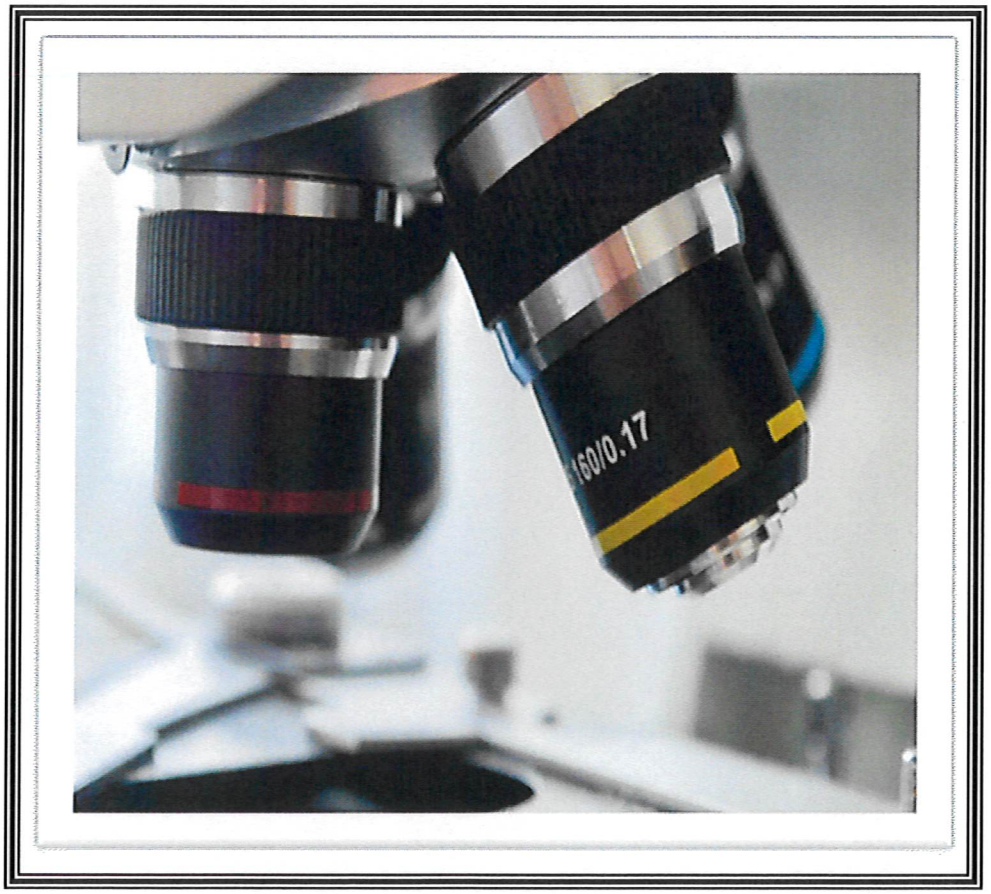
EINSTEIN
Albert Einstein College of Medicine

Montefiore

DEPARTMENT of PATHOLOGY

FACULTY RESEARCH INTERESTS

2023



REQUIREMENTS for a PhD in PATHOLOGY

A. Courses

Candidates for the Ph.D. Degree in Pathology will be expected to obtain a broad and strong foundation in the biological sciences. Course requirements include Mechanisms of Disease, Graduate Biochemistry, and one of these three: Molecular Genetics, Gene Expression or Molecular and Cellular Biology.

Additional courses will be selected depending upon individual interests and needs, and with the advice of the Student Advisory Committee. At least two courses per semester should be taken during the first two years. All students in the Ph.D. program will graduate with a minimum of seven courses. The Graduate Division offers a mandatory Grant Writing Course that will prepare students for the qualifying exam and for writing future grant applications.

B. Qualifying Examination

Students are required to take a qualifying exam after they have completed the first two years of course work. Students select a thesis project with their mentor and write a brief grant application in which background, methods and proposed experiments are outlined. Students also defend this proposal orally before a qualifying exam committee that consists of four faculty members.

C. Rotations

Rotations in three laboratories in any department are strongly advised during the first year. Students may also be permitted to undertake research in collaboration with faculty in other departments.

D. Other Requirements

The departmental Ph.D. Committee will constitute the Advisory Committee until the student chooses a Thesis Problem. A thesis advisory committee will then be established and will follow the Graduate Division requirements.

The Departmental Works-in-Progress meets every Friday. Seminars are held Tuesdays at noon during the academic year. Attendance at these activities is required. Additional seminars in specific areas are also offered.

Students are required to present a seminar as part of their thesis defense. The thesis defense will follow the seminar and will be conducted by a committee of six members with the rank of Assistant Professor or higher. At least one of the members will be faculty from the Pathology Department with a primary appointment and an additional member must have either a primary or secondary appointment in the Pathology Department. A former Einstein faculty member may serve on the Defense Committee if they are in Emeritus or Distinguished status, or hold a current faculty position elsewhere. One outside reviewer from another institution must be included.

Department of Pathology
Research Faculty 2023

Joan W. Berman, PhD	430-3194	Forchheimer 727
Tina Calderon, PhD	430-3194	Forchheimer 727
Laura Cheney, MD, PhD	430-3194	Forchheimer 727
David Entenberg, PhD	678-1116	Price 202
David Fooksman, PhD	430-7957	Forchheimer 131
Chandan Guha, MBBS, PhD	430-3556	Ullman 323/Golding 103
Rachel Hazan, PhD	430-3349	Forchheimer 526
Huan Huang, MD	430-2143	Forchheimer 721NE
John McAuliffe, MD, PhD	430-2161	Golding 604
Elizabeth Neyens, DVM	678-1177	Price 158
Maja Oktay, MD, PhD	678-1117	Price 202
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Louis M. Weiss, MD	430-2142	Forchheimer 501A
Shanye Yin, PhD	430-2355	Ullman 713

Department of Pathology
Emeritus

Jeffrey Segall, PhD	430-2484	Golding 603
Bridget Shafit-Zagardo, PhD	430-2189	Forchheimer 514

Department of Pathology
Associates 2023

Name	Laboratory
Jennifer Aguilan, PhD	Dr. Simone Sidoliti (Proteomics)
Outhiriaradjou Benard, PhD	Dr. Rachel Hazan
Yan Fen Ma, MD	Dr. Louis M. Weiss
Suryansh Shukla, MS	Dr. David Entenberg
Jing Zhu, PhD	Dr. Michael B. Prystowsky

Department of Pathology
Research Assistant Professors

Name	Laboratory
Yair Botbol, PhD	Dr. Ana Maria Cuervo (Macian)
Tadakimi Tomita, PhD	Dr. Louis M. Weiss

Department of Pathology
Postdoctoral Research Fellows 2023

Name	Laboratory
Nicole Barth, PhD	Dr. David Entenberg
Anastasia Chondronikola, DVM	Dr. Maya Oktay
Camille Duran, PhD	Dr. Maya Oktay
Rebekah Guevara, PhD	Dr. Louis M. Weiss
Burcu Karadal, MD	Dr. Maja Oktay
Viney Kumar, PhD	Dr. Rachel Hazan
Huizhi Liang, PhD	Dr. Rachel Hazan
Aline Luciano Horta, PhD	Dr. Louis M. Weiss
Andrew Miller, MD	Dr. Maja Oktay
Nabuqi Nabuqi, MD, PhD	Dr. David Fooksman
Mohd Nauman, PhD	Dr. Maja Oktay
Erika Pereira Zambalde, PhD	Dr. John McAuliffe
Vandana Thakur, PhD	Dr. Louis M. Weiss
Erika Zambalde, DVM	Dr. Maja Oktay

Department of Pathology
Predoctoral Students 2023

Name	Laboratory
Ranee Aflkpui	Dr. Ana Maria Cuervo (Macian)
Lina Ariyan	Dr. John McAuliffe
Brett Bell	Dr. Chandan Guha
Jeb English	Dr. Chandan Guha
Madeline Friedman	Dr. David Entenberg
Andrew Gausepohl	Dr. Joan W. Berman
Caitlin Hills	Dr. Joan W. Berman
Luis Ovando	Dr. David Fooksman
Rosa Park	Dr. David Fooksman
Kushbu Patel	Dr. Ana Maria Cuervo (Macian)
Vanessa Ruiz	Dr. Joan W. Berman
Michelle Schumacher	Dr. Chandan Guha
Veronica Veksler	Dr. Joan W. Berman
Justin Vercellino	Dr. Chandan Guha
Jessica Weiselberg	Dr. Joan W. Berman
Elizabeth Weyer	Dr. Louis M. Weiss

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Dr. Berman's laboratory examines the mechanisms that mediate HIV entry into the CNS and how viral and inflammatory factors damage neurons and other CNS cells. More than 38 million people worldwide are living with HIV (PWH). As a result of antiretroviral therapies (ART), PWH are living much longer, but exhibit many comorbidities that impact their quality of life. HIV enters the CNS early after peripheral infection and is mediated by the transmigration of infected monocytes across the BBB, establishing CNS viral reservoirs, neuronal damage, and low- level inflammation. Despite ART, HIV persists within the CNS, resulting in HIV associated neurocognitive disorders, orHIV-NCI, in 15-40% of PWH, even in those with an undetectable viral load. An understanding of mechanisms that mediate CNS infection and damage are critical to the development of therapeutic strategies.

To characterize the pathogenesis of neuroAIDS, our laboratory studies human monocyte and T cell transmigration across the human blood brain barrier (BBB), which monocyte subset preferentially crosses the barrier, and junctional proteins and chemotactic factors that mediate these processes. We examine tissues, cells, and fluids from PWH for biomarkers, junctional proteins, CCR2, inflammatory factors, functional properties, and predictors ofHIV-NCI. We use sophisticated molecular techniques to detect HIV RNA/DNA in cells we infect in vitro and in PBMC and tissues obtained from thesePWH. We correlate our findings with neuroimaging studies, neurocognitive testing, and clinical data from these patients. We also assess mediators of depression in PWH, and the impact of these on BBB integrity using in vitro studies and neorimaging.

