231	2604
Sree Karani Kondapuram	Agrawal	Forchheimer 231	2604
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Sandra Pagano	Hodgson	Price Center 211	1558
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Qichao Zhang	Cai	Forchheimer 216	2427

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Michael Broussalian	Huffman	Golding 201	7964
Jacky Chuen	Singh	Golding 203	2475
Jessica Fyodorova	Gamble	Golding 202	2192
Adam Haimowitz	Gamble	Golding 202	2943
Harrison Hector	Huffman	Golding 201	7964
Maxwell Horton	Pessin	Price Center 375	1029
Zimo Huang	Agrawal	Forchheimer 231	2604
Nazia Jamil	McDaid	Forchheimer 223	2192
Kyle Jewell	Huffman	Golding 201	7964
Spencer Kaminsky	McDaid	Forchheimer 223	2192
Sofia Kylova	Pessin	Price Center 375	1029
Austin Landgraf	Shinoda/Pessin	Price Center 355	1189
Katherine Nelson	Backer	Forchheimer 230	2124
Andrea Ramirez	Hodgson	Price Center 211	1558
Todd Richmann	Huffman	Golding 201	7964
Joshua Saltzberg	Gamble	Golding 202	2943
Daphne Solomon	Shinoda	Pice Center 355	1189
Natalie Thielsen	Kuang	Channin 628	2595
Alberto Williams-Medina	Huffman	Golding 201	7964
Elizabeth Yun	Gamble	Golding 202	2943
Bill Zhu	Huffman	Golding 201	7964

MOLECULAR PHARMACOLOGY - RESEARCH TECHNICIANS

Name	Mentor	Location	Phone
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Adriana Levine	Backer	Forchheimer 230	2124
Gracia Bualuti	McDaid	Forchheimer 233	2192

DEPARTMENT OF MOLECULAR PHARMACOLOGY

Jonathan M. Backer, M.D. – Chair The Backer Lab studies signaling by phosphoinositide 3-kinases, which regulate cell proliferation, motility, and transformation. Experimental approaches range from biochemical analysis to in vivo studies on metastasis in animals.

Praveen Agrawal, Ph.D. The Agrawal lab studies alteration in the cellular glycosylation associated with tumor progression, metastasis, and resistance to targeted and immunotherapy in melanoma and prostate cancer. Our studies utilize cutting-edge glycomic techniques, glycogene data mining of clinical samples, in vitro/in vivo functional screens, and metastasis models.

Michael Aschner, Ph.D. The focus of our laboratory is on understanding (1) gene x environment interactions in triggering neurodevelopmental and neurodegenerative disorders, (2) metal uptake and distribution in the brain and their cellular and molecular mechanisms of neurotoxicity.

Michael D. Brenowitz, Ph.D. Our laboratory seeks answers to questions related to the structure – function relationships that govern macromolecular function by combining quantitative analysis with innovative approaches.

Dongsheng Cai, M.D., Ph.D. The Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, neural epigenetics, and epigenetic reprogramming.

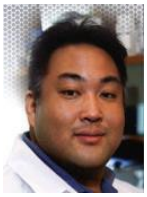
Jiahn Choi, Ph.D. Our research focuses on how intestinal stem cells and their niche adapt to environmental risk factors, particularly aging and western-style diet, and how these adaptations influence tissue homeostasis, inflammation, and cancer risk. Our goal is to uncover the regulatory mechanisms behind these adaptations and develop strategies to maintain mucosal homeostasis and prevent diet- and age-associated pathogenesis.

Edward Chu, M.D. The major focus of my research is to investigate the molecular mechanisms of cellular drug resistance in colorectal cancer that relate to the fluoropyrimidine class of anticancer agents and inhibitors to thymidylate synthase and to develop novel agents that can overcome and/or prevent the development of drug resistance. Our lab has worked on developing novel bifunctional siRNA molecules as well as small molecules and Chinese herbal medicine. In addition, I am actively involved in the early-phase clinical development of novel agents and/or combination regimens for the treatment of colorectal cancer, and my lab has been involved in conducting the key pre-clinical experiments and translational biomarker studies that serve as the rational basis for the first in man clinical studies.

Kelvin Davies, Ph.D. My laboratory investigates the molecular and biochemical determinants of benign and oncologic urogenital disease, with the goal of developing novel clinically translatable strategies for their treatment.

Eugen Dhimolea, Ph.D. The Dhimolea Lab studies the mechanisms through which cancer cells persist during treatment with pharmacological and immune therapies in the broader context of the tumor microenvironment. Our experimental approaches combine in vitro 3D cultures/co-cultures, and in vivo patient-derived xenografts and orthotopic tumor models, with molecular analyses and functional studies.

Matthew J. Gamble, Ph.D. Through the lens of chromatin biology, we explore the mechanisms which regulate transcription and splicing, and their dysregulation in cancer, using a host of cellular, computational and -omics based approaches.



Louis Hodgson, Ph.D. Hodgson Lab studies the mechanisms of the Rho family small GTPase coordination during cell adhesion, invasion and motility, in normal cells and diseased states including cancer and inflammation. We engineer fluorescent biosensors based on Förster Resonance Energy Transfer (FRET) to target posttranslational modification and protein activation events in living cells. We use high-resolution light microscopy, computational and direct multiplex imaging approaches to study GTPase signal cross talks in living cells.

Derek M. Huffman, Ph.D. The Huffman laboratory is focused on four areas: 1) Aging-metabolism interplay, 2) Aging drug synergy, 3) Role of systemic factors in aging, and 4) physiologic resilience and aging.

Young-Hwan Jo, Ph.D. The focus of our laboratory is to investigate the impact of bidirectional communication between the liver and brain on obesity and mental health.

Marina Konopleva, M.D., Ph.D. The focus of our laboratory is to characterize therapeutic vulnerabilities of acute leukemias, with emphasis on targeting cell death machinery, metabolism and leukemic stem cells. Our experiments utilize cell lines, primary samples and PDX models, biochemical and metabolomic assays and multi-parametric CyTOF analysis.

Chaoyuan Kuang, M.D., Ph.D. The Kuang Lab studies novel therapeutics for colorectal cancer. We utilize both preclinical and clinical models such as 2-D cell culture, 3-D patient derived organoids, mouse xenografts, and patient tumor specimens. Our goal is to discover the best new therapies to test in clinical trials and predictive biomarkers of colorectal cancer.

Sridhar Mani, M.D. Our laboratory focuses on the study of host-microbiome relationships as it relates to human and veterinary health and disease (inflammation, metabolism, and cancer).

Hayley M. McDaid, Ph.D. We are a senescence-centric lab whose broad goal is to understand and exploit the senescence that occurs in response to cancer therapy. Major areas include senescence biomarker identification, defining molecular dependencies of senescent cells, and developing novel cancer therapies that induce stable senescence.

Pabitra K. Parua, Ph.D. The research of the Parua lab is focused on dissecting the regulation of the RNA polymerase II (RNAPII) transcription cycle by kinase-phosphatase antagonisms. Our central interest is to uncover novel signaling networks governed by upstream stimuli and converge to regulate gene expression. Intriguingly, the prospective avenues are to explore how the aberrations of that critical molecular circuitry cause neoplasms.

Jeffrey E. Pessin, Ph.D. Our laboratory examines the molecular, cellular and integrative systems physiology of metabolism and energy expenditure focusing on the insulin signal transduction pathways regulating glucose uptake and lipogenesis.

Gaetano Santulli, M.D., Ph.D. In our laboratory, we investigate the biology of cardiovascular and metabolic disorders, focusing on intracellular calcium and microRNAs, with the ultimate goal to identify novel therapeutic targets.

Edward L. Schwartz, Ph.D. Our lab focuses on the identification of new targets and novel drugs to treat lung and prostate cancer, particularly tumors that have inactivating mutations in the RB1 tumor suppressor gene. This includes determining the critical signaling pathways downstream of RB1 and designing pharmacologic agents that would restore its function and cause tumor regressions.

David Sharp, Ph.D. Our research is focused on the roles of the microtubule cytoskeleton in basic aspects of cellular mechanics such as cell division, movement, and growth. We are also working to translate this basic research into novel therapies to promote tissue regeneration/repair.

Kosaku Shinoda, Ph.D. My lab is focused on the biology of adipocytes. Understanding the basic biology of adipocytes is fundamental to the treatment and prevention of type 2 diabetes and obesity. We use cutting-edge single-cell genomics and bioinformatics to map cellular lineage and the genetic program of adipocytes in disease states and under normal physiological conditions.

Kamini Singh, Ph.D. My laboratory investigates the gene expression and therapeutic vulnerabilities in cancer through the lens of ribosome. Using bulk and single cell ribosome footprinting approach we study the mechanism of mRNA translation, role of regulatory RNA elements, and the function of aberrant translation products in cancer progression, tumor microenvironment, and immune response.

Sylvia O. Suadicani, Ph.D. Research in our laboratory investigates the involvement of altered ATP, pannexin 1 and gap junction mediated signaling in mechanisms of disease, with particular focus on urogenital dysfunction and chronic pelvic pain.

Mia M. Thi, Ph.D. Primary focus of our laboratory is to understand the molecular and cellular mechanisms involved in how cells sense, transduce and signal mechanical stimuli and how cells work in synchrony to propagate locally generated signals throughout the skeletal tissue and others mechanosensitive tissues such as endothelium, urothelium by means of receptor, junctional, cytoskeletal and focal adhesion proteins under healthy and pathological conditions.

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Glycan Regulation of Tumor Progression, Metastasis, and Immune Evasion

Glycans, complex carbohydrates covalently attached to proteins, play critical roles in modulating protein folding, stability, trafficking, and receptor interactions. In cancer, aberrant glycosylation rewires key cellular processes, promoting tumor growth, metastasis, and resistance to therapy. Our research program focuses on elucidating the biochemical and structural mechanisms by which tumor-associated glycan modifications influence cancer progression, metastatic organotropism, and immune evasion, with the ultimate goal of uncovering new therapeutic vulnerabilities.

Glycan-Directed Mechanisms of Metastatic Organotropism in the Tumor Microenvironment

We investigate how tumor-intrinsic glycosylation programs intersect with the tumor microenvironment (TME) to drive site-specific metastatic colonization. Our recent studies using glycomic profiling of patient-derived melanoma and prostate cancer tissues revealed distinct glycan signatures, particularly fucosylated and sialylated structures, that correlate with brain, liver, and bone metastasis. Using in vivo intracardiac metastasis models, lectin microarrays, and glycoproteomic mass spectrometry, we are identifying the specific glycogenes (e.g., *B3GNT2*, *FUT4/7*, *ST3GAL4*) and glycoproteins that mediate organotropic dissemination. We are also investigating how these glycan–protein interactions influence extracellular matrix remodeling, microglial and macrophage responses, and tumor–endothelial crosstalk in metastatic niches. These studies are uncovering novel glycan-dependent mechanisms of melanoma brain metastasis (MBM) and prostate cancer bone metastasis.

Targeting Sialylated Glyco-Immune Checkpoints in Melanoma Immunotherapy Resistance

Despite the promise of immune checkpoint inhibitors (ICIs), many melanoma patients fail to respond or develop resistance. Our work has identified aberrant sialylation, driven by *ST3GAL4* and *ST3GAL1/2*, as a key immunoevasive mechanism in ICI-resistant tumors. We have demonstrated that α2,3-sialylated and sialyl Lewis X glycans enhance the function of immune checkpoint receptors (e.g., PD-1, TIGIT, CEACAM1), promote Siglec-9 engagement on myeloid cells, and suppress both innate and adaptive immune activation. Ongoing studies combine transcriptomics, sialyl-glycoprotein pull-downs, and immune cell co-culture assays to define how sialylated glyco-immune checkpoints shape the TME and contribute to adaptive immune suppression. Therapeutically, we are testing glycosyltransferase knockdown, sialylation inhibitors, and glyco-targeted combination therapies to overcome immunotherapy resistance in melanoma.

α1–3/4 Fucosyltransferases and E-Selectin–Mediated Bone Metastasis in Prostate Cancer

Bone-tropic prostate cancer cells exploit selectin-mediated adhesion to colonize the bone marrow niche. Our studies have identified elevated expression of α1–3/4 fucosyltransferases (*FUT4* and *FUT7*) in bone-metastatic prostate cancer models and patient samples. These enzymes promote the synthesis of sialyl Lewis X glycan, thereby enhancing tumor cell adhesion to E-selectin on bone marrow endothelial cells. We are using in vitro flow adhesion assays, RNA-seq, and lectin-IP-MS to define E-selectin-induced transcriptional programs and identify sialyl Lewis X modified glycoproteins that mediate extravasation and osteotropism. These insights are guiding therapeutic strategies to block metastatic seeding using glycoengineered inhibitors or anti-adhesion therapies.

Michael Aschner, Ph.D., Professor
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Research in our laboratory focuses on the interaction between genetics and the environment in triggering disease both during central nervous system (CNS) development and senescence. We are addressing metal uptake across the blood-brain barrier (BBB) and distribution in the brain (neurons and glia), specifically with methylmercury (MeHg) and manganese (Mn), as well as their cellular and molecular mechanisms of neurotoxicity. Our studies address mechanisms of transport and neurodegeneration in various experimental models (*C. elegans*, tissue cultures and rodents), as well as follow-up on the sequalae of heavy metal deposition in the brains of human neonates by means of magnetic resonance imaging (MRI).

