

DMB Departmental Overview



The mission of the Department of Developmental and Molecular Biology (DMB) is to investigate the underlying cellular and molecular mechanisms of development, aging, regeneration, and disease. DMB currently includes 24 research groups and more than 100 students, postdoctoral fellows, technicians, and faculty members, bringing in more than \$12M in annual grant funding including several pre- and post-doctoral fellowships per year.

The department's breadth is one of its greatest strengths. DMB investigators use diverse model systems - including human cells, mice, *Drosophila*, and zebrafish - to study hematologic, neurologic, cardiovascular, renal, virologic, metabolic, oncologic, and age-related diseases. These scientific areas foster lively interactions and form the foundation on which DMB stands.

DMB has a rich history of long-standing collaborations among groups, greatly enriching the academic environment. Faculty hold cross appointments in basic and clinical departments and serve as members and leaders across college-wide centers and institutes, including the Gottesman Institute for Stem Cell and Regenerative Medicine Research, the Institute for Geroscience, the Wilf Family Cardiovascular Research Institute, the Diabetes Center, the Liver Center, the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center, the Montefiore Einstein Comprehensive Cancer Center, and affiliated Cancer Dormancy and Blood Cancer Institutes.

Since 1965, the department has grown under the leadership of Drs. Jerard Hurwitz, E. Richard Stanley, Liang Zhu, and Teresa V. Bowman. Dr. Bowman, the current chair, continues to elevate, connect, and empower trainees, staff, and faculty to propel cutting-edge research and educational innovation.

DMB activities include weekly work-in-progress seminars, weekly faculty chalk talks, trainee-initiated DreaMBig sessions, biennial retreats, and a vibrant external faculty seminar series that expands scientific exposure and networking for faculty and trainees.



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Our research focuses on the control of hematopoiesis, focusing on hematopoietic stem and progenitor cells (HSPCs). Specifically, we explore how HSPC form during development, how these cells function to maintain healthy hematopoiesis lifelong, and how dysfunction in them leads to hematologic malignancies. The lab currently has three main themes: i) Defining regulators critical for *de novo* production of hematopoietic stem cells (HSC) and HSC-independent progenitors and their consequences on lifelong hematopoiesis ii) Deciphering how mutations found in human myelodysplastic syndromes (MDS) alter stem cell traits and influence differentiation choices, and iii) Understanding how RNA and DNA binding proteins that are mutated in MDS affect R-loop structures in the nucleus. My group is exploring these fundamental questions in hematology using a highly integrative strategy combining zebrafish genetics, human pluripotent stem cells, and genomics approaches.

Impact of the embryonic environment on the hematopoietic system: Our recent work dissecting developmental hematopoiesis demonstrated important functional differences between newly-formed HSCs and HSC-independent progenitors that form concomitantly during embryogenesis. We have several projects extending from this finding aimed at understanding the regulation of hematopoietic ontogeny and its impact on healthy and malignant adult hematopoiesis.

- Impacts of genetic and environmental factors on HSPC lineage bias, Clonal Hematopoiesis, and Immune Outputs - *Marta Mastrogiovanni, Ph.D.*
- Identifying the Origins of HSPC lymphoid bias and Tissue-Resident Lymphocytes - *Anastasia Nizhnik, Ph.D.*
- Dissecting the acute and long-term impacts of perinatal inflammation on the hematopoietic system- *Hanna Scholze*
- Characterizing the role of Ddx41 in nucleolar function and protein translation- *Keith Ameyaw*
- Tracing the spatiotemporal impact of the embryonic environment on HSPC subtype generation- *Victoria Lopez-Scarim*

Understanding the Role of RNA Binding Proteins in Regulating Hematopoietic Homeostasis: we have extensively explored how RNA and DNA binding proteins modulate hematopoiesis. A current focus related to this topic is aimed at understanding how DEAD-box helicase 41 (DDX41) helps maintain healthy hematopoiesis and how its loss contributes to myelodysplastic syndrome. We have demonstrated that DDX41 acts as a suppressor of R-loop accumulation and that homozygous loss of *ddx41* contributes to maladaptive HSPC expansion via activation of the cGAS-STING DNA-sensing inflammatory pathway. We have several ongoing projects aimed at understanding R-loop involvement in ineffective hematopoiesis as well as other factors that synergize with *DDX41* haploinsufficiency to promote MDS.