Substance use Disorder (SUD) has been shown to exacerbate neuroinflammation in many PWH. We examine underlying molecular mechanisms of HIV-mediated neuroinflammation and damage in the presence of ART and SUD. We specifically use methamphetamine (meth) and morphine, an opioid, as they are among the major drugs driving the HIV epidemic. Additionally, we study the effects of dopamine as a model of substance use because all illicit drugs increase CNS extracellular dopamine. We propose that meth or morphine use combines with HIV infection to exacerbate neuroinflammation and compromise BBB integrity, thereby increasing transmigration of uninfected and HIV-infected monocytes into the brain, leading toHIV-NCI.Additionally, HIV infection and SUD dysregulate myeloid cell function within the CNS. We also hypothesize that certain ART regimens may negatively impact cognitive function by synergizing with drugs of abuse to increase BBB permeability. We use state of the art in vitro and molecular techniques and to characterize these mechanisms and to test potential therapeutics to limit inflammation and to guide efficacy of ART.

We examine the effects of buprenorphine, an opioid substitution therapy, on neuroinflammation and viral seeding of the CNS in the context of HIV neuropathogensis. We use in vitro cultures of mature human monocytes as well as PBMC from PWH taking buprenorphine and examine their transmigration across the human BBB, and an EcoHIV animal model to examine the effects of buprenorphine in vivo on neurocognitive impairment (NCI) and monocyte entry into the CNS.

References

Williams, D.W., Byrd, D. Rubin, L., Anastos, K., Morgello,S. and **Berman, J.W.** (2014). CCR2 on CD14+CD16+ monocytes is a biomarker of HIV-associated neurocognitive disorders. Neurology, Neuroimmunology and Neuroinflammation. 1(3):e36.

Veenstra, M., Williams, D.W., Calderon, T.M., Anastos, K., Morgello, S. and **Berman, J.W**. (2017). Frontline Science: CXCR7 mediates $CD14^+CD16^+$ monocyte transmigration across the blood brain barrier: a potential therapeutic target for NeuroAIDS. Journal of Leukocyte Biology. 102(5): 1173-1185.

Veenstra, M., Leon-Rivera, R., Li, M., Gama, L., Clements, J.E. and **Berman J.W**. (2017). Mechanisms of CNS viral seeding by HIV^+ $CD14^+CD16^+$ monocytes: establishment and reseeding of viral reservoirs contributing to HIV-associated neurocognitive disorders. MBio. 8(5): pii: e01280-17.

Jaureguiberry-Bravo M, Lopez L**, Berman JW**. (2018) Frontline Science: Buprenorphine decreases CCL2-mediated migration of $CD14^+$ $CD16^+$monocytes. J Leukoc Biol. May 23 doi: 10.1002/JLB.3HI0118-015R. [Epub ahead of print]

Jaureguiberry-Bravo, M**.,** Kelschenbach, J., Murphy, A., Carvallo, L., Hadas, E., Tesfa, L., Scott, T.M., Rivera-Mindt, M., Cunningham, C.O, Arnsten, J.H., Volsky, D.J., and Berman, J.W. (2020) Treatment with buprenorphine prior to EcoHIV infection of mice prevents the development of neurocognitive impairment. J Leukoc Biol.109:675–68

León-Rivera, R., Morsey, B., Niu, M., Fox, H. S. & Berman, J. W. Interactions of Monocytes, HIV, and ART Identified by an Innovative scRNAseq Pipeline: Pathways to Reservoirs and HIV- Associated Comorbidities. mBio. (2020) Jul 28;11(4):e01037-20. doi: 10.1128/mBio.01037-20.

León-Rivera, R., Veenstra, M., Donoso, M., Tell, E., Eugenin, E.A., Morgello, S., Berman, J.W. (2021) Nervous System (CNS) Viral Seeding by Mature Monocytes and Potential Therapies To Reduce CNS Viral Reservoirs in the cART Era, mBio Mar 16;12(2):e03633-20.

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Dr. Calderon, as a member of Dr. Joan W. Berman's laboratory, examines the mechanisms by which substance abuse exacerbates neurological deficits in people living with HIV (PLWH). Peripheral blood monocytes are composed of multiple subpopulations, including a mature subset that expresses CD14, the LPS coreceptor, and CD16, the FcγIII receptor. Studies have shown that $CD14^+CD16^+$ monocytes are increased in the peripheral circulation of PLWH and these cells are preferentially infected with HIV compared to other monocyte subpopulations. HIV enters the central nervous system (CNS) very early after HIV infection, in part by the trafficking of infected $CD14^+CD16^+$ monocytes across the blood brain barrier (BBB) in response to chemokines, including CCL2 and CXCL12, and viral localization within the CNS persists despite antiretroviral therapy (ART). The continuous influx of uninfected and HIV infected $CD14^+CD16^+$ monocytes into the CNS replenishes viral reservoirs and contributes to chronic neuroinflammation, resulting in the development of a wide spectrum of cognitive, motor and behavioral abnormalities termed HIV-associated neurocognitive impairment (HIV-NCI) in 15-40% of PLWH, even with suppressive ART.

Neurological deficits elicited by HIV infection are often exacerbated by addictive substances of abuse, including methamphetamine and opioids. Some studies have shown that neurocognitive dysfunction is more severe in HIV infected substance abusers when compared to non-substance abusing infected individuals. The mechanisms by which uninfected and HIV infected $CD14^+CD16^+$ monocytes are chemoattracted to, and transmigrate across, the BBB in PLWH, in the presence or absence of substance abuse, are not fully characterized. We have reported that methamphetamine increases CCL2 and CXCL12 induced transmigration of uninfected and HIV infected $CD14^+CD16^+$ monocytes across our *in vitro* model of the human BBB. The less characterized CXCL12 receptor, CXCR7, is a major contributor to CXCL12 induced transmigration of uninfected and HIV infected $CD14^+CD16^+$ monocytes across the BBB and we are investigating the role of this receptor in methamphetamine induced effects on $CD14^+CD16^+$ monocyte transmigration. Increased $CD14^+CD16^+$ monocyte entry into the CNS in response to substances of abuse provides a possible mechanism for enhanced neurological damage in HIV infected substance abusers.

To characterize additional mechanisms that regulate $CD14^+CD16^+$ monocyte transmigration across the BBB, we performed single cell RNA sequencing (scRNAseq) on uninfected and HIV infected $CD14^+CD16^+$ monocytes which identified heterogeneous clusters of cells characterized by the expression of specific genes. We are characterizing the expression of proteins involved in transmigration and inflammation in monocyte clusters to identify mechanisms that contribute to the ability of these cells to transmigrate across the BBB in the presence or absence of substances of abuse. In addition, we will characterize the inflammatory properties of monocytes within each cluster, including cytokine and reactive oxygen species (ROS) production. These studies will contribute to the development of therapeutic strategies to inhibit uninfected and HIV infected $CD14^+CD16^+$ monocyte entry into the CNS of PLHW, with or without substance abuse, reducing the development and severity of HIV-NCI.

References

Calderon, TM, Williams, DW, Lopez L, Eugenin, EA, Cheney, L, Gaskill, PJ, Veenstra, M, Anastos, K, Morgello, S, Berman, JW. (2017) Dopamine increases $CD14^+CD16^+$ monocyte transmigration across the blood brain barrier: Implications for substance abuse and HIV neuropathogenesis. J Neuroimmune Pharmacol. 12(2): 353-370.

Veenstra, M, Williams, DW, **Calderon, TM**, Anastos, K, Morgello, S, Berman JW. (2017) Frontline Science: CXCR7 mediates $CD14^+CD16^+$ monocyte transmigration across the blood brain barrier: a potential therapeutic target for NeuroAIDS. J Leukoc Biol. 102(5): 1173-1185.

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Areas of Research: Investigating mechanisms of metastasis. Design and development of novel instrumentation and imaging technologies for biological research. Use of surgical engineering for expanding mouse models of cancer and metastasis. Development of and validation of clinical biomarkers for cancer progression and metastasis. Development of new technologies within the Gruss-Lipper Biophotonics Center.

Professional Interests: David Entenberg's expertise lies in the design and development of novel instrumentation and imaging technologies for biological research. With a background in laser-based experimental quantum physics, he brings skills in optical, mechanical, electrical, software, and instrument design.

His previous work has included the design and development of several robotics-based high-throughput automated biological assays utilizing real time PCR and MALDI-TOF protocols; novel microscopes including a fast switching, muti-channel TIRF microscope, a video rate multiphoton microscope; and a two-laser OPO-based multiphoton microscope.

Current and future projects are focused on development of tools and techniques for cancer research, using them to investigate mechanisms of tumor cell dissemination to and redissemination from the lung, and development and validation of machine vision and digital pathology-based biomarkers for metastasis.

Selected Publications - in the last 3 years

Kim, G. *et al.* Racial disparity in tumor microenvironment and distant recurrence in residual breast cancer after neoadjuvant chemotherapy. *NPJ Breast Cancer.* **9** (1), 52, PubMed PMID: 37311792, (2023).

Genna, A. *et al.* Macrophages Promote Tumor Cell Extravasation across an Endothelial Barrier through Thin Membranous Connections. *Cancers (Basel).* **15** (7), PubMed PMID: 37046751, (2023).

Entenberg, D. *et al.* Intravital imaging to study cancer progression and metastasis. *Nat Rev Cancer.* **23** (1), 25-42, PubMed PMID: 36385560, (2023).

Duran, C. L. *et al.* Cooperative NF-kappaB and Notch1 signaling promotes macrophage-mediated MenaINV expression in breast cancer. *Breast Cancer Res.* **25** (1), 37, PubMed PMID: 37024946, (2023).

Ye, X. *et al.* Combining TMEM Doorway Score and Mena(Calc) Score Improves the Prediction of Distant Recurrence Risk in HR+/HER2- Breast Cancer Patients. *Cancers (Basel).* **14** (9), PubMed PMID: 35565297, (2022).

Selvanesan, B. C. *et al.* Listeria delivers tetanus toxoid protein to pancreatic tumors and induces cancer cell death in mice. *Sci Transl Med.* **14** (637), eabc1600, PubMed PMID: 35320003, (2022).

Scheele, C. L. *et al.* Multiphoton intravital microscopy of rodents. *Nature Reviews Methods Primers.* **2** (1), 1-26 (2022).

Rodriguez-Tirado, C. *et al.* Interleukin 4 Controls the Pro-Tumoral Role of Macrophages in Mammary Cancer Pulmonary Metastasis in Mice. *Cancers (Basel).* **14** (17), PubMed PMID: 36077870, (2022).

Kim, G. *et al.* Racial disparity in distant recurrence-free survival in patients with localized breast cancer: A pooled analysis of National Surgical Adjuvant Breast and Bowel Project trials. *Cancer.* **128** (14), 2728-2735, PubMed PMID: 35578919, (2022).