Hypotheses presently tested include the following: *(1)* Modulation of *C. elegans* genes (*aat, skn-1, daf-16*) that are homologous to mammalian regulators of MeHg uptake and cellular resistance will modify dopaminergic neurodegeneration in response to MeHg exposure. *(2)* Under conditions of MeHg-induced oxidative stress, Nrf2 (a master regulator of antioxidant responses) coordinates the upregulation of cytoprotective genes that combat MeHg-induced oxidative injury, and that genetic and biochemical changes that negatively impact upon Nrf2 function increase MeHg's neurotoxicity. *(3)* PARK2, a strong PD genetic risk factor, alters neuronal vulnerability to modifiers of cellular Mn status, particularly at the level of mitochondrial dysfunction and oxidative stress.

Our studies are ultimately designed to *(1)* shed novel mechanistic insight into metal-induced neurodegeneration; *(2)* provide novel targets for genetic or pharmacologic modulation of neurodegenerative disorders; *(3)* increase knowledge of the pathway involved in oxidative stress, a common etiologic factor in neurodegenerative disorders; *(4)* develop improved research models for human disease using knowledge of environmental sciences.

Representative Publications:

Aschner M, Martins AC, Oliveira-Paula GH, Skalny AV, Zaitseva IP, Bowman AB, Kirichuk AA, Santamaria A, Tizabi Y, Tinkov AA. Manganese in autism spectrum disorder and attention deficit hyperactivity disorder: The state of the art. Curr Res Toxicol 2024;6:100170.

Ke T, Rajoo A, Tinkov AA, Skalny AV, Tizabi Y, Rocha JBT, Bowman AB, Aschner M. Intestinal microbiota protects against methylmercury-induced neurotoxicity. BioMetals 2023; 37(3):561-576.

Aschner A, Skalny AV, Paoliello MMB, Tinkova MN, Martins AC, Santamaria A, Lee E, Rocha JBT, Farsky SHP, Tinkov AA. Retinal toxicity of heavy metals and its involvement into retinal pathology. Food Chem Toxicol 2024; 188:114685.

Tizabi Y, Bennani S, El Kouhen N, Getachew B, Aschner M. Heavy Metals Interactions with Neuroglia and Gut Microbiota: Implications for Huntington's Disease. Cells 2024; 13(13):1144.

Jonathan M. Backer, M.D., Professor
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Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that mediate signaling downstream from receptor tyrosine kinases and G-protein coupled receptors (GPCRs). They are important regulators of cellular proliferation, motility, apoptosis, and vesicular trafficking. Mutational activation of PI3Ks is commonly found in human cancers. We are interested in how the altered regulation of PI3K contributes to human cancer.

1. PI3Ks in breast cancer. Class I PI3Ks are the sole source of the signaling lipid phosphoinositide-3,4,5-P_3 (PIP_3) in cells, which activates downstream kinases like Akt, small GTPases like Rac and Cdc42, and signaling enzymes like Phospholipase C. The PI3Kβ isoform of PI3K is unique among Class I PI3Ks in that it (a) is activated by binding to receptor tyrosine kinases, (b) is also activated by direct binding to Gβγ subunits downstream of activated GPCRs and to the small GTPase Rac1, and (c) specifically binds to the small GTPases Rab5, which regulates vesicular trafficking in the early endosome. We have identified point mutants that disrupt PI3Kβ binding to either Gβγ or Rab5, and have shown that these mutants block tumor cell invasion in cell culture and animal models of breast cancer metastasis.

Our current work focusses on the mechanisms by which PI3Kβ regulates breast cancer invasion, particularly its role in stromal cells such as macrophages and platelets. We have developed knock-in mice expressing the mutations that inhibit PI3Kβ binding to either Gβγ or Rab5, and we are studying how these mutations affect the behavior of primary macrophages and platelets. Using primary cells, we have shown that PI3Kβ mutations inhibit the ability of both platelets and macrophages to stimulate the invasive behavior of tumor cells. In a parallel set of experiments, we have shown that mutation or knockout of PI3Kβ in tumor cells inhibits invasion and metastasis, and also blocks macropinocytosis. This is a fluid-phase endocytic pathway that provides nutrients to support tumor growth under hypoxic or poorly vascularized conditions. Taken together, our findings suggest that PI3Kβ could be an important drug target in the treatment of tumor growth and metastasis.

2. S100A4 signaling in macrophages. In collaboration with Dr. Anne Bresnick (Biochemistry), we are studying the regulation of cellular motility and invasion by the dimeric calcium-binding protein S100A4. S100A4 is prometastatic when expressed in tumor cells. We have recently found that S100A4 also regulates invasion and matrix degradation by both tumor cells and macrophages, in part by regulating lysosomal exocytosis. Our current work uses genomic, proteomic and cell biological methods to study how macrophage S100A4 regulates vesicular trafficking pathways that contribute to macrophage motility and invasion.

Representative Recent Publications:

Graff RC, Haimowitz A, Aguilan JT, Levine A, Zhang J, Yuan W, Roose-Girma M, Seshagiri S, Porcelli SA, Gamble MJ, Sidoli S, Bresnick AR, Backer JM. Platelet PI3Kbeta regulates breast cancer metastasis. (2024) BioRxiv Sep 14:2024.09.10.612261.

Jakubik, CT, Weckerly, CC, Hammond, GRV, Bresnick, AR, and Backer, JM. PIP_3 abundance overcomes PI3K signaling selectivity in invadopodia. FEBS Letters 2022 596:417-426

Salloum, G., Jakubik, CT, Erami, Z., Heitz, SD, Bresnick, AR, and Backer, JM. PI3Kβ is selectively required for growth factor-stimulated micropinocytosis. (2019) J. Cell Sci. 132(16). pii: jcs231639

Heitz, SD, Hamelin, DJ, Hoffmann, RM, Greenbeerg, N, Salloum, G., Eramie, Z., Khalil, B., Shymanets,A, Steidle, EA, Gong, GQ, Nurrnberg, B, Burke, JE, Flanagan, JU, Bresnick, AR, and Backer, JM. A single discrete Rab5-binding site in phosphoinositide 3-kinase β is required for tumor cell invasion (2019) J. Biol. Chem 294:4621-4633.

Erami, Z., Heitz, SD. Bresnick AR, and Backer, JM. PI3Kβ links integrin activation and $PI(3,4)P_2$ production during invadopodial maturation (2019) Molecular Biology of the Cell 15:2367-2376.

Michael Brenowitz, Ph.D., Emeritus Professor
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Biology is a dynamic process. Among the myriad array of reversible association reactions that constitute life, small molecules bind to proteins, proteins self-associate and bind to other proteins and nucleic acids and nucleic acids fold and bind to each other in elaborate processing, signaling and regulatory cascades. What is common to association reactions is the physical chemistry that underlies their molecular interactions. For example, electrostatics mediate both the binding of proteins to DNA and the folding of RNA. Proteins that mimic the electrostatic character of DNA may competitively regulate DNA binding by other proteins. Small molecules utilize a diverse repertoire of interactions confer high affinity and specificity.

Prior to its closing with the new year, my laboratory sought answers to questions related to the structure – function relationships that govern macromolecular assembly reactions. Most recently, we developed a novel in-solution method to map small molecule-protein and protein-DNA interactions utilizing dose-dependent oxidation of proteins and their complexes to map the solvent accessibility of amino acid side chains with individual residue resolution. We applied this in-solution mapping technology to compare the binding of small-molecules to target proteins with the goal of facilitating drug discovery and the development of effective therapeutics and explored the DNA contacts made by disordered domains of the epigenetic regulator MeCP2 (methyl-CpG binding protein 2) whose disruption is a cause of the neurological disorder Rett Syndrome. I close by noting that with emeritus status, I am no longer recruiting researchers to my research program.

Representative Publications:

Sun, Y;, Houde, D., Iacob, R., Baird, J., Swift, R., Holliday, M., Shi, X., Sidoli, S., and Bre-nowitz, M. (2025) Hydrogen/Deuterium Exchange and Protein Oxidative Footprinting with Mass Spectrometry Collectively Discriminate the Binding of Small Molecule Therapeutics to Bcl-2, *Analytical Chemistry*, 97(8), 4329 - 4340

Chapman, J.R., Paukner, M., Leser, M., Becker, C., Tang, K., Koide, S., Ueberheide, B., Brenowitz, M. (2023) Systematic Fe(II)-EDTA Method of Dose-Dependent Hydroxyl Radical Generation for Protein Oxidative Footprinting, *Analytical Chemistry*, 95(50):18316-18325, PMID: 38049117

Bou-Assaf, G.M., Budyak, I.L., **Brenowitz, M.**, Day, E.S., Hayes, D., Hill, J., Majumdar, R., Ringhieri, P., Schuck. P., Lin, J.C. (2022) Best Practices for Aggregate Quantitation of Antibody Therapeutics by Sedimentation Velocity Analytical Ultracentrifugation, *J Pharm Sci.* 111, 2121-2133, PMID: 34986360

Khrapunov, S., Tao, Y., Cheng, H., Padlan, C., Harris, R., Galanopoulou, A.S., Greally, J.M., Girvin, M.E., **Brenowitz, M.** (2016) MeCP2 Binding Cooperativity Inhibits DNA Modification-Specific Recognition, *Biochemistry* 55, 4275 - 85

Dongsheng Cai, M.D., Ph.D., Professor
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Aging and overnutrition are two major etiological conditions for epidemiological diseases such as Alzheimer's disease, Parkinson's disease, diabetes, stroke and heart failure. The Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Our research has led to a series of paradigm-shifting research breakthroughs, for example, we pioneered discovering the role of the hypothalamus in regulating whole-body aging, identifying hypothalamic neural stem cells (htNSC), and developing htNSC exosomes for anti-aging and various disease treatments. These efforts have resulted in many high-profile publications, some of which are represented below. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, epigenetics, and epigenetic reprogramming, each representing an important front of today's biomedical science.

Representative Publications:

Zhang Y, Kim M, Jia B, Yan J, Hertz J, Han C, Cai D. Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. **Nature** (article), 548 (7665):52-57, 2017.

Zhang YL, Reichel JM, Han C, Zuniga-Hertz JP, Cai D. Astrocytic process plasticity and IKK/NF-kB in central control of blood glucose, blood pressure and body weight. **Cell Metabolism**. 25 (5); 1091-1102, 2017.

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Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Liu G, Cai D**.**Hypothalamic Programming of Systemic Aging Involving IKKÎ²/NF-ÎºB and GnRH. **Nature**, (article), 497 (7448): 211-6, 2013.

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Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKb/NF-kB and ER stress link overnutrition to energy imbalance and obesity. **Cell**, 135 (1): 61-73, 2008.

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Our research centers on understanding how intestinal stem cells and their surrounding niche adapt to environmental stressors—such as aging and diet—and how these adaptations influence tissue homeostasis, inflammation, and cancer risk. Our work integrates single-cell omics, *in vivo* imaging, and functional genomics to uncover how stem cell plasticity and niche interactions are reprogrammed in response to modifiable risk factors, including a Western-style diet.

We have demonstrated that western-style diet reshapes intestinal homeostasis by altering the primary stem cell population, thereby remodeling lineage differentiation and contributing to a pro-tumorigenic state.

Building on these findings, our ongoing research explores:

- Identifying regulatory mechanisms that drive remodeling of intestinal mucosa in response to environmental stimuli.
- Investigating the impact of aging on the adaptability of the intestinal mucosa following tissue damage.
- Deconvolving the mechanisms by which cellular adaptation contributes to pathogenesis, such as cancer.

By defining the mechanisms underlying mucosal remodeling and pathogenesis, our goal is to develop preventive strategies that preserve epithelial integrity and reduce the risk of diet- and age-associated diseases.