- Delineating RNASEH1-R-loop interactions in living cells - *Noura Ghazale, Ph.D.*
- Deciphering genotype-environmental interactions that drive HSPC dysfunction- *Maria Feliz Norberto (co-mentored with Sofia de Oliveira)*
- Defining the Spatial Architecture of Embryonic HSPC Niches- *Annie Carroll*
- Elucidating the Interplay Between *ddx41* and *cux1* Mutations in Hematopoietic Dysfunction - *Valerie Awad*

Through these studies, we anticipate identifying factors critical to HSPC biology, which can be used to increase production of HSPC from pluripotent stem cells and to inform therapeutic strategies with the ultimate goal of improving patient care for those suffering from a variety of hematologic disorders.

Lab website: <https://sites.google.com/view/tvbowmanlab/>

Selected Publications

- Weinreb JT, Ghazale N, Pradhan K, Gupta V, Potts KS, Tricoli B, Daniels NJ, Padgett RA, De Oliveira S, Verma AK, and Bowman TV[#]. Excessive R-loops Trigger an Inflammatory Cascade Leading to Aberrant HSPC Expansion. *Developmental Cell*, 2021; 56(5):627-640 e5. PMID: 33651979. PMCID: PMC8258699
- Ulloa BA, Habbsa S, Potts KP, Lewis A, McKinsty M, Payne SG, Flores J, Nizhnik A, Feliz Norberto M, Mosimann C, and Bowman TV[#]. Definitive Hematopoietic Stem Cells Minimally Contribute to Embryonic Hematopoiesis. *Cell Reports*, 2021; 36(11): 109703. doi: 10.1016/j.celrep.2021.109703. PMID: 34525360. PMCID: PMC8928453
- Weinreb JT, Gupta V, Sharvit E, Weil R, and Bowman TV[#]. Ddx41 inhibition of DNA damage signaling permits erythroid progenitor expansion in zebrafish. *Haematologica*, 2022; 107(3):664-654 doi:10.3324/haematol.2020.257246. PMID: 33763998. PMCID: PMC8883538
- Potts KS*, Cameron RC*, Barajas JM, Wallace L, Cervantes AL, Gupta V, Ghazale N, Pradhan K, McKinsty M, Bai X, Choudhary G, Shastri A, Verma A, Obeng E[#], and Bowman TV[#]. Selective targeting of splicing factor mutant HSPCs via STAT3 inhibition. *Cell Reports*, 2022; 41(11):111825. doi: 10.1016/j.celrep.2022.111825. PMID: 36516770. PMCID: PMC9994853



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Vascular calcification is common in patients with chronic kidney disease (CKD) and contributes to mortality. Unfortunately, no effective therapy is available to prevent or attenuate vascular calcification. Vascular smooth muscle cells (VSMCs), the key cell type in vascular calcification, undergo osteogenic differentiation to initiate mineralization in the vessel walls under pro-calcifying conditions such as hyperphosphatemia, which is a common complication of CKD.

Calcioprotein particles and vascular calcification

Calcioprotein particles (CPPs) have emerged as a promising therapeutic target. In CKD, excess CPPs build up in the blood and transform into pathogenic forms—primary and secondary CPPs, which have been shown in preclinical studies to cause vascular calcification by inducing inflammation, dysfunction of endothelial cells, and calcification of VSMCs. Whether and how serum CPPs lead to vascular calcification in CKD patients is an important knowledge gap. Our lab help fill this gap by testing the hypothesis that serum CPPs from CKD patients lead to macro-calcification, micro-calcification, and calcification of human VSMCs. Because vascular calcification resembles bone mineralization, agents that inhibit vascular calcification may adversely affect bone formation. By studying the function of vascular cells, we provide mechanistic insight that may serve as a basis for future CPP-related therapies to attenuate vascular calcification without impacting bone health. At a cellular level, VSMCs in arterial media and endothelial cells in the intima play pivotal roles in vascular calcification. VSMCs undergo osteogenic differentiation, a process that initiates mineralization in the vessel walls; and endothelial cells can regulate this process. Macro- and micro-calcification confer different cardiovascular risks, and studying micro-calcification allows for early detection and intervention. Using our novel methods of measuring serum CPP size and quantity, we determine the association between serum CPPs and macro-calcification in coronary arteries by leveraging the Chronic Renal Insufficiency Cohort. We also determine the association between serum CPPs and micro-calcification of aorta in a prospective longitudinal study of patients with CKD stage 4. Micro-calcification is measured by ^{18}F -sodium fluoride positron-emission tomography. Lastly, to gain mechanistic insights, we define the effects of CPPs derived from CKD patients on human primary vascular cells.