Karagiannis, G. S. *et al.* Assessment of MRI to estimate metastatic dissemination risk and prometastatic effects of chemotherapy. *NPJ Breast Cancer.* **8** (1), 101, PubMed PMID: 36056005, (2022).

Du, W. *et al.* SWIP-a stabilized window for intravital imaging of the murine pancreas. *Open Biol J.* **12** (6), 210273, PubMed PMID: 35702996, (2022).

Borriello, L. *et al.* Primary tumor associated macrophages activate programs of invasion and dormancy in disseminating tumor cells. *Nat Commun.* **13** (1), 626, PubMed PMID: 35110548, (2022).

Sharma, V. P. *et al.* SUN-MKL1 Crosstalk Regulates Nuclear Deformation and Fast Motility of Breast Carcinoma Cells in Fibrillar ECM Microenvironment. *Cells.* **10** (6), PubMed PMID: 34205257, (2021).

Sharma, V. P. *et al.* Live tumor imaging shows macrophage induction and TMEM-mediated enrichment of cancer stem cells during metastatic dissemination. *Nat Commun.* **12** (1), 7300, PubMed PMID: 34911937, (2021).

Duran, C. L. *et al.* Targeting Tie2 in the Tumor Microenvironment: From Angiogenesis to Dissemination. *Cancers (Basel).* **13** (22), PubMed PMID: 34830883, (2021).

Borriello, L. *et al.* A Permanent Window for Investigating Cancer Metastasis to the Lung. *J Vis Exp.* (173), PubMed PMID: 34279505, (2021).

Borriello, L. *et al.* Breast Cancer Cell Re-Dissemination from Lung Metastases-A Mechanism for Enhancing Metastatic Burden. *J Clin Med.* **10** (11), PubMed PMID: 34071839, (2021).

Asiry, S. *et al.* The Cancer Cell Dissemination Machinery as an Immunosuppressive Niche: A New Obstacle Towards the Era of Cancer Immunotherapy. *Front Immunol.* **12** 654877, PubMed PMID: 33927723, (2021).

Shanja-Grabarz, X. *et al.* Real-time, high-resolution imaging of tumor cells in genetically engineered and orthotopic models of thyroid cancer. *Endocr Relat Cancer.* **27** (10), 529-539, PubMed PMID: 32698130, (2020).

Niesner, R. A. *et al.* Life Through a Lens: Technological Development and Applications in Intravital Microscopy. *Cytometry A.* **97** (5), 445-447, PubMed PMID: 32378348, (2020).

Entenberg, D. *et al.* Validation of an Automated Quantitative Digital Pathology Approach for Scoring TMEM, a Prognostic Biomarker for Metastasis. *Cancers (Basel).* **12** (4), PubMed PMID: 32244564, (2020).

Entenberg, D. *et al.* in *Imaging from Cells to Animals In Vivo Series in cellular and clinical imaging* eds M. Barroso & X. Intes) 183 (CRC Press, 2020).

Coste, A. *et al.* Intravital Imaging Techniques for Biomedical and Clinical Research. *Cytometry A.* **97** (5), 448-457, PubMed PMID: 31889408, (2020).

Coste, A. *et al.* Hematogenous Dissemination of Breast Cancer Cells From Lymph Nodes Is Mediated by Tumor MicroEnvironment of Metastasis Doorways. *Front Oncol.* **10** 571100, PubMed PMID: 33194666, (2020).

Borriello, L. *et al.* The role of the tumor microenvironment in tumor cell intravasation and d issemination. *Eur J Cell Biol.* **99** (6), 151098, PubMed PMID: 32800278, (2020).

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The goals of our laboratory are to understand the regulation of plasma cell differentiation, migration, survival and function. Plasma cells are terminally-differentiated B cells that secrete high-affinity antibodies constitutively, following immunization and exposure to a pathogen. The longevity of the antibody response is highly dependent upon the differentiation and survival of plasma cells.

We have used intravital two-photon imaging, unique mouse models, transcriptomics, and cellular immunology techniques to study how these cells survive in the bone marrow microenvironment and what signals regulate this process. By live imaging, we have found these cells are motile, and quite dynamic, interacting with various cell types.

In some cases, plasma cells may undergo malignant transformation during differentiation leading to neoplasms in humans such as multiple myeloma. Despite their critical role in immune function and disease, many fundamental questions remain regarding the physiology of plasma cells in vivo.

By understanding the mechanisms controlling their survival in vivo, we hope to develop ways to make more effective vaccines, and also ways to disrupt myeloma cell survival for patients.

Selected Publications (* corresponding author)

1. Akhmetzyanova I, Aaron T, Galbo P, Tanaka M, Cheng, D, Zang X, Fooksman DR*. Tissue-resident macrophages promote multiple myeloma early dissemination and progression via IL-6 and TNFa. Blood Adv. in press.
2. Benet, Jing, Fooksman DR*. Plasma cell dynamics in the bone marrow niche. Cell Reports 2021. Feb 9;34(6) 108733. PMID 33567286.
3. Upadhaya S, Krichevsky O, Akhmetzyanova I, Sawai CM, Fooksman DR #* Reizis B Intravital imaging reveals motility of adult hematopoietic stem cells in the bone marrow niche. Cell Stem Cell. 2020 27(20): 336-345
4. Akhmetzyanova I, McCarron MC, Chesi M, Bergsagel PL, Parek S, Fooksman, DR#*. CD138 regulates dynamic switch between myeloma growth and dissemination. Leukemia. Aug 2019. PMID 31439945
5. Tikhonova AN, Dolgalev I, Hu H, Sivaraj KK, Hoxha E, Cuesta-Domínguez Á, Pinho S, Akhmetzyanova I, Gao J, Witkowski M, Guillamot M, Gutkin MC, Zhang Y, Marier C, Diefenbach C, Kousteni S, Heguy A, Zhong H, Fooksman DR, Butler JM, Economides A, Frenette PS, Adams RH, Satija R, Tsirigos A, Aifantis I. The bone marrow microenvironment at single-cell resolution. Nature Aug 2019. PMID 30971824
6. McCarron MJ, Park PW, Fooksman DR # *.CD138 mediates selection of mature plasma cells by regulating their survival. Blood. 2017 May 18;129(20):2749-275

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Areas of Research: Radiation Therapy, Low-intensity focused ultrasound (LOFU), Cancer Immunotherapy, acute radiation syndrome (ARS), Delayed effects of acute radiation exposure (DEARE), Radiation mitigators, Stem cells, Cell therapy, Immune dysfunction, Carbon ion radiation therapy, Hepatocyte transplantation

Preventing Cancer Recurrence after Radiation Therapy

Radiation therapy (RT) has been used as a standard treatment modality for many solid tumors. While tumoricidal properties of RT are instrumental for standard clinical application, irradiated tumors can potentially serve as a source of tumor antigens in vivo, where dying tumor cells would release various tumor antigens slowly over time. However, RT alone may not generate sufficient anti-tumoral immune responses, which results in cancer recurrence in the primary site or distant organs. Therefore, supplemental treatments are needed to enhance immune cell activity against tumors. Our laboratory has developed several strategies in combination with RT for cancer treatment and evaluated various cancer types in mouse models. For example, low-intensity focused ultrasound (LOFU) treatment generates thermal and physical stress to the cancer cells and enhances the exposure of tumor antigens. LOFU combined with RT, provides an active in-situ tumor vaccine and generates anti-tumoral immunity. Another strategy is to stimulate immune cell activity to recognize the tumor antigens released by RT. Our laboratory has identified that Fms-like tyrosine kinase 3 ligand (Flt3L) and anti-CD40 antibody can expand the number of dendritic cells and activate the antigen presenting cells, respectively. In this project, we are examining the timing of immune cell infiltration into the tumor after LOFU±RT and optimizing the schedule of each treatment in combination. The goal is to translate these pre-clinical studies to human clinical trials to treat various forms of cancer.

Mitigating Radiation-induced Organ Injury

In the event of nuclear plant leakage or nuclear terrorist attack, victims are exposed to high dose ionizing radiation in a short period of time and will experience acute radiation syndrome (ARS), which can lead to death. Furthermore, the surviving victims may suffer from delayed effects of acute radiation exposure (DEARE) in many organs. Radiation is also commonly used in treating cancer patients with the possibility of developing radiation-induced toxicity in the surrounding normal tissue. Although there are several drugs approved by FDA to treat hematopoietic ARS (H-ARS), not many therapeutic agents are available to mitigate damage to other sensitive organs after radiation exposure. The goal of this project is to have a better understating of molecular mechanisms by which high dose radiation causes organ damage and mortality, leading to the development of novel radiation protectors, mitigators, or medical countermeasures. The highly proliferative stem and progenitor cells that regenerate blood cells in bone marrow and intestinal stem cells in the crypts of the digestive system are particularly susceptible to damage by ionizing radiation. Our laboratory has established several mouse models and radiation regimens to study radiation-induced organ injury, such as whole-body irradiation (WBI) for H-ARS, partial body irradiation (PBI) for gastrointestinal ARS (GI-ARS), whole thoracic irradiation (WTI) to examine pneumonitis and fibrosis with lung injury, and targeted irradiation to the rectum for radiation proctitis. Our laboratory has identified several growth factors, chemical compounds, and specific stem cell populations as radiation mitigators in various mouse models. We will further evaluate their effectiveness and mechanism(s) of action, ultimately leading to FDA approval for radiation exposure in humans. We are also studying the functional immuno-radiobiology of the regenerative immune system after WBI in mice and whether T-cell immune senescence and dysfunction of myeloid population contributes to DEARE. These studies will provide a blueprint for developing optimized immuno-conditioning regimens for immunization protocols in radiation survivors that can be extended to immunocompromised and elderly population.

Carbon Ion Radiation Therapy for Pancreatic Cancer

Carbon ion radiotherapy (CIRT) is currently the world's most advanced radiotherapeutic technique. With its physical characteristics, CIRT causes less toxicity of normal tissue and organs surrounding the tumor and is more effective at killing tumor compared to photon radiotherapy, like X-ray. Carbon ion stops at a depth inside our body and releases all its energy in the form of a peak dose in the tumor. Since the track stops at a depth, the particle beam of carbon ion does not go through the body, thereby causing less harm to surrounding normal tissues. Carbon ions cause DNA damage in the irradiated cells resembling infection by a DNA virus which provokes the body's anti-viral defense system. In this project, we will study the immunological response of tumor, particularly in pancreatic

cancer, and its microenvironment after CIRT in animal models with comparison to traditional X-ray therapy. This information will enhance the planning and usage of CIRT to cancer patients.