Selected Publications

MP Verhagen, R Joosten, M Schmitt, N Välimäki, A Sacchetti, K Rajamäki, **J Choi,** P Procopio, S Silva, B van der Steen, TPP van den Bosch, D Seinstra, AC. de Vries, M Doukas, LH. Augenlicht, LA. Aaltonen, R Fodde, "Non-stem cell lineages as an alternative origin of intestinal tumorigenesis in the context of inflammation," ***Nature Genetics***, 56: 1456 – 1467, 2024. PMCID: PMC11250264

J Choi*, LH. Augenlicht, "Intestinal stem cells: guardians of homeostasis in health and aging amid environmental challenges," ***Experimental & Molecular Medicine***, 1-6, 2024 (*corresponding author). PMCID: PMC10985084

J Choi, X Zhang, W Li, M Houston, K Peregrina, R Dubin, K Ye, LH. Augenlicht, "Dynamic intestinal stem cell plasticity and lineage remodeling by a nutritional environment relevant to human risk for tumorigenesis," ***Molecular Cancer Research,*** 21 (8): 808–824, 2023, editorially selected for highlight and commentary. PMCID: PMC10390890

J Choi*, M Houston, R Wang, K Ye, W Li, X Zhang, DM. Huffman, LH. Augenlicht, "Intestinal stem cell aging at single-cell resolution: Transcriptional perturbations alter cell developmental trajectory reversed by gerotherapeutics," ***Aging Cell***, 22, e13802, 2023 (*corresponding author). PMCID: PMC10186593

M Nauman, S Varshney, **J Choi**, LH. Augenlicht, P Stanley, "EOGT enables residual Notch signaling in mouse intestinal cells lacking Pofut1," ***Scientific Reports,*** 13:17473, 2023. PMCID: PMC10576774

J Choi, N Rakhilin, P Gadamsetty, DJ Joe, T Tabrizian, SM Lipkin, DM Huffman, X Shen, N Nishimura, "Intestinal crypts recover rapidly from focal damage with coordinated motion of stem cells that is impaired by aging," ***Scientific Reports***, 8(1):10989, 2018. PMCID: PMC6054609

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My research lab has focused on developing novel agents and/or combination regimens for the treatment of colorectal cancer.

Translational regulation of gene expression: My lab was the first to demonstrate that the expression of the folate-dependent enzyme thymidylate synthase was controlled by a translational autoregulatory mechanism whereby the thymidylate synthase protein binds to cis-acting regulatory elements on the cognate TS mRNA and regulates translation. This was a seminal finding as this was the first description of this type of translational autoregulatory mechanism in a eukaryotic organism. Moreover, the acute induction of TS expression in response to TS inhibitor compounds represents a novel mechanism of acute cellular drug resistance. My lab then followed up on this observation to demonstrate that the expression of another folate-dependent enzyme dihydrofolate reductase is controlled in an identical translational autoregulatory manner. It has now been well-established that translation autoregulation is a common mechanism by which cellular gene expression can be controlled in a very efficient and rapid manner.

Development of siRNAs as novel therapeutic molecules: The Chu lab has been investigating the potential role of siRNA's as novel therapeutic molecules for the treatment of colorectal cancer. The goal of these studies is to identify novel molecules to prevent and/or overcome the development of cellular drug resistance to inhibitor compounds that target thymidylate synthase, a well- established target for cancer chemotherapy. The Chu lab observed that siRNA's were significantly more potent and specific in their ability to repress TS mRNA translation, resulting in potent inhibition of TS synthesis. Moreover, these molecules were able to completely restore chemosensitivity to anticancer agents that target TS, including the fluoropyrimidines and TS antifolate inhibitors.

Chinese herbal medicine: Our lab identified bruceantinol (BOL), a natural quassinoid isolated from the plant *Brucea javanica*, as a potent inhibitor of CRC growth. BOL suppressed >90% of tumor growth in both HCT116 xenograft-bearing athymic mice and a syngeneic MC38 tumor model. However, at high doses, BOL treatment was associated with spleen and body weight loss suggesting normal host toxicities. Using multiple biochemical and molecular techniques, we demonstrated that BOL binds to STAT3 resulting in inhibition of STAT3 phosphorylation, and our data suggests that direct targeting of STAT3, by itself, has little to no effect on CRC cell growth. Previous studies have suggested that the mechanism of action of quassinoids may be mediated through inhibition of protein synthesis. A comparison between cycloheximide, a well-established inhibitor of protein synthesis, and BOL revealed similarities as well as significant differences with regard to alterations in protein expression. Newly developed BOL-resistant CRC cells were not cross resistant to cycloheximide suggesting BOL may inhibit protein synthesis in a completely different manner.

The overarching hypothesis of our research is that quassinoids inhibit cancer cell growth through suppression of protein synthesis with subsequent inhibition of cancer-dependent signaling pathways. We believe that they can be developed as novel therapeutic molecules for the treatment of mCRC. Our research has 3 main aims: Aim 1: Investigate the biological activity of BOL and its analogs on protein synthesis; Aim 2: Design and develop novel therapeutic quassinoid analogs. Preliminary data demonstrates that the C15 side chain influences the ability of BOL to inhibit protein synthesis as well as STAT3. We will synthesize novel quassinoid-based analogs to increase in vitro cytotoxicity and in vivo antitumor activity and enhance target selectivities; and Aim 3: Develop novel nanoparticle technologies for BOL delivery. Preliminary data reveal that encapsulation of BOL into nanomicelles reduced BOL toxicities without affecting antitumor activity. The ADME properties of the BOL-nanomicelles will be further characterized.

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Our laboratory is dedicated to advancing the field of Urology through extensive research spanning several areas of interest. Our primary objective is to enhance our understanding of the molecular mechanisms that contribute to urogenital pathologies. By doing so, we aim to identify innovative and clinically applicable strategies for treating these conditions.

To achieve our goals, we employ state-of-the-art investigative techniques and have developed extensive expertise in utilizing 'omic' technologies to unravel the underlying mechanisms of urogenital diseases. We have received international recognition for conducting urogenital physiologic studies using small rodent animal models. For instance, our lab is adept at determining bladder function through cystometry, and is renowned for its pioneering use of animal models to scientifically document erectile function using cavernosometry.

Our research approach adopts a highly interdisciplinary perspective, and encompasses both benign and oncologic urogenital diseases. We have fostered successful collaborations with research groups from diverse disciplines that have brought fresh insights to the field of Urology. As a result, we have identified several compelling areas of research interest, including: **i)** Investigating mechanisms to facilitate cavernous/peripheral nerve regeneration as a potential treatment for erectile dysfunction following radical prostatectomy. **ii)** Exploring the utilization of nanoparticles as a dermal delivery system for various agents used in the treatment of urogenital diseases. **iii)** Elucidating the role of the MaxiK channel expressed in the urothelium in regulating bladder activity. **iv)** Uncovering the molecular mechanisms responsible for the development of priapism associated with sickle cell disease. **v)** Examining the influence of the microbiome on the development of kidney stone disease. viInvestigating the role of opiorphin in sperm motility. **vii)** Understanding the mechanism behind hyperglycemic memory in the diabetic bladder. **viii)** Examining the role and potential mechanism of opiorphin in the development of prostate cancer, which represents our most recent research focus.

By actively pursuing these diverse research interests, we aim to contribute significantly to the field of Urology and make tangible advancements in the diagnosis, treatment, and management of urogenital pathologies.

Representative Recent Publications (2021-)

Mukherjee, A., Park, A., Wang, L. and **Davies, K.P. (2021)** The role of opiorphin genes in prostate cancer growth and progression. Future Oncol. 2021 Jun;17(17):2209-2223. PMID: 33593085

Baker, L., Tar, M., Villegas, G., Charafeddine, R.A., Kramer, A., Vafaeva, O., Nacharaju, P., Friedman, J., **Davies, K.P.** *, and Sharp, D.J*. *=co-senior authors. **(2021)** Fidgetin-like 2 is a novel negative regulator of axonal growth and can be targeted to promote functional nerve regeneration after injury. JCI Insight. 10;6(9):138484. PMID: 33872220

Tar, M.T., Friedman, J.M., Draganski, A. and **Davies, K.P**. **(2022)** Topically delivered nitric oxide acts synergistically with an orally administered PDE5 inhibitor in eliciting an erectile response in a rat model of radical prostatectomy. Int J Impot Res.; Int J Impot Res 34(6):573-580. PMID: 34017115

Mukherjee, A., Park, A. and **Davies, K.P. (2022)** *PROL1* is essential for xenograft tumor development in mice injected with the human prostate cancer cell-line, LNCaP, and modulates cell migration and invasion. Journal of Men's Health 18(2):044, PMID: 35547856

Villegas, G., Tar, M.T. and **Davies, K.P. (2022)** Erectile dysfunction resulting from pelvic surgery is associated with changes in cavernosal gene expression indicative of cavernous nerve injury. Andrologia 54(1):e14247. PMID: 34514620

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Our laboratory is interested on the cell-autonomous and microenvironmental mechanisms that enable tumor cells to survive during treatment.

1) Despite the advances in cancer treatment, administered therapeutics often fail to eradicate the tumor cells in patients. One key focus area for our lab is the biology of the tumor cells that persist (residual tumor) after the initial acute cytotoxic effect of treatment and represent a reservoir for the eventual relapse. The goal of our research program is to functionally dissect the mechanisms that enable cancer cell persistence to multiple treatments and prevent the curative outcome. Our previous work has demonstrated that post-treatment residual cancer cells evade drug-induced cytotoxicity by adopting a distinct cellular state of reversible dormancy. This molecular program in persistent cancer cells resembles the adaptive diapause in epiblast stem cells, a dormant stage of suspended development in pre-implantation embryos triggered by stress and associated with suppressed Myc activity and overall biosynthesis. We aim to identify the molecular mechanisms that allow the tumor cells to enter, survive during and exit this diapause-like dormant state. We are also interested on the molecular similarities and unifying principles across treatment-induced adaptive dormancy and other survival states of quiescence in nature, such as the paused pluripotency during embryonic development. To this end, we combine the use of versatile in vitro (e.g. 3D monotypic and heterotypic organoid cultures) and in vivo (subcutaneous, orthotopic, or patient-derived xenografts) cancer models with molecular and functional studies.

2) Tumor cells reside in a complex 3-dimensional tissue microenvironment and interact with other, non-malignant, cell types (e.g. mesenchymal, immune cells etc.) and with extracellular matrix (ECM) molecules. Our previous work has focused on the reciprocal cross play between tumor cells and stromal cells as well as the ECM remodeling within the tissue microenvironment. We have observed that the interactions between tumor cells and the surrounding stroma (non-malignant cells and ECM) can profoundly affect the sensitivity of tumor cells to various classes of therapeutics (e.g. hormonal agents in breast and prostate cancer). Our current work focuses on dissecting the molecular interactions between tumor cells and the other elements of the microenvironment in the context of cancer therapy. Our goal is to increase the efficacy of pharmacological and immune therapies through manipulation of the tumor microenvironment.

3) Anti-microtubule chemotherapy drugs are among the most widely used treatments against cancer. Despite their success, treatment persistence and resistance limit their efficacy. Our recent work has uncovered key mediators of anti-microtubule drug resistance. We are currently developing novel preclinical drug candidates that target these resistance mechanisms and sensitize cancer cells to anti-microtubule agents.

Recent Relevant Publications:

- **Dhimolea E***, de Matos Simoes R, Kansara D, Al'Khafaji A, Bouyssou J, Weng X, Sharma S, Raja J, Awate P, Shirasaki R, Tang H, Glassner BJ, Liu Z, Gao D, Bryan J, Bender S, Roth J, Scheffer M, Jeselsohn R, Gray NS, Georgakoudi I, Vazquez F, Tsherniak A, Chen Y, Welm A, Duy C, Melnick A, Bartholdy B, Brown M, Culhane AC, Mitsiades CS*. An Embryonic Diapause-like Adaptation with Suppressed Myc Activity Enables Tumor Treatment Persistence. *Cancer Cell.* 2021 Feb 8;39(2):240-256. [corresponding authors]

- **Dhimolea E***, de Matos Simoes R, Kansara D, Weng X, Sharma S, Awate P, Liu Z, Gao D, Mitsiades N, Schwab JH, Chen Y, Jeselsohn R, Culhane AC, Brown M, Georgakoudi I, Mitsiades CS*. Pleiotropic Mechanisms Drive Endocrine Resistance in the Three-Dimensional Bone Microenvironment. *Cancer Res.* 2021 Jan 15;81(2):371-383. [corresponding authors]

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MacroH2As, histone variants with diverse roles in gene expression and DNA damage responses – The macroH2A histone variants (which include macroH2A1.1, macroH2A1.2 and macroH2A2) have roles in tumor suppression, cellular senescence, activation and repression of transcription, promotion of DNA repair and suppression of the reprogramming of differentiated cells into stem cells. MacroH2As are typified by a histone-like region fused by a flexible linker to a C-terminal macrodomain, a ligand-binding domain whose functions is modulated by binding to poly(ADP-ribose) produced by a family of poly(ADP-ribose) polymerases. MacroH2A1 regulates the expression of genes found within its large chromatin domains which can span hundreds of kilobases. Through changes in its expression and/or alterations in its genomic localization, disruption of macroH2A1's tumor suppressive functions are common in cancer; alterations of macroH2A transcription and splicing occur in a variety of cancers including those of lung, breast, colon, ovaries, endometrium, bladder, testicles, and melanocytes. Consistently, macroH2A1 loss in primary cells is sufficient to trigger an oncogenic gene expression profile. We are interested in many aspects of macroH2A biology. 1) How are macroH2As targeted to specific regions of the genome? 2) How does macroH2A1.1 in collaboration with PARPs regulate gene expression? 3) How does macroH2A1 regulate chromatin accessibility at enhancers? 4) How does macroH2A participate in DNA repair? 5) What regulates macroH2A1's alternative splicing?