Atypical FAT1 cadherin (FAT1) and vascular calcification

FAT1 is a transmembrane protein that limits proliferation and phenotypic switching of VSMCs; however, the effects of FAT1 on vascular calcification are unknown. Our preliminary data show that arteries from mice lacking FAT1 had increased expression of Krüppel-like factor 4 (KLF4), a transcription factor that contributes to osteogenic differentiation, and that loss of FAT1 enhanced phosphate-induced calcification of VSMCs. Thus, we hypothesize that FAT1 limits osteogenic differentiation of VSMCs and vascular calcification in CKD. We will test the hypothesis in two specific aims: a mechanistic aim to assess whether FAT1-mediated inhibition of KLF4 is important to limit VSMC calcification, and an in vivo aim to test if FAT1 limits vascular calcification in mice with CKD. Our innovative approach will use a novel murine model of CKD to study vascular calcification.

Atypical FAT1 cadherin and diabetic kidney disease

Diabetic kidney disease (DKD) is characterized by an impaired glomerular filtration barrier, leading to albuminuria and impaired kidney function. Podocytes maintain the integrity of this barrier; however, the underlying molecular mechanisms are not fully elucidated. The cadherin FAT1 is expressed in podocytes, and humans and mice with *FAT1* loss-of-function mutations develop albuminuria; yet whether FAT1 function in podocytes contributes to the pathogenesis of DKD is unknown. We hypothesize that podocyte FAT1 protects against DKD. We will test whether FAT1 protein expression is lower in podocytes of patients with DKD, compared to that of healthy kidneys, or patients with non-diabetic proteinuric kidney disease. In addition, we will assess whether *FAT1* variants associated with albuminuria in a genome-wide association study are linked to decreased *FAT1* expression. Lastly, we will test whether loss of FAT1 in podocytes exacerbates DKD using mouse models.

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Macrophage Phagocytosis, Motility and Invasion in Health and Disease

Macrophages play important roles in host defense against invading micro-organisms and they are also key players in initiating and maintaining an immune response. However, macrophages can also play negative roles, such as in chronic inflammatory disease. Also, tumor-associated macrophages (TAMs), which are present in large numbers in many tumors, appear to play an important role in promoting the progression of solid tumors to an invasive, metastatic phenotype. Macrophages are therefore a prime target for therapies.

Studying the molecular mechanisms of phagocytosis and chemotaxis

Alterations in the actin cytoskeleton are necessary for macrophage functions like phagocytosis and chemotaxis. The directed movement of cells in response to chemoattractants involves several complex, interrelated processes, including directional or chemotactic sensing, polarity, and motility. These processes are mediated by complex, interacting signaling pathways that appear to have many similarities but yet have distinct characteristics depending on the specific chemoattractants and receptors involved. Many of the signaling cascades utilized for phagocytosis are also required for chemotaxis yet they result in the appearance of different structures. We are deciphering the differences in signaling requirements for these different functions to develop tools to specifically inhibit one process such as inappropriate recruitment in inflammatory diseases while maintaining the beneficial macrophage functions needed to fight infection. In addition to traditional approaches, we have developed new technologies and probes for single live cell imaging necessary for dissecting these processes such as biosensors to monitor localized protein activity in live cells, including the development of isoform specific single chain RhoGTPase biosensors.