Hepatocyte Transplantation for Treating Inherited and Chronic Liver Diseases

Hepatocyte transplantation is a very attractive alternative for liver transplant to treat patients with inherited and chronic liver diseases in consideration of the limited number of liver donors. However, benefits of hepatocyte transplantation are hindered by the low efficacy of the transplanted hepatocytes to engraft and proliferate in the host liver. Our laboratory has pioneered the development of preparative hepatic irradiation in combination with growth factors to enhance the engraftment and repopulation of transplanted hepatocytes using rodent model. To mimic the clinical operation, a state-of-the-art image-guided hepatic irradiation model is utilized by using the small animal radiation research platform (SARRP). We are currently investigating several potential growth factors combined with irradiation to enhance the replaced area of transplanted hepatocytes in the host liver. We are also interested in exploring the use of progenitor cells as alternatives for hepatocytes for transplantation.

SELECTED PUBLICATIONS:

1. Orthovoltage X-Rays Exhibit Increased Efficacy Compared with γ-Rays in Preclinical irradiation. Bell BI, Vercellino J, Brodin NP, Velten C, Nanduri LSY, Nagesh PKB, Tanaka KE, Fang Y, Wang Y, Macedo R, English J, Schumacher MM, Duddempudi PK, Asp P, Koba W, Shajahan S, Liu L, Tomé WA, Yang WL, Kolesnick R, Guha C. Cancer Res. 2022. 82(15):2678-2691.

2. Mitigation of total body irradiation-induced mortality and hematopoietic injury of mice by a thrombopoietin mimetic (JNJ-26366821). Kumar VP, Holmes-Hampton GP, Biswas S, Stone S, Sharma NK, Hritzo B, Guilfoyle M, Eichenbaum G, Guha C, Ghosh SP. Sci Rep. 2022. 12(1):3485.

3. Normal Tissue Injury Induced by Photon and Proton Therapies: Gaps and Opportunities. Prasanna PG, Rawojc K, Guha C, Buchsbaum JC, Miszczyk JU, Coleman CN. Int J Radiat Oncol Biol Phys. 2021. 110(5):1325-1340.

4. Evaluating dosimetric constraints for carbon ion radiotherapy in the treatment of locally advanced pancreatic cancer. Lin LC, Jiang GL, Ohri N, Wang Z, Lu JJ, Garg M, Guha C, Wu X. Radiat Oncol. 2020. 15(1):101.

5. Nestin+NG2+ Cells Form a Reserve Stem Cell Population in the Mouse Prostate. Hanoun M, Arnal-Estapé A, Maryanovich M, Zahalka AH, Bergren SK, Chua CW, Leftin A, Brodin PN, Shen MM, Guha C, Frenette PS. Stem Cell Reports. 2019. 12(6):1201-1211.

6. Radiation-primed hepatocyte transplantation in murine monogeneic dyslipidemia normalizes cholesterol and prevents atherosclerosis. Barahman M, Zhang W, Harris HY, Aiyer A, Kabarriti R,
Kinkhabwala M, Roy-Chowdhury N, Beck AP, Scanlan TS, Roy-Chowdhury J, Asp P, Guha C. J Hepatol. 2019. 70(6):1170-1179.

7. Macrophage-derived extracellular vesicle-packaged WNTs rescue intestinal stem cells and enhance survival after radiation injury. Saha S, Aranda E, Hayakawa Y, Bhanja P, Atay S, Brodin NP, Li J, Asfaha S, Liu L, Tailor Y, Zhang J, Godwin AK, Tome WA, Wang TC, Guha C, Pollard JW. Nat Commun. 2016. 7:13096. doi: 10.1038/ncomms13096.

8. Low-Intensity Focused Ultrasound Induces Reversal of Tumor-Induced T Cell Tolerance and Prevents Immune Escape. Bandyopadhyay S, Quinn TJ, Scandiuzzi L, Basu I, Partanen A, Tomé WA, Macian F, Guha C. J Immunol. 2016. 196(4):1964-76.

9. An autologous in situ tumor vaccination approach for hepatocellular carcinoma. 2. Tumor-specific immunity and cure after radio-inducible suicide gene therapy and systemic CD40-ligand and Flt3-ligand gene therapy in an orthotopic tumor model. Kawashita Y, Deb NJ, Garg MK, Kabarriti R, Fan Z, Alfieri AA, Roy-Chowdhury J, Guha C. Radiat Res. 2014. 182(2):201-10.

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Cell-cell adhesion is a primary modulator of morphogenetic events during normal embryonic development and cancer evolution. Metastatic dissemination of epithelial tumor cells is also strongly influenced by the activity of cell-cell adhesion molecules, in particular members of the cadherin family. My laboratory has shown that N-cadherin upregulation in breast cancer cells promotes metastasis despite persistent E-cadherin expression. N-cadherin pro-metastatic function is due to a cooperative interaction with the FGFR, resulting in epithelial to mesenchymal transition (EMT), cancer stemness and resistance to apoptosis. Specifically, we showed that N-cadherin/FGFR upregulates the Slug EMT transcription factor, which in turn promotes cancer cell survival at metastatic sites, by suppressing the pro-apoptotic protein, Puma. We also showed that EMT was accompanied by upregulation of the cell cycle inhibitor, p21CIP1, which drives metastasis due to stemness induction via Wnt signaling activation. Moreover, increases in cell motility by N-cadherin were due to suppression of Akt3 which interestingly promotes tumorigenesis. By contrast, an Akt3 isoform lacking the serine regulatory phosphorylation site, was found to inhibit tumorigenesis. This was due to EGFR attenuation, resulting in ERK inhibition, which in turn activates Bim/Bax pro-apoptotic proteins, resulting in apoptotic suppression of tumorigenesis. More recently, we investigated the role of redox signaling in breast cancer metastasis with emphasis on hypoxia. We showed that the loss of the ROS scavenging enzyme, GPx2, dramatically enhances metastasis and causes worse clinical outcomes. Using single cell RNA sequencing of the primary tumor and metastases, we were able to uncover novel mechanisms driving metastasis with insights into therapeutic targets. Hence our work has high potential to lead to a breakthrough and accelerate progress toward ending breast cancer.

Selected Publications

Suyama K, Shapiro I, Guttman M and **Hazan**, RB (2002) A signaling pathway leading to metastasis is controlled by N-cadherin and the FGF receptor. Cancer Cell. 2: 301-314. PMID: 12398894

Hulit J, Suyama k, Chung S, Keren R, Agiostratidou G, Shan W, Dong X, Williams TM, Lisanti MP, Knudsen K, **Hazan** RB (2007). N-cadherin signaling potentiates mammary tumor metastasis via enhanced ERK activation. Cancer Research. 67:3106-16.

Agiostratidou G, Li M, Suyama K, Keren R, Chung S, Qian BB, Hulit J, Bouzahzah B, Loudig O, Phillips G, Locker J and **Hazan** RB (2009). Loss of R-cadherin facilitates breast tumor progression and metastasis. Cancer Research. 69:5030-38

Chung, S., Yao, J., Suyama, K., Bajaj, S., Qian, X., Loudig, O., Eliseo, E., Phillips, G., **Hazan**. R.B. (2013). N-cadherin promotes breast cancer cell migration through Akt3 suppression. Oncogene. 32(4): 422-30. PMID: 22410780

Qian, X., Hulit, J., Suyama, K., Belbin, T., Smirnova, T., Segall, J., Phillips, G., Norton L., **Hazan**. R.B. (2013). p21 CIP1 mediates reciprocal switching between proliferation and invasion during metastasis. Oncogene. 2012 Jul 2. PMID: 22751124

Qian X, Anzovino A, Hulit J, Kim S , Suyama K, Chandiramani N, McDaid HM, Nagi C, Phillips GR, Norton L, **Hazan** RB. (2014). N-cadherin/FGFR Signaling Promotes Epithelial to Mesenchymal Transition and Tumor Initiating Potential in ErbB2-driven Breast Cancer. Oncogene. PMID: 23975425

Kim S, Yao J, Suyama K, Qian X, Qian BZ, Bandyopadhyay S, Loudig OD, De Leon-Rodriguez C, Zhou ZN, Segall JE, Macian F, Norton L, **Hazan** RB. (2014). Slug Promotes Survival during Metastasis through Suppression of Puma-Mediated Apoptosis. Cancer Research. PMID: 2483072

Suyama K, Yao J, Liang H, Benard O, Loudig O, Amgalan D, McKimpson W, Phillips GR, Segall J, Wang Y, Fineberg S, Norton L, Kitsis R, and **Hazan** RB. (2017) an Akt3 splice variant lacking the serine 472 phosphorylation site promotes apoptosis and suppresses mammary tumorigenesis, *Cancer Research*. PMID: 29038347

Benard O, Qian X, Liang H, Ren Z, Suyama K, Norton L, **Hazan RB** (2019). p21 CIP1 promotes mammary cancer initiating cells via activation of Wnt/TCF1/Cyclin D1 signaling. Mol Cancer Res. 2019.PMID: 30967481

Ren Z, Liang H, Galbo PM, Dharmaratne M, Kulkarni AS, Fard AT, Aoun ML, Suyama K, Benard O, Zheng W, Albanese J, Zheng D, Mar JC, Singh R, Prystowsky MB, Norton L, **Hazan RB** (2021) Redox signaling by Glutathione Peroxidase 2 links vascular modulation to metabolic plasticity of breast cancer (PNAS in revision)

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Dr. Huang's research interests focus on the pathogenesis of Chagas' disease and immunity against *Trypanosoma cruzi* infection.

Trypanosoma cruzi (*T. cruzi*) is a parasite, which causes Chagas disease. The focus of my research includes molecular biology of the parasite, pathogenesis of Chagas disease and the genetic techniques in this organism. My laboratory studies protein kinases and kinase signaling pathways in *T. cruzi*, identifying and characterizing components in cAMP-dependent protein kinase (PKA) and mitogen activated protein kinase pathways in *T. cruzi*. The knowledge can be used for drug development. My group has also advanced molecular genetics in *T. cruzi* by designing a modified pTREX vector which uses an N-terminal fusion of a ligand-controlled destabilization domain (ddFKBP) to a gene/protein of interest. This vector system allows rapid and reversible protein expression and efficient functional analysis of proteins in different *T. cruzi* life cycle stages. In addition, my group is creating transgenic *T. cruzi* for the study of disease mechanism and for vaccine strains. The inducible suicide vector systems in *T. cruzi* have been established using the degradation domain based on the Escherichia coli dihydrofolate reductase (ecDHFR) linked with toxic or detrimental proteins. These vector systems can be introduced into this organism to create attenuated live parasites, which can be induced to undergo a self-destruction process. Using the transgenic *T. cruzi* strains, which induce strong protection against re-infection in mice, effective immunity against *T. cruzi* infection is being investigated. Infection with *T. cruzi* is lifelong. A drug that can modulate immune responses and reduce parasite burden will be ideal to use in patients with Chagas disease. As the activity of resolvins is immunoresolvent but not immunosuppressive, we determined if they could have such a therapeutic effect. For that purpose, we tested the consequences of treatment with resolvin D1 in a murine model of *T. cruzi* infection. The treatment significantly improves the mice infected with *T. cruzi*. We have recently published an article describing the benefits of resolvin D1 treatment for mice infected with *T. cruzi*.