Genomic context and enhancer function – Enhancers are key regulatory elements that can affect the transcription of their target gene even when found many kilobases upstream or downstream of the promoters they regulate. Consequently, enhancers can reside both in intergenic regions of the genome and within gene bodies. Our recent work demonstrates that the rule governing enhancer function are distinct for intergenic and gene body enhancers. In order to regulate transcription enhancers must maintain the accessibility of their chromatin, mediate the recruitment of critical cofactors and interact with target promoters over long linear distances through looping. We have shown that the histone variant macroH2A1 promotes the accessibility specifically of intergenic enhancers. In addition, we have demonstrated that acetylation of histone H2B on lysine 120 is critical for the recruitment of the transcriptional cofactor, BRD4, to intergenic enhancers but not gene body enhancers. By utilizing machine learning models, we continue to explore the distinct factors that regulate the function of these two classes of enhancers.

Interplay between transcriptional elongation rates and alternative splicing – Alternative splicing is a crucial aspect of gene expression, allowing a gene to yield functionally distinct product. Splicing dysregulation is central to several cancers and developmental diseases. Alternative splicing can be regulated through the recruitment of splicing factors which promote or repress distinct splicing events. Splicing largely occurs co-transcriptionally, and so, splicing outcomes are also affected by aspects of the transcription process and chromatin environment. The local elongation rate of RNA polymerase II is one aspect of transcription with important consequences on splicing outcomes. A barrier to progress in the field has been the lack of a high-throughput assay to measure splicing rates in mammalian cells. To address this, we have developed SKaTER-seq (Splicing Kinetics and Transcript Elongation Rates through sequencing). With this assay, we are exploring a myriad of factors that regulate splicing, including elongation rate, gene architecture, binding sites for RNA binding factors, chromatin structure and histone modifications. With this powerful approach we will determine the underlying causes of spicing alterations in disease.

Representative Publications:

Casill, A.D., Haimowitz, A.J., Kosmyna, B., Query, C.C., Ye, K., Gamble, M.J. (2021) Spatial organization of transcript elongation and splicing kinetics. bioRxiv doi: https://doi.org/10.1101/2021.01.28.428713

Hamilton, G.A., Ruiz, P.D., Ye, K., Gamble, M.J. Acetylation of histone H2B on lysine 120 regulates BRD4 binding to intergenic enhancers. bioRxiv doi: https://doi.org/10.1101/2025.02.07.637147

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P21 Rho family of small GTPases are critically important in normal and disease processes including cancers, developmental defects, arthrosclerosis, and autoimmune dysfunction. RhoGTPases control processes including cell polarity, motility, and invasion/migration through their actions on downstream targets important for cytoskeleton and adhesion dynamics, proliferation and vesicular transport pathways. The coordination of multiple RhoGTPases is thought to regulate a variety of cellular signaling outcomes; however, it has been difficult if not impossible to dissect the spatiotemporal dynamics of signal regulation by conventional imaging or biochemical techniques.

Our laboratory specializes in development of Förster Resonance Energy Transfer (FRET)-based fluorescent biosensors to visualize the spatiotemporal dynamics of protein activations in living cells in real time. FRET biosensors enable direct visualization signaling pathways at the resolution limits of light microscopy, previously inaccessible by traditional biochemical methods. Understanding the regulatory mechanism of GTPases is important and has potential impact in many areas including cancer metastasis and cell migration. Regulatory and coordinating effects of multiple GTPases at the leading edge of cell migration have yet not yet been fully elucidated. This is an exceptionally rich area of study in the field of cell and cancer biology.

Our laboratory has pioneered the direct-multiplex FRET visualization approach where we monitor two or more protein activities simultaneously using orthogonal pairs of FRET biosensors in living cells. These biosensors are engineered to maximize signal-to-noise ratio (SNR) and dynamic range of response and are optimized especially for simultaneous imaging in living cells using state-of-the-art high-resolution, multichannel microscope system.

Representative Publications:

Hülsemann, M., Donnelly, S.K., Verkhusha, P., Mao, S.H., DesMarais, V., Segall, J., and Hodgson, L. TC10 GTPase regulates breast cancer invasion and metastasis. (2021), Communications Biology: 4: 1091.

Shcherbakova, D.M., Cox Cammer, N., Huisman, T.M., Verkhusha, V.V. and Hodgson, L. (2018) Direct multiplex imaging and optogenetics of RhoGTPases enabled by near-infrared FRET. Nature Chemical Biology: Jun;14(6):591-600.

Donnelly, S.K., Cabrera, R., Chiang, S., Christin, J.R., Wu, B., Guo, W., Bravo-Cordero, J.J., Condeelis, J.S., Segall, J.E., and Hodgson, L. (2017) Rac3 regulates breast cancer invasion and metastasis by controlling adhesion and matrix degradation. J. Cell Biology: Dec 4;216(12):4331-4349.

Moshfegh Y, Bravo-Cordero JJ, Miskolci V, Condeelis J and Hodgson L. A Trio-Rac1-PAK1 signaling axis drives invadopodia disassembly. (2014) Nature Cell Biology, Vol.16, 574-86.

Bravo-Cordero, J. J., Oser, M., Chen, X., Eddy, R., Hodgson, L. and Condeelis, J. A novel spatiotemporal RhoC activation pathway locally regulates cofilin activity at invadopodia. (2011) Current Biology: .Vol. 21(8), 635-44.

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1. Aging and metabolism – A major goal of my research are to understand the interplay between aging and metabolism. We have recently published that the **IGF-1R** is a viable target via IGF-1R mAb treatment to delay aging in female mice, a pattern consistent with several genetic models of low IGF-1 signaling. In related studies, we have uncovered novel mechanisms of insulin and **IGF-1 signaling in the brain**, with implications for treating age-related metabolic decline and type 2 diabetes. Studies are further investigating the potential utility of growth factors targeted to the brain via the intranasal route may harbor therapeutic potential for cognitive decline. We have also investigated the role of metabolites in aging, identifying sarcosine, which is a byproduct of **glycine-N methyltransferase (GNMT)**, is upregulated by dietary restriction, and may be a key mediator of its effects. A focus of the lab is to further understanding the role of GNMT in metabolism and aging biology.

2. A geroscience approach to identify aging drug synergy –While single drugs can improve lifespan and healthspan, there is now evidence that combinatorial strategies designed to simultaneously target multiple aging pillars can result in greater efficacy than single agents. However, given the sheer number of potential aging drug combinations, a **systems geroscience approach** that integrates multi-level data could potentially make powerful, informed predictions regarding probability of synergistic effects between seemingly unrelated compounds. We are currently leveraging this approach in a mouse model of AD to determine the ability to identify aging drug synergy.

3. Role of cell non-autonomous factors in aging – We use several strategies, including **heterochronic parabiosis**, to understanding the role of systemic factors in tissue and cellular aging. We are currently pursuing studies to identify the systemic factor(s) responsible for driving features of intestinal decline as well as vascular aging.

4. Physiologic resilience and aging –Resilience is the ability in which an organism can respond to a physical challenge or stress and return to homeostasis, and. the gradual loss of resilience with age may underlie the onset of chronic disease, multimorbidity, frailty and death. We are developing a battery of simple, short-term assays to characterize resilience in rodents and are now using these assays in combination with molecular approaches to better understand the **molecular mechanisms underlying physiologic resilience** in mice and its loss with age.

Representative Publications

Mao K, Farias Quipildor G, Tabrizian T, Guan F, Walters RO, Delahaye F, Hubbard GB, Ikeno Y, Ejima K, Li P, Allison DB, Beltran P, Cohen P, Barzilai N, **Huffman DM**. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat Commun* 2018 Jun 19;9(1):2394. PMC6008442

Walters RO, Arias E, Diaz A, Burgos ES, Guan F, Tiano S, Mao K, Green CL, Qiu Y, Shah H, Wang D, Hudgins AD, Tabrizian T, Tosti V, Shechter D, Fontana L, Kurland IJ, Barzilai N, Cuervo AM, Promislow DEL, **Huffman DM.** Sarcosine is uniquely modulated by aging and dietary restriction in rodents and humans *Cell Rep* 2018 Oct 16;25(3):663-676.e6. PMC6280974

Farias-Quipildor G, Mao K, Hu Z, Novaj A, Cui MH, Gulinello M, Branch CA, Gubbi S, Patel K, Moellering DR, Tarantini S, Kiss T, Yabluchanskiy A, Ungvari Z, Sonntag WE, **Huffman DM**. Central IGF-1 reduces depressive-like behavior and improves cognitive and physical performance with aging preferentially in male mice *Geroscience* 2019 May 10 PMC6544744

Farias-Quipildor G, Mao K, Beltran P, Barzilai N, **Huffman DM**. Modulation of Glucose Production by Central Insulin Requires IGF-1 Receptors in AgRP Neurons. *Diabetes* 2021 (*in press*)

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My research program focuses on studying the neurobiology of energy metabolism. First, my ongoing research examines whether liver-derived interoceptive signals can influence emotions. Proper integration and transportation of interoceptive signals from organs to the brain via vagal sensory neurons appear to be critical for psychological experiences ranging from various feelings and emotions to motivations and adaptive behaviors. Optimal sensing and integration of internal body signals are crucial for many essential physiological functions. I specifically seek to determine if there is a specialized anatomical organization of liver-innervating vagal sensory neurons and determine the roles of liver-projecting vagal sensory neurons in controlling energy homeostasis and emotions. This research area is novel and remains to be explored.

Second, I seek to define the role of the parasympathetic nervous system of the liver in controlling energy metabolism and hepatic steatosis. In this study, I use a unique, coordinated, and multidisciplinary combination of state-of-the-art techniques, including viral tracing, virus-mediated gene delivery, *in vivo* fiber photometry, and functional readouts of liver function to identify and characterize the roles of parasympathetic cholinergic innervation in the control of hepatic metabolism in lean and obese mice.

Lastly, my study aims to assess the role of central melanocortin tone in the function of hypothalamic pro-opiomelanocortin (POMC) neurons projecting to the medial amygdala and the dorsal motor nucleus of the vagus in mice. The primary goal of this study is to produce meaningful, applicable results demonstrating that α-melanocyte-stimulating hormone maturation in hypothalamic POMC neurons is critical in affecting the ability of hypothalamic POMC neurons to regulate energy balance, insulin resistance, and hepatic steatosis in obese mice.

This laboratory uses multiple cutting-edge techniques such as conditional viral tracing, wired and wireless optogenetics, pharmacogenetics, *in vivo* calcium imaging, *in vivo* fiber photometry, CRISPR/Cas-9 gene knockdown, and electrophysiology.

Representative publications:

Hwang, JY, Lee, SB, Okada, J, Liu, L, Pessin, JE, Chua, SC, Schwartz, GJ, and Jo, YH (2025), Liver-innervating vagal sensory neurons play an indispensable role in the development of hepatic steatosis and anxiety-like behavior in mice fed a high-fat diet. *Nature Commun.,* 16, 991, doi.org/10.1038/s41467-025-56328-5; PMID: 39856118

Hwang, JY, Okada, J, Liu, L, Pessin, JE, Schwartz, GJ, and Jo, Y.H. (2024) The development of hepatic steatosis depends on the presence of liver-innervating parasympathetic cholinergic neurons in mice fed a high-fat diet. *Plos Biol.* 22 (11): e3002865; PMID: 39436946

Jo, Y.H. (2024), Differential transcriptional profiles of vagal sensory neurons in female and male mice. *Front. Neurosci*. Volume 18, 2024: doi: 10.3389/fnins.2024.1393196

Min, H-Y, Hwang, J-Y, Choi, Y, and Jo, YH, Knockdown of the *Magel2* gene in hypothalamic POMC neurons innervating the medial amygdala reduces susceptibility to diet-induced obesity with increased locomotor activity, *Life Science Alliance,* (2022), DOI: 10.26508/lsa.202201502

Kwon, E., Joung H.-Y., Liu, S. M., Chua, S. C., Jr., Schwartz, G. J., and Jo, Y. H. Optogenetic stimulation of the liver-projecting melanocortinergic pathway promotes hepatic glucose production. *Nature Commun.* (2020), 11(1):6295. doi: 10.1038/s41467-020-20160-w

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Targeting BCL-2 family proteins in leukemias. Our lab has a long-standing interest in targeting BCL-2 family proteins in leukemia. Pre-clinical studies have demonstrated high activity of BCL-2 inhibitor venetoclax in acute leukemias,and have transitioned into clinical trials and eventually FDA approval of this agent used in combinations for older unfit for chemotherapy AML patients. In the laboratory, we have focused on mechanisms of resistance to venetoclax, and have identified FLT3/MCL-1 and RAS/MAPK/MCL-1 pathways (*STTT* 2022). My lab has performed pre-clinical studies indicating synergy of monoclonal antibodies and engagers of innate immunity and Azacitidine/venetoclax, and clinical trials are currently underway. In ALL and more recent in subsets of AML, we have demonstrated a role of BCL-XL in addition to BCL-2, in control of apoptotic threshold. Studies with dual Bcl-2/XL inhibitor and novel -2/XL degraders are ongoing in AML and ALL models.