Determining the mechanism of Tunneling Nanotube formation and function

Cell-to-cell signaling is an important biological function that allows cross talk between cells regulating their activity and function. While soluble factors can mediate interactions between different cells, there are other mechanisms for intercellular communication, such as exosomes and tunneling nanotubes (TNTs) that may play important roles in tumor microenvironment. Tunneling Nanotubes (TNTs) are newly identified thin membranous F-actin containing structures that can be hundreds of microns in length that connect cells together into networks that can sustain and enhance signal propagation between cells. We have defined the roles for actin nucleating proteins along with other regulators in the formation of TNTs and have found that this pathway is conserved in macrophages and breast cancer cells. We have detected that TNTs form between macrophages and tumor cells and can promote macrophage-dependent tumor cell functions, including invasion, chemoresistance and in tumor cell extravasation *in vitro*. We are currently exploring how these unique cell connections are induced and virtually nothing is known about how these structures are regulated.

Determining the role of macrophages in the tumor microenvironment

The tissue microenvironment plays a critical role in tumor progression, but most studies on tumor metastasis involve the use of endpoint assays or *in vitro* studies on cell lines. It appears that macrophages and tumor cells interact in the tumor microenvironment leading to co-invasion into the stroma, entrance into the blood stream, and seeding at the metastatic niche. We have developed a number of *in vitro* assays that reconstitute paracrine interaction between macrophage and carcinoma cells that mimic *in vivo* interactions in the tumor microenvironment. We are currently using these assays to understand the roles of macrophage mediated enhancement of tumor cell invadopodia in stromal invasion. We have also determined the importance of TNTs in the macrophage - tumor cell interaction in carcinoma cell invasion and extravasation *in vivo* using both zebrafish and mouse models.

Lab website: Currently being updated

Selected Recent Publications:

- Genna, A., Duran, C., Entenberg, D., Condeelis, J., and Cox, D. (2023) Macrophages Promote Tumor cell Extravasation across an Endothelial Barrier through Thin Membranous Connections. *Cancers*, special issue “The Role of Tunneling Nanotubes in Intercellular Communication and Pathophysiology of Cancer” 15(7):2092. doi: 10.3390/cancers15072092.
- Zambalde, E.P., Aryian, L.A., Puerta-Martinez, F., Zhu, Y.U., Patil, P., Panarelli, N., Li, J., Yung, Y., Adkisson, C., Petersen, J., Cox, D., Gil-Henn, H., Eddy, R.E., Stanger, B.Z., Entenberg, D., Oktay, M.H., Condeelis, J.S., and McAuliffe, J.C. (2026) TMEM Doorways Enable Metastasis in PDAC and Can Be Targeted by Tie2 Inhibition. *Clinical Cancer Research* 45(1):126. doi: 10.1186/s13046-026-03730-6.



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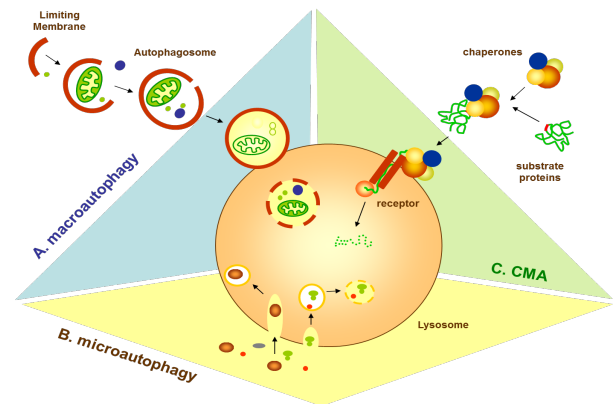
Autophagy in Aging and Age-related diseases

The **main focus** of our laboratory is understanding how proteins are transported into lysosomes for their degradation (*autophagy*) and how impaired autophagy contributes to aging and age-related diseases. A common feature of aging cells is the accumulation of abnormal or damaged proteins in their cytosol that impair cellular function. Protein accumulation results, at least in part, from impaired protein degradation with age. We have previously identified the activity of two selective pathways for the degradation of cytosolic proteins in lysosomes, known as chaperone-mediated autophagy (CMA), or in endosomes, known as endosomal microautophagy (eMI). **The main goal of our research** is to identify the defect(s) that lead to the decreased activity of CMA, eMI and other forms of selective autophagy with age and in age-related pathologies, and to determine if the correction of these defects in old organisms leads to improvement in healthspan.