Selected References:

- Bao Y, Weiss LM , Ma YF, Lisanti MP, Tanowitz HB, Das BC, Zheng R and **Huang H**. (2010) Molecular cloning and characterization of Mitogen-activated protein kinase 2 in Trypanosoma cruzi. Cell Cycle 2010 Jul 15;9(14):2888-96. Epub 2010 Jul 13.
- Ma YF, Weiss LM, **Huang H**. (2012). A method for rapid regulation of protein expression in Trypanosoma cruzi. Int J Parasitol. 42:33-37.
- Ma YF, Weiss LM, **Huang H** (2015). Inducible suicide vector systems for *Trypanosoma cruzi*. Microbes and Infection 17: 440-450 (Editor recommended).
- Ma YF, Weiss LM, **Huang H** (2016). Strategy for the development of vaccines against Chagas disease. HSOA Journal of Vaccine Research and Vaccination 1:001.
- Podešvová L, **Huang H**, Yurchenko V(2017). Inducible protein stabilization system in Leishmania mexicana. Mol Biochem Parasitol. 214:62-64
- Horta AL, Williams T, Han B, Ma Y, Menezes APJ, Tu V, Talvani A, Weiss LM, **Huang H** (2020). Resolvin D1 Administration is Beneficial in *Trypanosoma cruzi* Infection. Infect Immun. 88(6):e00052-20. PMID: 32152197.
- Williams T, Guerrero-Ros I, Ma Y, Matos Dos Santos F, Scherer PE, Gordillo R, Horta A, Macian F, Weiss LM, **Huang H** (2020). Induction of effective immunity against *Trypanosoma cruzi*. Infect Immun. 88(4):e00908-19, PMID: 31907197.

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Areas of Research: Investigating mechanisms of metastasis in pancreatic adenocarcinoma, receptor tyrosine kinase inhibition, tumor microenvironment, invasion and migration.

Professional Interests: Dr. John McAuliffe is an Associate Professor and surgeon-scientist in the Department of Surgery and Pathology.

His surgical practice includes Pancreatic, Biliary, Neuroendocrine, Thyroid, and Adrenal benign and malignant diseases.

Dr. McAuliffe's laboratory seeks to better understand the mechanisms underlying pancreas cancer metastasis with the ultimate goal of translation to clinical trial. His laboratory focuses on the trans-endothelial migration of pancreatic adenocarcinoma and Tie2 signaling. He utilizes transgenic mouse models, cell culture, human samples, and intravital microscopy to evaluate tumor associated macrophage and cancer cell signaling through Tie2 in cancer cell invasion, migration, intravasation, epithelial-mesenchymal transition, stemness, and dormancy in pancreatic adenocarcinoma. Dr. McAuliffe has observed TMEM doorways in human and mouse pancreatic cancer.

Selected Publications - in the last 3 years

1. Michael I. D'Angelica, Ryan J. Ellis, Jason B. Liu, Brian C. Brajcich, Mithat Gonen, Vanessa M. Thompson, Mark E. Cohen, Susan K. Seo, Emily C. Zabor, Michele L. Babicky, David J. Bentrem, Stephen W. Behrman, Kimberly A. Bertens, Scott A. Celinski, Carlos H.F. Chan, Mary Dillhoff, MD; Matthew E.B. Dixon, Carlos Fernandez del Castillo, Sepideh Gholami, Michael G. House, Paul J. Karanicolas, Harish Lavu, Shishir K. Maithel, **John C. McAuliffe**, Mark J. Ott, Bradley N Reames, Dominic E. Sanford, Umut Sarpel, Courtney L. Scaife, Pablo E. Serrano, Travis Smith, Rebecca A. Snyder, Mark S. Talamonti, Sharon M. Weber, Adam C. Yopp, Henry A. Pitt, Clifford Y. Ko. Piperacillin-Tazobactam Compared with Cefoxitin as Antimicrobial Prophylaxis for Pancreatoduodenectomy. JAMA 2023. *In Press.*

2. Zhang FG, Ow TJ, Lin J, Smith RV, Schiff BA, Debiase CA, **McAuliffe JC**, Bloomgarden N, Mehta V. Complications Related to Thyroidectomy Among Patients with Hyperthyroidism: Exploring the Feasibility of Ambulatory Surgery. JAMA Otolaryngology Head and Neck Surgery. 2023. *In Press.*

3. Du W, Adkisson C, Ye X, Duran CL, Chellakkan Selvanesan B, Gravekamp C, Oktay MH, **McAuliffe JC**, Condeelis JS, Panarelli NC, Norgard RJ, Sela Y, Stanger BZ, Entenberg D. SWIP-a stabilized window for intravital imaging of the murine pancreas. Open Biology. 2022 Jun; 12(6):210273

4. Selvanesan BC, Chandra D, Quispe-Tintaya W, Jahangir A, Patel A, Meena K, Alves Da Silva RA, Friedman M, Gabor L, Khouri O, Libutti SK, Yuan Z, Li J, Siddiqui S, Beck A, Tesfa L, Koba W, Chuy J, **McAuliffe JC**, Jafari R, Entenberg D, Wang Y, Condeelis J, DesMarais V, Balachandran V, Zhang X, Lin K, Gravekamp C. Listeria delivers tetanus toxoid protein to pancreatic tumors and induces cancer cell death in mice. Sci Transl Med. 2022 Mar 23;14(637):eabc1600.

5. Maddipati R, Norgard RJ, Baslan T, Rathi KS, Zhang A, Saeid A, Higashihara T, Wu F, Kumar A, Annamalai V, Bhattacharya S, Raman P, Adkisson CA, Pitarresi JR, Wengyn MD, Yamazoe T, Li J, Balli D, LaRiviere MJ, Ngo TC, Folkert IW, Millstein ID, Bermeo J, Carpenter EL, **McAuliffe JC**, Oktay MH, Brekken RA, Lowe SW, Iacobuzio-Donahue CA, Notta F, Stanger BZ. MYC levels regulate metastatic heterogeneity in pancreatic adenocarcinoma. Cancer Discov. 2022 Feb; 12(2):542-561.

6. Romero-Velez G, Pereira X, Mandujano CC, Parides MK, Muscarella P, Melvin WS, Love C, **McAuliffe JC**. The Utility of HIDA in the Tokyo Guidelines Era for Acute Cholecystitis. Journal of Surgical Research. 2021 Dec;268:667-672.

7. Romero-Velez G, Rodriguez Quintero JH, Pereira X, Nussbaum JE, **McAuliffe JC**. SARS-CoV-2 During Abdominal Operations: Are Surgeons at Risk? Surg Laparosc Endosc Percutan. 2021 June 29;31(6):674-678

8. Romero-Velez G, Pereira X, Panarelli N, Yang J, **McAuliffe JC**. Neuroendocrine tumor of the common bile duct associated with von Hippel-Lindau Disease: A Rare Diagnosis. ACG Case Rep J. 2021 Feb 26;8(2):e00512.

9. Shanja-Grabarz X, **McAuliffe JC**, Kanneganti M, Friedmann P, Levine R, Huang R, In H. Colorectal Cancer Surgery Outcomes in the Non-Elective Setting: A Target for Improvement. J Gastrointest Surg. 2021 May;45)5):1475-1482.

10. Romero-Velez G, Laird A, Libutti S, **McAuliffe JC.** Outcomes of Adrenalectomy for Aldosteronoma in the Hispanic and Black Populations. World J Surg. 2021 May;45(5):1475-1482.

11. Bliton J, Parides M, Muscarella P, **McAuliffe JC**, Papalezova K, In H. Clincal Stage of Cancer Affects Perioperative Mortality for Gastrointestinal Cancer Surgeries. J Surg Res. 2020 Dec 9;260:1-9.

12. Creasy JM, Cunanan KM, Chakraborty J, **McAuliffe JC**, Chou J, Gonen M, Kingham VS, Weiser MR, Balachandran VP, Drebin JA, Kingham TP, Jarnagin WR, D'Angelica MI, Do RKG, Simpson AL. Differences in Liver Parenchyma are Measurable with CT Radiomics at Initial Colon Resectionin Patients that Develop Hepatic Metastases from Stage II/III Colon Cancer. Ann Surg Oncol. 2020 Sep 20.

13. Yeung A, Friedmann P, In H, Bloomgarden N, **McAuliffe JC**, et al. Evaluation of Adrenal Vein Sampling use and Outcomes in Patients With Primary Aldosteronism. J Surg Res 2020 Aug 19;256:673-679.

14. Mehta VV, Friedmann P, **McAuliffe JC**, Muscarella P, In H. Pancreatic Cancer Surgery Following Emergency Department Admission: Understanding Poor Outcomes and Disparities in Care. J Gastrointest Surg 2020 May 6. Online ahead of print.

15. Datta J, Smith JJ, Chatila WK, **McAuliffe JC**, et al. Co-Altered Ras/B-raf and TP53 is Associated with Extremes of Survivorship and Distinct Patterns of Metastasis in Metastatic Colorectal Cancer Patient. Clin Cancer Res. 2020 Mar 1;26(5):1077-1085.

16. **McAuliffe JC**, McAuliffe RH, Romero-Velez G, Statter M, Melvin WS, Muscarella P. Feasibility and Efficacy of Gamification in General Surgery Residency: Preliminary Outcomes of Residency Teams. Am J Surg. 2020 Feb;219(2):283-288.