Targeting mitochondrial metabolism in leukemias. Based on pre-clinical findings of high OxPhos dependency in AML, I led a first-in-human Phase I clinical trial of oxidative phosphorylation (OxPhos) inhibitor IACS-010759 in relapsed/refractory AML, which showed target modulation, but was discontinued due to toxicities. The ongoing studies are focusing on exploration of other OxPhos inhibitors in combination with chemotherapy and target agents. We demonstrated metabolic dependency of Notch-mutated T-ALL on OxPhos and sensitivity to IACS-010759, alone and in combination with chemotherapy (*Nature Comm* 2022) and MCT1 inhibitors. We have an ongoing collaboration on novel mitochondrial inhibitors. We continue studies aimed at understanding the role of glutamine metabolism, and targeting glutaminase in combination with BCL-2 and FLT3 inhibitors in AML.

Biology and therapy of blastic plasmacytoid dendritic cell neoplasm (BPDCN). My lab is studying combined BCL-2 and anti-CD123 targeting in BPDCN, a rare hematologic malignancy with poor outcomes. Studies in my lab have shown pre-clinical activity of allogeneic UCARTCD123 CAR-T cells (*Nature Comm 2022*) and CD123 ADC IMGN123 in models of BPDCN. Both strategies have translated into ongoing clinical trials. We are developing CART targeting novel antigens in BPDCN.

Studying the role of CD200 as a novel AML LSC marker conveying immune-suppressive properties of ASML cells. We identified CD200 as a highly expressed marker on AML LSC, and demonstrated that overexpression reduced cytokine production and metabolism of T-, NK-cells and macrophages (*JITC 2021*). Targeting CD200 using a tool anti-CD200 IgG1-antibody induced single agent activity and eliminated AML in immune-reconstituted AML in vivo models, and potentiated efficacy of Azacitidine/venetoclax in immune-deficient AML PDX models. We are currently developing a novel anti-CD200 antibody.

Immuno-oncology. My lab is performing pre-clinical studies to determine efficacy and feasibility of proceeding towards clinical trials of several immune conjugates and CARTs against AML stem cell antigens. Using proteomics, we have several novel testis-specific antigens expressed in AML and are developing targeting antibodies.

Representative Recent Publications:

Pan R.et al. Selective BCL-2 Inhibition by ABT-199 Causes On Target Cell Death in Acute Myeloid Leukemia. Cancer Discov 4(3):362-75, 3/2014.

Zhang Q. et al. Activation of RAS/MAPK pathway confers MCL-1 mediated acquired resistance to BCL-2 inhibitor venetoclax in acute myeloid leukemia. Signal Transduct Target Ther 7(1):51, 2/2022.

DiNardo CD, Konopleva MY. A venetoclax bench-to-bedside story. Nat Cancer 2(1):3-5, 1/2021.

Baran N. et al. Inhibition of mitochondrial complex I reverses NOTCH1-driven metabolic reprogramming in T-cell acute lymphoblastic leukemia. Nat Commun. 13(1):2801, 5/2022.

Cai T. et al. Targeting CD123 in blastic plasmacytoid dendritic cell neoplasm using allogeneic anti-CD123 CAR T cells. Nat Commun 13(1):2228, 4/2022.

Pemmaraju N. et al. Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm. N Engl J Med 380(17):1628-1637, 4/2019.

Herbrich S. et al. Overexpression of CD200 is a Stem Cell-Specific Mechanism of Immune Evasion in AML. J Immunother Cancer 9(7):e002968, 7/2021.

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Our lab studies biology and therapies for colorectal cancer (CRC). We use unique, patient-derived models of cancer in lab, and a combination of dry-lab and wet-lab approaches. Our techniques can be applied to mechanistic discovery as well as therapeutic validation of drugs. Ultimately, we hope to translate our findings into novel clinical trials.

Combination Therapy to Overcome Drug Resistance in CRC: We have multiple ongoing projects on the discovery and validation of new combination therapies to overcome drug resistance and prolong survival for CRC. We are currently most interested in combinations involving CDK9 inhibitors, KRAS inhibitors, and other small molecules.

CDK9 inhibitors modulate the transcriptional landscape of colorectal cancer to suppress MAPK signaling and synergizes with BRAF inhibitors to treat BRAF-mutant colorectal cancer. **Kuang C**, Wei N, Mohammadi M, Bhat MA, Li T, Patil P, Wiltz O, Huang R, Ooka K, Quintal M, Chu E. Cancer Research. 2024 Mar 22;84(6_Supplement):1218-.

CDK9 inhibitors for the treatment of solid tumors. Mo C, Wei N, Li T, Ahmed Bhat M, Mohammadi M, **Kuang C**. Biochem Pharmacol. 2024 Nov;229:116470. doi: 10.1016/j.bcp.2024.116470. Epub 2024 Aug 8. PMID: 39127153.

Targeting KRAS in Colorectal Cancer: A Bench to Bedside Review. Bteich F, Mohammadi M, Li T, Bhat MA, Sofianidi A, Wei N, **Kuang C**. Int J Mol Sci. 2023 Jul 27;24(15):12030. doi: 10.3390/ijms241512030. PMID: 37569406.

High Throughput Screening Identifies Small Molecules that Synergize with MRTX1133 Against Acquired Resistant KRAS G12D Mutated CRC. Thielen N, Wei N, Nagai E, Chu E, Kitamura S, **Kuang C**. bioRxiv [Preprint]. 2025 Jul 2:2025.06.27.662039. doi: 10.1101/2025.06.27.662039.

Development of novel patient derived models for drug discovery: We are collecting cancer specimens from our diverse patients in the Montefiore Einstein Comprehensive Cancer Center to establish novel preclinical cancer models that will be used for cancer drug experiments. We will combine this biobank with rigorous molecular and clinical annotation to facilitate personalized drug discovery and validation.

Senescent fibroblasts in the tumor stroma rewire lung cancer metabolism and plasticity. Lee JY, Reyes N, Woo SH, Goel S, Stratton F, **Kuang C**, Mansfield AS, LaFave LM, Peng T. bioRxiv [Preprint]. 2024 Jul 30:2024.07.29.605645. doi: 10.1101/2024.07.29.605645. PMID: 39131266.

Clinical Trials for CRC: We are interested in developing promising interventions being studied in preclinical models into new clinical trials. In addition to ongoing work to translate our own lab findings, we have established collaborations with other scientists to turn their treatments into new therapeutic trials.

CBX-12 for the Treatment of Metastatic Chemotherapy-Refractory Microsatellite Stable Colorectal Cancer. ClinicalTrials.gov ID: NCT06730100. https://clinicaltrials.gov/study/NCT06730100. **PI: Kuang C**.

Design of a phase 1 trial of Listeria monocytogenes 11-T856-1313 tetanus toxoid (Lm-LLO-TT) for pancreatic ductal adenocarcinoma (PDAC). Bhawneet Chadha et al. JCO 43, e15115-e15115(2025).

Pembrolizumab plus azacitidine in patients with chemotherapy refractory metastatic colorectal cancer: a single-arm phase 2 trial and correlative biomarker analysis. **Kuang C**, Park Y, Augustin RC, Lin Y, Hartman DJ, Seigh L, Pai RK, Sun W, Bahary N, Ohr J, Rhee JC, Marks SM, Beasley HS, Shuai Y, Herman JG, Zarour HM, Chu E, Lee JJ, Krishnamurthy A. Clin Epigenetics. 2022 Jan 6;14(1):3. doi: 10.1186/s13148-021-01226-y. PMID: 34991708.

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Host-Microbial genetics, orphan nuclear receptors, metabolites, and disease

Pregnane X Receptor (PXR) [a.k.the Steroid and Xenobiotic Receptor (SXR)] is a master nuclear receptor regulator of host xenobiotic/endobiotic metabolism, detoxification, and inflammation. We have shown that the receptor plays a major role in relaying host microbial signals in the intestines with innate immunity. Specifically, we have shown that microbial metabolites of L-tryptophan, indoles, and indole propionates, activate PXR in intestinal epithelial cells to promote intestinal immune homeostasis via a TLR4 specific pathway[*]. This discovery has led our laboratory into new directions primarily focused on molecular mechanisms governing host-microbial and microbial-microbial relationships in the intestines.

1. Discovery of endobiotic PXR ligands and use of microbial metabolite mimicry to design drugs combating intestinal inflammation and cancer. We have embarked on chemical biological approaches to discovery of indole propionate analogs as potent PXR ligand agonists, with the eventual hope of designing small molecule drugs (microbial metabolite mimicry) combating intestinal inflammation and inflammation-induced cancer[**]. More recently, the role for indole metabolites connects the gut microbes to neuronal function partly via PXR[***]. We are also interested in covering all other human receptors regarding microbial metabolite effects.

2. Discovery of new (novel) microbes and mechanisms governing its regulation of innate immunity. We have diversified our interests to the study of how and why novel bacterial strains arise during inflammation, and how they execute a phenotype in mice[$]. Finally, our goal is to derive probiotic approaches, harnessing our internal microbiome, for the treatment of a variety of health conditions. These projects have led to multidisciplinary approaches of designing probiotic drug delivery systems using physics of bacterial spreading, molecular microbiology, and host biology[$$]. We are also interested in bar coded recording of transcriptional events in probiotics and pathogens.

Selected Publications:

[*] Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benechet AP, Qiu Z, Maher L, Redinbo MR, Phillips RS, Fleet JC, Kortagere S, Mukherjee P, Fasano A, Le Ven J, Nicholson JK, Dumas ME, Khanna KM, Mani S. Symbiotic Bacterial Metabolites Regulate Gastrointestinal Barrier Function via the Xenobiotic Sensor PXR and Toll-like Receptor 4. Immunity 41(2): 296-310 (2014)

[**] Dvorak Z et al (40 authors), Mani S*. Targeting the Pregnane X Receptor Using Microbial Metabolite Mimicry. EMBO Molecular Medicine (Cover Page Citation) 12(4):e11621(2020)

[**] Dvorak Z, Sokol H, Mani S. Drug Mimicry: Promiscuous Receptors PXR and AhR, and Microbial Metabolite Interactions in the Intestine. Trends Pharm Sci (Cover Page Citation) 41(12): 900-908 (2020)

[***] Serger E et al (primary work from the Giovanni lab, Imperial College, London). The gut metabolite indole-3 propionate promotes nerve regeneration and repair. Nature Jun 22 doi:10.1038/s41586-022-04884-x (online ahead of print 2022)

[$] De A, Chen W, Li H, Wright JR, Lamendella R, Lukin DJ, Szymczak WA, Sun K, Kelly L, Ghosh S, Kearns DB, He Z, Jobin C, Luo X, Byju A, Chatterjee S, San Yeoh B, Vijay-Kumar M, Tang JX, Prajapati M, Bartnikas TB, Mani S. Bacterial Swarmers Enriched During Intestinal Stress Ameliorate Damage. Gastroenterology 161(1):211-224. doi: 10.1053/j.gastro.2021.03.017 (2021)

[$$] Chen W, Mani N, Karani H, Li H, Mani S, Tang JX. Confinement discerns swarmers from planktonic bacteria. Elife 10:e64176 (2021)

Ondrová K et al (17 authors), Mani S*, Dvořák Z*. Monoterpenoid aryl hydrocarbon receptor allosteric antagonists protect against ultraviolet skin damage in female mice. Nat Commun. 2023 May 11;14(1):2728. doi: 10.1038/s41467-023-38478-6.

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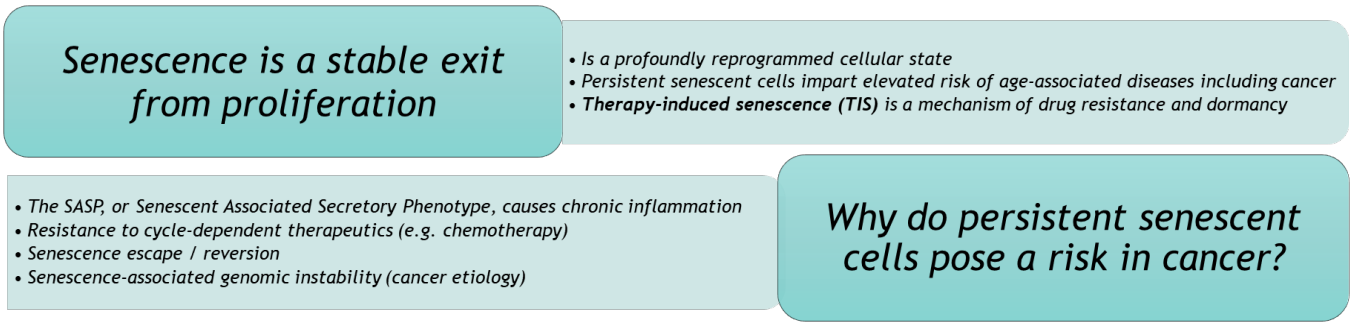
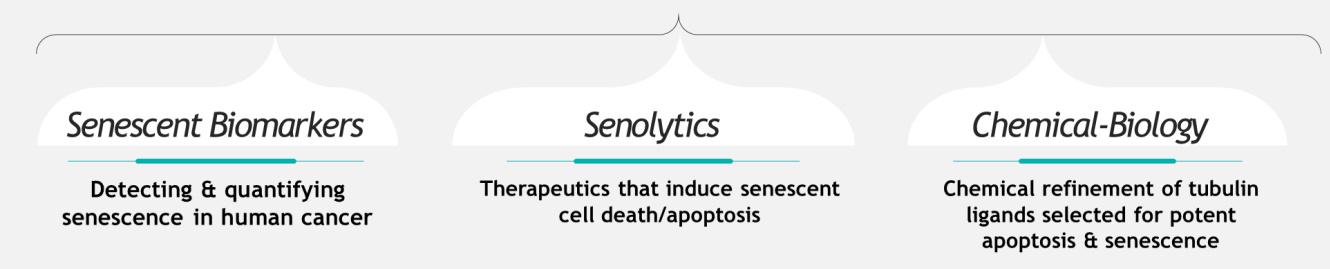
WE ARE A SENESCENCE-CENTRIC LAB WHOSE BROAD GOAL IS TO UNDERSTAND AND EXPLOIT THE SENESCENCE THAT OCCURS IN RESPONSE TO CANCER THERAPY



- *We were one of the first groups to propose that chemotherapy-induced senescence (CIS) is an underappreciated mechanism of drug resistance and cause of tumor dormancy.*
- *Our interests in senescence began with studies on the tubulin ligand,* ***discodermolide*** *and the discovery that it is a potent inducer of senescence. We refined the chemical structure of discodermolide to leverage both apoptosis and senescence-inducing capabilities and are evaluating novel analogs for antitumor efficacy.*
- *We posit that cycles of recurrent senescence and escape may act as evolutionary bottlenecks through which somatic mutations occur. This could represent an important, though overlooked mechanism of carcinogenesis and cancer evolution (in response to therapy). We have generated drug-resistant cancer cell lines that escaped consecutive cycles of therapy-induced senescence to investigate the role of senescence in shaping the genomic landscape of cancer.*
- *Detecting and therapeutically targeting dormant senescent cells remains an area of unmet clinical need. By eliminating the senescent cells that accumulate during cancer therapy, we can reduce the risk of relapse. We have identified molecules with promising senolytic potential (ability to induce senescent cell death). We are leveraging proteomic approaches to identify senescent signatures in vivo and exploring the potential for senescence-enriched cell surface proteins to be used in antibody-conjugate senolytic applications.*

PROJECTS AVAILABLE IN THE McDAID LAB



CANCER PHARMACOLOGY - TUMOR DORMANCY - BIOMARKER DISCOVERY

-Chao SK, Lin J, Brouwer-Visser J, Smith AB 3rd, Horwitz SB, **McDaid HM** (2010). Resistance to discodermolide, a microtubule-stabilizing agent and senescence inducer, is 4E-BP1-dependent. Proc Natl Acad Sci U S A.;108(1):391-6. PMCID: PMC3017154

-Chao SK, Horwitz SB, **McDaid HM** (2011). Insights into 4E-BP1 and p53 mediated regulation of accelerated cell senescence. Insights into 4E-BP1 and p53 mediated regulation of accelerated cell senescence. Oncotarget. Jan-Feb;2(1-2):89-98. PMCID: PMC3248149

-Samaraweera L, Adomako A, Rodriguez-Gabin A and **McDaid HM**. (2017) A Novel Indication for Panobinostat as a Senolytic in NSCLC and HNSCC. Sci Rep;7(1):1900. PMID: 28507307

-Guo B, Rodriguez-Gabin A, Zhang N, Ye K, Atsaoylu O, Horwitz SB, Smith AB III, and **McDaid HM** (2020). Structural Refinement of the Tubulin Ligand Discodermolide to Attenuate Chemotherapy-Mediated Senescence. Molecular Pharmacology. August 2020, 98 (2) 156-167. PMID: 32591477

-Yang CH, Horwitz SB and **McDaid HM** (2022). Utilization of Photoaffinity Labeling to Investigate Binding of Microtubule Stabilizing Agents to P-glycoprotein and -Tubulin. Journal of natural products. Nat Prod. 2022 Mar 25;85(3):720-728. PMID: 35240035

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Area of Research: Regulation of gene expression; Control of RNA polymerase II transcription cycle; Kinase-phosphatase antagonism in regulating chromatin structure, antisense transcription, and transcription elongation; Unraveling the molecular mechanisms of dependencies of cancer cells on the dysregulated transcription.

Professional Interests

The proper regulation of RNA Polymerase II (Pol II)-dependent transcription—that normally maintains appropriate expression levels of protein-coding genes and non-coding RNAs—is crucial to keep cells healthy and prevent diseases. Pol II transcription is strictly regulated at three main stages: initiation, elongation, and termination by numerous regulatory factors, including kinases and phosphatases, chromatin structure, and antisense transcripts. Dysregulation of Pol II elongation and the production of antisense transcripts are associated with various diseases, including cancer, diabetes, cardiac and neurodegenerative disorders. Therefore, a better understanding of the fundamentals of the regulation of these processes is of paramount importance for improved diagnostic markers and therapeutic treatments. We investigate Pol II transcription regulation in the fission yeast *Schizosaccharomyces pombe* and human cells. Our research leverages integrated approaches, including biochemistry, cellular and molecular biology, classical genetics, and chemical genetics—a technique to sensitize a kinase to unnatural ATP analogs—combined with genomics and proteomics.

To obtain mechanistic insights into promoter-proximal pausing – Most of the genes in metazoan (and ~20% genes in fission yeast) are regulated by an early regulatory event, known as promoter-proximal pausing—Pol II is paused shortly after initiation around 20-80 nucleotides downstream of the transcription start site (TSS). Properly regulated release of stalled Pol II from the promoter-proximal pause site results in the synthesis of full-length transcripts. Mis-regulation of pausing or its release can result in abnormal gene expression. Given this early regulatory event's decisive role in tuning Pol II transcription, dissecting the underlying molecular mechanisms is of utmost importance for understanding transcriptional homeostasis and its disruption in human diseases. Emerging studies suggest that the distinct kinase-phosphatase switch mechanisms control the phosphorylation of effector proteins, modulating the pause establishment, maintenance, and release. These critical kinase-phosphatase networks are mostly unknown and need to be identified and characterized precisely. We seek to investigate the regulation of promoter-proximal pausing in fission yeast and human cells to understand how the coordination between kinases and phosphatases ensures the pause establishment and synchronized release beneficial for healthy cells.

To investigate the coupling of transcription elongation and co-transcriptional processes – The variations in the rate of Pol II elongation have been implicated in controlling co-transcriptional processes such as 5'- and 3'-end processing, antisense transcription, alternative polyadenylation (APA), and splicing of pre-mRNA. However, much is still unknown, how the elongation rate is controlled and, consequently, the coupled process. The current hypothesis is that normal speeds of Pol II elongation favor the recruitment of factors necessary to execute a particular step, whereas slower Pol II promotes aberrant recruitment of factors, resulting in premature outcomes; conversely, faster rates impair the timely execution of exact steps. The primary objective here is to examine unidentified and uncharacterized connections among kinase-phosphatase antagonisms, rate of elongation, post-translational modifications (PTMs) of histones, pre-mRNA splicing, and transcription polarity.

To uncover how spatial and temporal phosphorylation events influence termination – The elongation to termination transition, a crucial step near the end of transcription, prepares Pol II for efficient and accurate termination following a series of sequential events: (1) deacceleration of elongating Pol II while crosses the cleavage and polyadenylation signal (CPS), leading to (2) accumulation of Ser2 phosphorylation of Pol II carboxy-terminal domain (CTD), which in turn facilitates (3) the recruitment of factors involved in pre-mRNA 3'-end formation and termination. A long-standing puzzle was how the transition from elongation to termination is initiated. Recently we identified a novel bistable switch mechanism comprising cyclin-dependent kinase 9 (Cdk9) and protein phosphatase 1 (PP1) that rapidly reverses phosphorylation at the CTD of an essential elongation factor, Spt5 (and possibly other Cdk9 substrates) during the traversal of the elongation machinery through the CPS, leading to Pol II slowing. The Spt5 CTD phosphorylation is inversely correlated with Pol II CTD Ser2 and Thr4 phosphorylation at the 3'-end of genes. However, how their reciprocal relations functionally link to influence the termination remains less understood. We will assess the spatial and temporal connections of various phosphorylation events and characterize their molecular roles in transcription termination.

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One major project in our laboratory is to understand the basis for the dysregulation of glucose and lipid metabolisms in the liver. It is well established that in insulin resistant states the regulation of gluconeogenesis is altered such that hepatic glucose production is enhanced in the fasted state with reduced suppression in the fed state. In parallel, hepatic *de novo* lipogenesis is elevated in fasted state and further increased in the fed state. Numerous studies have examined the regulation of DNA binding transcription factors, transcription factor co-activators and co-repressors in the control of liver lipogenic gene expression. Despite the intensive investigation of these trans-factors, none of these proteins directly interacts with DNA-dependent RNA polymerase II. One critical complex termed the Mediator connects multiple trans-factors to the DNA-dependent RNA polymerase II. In mammalians Mediator is composed of at least 30 individual subunits that are assembled from four sub-complexes, head, middle, tail and kinase sub-modules. In yeast, it was originally suggested that the Mediator is a constitutive component of the expression machinery. However, we recently demonstrated that the CDK8/CycC complex a component of the kinase sub-module (CDK8/CycC, Med12 and Med13) undergoes dynamic regulation by insulin and nutritional states. We are currently studying the molecular pathways and functional consequences of the Mediator structural reorganization in both rodent models and in human liver biopsy speciments. In parallel, to these efforts we are also performing comprehensive time-dependent nutritional, developmental/age, circadian cycle, and sex dependent changes in genome-wide chromosomal (Hi-C, Histone/Mediator ChIP-seq, ATAC-seq, DNA methylation) and expression (PRO-seq, RNA-seq) from normal C57BL6/J mouse livers.

A second major project is based upon our observations that deficiency of a specific SNARE protein responsible for intracellular membrane trafficking (SNAP23) functions to control macroautophagy and cell death in adipocytes. For example, adipocyte-specific SNAP23 knockout mice display a temporal development of severe general lipodystrophy associated with adipose tissue inflammation, insulin resistance, hyperglycemia, liver steatosis and early death. We have found that this loss of adipocytes results from an adipocyte specific apoptosis process resulting from increased levels of the pro-apoptotic protein Bax due to impaired lysosome-mediated degradation. Moreover, SNAP23 deficiency altered the trafficking of ATG9 and knockdown of ATG9 phenocopied the same increase and activation of Bax protein and apoptotic cell death. These events were specific for Bax, as the induction of apoptotic cell death was blocked by BAX knockdown in the context of either SNAP23 or ATG9 deficiency. We are now examining the SNAP23/ATG9 selective versus canonical macroautophagy pathway responsible for Bax activation by using the BAX activation specific antibody 6A7 in combination with shRNA knockdown and/or sgRNA knockout to identify other autophagy family members and SNARE proteins mediating BAX degradation/activation and apoptotic cell death.

Representative Publications:

Song Z, Xiaoli AM, Li Y, Siqin G, Wu T, Strich R, Pessin JE, Yang F. The onserved Mediator subunit Cyclin C (CCNC) is required for brown adipocyte development and lipid accumulation. Mol Metab, In Press, 2022.

Picarda E, Galbo PM Jr, Zong H, Rajan MR, Wallenius V, Zheng D, Börgeson E, Singh R, Pessin J, Zang X. The immune checkpoint B7-H3 (CD276) regulates adipocyte progenitor metabolism and obesity development. Sci Adv. 2022 Apr 29;8(17):eabm7012.

Tang Y, Zong H, Kwon H, Qiu Y, Pessin JB, Wu L, Buddo KA, Boykov I, Schmidt CA, Lin CT, Neufer PD, Schwartz GJ, Kurland IJ, Pessin JE. TIGAR deficiency enhances skeletal muscle thermogenesis by increasing neuromuscular junction cholinergic signaling. Elife. 2022 Mar 7;11:e73360. doi: 10.7554/eLife.73360.

Youn DY, Xiaoli AM, Zong H, Okada J, Liu L, Pessin JB, Pessin JE, Yang F. The Mediator complex kinase module is necessary for fructose regulation of liver glycogen levels through induction of glucose-6-phosphatase catalytic subunit (G6pc). Mol Metab. 2021 Jun;48:101227. doi: 10.1016/j.molmet.2021.101227. Epub 2021 Mar 31.PMID: 33812059

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The Santulli Lab studies the functional role of microRNAs and calcium fluxes in the pathophysiology of cardiovascular and metabolic disorders. The Lab is funded by the National Institute of Health (NIH): indeed, the PI has 5 R01 Grants (2 as PI: NIDDK and NHLBI) and 1 T32 (Cardiovascular Research). The lab is also supported by the American Heart Association (AHA, 1 Innovative Project Award, 4 postdoctoral fellowships), the Weill-Caulier and Hirschl Trusts, and the Diabetes Research Foundation.
Website: https://sites.einsteinmed.edu/santulli-lab/latest-publications

The main current projects, focusing on translational research, are:

- **Intracellular calcium modulates cardiomyocyte function and fibroblast activation in myocardial infarction and heart failure.** We are investigating the functional contribution of intracellular calcium release channels in the regulation of cardiomyocyte fitness and in the phenoconversion of fibroblasts to myofibroblast following cardiac ischemia.
- **Mechanistic role of intracellular calcium in mediating mitochondrial function in pancreatic beta cells.** We are studying the fundamental mechanisms underlying the key role of intracellular calcium release channels in diabetes, both in humans (including human islets) and murine models of diabetes mellitus and obesity.
- **Role of non-coding RNAs in the regulation of endothelial dysfunction.** We have been the first group to propose that COVID-19 is an endothelial disease (*J Clin Med*. 2020;9:1417) and we are currently dissecting the functional role of non-coding RNAs and microRNAs in the regulation of endothelial cells in several settings.