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The College of Medicine supports a broad array of Shared Scientific Facilities and Cores designed to advance the research efforts of its investigators. The Histology and Comparative Pathology Facility provides comprehensive research pathology support to Einstein and Montefiore investigators, as well as diagnostic support to the Institute of Animal Studies. The facility performs most aspects of tissue evaluation from necropsy to histologic evaluation and special/immunohistochemical staining. The Core Facility supports quality translational research by evaluating how the genetic background, environment and sex of animals affect study results or gene phenotype. Expertise fields are ocular & liver pathology & toxicology, and carcinogenicity. The goal of the facility is to provide a high-quality pathology service as well as to be a resource for understanding and translating in vivo data. Finally, the facility is increasing its digital pathology capabilities to serve faculty members, researchers & students with advanced digital and AI tools for future collaborations.

Selected Publications

1. Proposal of A 2-Tier Histologic Grading System for Canine Cutaneous Mast Cell Tumors to More Accurately Predict Biological Behavior. Veterinary Pathology. 2011 Jan; 48(1):147-55. Epub 2010 Nov 9. Kiupel M, Webster JD, Bailey KL, Best S, DeLay J, Detrisac CJ, Fitzgerald SD, Gamble D, Ginn PE, Goldschmidt MH, Hendrick MJ, Howerth EW, Janovitz EB, Langohr I, Lenz SD, Lipscomb TP, Miller MA, Misdorp W, Moroff S, Mullaney TP, **Neyens E**, O'Toole D, Ramos-Vara J, Scase TJ, Schulman FY, Sledge D, Smedley RC, Smith K, W Snyder P, Southorn E, Stedman NL, Steficek BA, Stromberg PC, Valli VE, Weisbrode SE, Yager J, Heller J, Miller R.

2. A Clinicopathological Study Of 52 Feline Epulides. Veterinary Pathology. 2007 Mar; 44(2):161-9. De Bruijn ND, Kirpensteijn J, **Neyens**, Van Den Brand JM, Van Den Ingh TS.

3. Pilot Study of Intraregional Deionized Water Adjunct Therapy for Mast Cell Tumors In Dogs. Veterinary Record. 2004 Jan 17; 154(3):90-1. **Neyens E**, Kirpensteijn J, Grinwis GC, Teske E.

4. The application, challenges, and advancement toward regulatory acceptance of digital toxicologic pathology: Results of the 7th ESTP International expert workshop (September 20-21, 2019). V. Schumacher, F. Aeffner, E. Barale-Thomas, C. Botteron, J. Cartner, L. Elies, J. Engelhardt, P. Fant, T. Forest, P. Hall, D. Hildebrand, R. Klpfleish, T. Lucotte, H. Marxfeld, L. Mckinney, P. Moulin, **E. Neyens**, X. Palazzi, A. Piton, E. Riccardi, D. Roth, S. Rousselle, J. Vidal, B. Williams.

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Areas of Research: Translational and basic research (bench to bedside/ bedside to bench) in tumor microenvironment related to pro-metastatic changes including induction of invasive and stem cell phenotype in cancer cells. The effect of chemotherapy on tumor microenvironment in pre-clinical mouse models, and patient-derived samples. The analyses of disease outcome data from clinical trials comparing pre- and post-operative chemotherapy relative to patient ethnicity and race.

Professional Interests: Maja Oktay is a physician scientist. She is board certified anatomical pathologist and cytopathologist with a Ph.D. and post-doctoral training in cancer cell biology and cell signaling pathways. Her major interests are in cancer cell biology, the biology of breast cancer progression and metastasis, development of prognostic and predictive molecular biomarkers as well as identification of therapeutic targets for cancer cell dissemination. In addition, she is interested in the effect of commonly used chemotherapy on tumor microenvironment in patients of all racial backgrounds. Her work is based on the analysis of the cancer microenvironment using patient-derived material as well as mouse models of cancer in combination with digital pathology and intravital multiphoton imaging. Dr. Oktay's team is now focusing on elucidating the cellular and molecular mechanisms involved in the emergence of disseminating cancer stem cells, cancer cell dissemination from metastatic foci and chemotherapy-mediated induction of invasive and stem program in breast cancer cells with the overarching goal to improve the outcome of patients treated with chemotherapy.

Selected References

Borriello L, Condeelis J, Entenberg D, Oktay MH. Breast Cancer Cell Re-Dissemination from Lung Metastases-A Mechanism for Enhancing Metastatic Burden. J Clin Med. 2021 May 27;10(11):2340. doi: 10.3390/jcm10112340. PMID: 34071839

Kim G, Pastoriza JM, Condeelis JS, Sparano JA, Filippou PS, Karagiannis GS, Oktay MH. The Contribution of Race to Breast Tumor Microenvironment Composition and Disease Progression. Front Oncol. 2020 Jun 30;10:1022. doi: 10.3389/fonc.2020.01022. eCollection (2020)

Entenberg D, Oktay MH, D'Alfonso T, Ginter PS, Robinson BD, Xue X, Rohan TE, Sparano JA, 24 Jones JG, Condeelis JS. Validation of an Automated Quantitative Digital Pathology Approach for Scoring TMEM, a Prognostic Biomarker for Metastasis. Cancers (Basel). Mar 31;12(4):846. doi: 10.3390/cancers12040846 (2020)

Sanchez LR, Borriello L, Entenberg D, Condeelis JS, Oktay MH, Karagiannis GS. The emerging roles of macrophages in cancer metastasis and response to chemotherapy. J Leukoc Biol. Aug;106(2):259-274. doi: 10.1002/JLB.MR0218- 056RR. Epub 2019 Feb 5. (2019)

Ginter PS, Karagiannis GS, Entenberg D, Lin Y, Condeelis J, Jones JG, Oktay MH. Tumor microenvironment of metastasis (TMEM) doorways are restricted to the blood vessel endothelium in both primary breast cancers and their limph node metastases. Bancers (Basel), Oct8;11(10).pii:E1507.doi:10.3390/cancers11101 507. (2019)

Karagiannis GS, Condeelis JS, Oktay MH. Chemotherapy-Induced Metastasis: Molecular Mechanisms, Clinical Manifestations, Therapeutic Interventions. Cancer Res. Sep 15;79(18):4567- 4576. Doi: 10.1158/0008-5472.CAN-19-1147. Epub 2019 Aug 20. Review. (2019)

Karagiannis GS, Pastoriza JM, Borriello L, Jarfari R, Coste A, Condeelis JS, Oktay MH, Entenberg D. Assessing TMEM Doorway-Mediated Vascular Permeability Associated with Cancer Cell Dissemination Using Intravital Imaging and Fixed Tissue Analysis. JoVE. Jun 26;(148). Doi: 10.3791/59633. (2019)

Sanchez LR, Borriello L, Entenberg D, Condeelis JS, Oktay MH, Karagiannis GS. The emerging roles of macrophages in cancer metastasis and response to chemotherapy. J Leukoc Biol. doi: 10.1002/JLB.MR0218-056RR. (2019)

Pastoriza JM, Kargiannis GS, Lin J, Lanjewar S, Entenberg D, Condeelis JS, Sparano JA, Xiaonan X, Rohan TE, Oktay MH. Black race and distant recurrence after neoadjuvant or adjuvant chemothrapry in breast cancer. Clin Exp Metastasis. Aug 22. doi: 10.1007/s10585-018- 9932-8. (2018)

Entenberg D, Voiculescu S, Guo P, Borriello L, Wang Y, Karagiannis GS, Jones J, Baccay F, Oktay MH, Condeelis J. A permanent window for the murine lung enables high-resolution imaging of cancer metastasis. Nat Methods.;15(1):73-80. Epub 2017/11/28. doi: 10.1038/nmeth.4511. (2018)

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Genetic differences play an important role in normal human development and disease. These differences can also play a role in the progression of disease and in individual responses to therapy. The research mission of our laboratory is to use of modern genomics to help understand the roles of human genetic variation in these processes. We have developed functional variant assays to understand the phenotypic effects of genetic variants.

Genetic variation in human populations. We have characterized genetic variation in a number of human populations (Hispanics and Latinos, Jewish HapMap Project) to understand the origins and migrations of these populations. Currently, we are exploring the role of bottlenecks in the formation of some of these populations. We are carrying the work forward to understand disease susceptibilities within these groups. A key feature of this work is translating new findings into clinical practice to promote personalized medicine.

Human developmental disorders. We study the genetic basis of rare genetic disorders, notably disorders found in isolated populations and disorders of sex development, to identify not only the mutational basis, but also the molecular mechanisms. We identified mutations in genes in the MAP kinase pathway in abnormal testicular development and now are investigating the roles of members of this pathway in normal testicular development and testicular cancer.

Cancer genetics and genomics. We have explored the roles of low and high-penetrance variants in risk of human cancers and have developed models for predicting risk through the use of flow variant assays developed in our lab. Through genome wide association studies, we have identified common variants that increase risk of adverse outcomes (erectile dysfunction, urinary dysfunction, proctitis) for men treated with radiation therapy for prostate cancer. We have also developed a molecular signature based on acquired somatic copy number alterations that is highly predictive of risk of prostate cancer metastasis and may account for this increased risk among African-American men. We have also developed a rapid, novel and accurate approach for identifying germline defects in DNA repair pathways that increase risk for common cancers.

Recent publications

- Atzmon G, Hao L, Pe'er I, Velez C, Pearlman A, Palamara PF, Morrow B, Friedman E, Oddoux C, Burns E, **Ostrer H**. Abraham's children in the Genome Era: Major Jewish Diaspora populations comprise distinct genetic clusters with shared Middle Eastern ancestry. Am J Hum Genet. 86:850-9, 2010.
- Campbell CL, Palamara PF, Dubrovsky M, Botigué LR, Fellous M, Atzmon G, Oddoux C, Pearlman A, Hao L, Henn BM, Burns E, Bustamante CD, Comas D, Friedman E, Pe'er I, **Ostrer H**. North African Jewish and non-Jewish populations form distinctive, orthogonal clusters. Proc Natl Acad Sci U S A. 109:13865-70, 2012.
- Pearlman A, Radi O, Zuffardi O, Giussani U, Pallotta R, Camerino G, **Ostrer H.** Mutations in MAP3K1 tilt the balance from SOX9/FGF9 to WNT/β-catenin signaling. Hum Mol Genet. 23:1073-83, 2014.
- Kerns SL, **Ostrer H**, Rosenstein BS. Radiogenomics: using genetics to identify cancer patients at risk for development of adverse effects following radiotherapy. Cancer Discov. 4:155-65, 2014.
- Loke J, Pearlman A, Upadhyay K, Tesfa L, Shao Y, **Ostrer H**. Functional variant analyses (FVAs) predict pathogenicity in the BRCA1 DNA double-strand break repair pathway. Hum Mol Genet. 24:3030-7, 2015.
- Syeda MM, Upadhyay K, Loke J, Pearlman A, Klugman S, Shao Y, **Ostrer H.** Prediction of breast cancer risk based on flow-variant analysis of circulating peripheral blood B cells. Genet Med. 2017 Mar 16. doi: 10.1038/gim.2016.222.
- Chamberlin A, Huether R, Machado AZ, Groden M, Liu HM, Upadhyay K, O V, Gomes NL, Lerario AM, Nishi MY, Costa EMF, Mendonca B, Domenice S, Velasco J, Loke J, **Ostrer H**. Mutations in MAP3K1 that cause 46,XY disorders of sex development disrupt distinct structural domains in the protein. Hum Mol Genet. 28:1620-1628, 2019, PMID: 30608580.
- Pearlman A, Upadhyay K, Cole K, Loke J, Sun K, Fineberg S, Freedland SJ, Shao Y, **Ostrer H**. Robust genomic copy number predictor of pan cancer metastasis Genes and Cancer 9:66-77, 2018, PMID: 29725504.
- Fofanov VY, Upadhyay K, Pearlman A, Loke J, O V, Shao Y, Freedland S, **Ostrer H**. Rapid next-generation sequencing method for prediction of prostate cancer risks. J Mol Diagn. 21:49-57, 2019 PMID: 30553750.

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Head and neck squamous cell cancer (HNSCC) afflicts approximately 50,000 people in the United States each year. Risks for the development of this disease include tobacco use, alcohol use, and viral infection with high-risk human papilloma virus (HPV). Treatment failure occurs in 40-50% of patients who present with loco-regionally advanced disease, resulting in significant mortality rates. Morbidity in this disease is also significant secondary to tumor and treatment effects on patients' ability to speak, breathe, and swallow. Treatments for HNSCC have remained relatively unchanged for several decades, relying on surgery, radiation, and cisplatin-based chemotherapy to achieve optimal results. The only targeted molecular agent approved by the FDA to treat HNSCC – Cetuximab - targets the EGFR receptor and provides only modest benefit. Currently, there are no molecular biomarkers that are used to modify the treatment course recommended for the management of HNSCC, however, several new discoveries are providing potentially useful biomarkers and molecular targets in this disease.

Dr. Ow's research is focused on the translation of genetic and molecular determinants in HNSCC into clinically useful biomarkers and therapeutic targets. Specifically, Dr. Ow is studying factors that contribute to radiation and chemo-resistance in this disease, as well as genomic alterations acquired during the process of locoregional recurrence, nodal metastasis, and distant failure. As a translational scientist, Dr. Ow has active projects using *in vitro* models of HNSCC, as well as clinical and translational research. The ultimate goal of this work is to identify novel ways to improve the survival and functional outcomes among patients with HNSCC.

Selected References

- Ben-Dayan MM, **Ow TJ**, Belbin TJ, Wetzler J, Smith RV, Childs G, Diergaarde B, Hayes DN, Grandis JR, Prystowsky MB, Schlecht NF. Nonpromoter methylation of the CDKN2A gene with active transcription is associated with improved locoregional control in laryngeal squamous cell carcinoma. *Can Med*. 2017;6(2):397-407; PMID: 28102032; PMCID: PMC5313649
- Osman AA, Neskey DM, Katsonis P, Patel AA, Ward AM, Hsu TK, Hicks SC, McDonald TO, **Ow TJ**, Ortega Alves M, Pickering CR, Skinner HD, Zhao M, Sturgis EM, Kies MS, El-Naggar A, Perrone F, Licitra L, Bossi P, Kimmel M, Frederick MJ, Lichtarge O, Myers JN. Evolutionary Action Score of TP53 Coding Variants (EAp53) is Predictive of Platinum Response in Head and Neck Cancer Patients. Cancer Res. 2015 Apr 1;75(7):1205-15. doi: 10.1158/0008-5472.CAN-14-2729. Epub 2015 Feb 17. PMID: 25691460
- Neskey DM, Osman AA, **Ow TJ**, Katsonis P, O McDonald T, Hicks SC, Hsu Teng-Kuei, Pickering CR, Ward A, Patel A, Yordy JS, Skinner HD, Giri U, Sano D, Story MD, Beadle BM, El-Naggar AK, Kies MS, William WN, Caulin C, Frederick MJ, Kimmel M, Lichtarge O, Myers JN. Evolutionary Action score of TP53 (EAp53) identifies high risk mutations associated with decreased survival and increased distant metastases in head and neck cancer. Cancer Res. 2015 Apr 1;75(7):1527-36. doi: 10.1158/0008-5472.CAN-14-2735. Epub 2015 Jan 29. PMID: 25634208
- **Ow TJ,** Hanna EY, Roberts DB, Levine NB, El-Naggar AK, Rosenthal DI, Demonte F, Kupferman ME. Optimization of long-term outcomes for patients with esthesioneuroblastoma. *Head Neck*. 2014 Apr;36(4):524-30.
- Skinner, HD; Sandulache, VC; **Ow, TJ**; Meyn, RE; Yordy, JS; Beadle, BM; Fitzgerald, AL; Giri, U; Ang, KK; Myers, JN. TP53 disruptive mutations lead to head and neck cancer treatment failure through inhibition of radiation-induced senescence. *Clin Cancer Res*. 2012 Jan 1;18(1):290-300. Epub 2011 Nov 16.
- **Ow, TJ***; Sano, D.*; Xie, TX*; Zhao, M; Pickering, CR; Zhou, G; Sandulache, VC; Wheeler, DA; Gibbs, RA; Caulin, C; Myers, JN. Disruptive *TP53* Mutation is Associated with Aggressive Disease Characteristics in an Orthotopic Murine Model of Oral Tongue Cancer . *Clin Cancer Res*. 2011 Nov 1;17(21):6658-70. *Co-First Authors
- Sandulache VC, **Ow TJ**, Pickering CR, Frederick MJ, Zhou G, Fokt I, Davis-Malesevich M, Priebe W, Myers JN. Glucose, not glutamine, is the dominant energy source required for proliferation and survival of head and neck squamous carcinoma cells. *Cancer*, 2011 Jul 1;117(13):2926-38.
- **Ow TJ,** Sandulache VC, Skinner HD, Myers JN. Integration of cancer genomics with treatment selection: from the genome to predictive biomarkers. *Cancer*. 2013 Nov 15;119(22):3914-28.

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In 1999 we developed a multidisciplinary group including surgery, oncology, pathology, molecular biology, protein chemistry, computational biology and biostatistics to study Head and Neck Squamous Cell Carcinoma (HNSCC). Our initial studies on molecular classification of HNSCC using microarray technology demonstrated that patient segregation by gene expression profiling is a better predictor of outcome than established clinicopathological variables. The Head and Neck Program includes multiple laboratories with research exploring basic mechanisms of tumor behavior, developing biomarkers and identifying molecular classifiers that define distinct subsets of patients. Studies in the Prystowsky Laboratory focus on identifying proteomic signatures that predict tumor behavior. The Head and Neck program goals are:

- To develop new diagnostics that will identify optimal treatments at initial diagnosis.
- To identify potential new targets for drug development.

References

Childs G, Fazzari M, Kung G, Kawachi N, Brandwein-Gensler M, McLemore M, Chen Q, Burk RD, Smith RV, **Prystowsky MB**, Belbin TJ. Schlecht NF (2009) Low level expression of microRNA's let7-d and miR-205 are prognostic markers of head and neck squamous cell carcinoma. *Amer J Pathol* 174(3):736-745.

Prystowsky MB, Adomako A, Smith RV, Kawachi N, McKimpson W, Atadja P, Chen Q, Schlecht NF, Parish JL, Childs G, Belbin TJ (2009) The histone deacetylase inhibitor LBH589 inhibits expression of mitotic genes causing G2/M arrest and cell death in head and neck squamous cell carcinoma cell lines. Journal of Pathology, 218:467-477.

Smirnova T, Adomako A, Locker J, Van Rooijen N, **Prystowsky MB**, Segall JE (2011) *In vivo* invasion of head and neck squamous cell carcinoma cells does not require macrophages. Am J Pathol 178:2857-2865.

Harris T, Jimenez L, Kawachi N, Fan J-B, Chen J, Belbin T, Ramnauth A, Loudig O, Keller CE, Smith R, **Prystowsky MB**, Schlecht NF, Segall JE, Childs G (2012) Low-Level expression of miR-375 Correlates with Poor Outcome and Metastasis While Altering the Invasive Properties of Head and Neck Squamous Cell Carcinomas Am J Pathol, 180:917-928.

Schlecht N, Brandwein-Gensler M, Smith RV, Kawachi N, Broughel D, Lin J, Keller CE, Reynolds PA, Gunn-Moore FJ, Harris T, Childs G, Belbin TJ, **Prystowsky MB** (2012) Cytoplasmic ezrin and moesin correlate with poor survival in head and neck squamous cell carcinoma. Head and Neck Pathology 6:232-243.

Salazar CR, Anayannis N, Smith RV, Wang Y, Haigentz M, Garg M, Schiff BA, Kawachi N, Elman J, Belbin TJ, **Prystowsky MB**, Burk RD, Schlecht NF (2014) Combined P16 and Human Papillomavirus testing predicts head and neck cancer survival. Int J Cancer. 135: 2404–2412.

Harris TM, Du P, Kawachi N, Belbin TJ, Wang Y, Schlecht NF, Ow TJ, Keller CE, Childs GJ, Smith RV, Angeletti RH, **Prystowsky MB**, Lim J. (2015) Proteomic Analysis of Oral Cavity Squamous Cell Carcinoma Specimens Identifies Patient Outcome—Associated Proteins. Archives of Pathology & Laboratory Medicine 139:494-507.

Schlecht NF, Ben-Dayan M, Anayannis N, Lleras RA, Thomas C, Wang Y, Smith RV, Burk RD, Harris TM, Childs C, Ow TJ, **Prystowsky**, **MB**, Belbin TJ (2015) Epigenetic changes in the CDKN2A locus are associated with differential expression of P16INK4A and P14ARF in HPV positive oropharyngeal squamous cell carcinoma. Cancer Medicine 4:342-353. DOI: 10.1002/cam4.374

Jimenez L, Sharma VP, Condeelis J, Harris TM, Ow TJ, **Prystowsky MB**, Childs G, Segall JE (2015) MicroRNA-375 Suppresses Extracellular Matrix Degradation and Invadopodial Activity in Head and Neck Squamous Cell Carcinoma. Archives of Pathology & Laboratory Medicine. 139:1349-1361

Ben-Dayan M, MacCarthy T, Schlecht NF, Belbin TJ, Childs G, Smith RV, **Prystowsky MB,** Bergman A (2015) Cancer as the disintegration of robustness: population-level variance in gene expression identifies key differences between tobacco- and HPV-associated oropharyngeal carcinogenesis. Archives of Pathology & Laboratory Medicine 139:1362-1372.