Representative Recent Publications:

-Natural Killer T Cells Link Stress Hyperglycemia to Cognitive Decline in HFpEF. ***Circulation Research***. 2025

-Prediabetes Increases the Risk of Frailty in Prefrail Older Adults with Hypertension: Beneficial Effects of Metformin. ***Hypertension***. 2024 – with cover.

-The SGLT2 inhibitor canagliflozin attenuates mitochondrial oxidative stress and alterations of calcium handling induced by high glucose in human cardiac fibroblasts. ***Cell Cycle***. 2025

-Beneficial effects of metformin treatment in hyperglycemic patients affected by ischemia with no obstructive coronary artery. ***Cardiovascular Research***. 2025

-Low LDL-cholesterol drives the risk of bleeding in patients treated with aspirin: A 15-year study in a real-world large population. ***Pharmacological Research***. 2025

-The Dual Endothelin-1 Antagonist Aprocitentan Alleviates Mitochondrial Oxidative Stress in Human Cardiac Fibroblasts. ***European Heart Journal - Cardiovascular Pharmacotherapy***. 2024

-Ketone bodies rescue mitochondrial dysfunction via epigenetic remodeling. ***JACC (Basic Transl Sci)***. 2023

-Infiltrating macrophages amplify doxorubicin-induced cardiac damage. ***Cell Mol Life Sci.*** 2023

-Choline supplementation improves cognitive performance: Novel insights on endothelial function. ***Eur J Prev Cardiol***. 2023

-Extended-release metformin improves cognitive impairment in frail older women with hypertension and diabetes. ***Cardiovasc Diabetology*** 2023

-IP3 receptor orchestrates maladaptive vascular responses in heart failure. ***JCI***. 2022

-Empagliflozin improves cognitive impairment in type 2 diabetes and heart failure with preserved ejection fraction (HFpEF). ***Diabetes Care***. 2022

-SGLT2 inhibition via Empagliflozin improves endothelial function and reduces mitochondrial oxidative stress: Insights from frail hypertensive and diabetic patients. ***Hypertension*** 2022

-Glycation of Ryanodine Receptor in circulating lymphocytes predicts the response to cardiac resynchronization therapy. ***Journal of Heart and Lung Transplantation***. 2022

-Role of endothelial miR-24 in COVID-19 cerebrovascular events. ***Critical Care***. 2021.

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Small cell lung cancer (SCLC) is characterized by aggressive growth, frequent metastases, the rapid development of chemotherapy resistance, and an overall five-year survival of less than 5%. Dozens of drugs have been tested for clinical activity in SCLC, including more than 40 agents that have failed in phase III trials. The identification of driver mutations and their corresponding targeted drugs have led to significant improvements in the treatment of other solid tumors; however, similar advances have not been made in the treatment of SCLC. A unique feature of SCLC is the near uniform (>95%) bi-allelic inactivation of tumor suppressor genes RB1 and TP53 to drive tumorigenesis. This defining feature of the disease has not led to a targeted therapy, however, since genetically inactivated RB1 and TP53 cannot be reactivated, nor is it feasible to clinically reintroduce the wild-type genes into tumor cells in vivo. Our lab identifies key signaling pathways that are activated in RB1-deficient cells, and then to design and test pharmacologic agents that inhibit these pathways, restoring the lost function(s) of RB1, and causing tumor regressions.

1. pRb regulates the E3 ubiquitin ligase SCF-Skp2/Cks1 (Skp2). pRB has been shown to exert significant cell cycle control that is transcription-independent, and this is due to pRB's regulation of protein stability by direct effects on the ubiquitin-ligase proteasomal degradation pathway. One repression target of pRB is the SCF E3 ligase, SCFSkp2/Cks1, and the knockout of the Skp2 substrate-recruiting subunit of SCFSkp2/Cks1 effectively blocked pituitary, lung, and prostate tumorigenesis in Rb1-deficient mice. Protein targets of Skp2 include the cyclin-dependent kinase inhibitor p27 (CDKN1b), a key cell cycle regulator which inhibits progression from G1 phase into S phase of the cell cycle. We are using a series of genetically- modified mouse models to determine the molecular role of Skp2, p27, and related proteins in SCLC tumorigenesis.

2. While not as common as in SCLC, prostate cancers can also have mutations that inactivate the RB1 gene, and these are often aggressive, metastatic, and drug-resistant tumors. Using similar strategies as in our lung cancer studies, we are studying Skp2 inhibitors as potential treatments of advanced prostate cancer.

3. A challenge in the identification of inhibitors of Skp2 is that the ubiquitin ligases have biochemically distinct active sites, and lack the tight, well-defined pockets of traditional enzymes or receptors. Instead, studies have targeted the coordinated series of protein-protein interactions (PPIs) that are required for ligase activity. Using in silico modeling, virtual library screening, and medicinal chemistry syntheses, we are identifying and testing small molecule inhibitors of Skp2 activity for their antitumor effects in mouse and human cancer models.

Recent Publications:

Zhao H, Iqbal N, Sukrithan V, Nicholas C, Xue Y, Yu C, Locker J, Zou J, Schwartz EL and Zhu L. Targeted inhibition of the E3 ligase SCFSkp2/Cks1 has antitumor activity in RB1-deficient human and mouse small cell lung cancer (SCLC). Cancer Research, 2020; 80:2355-2367.

Wang J, Aldahamsheh O, Ferrena A, Borjihan H, Singla A, Yaguare S, Singh S, Viscarret V, Tingling J, Zi X, Lo Y, Gorlick R, Zheng D, Schwartz EL, Zhao H, Yang DS, Geller DS and Hoang BH. The interaction of Skp2 with p27 enhances the progression and stemness of osteosarcoma. Annals NY Acad Sci, 2021; 1490:90-104.

Gupta P, Zhou H, Hoang B, Schwartz EL. Targeting the untargetable: RB1-deficient tumors are vulnerable to Skp2 ubiquitin ligase inhibition. Brit J Cancer 2022: 27:969-975.

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My career-long research objective has been to elucidate the molecular machinery that assembles and regulates the functions of the microtubule cytoskeleton. Work in my laboratory is presently focused on understanding the roles and regulation of microtubules in cellular motility and modifications thereof such as neuronal axon growth and guidance. We have identified new and unique functions in this process for a number of microtubule severing and depolymerizing enzymes and are currently testing the hypothesis that the differential localization and regulation of these allows the microtubule cytoskeleton to selectively tune and coordinate different parameters of cell movement. Additionally, we have found that these enzymes can be targeted in vivo using nanoparticle encapsulated siRNA to predictably alter cellular motility in a variety of clinical contexts related to tissue regeneration and repair. Tested applications include cutaneous wound healing, cardiovascular repair after myocardial infarction, and neural regeneration in both the CNS and PNS. This has led to the formation of the biotech startup, MicroCures Inc., as a commercialization vehicle for our technology.

Selected Publications:

a. Rogers, G.C., Rogers, S.L., Schwimmer, T.A., Ems-McClung, S.C., Walczak, C.E., Vale, R.D., Scholey, J.M., and Sharp, D.J. (2004). Two mitotic kinesins cooperate to drive sister chromatid separation during anaphase. Nature 427, 364-370. http://www.ncbi.nlm.nih.gov/pubmed/14681690

b. Mennella, V., Rogers, G.C., Rogers, S.L., Buster, D.W., Vale, R.D., and Sharp, D.J. (2005). Functionally distinct kinesin-13 family members cooperate to regulate microtubule dynamics during interphase. Nature Cell Biology 7, 235-245. http://www.ncbi.nlm.nih.gov/pubmed/15723056

c. Zhang, D., Grode, K.D., Stewman, S.F., Diaz-Valencia, J.D., Liebling, E., Rath, U., Riera, T., Currie, J.D., Buster, D.W., Asenjo, A.B., Sosa, H.J., Ross, J.L., Ma, A., Rogers, S.L. and Sharp, D.J. (2011). Drosophila katanin is a microtubule depolymerase that regulates cortical-microtubule plus-end interactions and cell migration. Nature Cell Biology 13, 361-370.

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1. ***Single Cell Genomics of Beige Adipose Tissue.*** Brown adipose tissue (BAT) is specialized adipose tissue that dissipates energy for thermogenesis through UCP1 (Uncoupling Protein-1), whereas the function white adipose tissue (WAT) is storage of excess energy. Studies suggest that loss of BAT is linked to obesity and insulin resistance in humans. Thus, increasing energy expenditure through regeneration of BAT could be effective to counteract obesity and type 2 diabetes. Certain physiological cues, such as cold exposure, convert WAT into UCP1-positive, mitochondria-rich, energy consuming BAT-like adipocyte. This "browned" adipocyte is referred to as a "beige adipocyte" and recent studies indicate that predetermined progenitor cells exist as a source of beige adipocytes. We are working to determine the marker genes and functional characteristics of beige progenitor cells by single cell RNA sequencing.

2. ***The Molecular Mechanisms of Adipose Tissue Aging.*** We are studying the molecular mechanism of the decline in brown fat's mass and function during normal aging and whether preserving brown adipocytes can improve energy balance, insulin sensitivity, and metabolic homeostasis. We have recently found evidence suggesting that mitochondrial fission, also called fragmentation, in brown adipocytes is diminished during aging. It has been hypothesized that mitochondrial fission gives mitochondria better access to energy substrates. This research could lead to strategies to prevent brown fat's decline with age or even to increase the number of brown fat cells and boost their ability to improve glucose metabolism, burn more calories, and prevent weight gain.

3. ***Nanopore Sequencing of Human Adipose Tissues.*** Sequencing RNA in a biological sample can determine the transcriptional state of cells and tissues. However, current methods have limitations due to short read lengths and PCR amplification biases. We utilize nanopore direct RNA sequencing, a highly parallel, real-time, single-molecule method that circumvents these biases and identifies novel gene isoforms and alternative splicing events specific to developing human adipose tissues.

Representative Publications:

1) Landgraf A, Okada J, Horton M, Liu L, Solomon S, Qiu Y, Kurland IJ, Sidoli S, Pessin JE. **Shinoda K*.** (2025) Widespread discordance between mRNA expression, protein abundance and *de novo* lipogenesis activity in hepatocytes during the fed-starvation transition. ***bioRxiv*** doi: 10.1101/2025.04.15.649020. *corresponding author
2) Okada J, Landgraf A, Xiaoli AM, Liu L, Horton M, Schuster VL, Yang F, Sidoli S, Qiu Y, Kurland IJ#, Eliscovich C#, **Shinoda K#**, Pessin JE#. (2025) Spatial hepatocyte plasticity of gluconeogenesis during the metabolic transitions between fed, fasted and starvation states. ***Nature Metabolism***, 7, 1073-1091. #senior author
3) Deutsch, A. and **Shinoda, K***. (2021) The genesis of brown fat-a smooth muscle origin story revisited. ***Nature Metabolism***, 3, 449-450. *corresponding author
4) Oguri, Y*., **Shinoda, K***., Kim, H*., Alba, DL., Bolus, RW., ... Spiegelman, B.M. and Kajimura, S. (2020) CD81 controls beige fat progenitor cell growth and energy balance via FAK signaling. ***Cell***, 182, 563-577. *co-first author
5) Deutsch, A., Feng, D., Pessin J.E. and **Shinoda, K***. (2020) The Impact of Single-Cell Genomics on Adipose Tissue Research. ***Int J Mol Sci.***, 21, 4773 *corresponding author
6) Benitez, G.J. and **Shinoda, K***. (2020) Isolation of adipose tissue nuclei for single-cell genomic applications. ***Journal of Visualized Experiments***, 12, 160. *corresponding author
7) Deutsch, A., McLellan B.N. and **Shinoda, K***. (2020) Single-cell transcriptomics in dermatology. ***JAAD International***, 1, 182-188. *corresponding author

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Activation of mRNA translation is a common feature of cancer cell. Through the lens of ribosomes, we explore the mechanistic underpinnings of mRNA translation reprogramming in MYC and KRAS driven cancer model, the tumor microenvironment, and immune response to cancer.

Project 1: Decoding Pancreatic Cancer and Immunity: Through the Lens of the Ribosome

Our previous work has demonstrated that mRNA translation, including EIF4A-dependent regulation of oncogenes like MYC and KRAS, plays a pivotal role in cancer progression. By integrating RNA-seq, ribosome footprinting, TSS mapping, surface proteomics, and MHC I immunopeptidomics, we uncovered translational reprogramming and neoantigen formation during pancreatic cancer progression. Building on these insights, we now aim to define how translational control drives tumor evolution and immune recognition, with the goal of identifying novel biomarkers and developing T cell–based immunotherapies.