Ben-Dayan MM, Ow TJ, Belbin TJ, Wetzler J, Smith RV, Childs G, Diergaarde B, Hayes DN, Grandis JR, **Prystowsky MB**, Schlecht NF. (2017) Non-promoter Methylation of the CDKN2A Gene with Active Transcription is Associated with Improved Locoregional Control in Laryngeal Squamous Cell Carcinoma. Cancer Medicine 6:397-407. PMID:28102032

Jimenez L, Lim J, Burd B, Harris T, Ow TJ, Kawachi N, Belbin T, Angeletti R, **Prystowsky MB**, Childs G, Segall J. (2017) miR-375 regulates invasion related proteins vimentin and L-plastin. Am J Pathology 187:1523-1536.

Anayannis N, Schlecht NF, Ben-Dayan M, Smith RV, Belbin TJ, Ow TJ, Blakaj DM, Burk RD, Leonard SM, WoodmanCB, Parish JL, **Prystowsky MB**. (2018) Association of an intact *E2* gene with higher HPV viral load, higher viral oncogene expression, and improved clinical outcome in HPV16 positive Head and Neck Squamous Cell Carcinoma. PLoS ONE 13: e0191581.

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TOXOPLASMOSIS: *Toxoplasma gondii* is a ubiquitous Apicomplexan protozoan parasite that infects humans, mammals and birds. Despite recent progress in understanding the biology of the rapidly replicating form (tachyzoite), very little is known about the cyst form (bradyzoite). The bradyzoite stage plays a critical role in maintenance of latent infection, the relapse of infections and the development of chronic neurologcial disease. Our research is focused on the identification of cyst wall (bradyzoite) proteins and how they function.

MICROSPORIDIOSIS: Microsporidia are "emerging" human and veterinary pathogens that contain a unique organelle, the polar tube, which is involved in invasion. While the description of the polar tube occurred over 100 years ago, the biochemical components of this structure and its formation during invasion remain to be definitively determined. Our research is focused on the: (1) characterization of the structure and composition of the polar tube and spore wall; and (2) the identificiation of therapeutic agents for microsporidiosis.

REFERENCES

Weiss LM and Kim K (eds.) *Toxoplasma gondii* the model Apicomplexan: Methods and Applications, Elsevier Press (Academic Press), 3rd edition, 2020.

Weiss LM and Becnel JJ (eds.) Microsporidia: Pathogens of Opportunity, Wiley-Blackwell, 2014. [Translated into Chinese 2020]

Han B, Pan G, **Weiss LM**. Microsporidiosis in humans. Clin Microbiol Rev. 2021 Jun 30:e0001020. doi: 10.1128/CMR.00010-20.

Mayoral J, Guevara RB, Rivera-Cuevas Y, Tu V, Tomita T, Romano JD, Gunther-Cummins L, Sidoli S, Coppens I, Carruthers VB, **Weiss LM**. Dense granule protein GRA64 interacts with host cell ESCRT proteins during *Toxoplasma gondii* infection. mBio. 2022 Jun 22:e0144222. doi: 10.1128/mbio.01442-22

Tomita T, Mukhopadhyay D, Han B, Yakubu R, Tu V, Mayoral J, Sugi T, Ma Y, Saeij JPJ, **Weiss LM**. Toxoplasma gondii matrix antigen 1 is a secreted immunomodulatory effector. mBio. 2021 May 18;12(3):e00603-21.

Flores J, Takvorian PM, **Weiss LM**, Cali A, Gao N. Human microsporidian pathogen *Encephalitozoon intestinalis* impinges on enterocyte membrane trafficking and signaling. J Cell Sci. 2021 Feb 15:jcs.253757. doi: 10.1242/jcs.253757.

Mayoral J, Tomita T, Tu V, Aguilan JT, Sidoli S, **Weiss LM**. Toxoplasma gondii PPM3C, a secreted protein phosphatase, affects parasitophorous vacuole effector export. PLoS Pathog. 2020 Dec 28;16(12):e1008771. doi: 10.1371/journal.ppat.1008771.

Mayoral J, Shamamian P Jr, **Weiss LM**. In vitro characterization of protein effector export in the bradyzoite stage of *Toxoplasma gondii.* mBio. 2020 Mar 10;11(2):e00046-20. doi: 10.1128/mBio.00046-20.

Tu V, Mayoral J, Yakubu RR, Tomita T, Sugi T, Han B, Williams T, Ma Y, **Weiss LM.** MAG2, a *Toxoplasma gondii* bradyzoite stage-specific cyst matrix protein. mSphere. 2020 Feb 19;5(1). pii: e00100-20. doi: 10.1128/mSphere.00100-20.

Tu V, Tomita T, Sugi T, Mayoral J, Han B, Yakubu RR, Williams T, Horta A, Ma Y, **Weiss LM**. The *Toxoplasma gondii* cyst wall interactome. mBio. 2020 Feb 4;11(1). pii: e02699-19. doi: 10.1128/mBio.02699-19.

Han B, Ma Y, Tu V, Tomita T, Mayoral J, Williams T, Horta A, Huang H, **Weiss LM** Microsporidia interact with host cell mitochondria via voltage-dependent anion channels using sporoplasm surface protein 1. MBio. 2019 Aug 20;10(4). pii: e01944-19.

Han B, Polonais V, Sugi T, Yakubu R, Takvorian PM, Cali A, Maier K, Long M, Levy M, Tanowitz HB, Pan G, Delbac F, Zhou Z, **Weiss LM.** The role of microsporidian polar tube protein 4 (PTP4) in host cell infection. PLoS Pathog. 2017: 20;13(4):e1006341. . doi: 10.1371/journal.ppat.100634

Tomita T, Sugi T, Yakubu R, Tu V, Ma Y, **Weiss LM**. Making Home Sweet and Sturdy: *Toxoplasma gondii* ppGalNAc-Ts glycosylate in hierarchical order and confer cyst wall rigidity. mBio. 2017 8(1). pii: e02048-16. . doi: 10.1128/mBio.02048-16

Sugi T, Ma YF, Tomita T, Murakoshi F, Eaton MS, Yakubu R, Han B, Tu V, Kato K, Kawazu S, Gupta N, Suvorova ES, White MW, Kim K, **Weiss LM**. *Toxoplasma gondii* cyclic AMP-dependent protein kinase subunit 3 is involved in the switch from tachyzoite to bradyzoite development. mBio. 2016: e00755-16. doi: 10.1128/mBio.00755-16

Tu V, Mayoral J, Sugi T, Tomita T, Han B, Ma YF, **Weiss LM**. Enrichment and proteomic characterization of the cyst wall from in vitro *Toxoplasma gondii* cysts. mBio. 2019 Apr 30;10(2). pii: e00469-19. doi: 10.1128/mBio.00469-19.

Tomita T, Bzik DJ, Ma YF, Fox BA, Markillie LM, Taylor RC, Kim K, **Weiss LM**. The *Toxoplasma gondii* cyst wall protein CST1 is critical for cyst wall integrity and promotes bradyzoite persistence. PLoS Pathog. 2013; 9(12):e1003823. doi: 10.1371/journal.ppat.1003823

Alvarado JJ, Nemkal A, Sauder JM, Russell M, Akiyoshi DE, Shi W, Almo SC, **Weiss LM**. Structure of a microsporidian methionine aminopeptidase type 2 complexed with fumagillin and TNP-470. Mol Biochem Parasitol. 2009; 168(2):158-167.

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Dr. Yin's laboratory focuses on unraveling the genetic and molecular basis of chronic lymphocytic leukemia (CLL), the most common type of leukemia in adults. Our lab has pioneered the functional study of CLL driver mutations using genetically engineered mouse models, providing critical fresh insights into the mechanisms through which these mutational events drive CLL. Specifically, my research on the *Sf3b1-Atm* mouse model revealed the effect of *Sf3b1* mutation status on 3' splice site changes, leading to alterations in diverse pathways, including BCR signaling. Importantly, these findings have been confirmed in human CLL cells, underscoring their clinical relevance. Furthermore, we uncovered how a hotspot mutation in the *Ikzf3* model affects target selection, resulting in transcriptional activation of BCR signaling, shedding light on the underlying mechanisms of CLL. In addition, my investigations into the *Dnmt3a* mouse model elucidated how methylation changes associated with *Dnmt3a* loss activate notch signaling. Most recently, using CRISPR screens, I made significant strides in identifying the cooperative oncogenicity of CLL drivers. These findings suggest that a diverse array of mutations can drive B cells toward CLL, but ultimately converge on a limited set of B cell-relevant pathways. Collectively, our work has shed light on the step-by-step process through which CLL develops and has uncovered potential vulnerabilities that could be exploited for targeted therapies.

Selected Publications

1. Ten Hacken E*, Yin S*, Redd RA, Hernández Sánchez M, Clement K, Brunsting Hoffmann G Regis FFD, Witten E, Li S, Neuberg D, Pinello L, Livak KJ, Wu CJ. Loss-of-function lesions impact B-cell development and fitness but are insufficient to drive CLL in mouse models. Blood Adv. 2022 Dec 7. PMID: 36477552.
2. Lazarian G*, Yin S*, Hacken E*, Sewastianik T, Uduman M, et al. A hotspot mutation p.L162R in IKZF3 drives B cell neoplasia via transcriptional dysregulation. *Cancer Cell*. 2021 Mar 8;39(3):380-393.
3. Biran A*, Yin S*, Kretzmer H, Hacken, Parvin S, Carrasco R, Meissner A, Wu C. B cell-restricted depletion of Dnmt3a activates Notch and Myc signaling, causing chronic lymphocytic leukemia. *Cancer Research.* 2021 Dec 15;81(24):6117-6130.
4. Yin S, Gambe RG, Sun J, Martinez AZ, Cartun ZJ, et al. A Murine Model of Chronic Lymphocytic Leukemia Based on B Cell-Restricted Expression of *Sf3b1* Mutation and *Atm* Deletion. *Cancer Cell.* 2019 Jan 14;35(2):283-296 [Cover story].