Project 2: Translation Elongation Factor Isoform-Specific Control of mRNA Translation in Pancreatic Cancer. We are investigating the role of translation elongation factors EEF1A1 and EEF1A2 in pancreatic cancer using isoform-specific inhibitors Ternatin-4 and Plitidepsin, revealing unique molecular and translational effects. Ribosome profiling and RNA-seq uncovered isoform-specific regulation of mRNAs, with Ternatin-4 affecting lipid metabolism and Plitidepsin modulating collagen-related pathways. These findings point to a novel therapeutic avenue targeting translation elongation in pancreatic cancer.

Representative Recent Publications:

1. J. Park, J. Wu, K. J. Szkop, J. Jeong, D. Husmann, N. M. Flores, J. W. Francis, Y. J. C. Chen, A. M. Benitez, E. Zahn, S. Song, J. A. Ajani, L. Wang, **K. Singh,** O. Larrson, B. A. Garcia, I. Topisirovic, P. K. Mazur, and O. Gozani "SMYD5 methylation of rpL40 links ribosomal output to gastric cancer malignant progression"**.** **Nature 2024** Aug;632(8025):656-663.
2. T. U. Nguyen, H. Hector, E. N. Pederson, J. Lin, Z. Ouyang, H. G. Wendel, **K. Singh** "Rapamycin-Induced Feedback Activation of eIF4E-EIF4A De-pendent mRNA Translation in Pancreatic Cancer". **Cancers, 2023** Mar; 15(5): 1444.
3. P. Mohan, J. Pasion, G. Ciriello, N. Lailler, E. de Stanchina, A. Viale, A. V. Berg, A. Diepstra, H. G. Wendel, V. R. Sanghvi, and **K. Singh** "Frequent 4EBP1 amplification induces synthetic dependence on FGFR signaling in cancer". **Cancers, 2022** 14(10), 2397.
4. **K. Singh**[*,**], M. G. Martinez*, J. Lin*, J. Gregory*, R. Abdelaal, K. Kang, K. Brennand, A. Grünweller, Z. Ouyang, H. Phatnani, M. Kielian, and H. G. Wendel, "Transcriptional and Translational Dynamics of Zika and Dengue Virus Infection" **Viruses 2022,** 14(7), 1418. [* Equal contribution; ** Corresponding author]
5. D. Salloum*, **K. Singh*,** N. R. Davidson, L. Cao, D. Kuo, V. R. Sanghvi, M. Jiang, A. Viale, G. Ratsch, and H. G. Wende, "A Rapid Translational Immune Response Program in CD8 Memory T Lymphocytes", **Journal of Immunology, 2022**, 209 (6) [*Equal Contribution].
6. **K. Singh**, J. Lin, N. Lecomte, P. Mohan, A. Gokce, V. R. Sanghvi, M. Jiang, O. Grbovic-Huezo, A. Burčul, S. G. Stark, P. B. Romesser, Q. Chang, J. P. Melchor, R. K. Beyer, M. Duggan, Y. Fukase, G. Yang, O. Ouerfelli, A. Viale, E. de Stanchina, A. W. Stamford, P. T. Meinke, G. Ratsch, S. D. Leach, Z. Ouyang, and H. G. Wendel, "Targeting eIF4A Dependent Translation of KRAS Signaling Molecules". **Cancer Research, 2021**, 81, 8.
7. **K. Singh**, J. Lin, Y. Zhong, A. Burčul, P. Mohan, M. Jiang, A. Viale, J. R. Cross, L. Sun, V. Yong, R. Hendrickson, G. R.tsch, Z. Ouyang, and H. G. Wendel, "c-MYC regulates mRNA translation efficiency and start site selection in lymphoma". **Journal of Experimental Medicine, 2019,** 216 (7): 1509.
8. **K. Singh*,**A. L. Wolfe*, Y. Zhong, P. Drewe, V. K. Rajasekhar, V. R. Sanghvi, K. J. Mavrakis, J. E. Roderick, J. V. Meulen, J. H. Schatz, C. M. Rodrigo, M. Jiang, C. Zhao, P. Rondou, E. de Stanchina, J. Teruya-Feldstein, M. A. Kelliher, F. Speleman, J. A. Porco Jr., J. Pelletier, G. R.tsch, and H. G. Wendel, "RNA G-quadruplexes cause eIF4A dependent oncogene translation in cancer". **Nature, 2014,** 513 p. 65–70. [*Equal Contribution].

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Cellular communication is essential for proper coordination of organ function. It involves release of signaling molecules, activation of receptors and channels, and direct signaling through gap junctions. Among these key players is ATP and its receptors, pannexin 1 channels and connexin43 (Cx43) gap junction channels. We are interested in the role played by ATP (purinergic) and Cx43 signaling in disease conditions. The Suadicani lab works collaboratively with the labs of Dr. Mia Thi, Dept. of Orthopaedic Surgery, Dr. Kelvin Davies, Dept. of Urology, and Dr. David Spray, Dept. of Neuroscience.

1. Urothelial ATP signaling in bladder dysfunction. Urothelial cells line the interior of the urinary bladder and serve both as a protective barrier against urine contents and sensors of bladder distension. Urothelial cells release ATP in response to bladder distension, and ATP signaling from the bladder to the CNS regulate micturition. We have shown that pannexin 1 (Panx1) channels play key roles in urothelial mechanosensation and ATP signaling. Panx1 has also been shown to mediate inflammasome activation. We are now investigating the extent that Panx1 dysregulation contributes to bladder dysfunction in type 1 diabetes and to pelvic pain and urinary symptoms in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS).

2. Pannexin 1 and ATP signaling in female sexual dysfunction. The mechanosensitivity of female genital organs and its importance for perception and response to penetrative sexual stimulation are well recognized. However, little is known of the molecular mediators and mechanisms involved in vaginal mechanosensory transduction. We show that Panx1 is expressed in vaginal epithelium and mediates ATP release in response to vaginal stimulation, a response that was altered in animal models of diabetes and menopause, conditions known to be associated with female genital arousal dysfunction (FGAD). We are now investigating the mechanisms that lead to Panx1 dysregulation in the vaginal epithelium and whether Panx1 channels may provide novel therapeutic targets to manage FGAD.

3. Pannexin 1 and Cx43 channels in sensory neuron and glia signaling. Neuronal activity is modulated by glial cells. We have shown that glial communication involves Panx1-mediated ATP signaling and that bidirectional satellite glial cell-neuron signaling in sensory ganglia is altered in animal models of inflammatory pain. We are currently investigating the involvement of altered glial Panx1 and Cx43 signaling in chronic pelvic pain and in mechanisms underlying development of urogenital complications (i.e. erectile dysfunction, bladder overactivity and urinary incontinence) from pelvic surgeries.

4. ATP signaling in the diabetic bone. Diabetes affects the skeletal system, leading to reduced bone density and increase risk for bone fractures. ATP signaling plays a central role in bone homeostasis. We have shown that Panx1 and the purinergic P2X7 receptor form a mechanosignaling complex, and that altered expression of this complex in diabetic bone results in impaired ATP release and response to mechanical loading, which might be implicated in the diabetic skeletal complications. Our studies are now focusing on investigating mechanisms that regulate Panx1-P2X7R expression in the healthy and diabetic bone.

Representative Publications:

Lemes JBP, Malange KF, Carvalho NS, Neves AF, Urban-Maldonado M, Kempe PRG, Nishijima CM, Fagundes CC, Lotufo CMDC, Suadicani SO, Parada CA (2024) - Blocking Pannexin 1 Channels Alleviates Peripheral Inflammatory Pain but not Paclitaxel-Induced Neuropathy. J Integr Neurosci. 20;23(3):64

Harroche J, Urban-Maldonado, M, Thi, MM, Suadicani, SO (2020) - Mechanosensitive Vaginal Epithelial Adenosine Triphosphate Release and Pannexin 1 Channels in Healthy, in Type 1 Diabetic, and in Surgically Castrated Female Mice. J Sex Med; 17: 870-880.

Spray, DC, Iglesias, R, Shraer, N, Suadicani, SO, Belzer, V, Hanstein, R, Hananai, M (2019) - Gap junction mediated signaling between satellite glia and neurons in trigeminal ganglia. Glia; 67: 791-801.

Seref-Ferlengez, Z, Urban-Maldonado, M; Sun, HB, Schaffler, MB; Suadicani, SO and Thi, MM (2019) - Role of pannexin 1 channels in load-induced skeletal response. Ann N Y Acad Sci. 1442(1):79-90.

Negoro, H., Urban-Maldonado, M., Liou, L.S., Spray, D.C., Thi, M.M. and Suadicani, S.O. (2014) - Pannexin 1 channels play essential roles in urothelial mechanotransduction and intercellular signaling. PLoS ONE 9(8): e106269.

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Identifying the "mechanosomes", which is the complex responsible for sensing, transduction and signaling in response to mechanical stimuli, is essential to elucidate molecular and cellular machinery underlying mechanosignaling in mechanosensitive tissue. Some of the mechanosome components identified until now includes Panx1 hemichannel, purinergic receptor P2X7R, Piezo1 channel and integrin αVβ3. We are particularly interested in understanding how an altered mechanosome complex contributes to pathological conditions in mechanosensitive tissues such as bone and bladder, where proper mechanosignaling is crucial for tissue health. **The Thi lab works collaboratively with the labs of Dr. Sylvia Suadicani, Dept. of Urology and Dr. David Spray, Dept. of Neuroscience at Einstein and Dr. Mitchell Schaffler, Dept. of Biomedical Engineering at City College of New York, on projects listed below.**

1. **Mechanosomes in sugar coated bone.** We have shown that type 1 diabetes (T1D) alters Panx1-P2X7R mechanosignaling complex in osteocytes, key mechanosensing cells in bone, and disrupts proper load-induced bone adaptation and thereby contributes to bone loss in T1D. We further hypothesized that load-induced regulation of bone mass occurs not only at the local bone level but remotely involving direct signaling between the bone and the nervous system. Given that diabetes affects the nervous system, particularly sensory nerves, a critical gap remains in our understanding of how diabetes impairs this neural regulation of load-induced bone responses. Our studies also indicate that the Panx1-P2X7R complex has broader roles: it's involved in bone neuro-mechanosensory signaling and mediates load-induced inflammasome activation. Our current research is dedicated to exploring how diabetes impacts these two additional functions.

2. **Structural, molecular and functional specialization of osteocyte mechanosomes.** Osteocytes, as the primary mechanosensing cells in bone, orchestrate crucial bone functions, including bone formation (modeling), bone maintenance and repair (remodeling), and bone loss. However, the exact mechanisms by which they achieve this mechanical sensing remain unclear. We have discovered that the osteocyte cell processes function as uniquely sensitive mechanosensory elements through specialized mechanosome complex (Panx1, P2X7R, αVβ3 and CaV3.2 T-type calcium channel). Our current work explores how these osteocytes function as mechanosensors in both healthy and diseased bone, considering differences between male and female physiology.

3. **Mechanosomes in diabetic bladder dysfunction (DBD).** Type 1 Diabetes Mellitus (T1DM) causes a progressive decline in bladder function, leading it from a normal state to becoming overactive, and eventually underactive. The specific factors and mechanisms driving these sequential changes remain poorly understood. Our research indicates that Panx1 plays an essential role in the urothelium's (bladder lining) ability to sense, transduce signals, and communicate in response to mechanical stimuli. This suggests that changes in Panx1 expression directly affect the bladder's sensitivity to distention. Currently, we are focusing on understanding the precise role of urothelial Panx1 channels in the emergence and temporal progression of Diabetic Bladder Dysfunction (DBD).

Representative Publications

Lewis KJ, Boorman-Padgett JF, Castaneda M, Spray DC, Thi MM, Schaffler MB. A Fluorescent Intravital Imaging Approach to Study Load-Induced Calcium Signaling Dynamics in Mouse Osteocytes. J Vis Exp. 2023 Feb 24;(192).

Lewis KJ, Frikha-Benayed D, Louie J, Stephen S, Spray DC, Thi MM, Seref-Ferlengez Z, Majeska RJ, Weinbaum S, Schaffler MB. Osteocyte calcium signals encode strain magnitude and loading frequency in vivo. Proc Natl Acad Sci U S A. 114(44):11775-11780, 2017.

Seref-Ferlengez Z, Maung S, Schaffler MB, Spray DC, Suadicani SO, Thi MM. P2X7R-Panx1 Complex Impairs Bone Mechanosignaling under High Glucose Levels Associated with Type-1 Diabetes. PLoS One. 2016 May 9;11(5):e0155107.

Negoro H, Urban-Maldonado M, Liou LS, Spray DC, Thi MM, Suadicani SO. Pannexin 1 channels play essential roles in urothelial mechanotransduction and intercellular signaling. PLoS One. 2014 Aug 29;9(8):e106269.