Chaperone-mediated autophagy (CMA) and **endosomal-microautophagy (eMI)** are responsible for the degradation of a large part of the proteome. CMA is mainly activated under conditions of stress, such as nutrient deprivation and oxidative stress, whereas mammalian eMI is inhibited by nutrient deprivation. Substrate proteins are selectively recognized by cytosolic chaperones (hsc70 and cochaperones) that stimulate their binding either to a glycoprotein receptor in the lysosomal membrane (LAMP-2A) (in the case of CMA) or to lipids in the membrane of late endosomes (in the case of eMI).

Our current efforts are directed to:

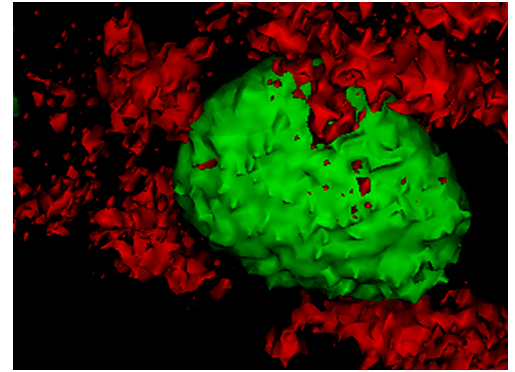
1. Characterization of the different components involved in chaperone-mediated autophagy and endosomal microautophagy.- We can isolate intact lysosomes and late endosomes from several tissues (liver, kidney and spleen) of rodents. For the identification of new CMA and eMI components we have developed a photoswitchable reporter (for CMA) and a split-venus based reporter (for eMI). We are using genome-wide CRISPRinterference screen, immunochemical approaches and a organelle proteomic approaches to complete the molecular dissection of these two pathways.



Autophagic pathways in mammalian cells

2. Understanding the consequences of the age-related defect in chaperone-mediated autophagy and endosomal-microautophagy.- We have generated conditional and inducible transgenic mouse models incompetent for CMA in different tissues and are investigating possible tissue-dependence differences in the requirements for functional CMA. We are also analyzing the cellular response to CMA blockage and the different compensatory mechanisms elicited. We have found that blockage of CMA leads to important alterations in cellular quality control and cellular metabolism and deficiencies in the response to different stressors. Mouse models with defective CMA display multi-tissue degeneration (neurodegeneration, retinal degeneration, muscle mass loss), metabolic alterations (fatty liver, dislipidemia, dysfunctional adipose tissue), loss of stemness, inadequate immune response, loss of circadian rhythms and higher propensity to oncogenic transformation.

3. Consequences of impaired autophagy in age related-disorders.- We have been analyzing changes in autophagy in three main groups of age-related diseases: neurodegeneration, metabolic disorders and cancer. By combining metabolic assays, cellular fractionation procedures and our in vitro lysosomal transport assays in different animal and cellular models of these diseases, we have found that autophagy malfunctions in conditions such as diabetes, obesity and also that the age-related decline in autophagy could be an early step in oncogenic transformation. We have identified a primary defect in CMA in some familial forms of Parkinson's disease and of tauopathies such as Alzheimer's disease. We are interested in identifying the primary defect, the compensatory mechanisms elicited and developing approaches to modulate autophagy with therapeutic purposes in age-related disorders



CMA mediates lipid (green) mobilization.

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- Harrison R, Gjergjova F, Pelka S, Macho-Gonzalez A, Chavda B, Lindenau K, Gazteluiturri Garcia A, Khawaja RR, Aguilan JT, Sidoli S, Kaushik S, Botbol Y, Cuervo AM*, Macian F. Chaperone-mediated autophagy is required for regulatory T cell function. *Nat Commun.* 2026 May 22. doi: 10.1038/s41467-026-73417-1
- Khawaja RR, Griego E, Lindenau K, Salek A, ... Tasset I, Kaushik S, Gan L, Castillo P*, Cuervo AM*. Chaperone-mediated autophagy regulates neuronal activity by sex-specifically remodeling the synaptic proteome. *Nature Cell Biology*, 2025 doi: 10.1038/s41556-025-01771-1
- Khawaja RR, Martín-Segura A, Santiago-Fernández O, Sereda R, Kaushik S, Cuervo AM*. Sex- and cell type-specific loss of chaperone-mediated autophagy across tissues with aging. *Nature Aging* 5(2):188-192 doi: 10.1038/s43587-024-00799-6.
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Reviews:

- Kaushik S, Tasset I, Arias E, Pampliega O, Wong E, Martinez-Vicente M, Cuervo AM. Autophagy and the Hallmarks of Aging. *Ageing Res Rev.* doi: 10.1016/j.arr.2021.101468, 2021
- Kaushik K, Cuervo AM. The coming of age of Chaperone-mediated autophagy. *Nat. Rev. Cell. Mol. Biol.* Doi: doi.org/10.1038/s41580-018-0001-6, 2018



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Epigenetic regulation of stem cells, development and cancer

We seek to understand the epigenetic mechanisms governing the biology of stem cells, development and cancer. We study how the DNA methylation and demethylation machineries reshape the epigenome and regulate stem cell biology during development and in disease. We integrate mouse genetics with cellular, molecular, biochemical and bioinformatics approaches to define epigenetic pathways and mechanisms regulating stem cell specification, self-renewal, pluripotency and multipotency. We focus on the Tet family of DNA dioxygenases (Tet1, Tet2 and Tet3) which promote DNA demethylation by converting 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and other derivatives. Tet enzymes also partner with chromatin regulatory complexes to promote gene activation and repression independent of their catalytic activity. We study how these dual functions of Tets regulate gene expression, and define their molecular and biological requirements in development and their implications in human diseases like cancer.

- *Embryonic stem cell (ESC) biology:* We study the enzymatic dependent and independent roles of Tets in gene regulation in ESCs and dissect their biological significance in pluripotency and development. We have identified noncatalytic roles of Tet enzymes in partnering with Sin3a and PRC2 for H3K27 modification. This is essential for establishing bivalency at developmental genes and is critical for silencing mesodermal and trophodermal genes as well as cell cycle progression in ESCs.
- *Neural and hematopoietic lineage specification during development:* We study how Tet enzymes regulate lineage specification and organogenesis during embryogenesis with a focus on the hematopoietic and neural lineages. We have shown that Tets regulate hematopoietic and neural stem cell specification, self-renewal and multipotency.
- *Hematopoietic stem cells (HSCs) and cancer:* We investigate how Tet2, which is commonly mutated in human blood malignancies, regulates HSCs. We have identified enzymatic and nonenzymatic requirements for Tet2 in regulating the myeloid and lymphoid lineages, respectively.

Our work defines novel mechanisms of epigenetic regulation by Tet enzymes and 5hmC in development. It has implications in identifying new markers and targets for stem cell applications and for treatment of diseases.

For more details on our research please visit our lab website: <https://www.dawlatylaboratory.com>

Selected publications:

- Ebert BC, MacArthur IC, Ketchum H, Musheev M, Christof Niehrs C, Suzuki M, and Dawlaty MM, Establishment of neuronal and glial competence of neural stem cells requires distinct enzymatic activities of TET enzymes, Stem Cell Reports, July (2025). PMID: 40749667
- Ketchum H*, Morganti C*, Yanase C, Ebert B, Ito, K**, and Dawlaty, MM**. Tet3 regulates hematopoietic stem cell homeostasis during embryonic and adult hematopoiesis. HemaSphere, May (2025). PMID: 40330736
- MacArthur IC, Ma L, Huang C, Bhavsar H, Masako S, and Dawlaty MM, Developmental DNA demethylation is a determinant of neural stem cell identity and gliogenic competence, **Science Advances**, August (2024) PMID: 39196941

- Ketchum HC, Masako S, and Dawlaty MM, Catalytic-dependent and independent roles of TET3 in the regulation of specific genetic programs during neuroectoderm specification, *Communications Biology*, April (2024), PMID: 38580843
- Flores JC, Sidoli S, and Dawlaty MM, Tet2 regulates Sin3a recruitment at active enhancers in embryonic stem cells, *iScience*, June (2023), PMID: 37456851
- Flores JC*, Ito Ky*(co-first), Huang C, Tang Q, Yanase C, Ito K** and Dawlaty MM**, Comparative analysis of Tet2 catalytic deficient and knockout bone marrow over time, *Exp. Hematology*, May (2023), PMID: 37225048.
- Chrysanthou S*, Tang Q* (co-first), Lee J, Taylor SJ, Zhao Y, Steidl U, Zheng D, Dawlaty MM, The DNA dioxygenase Tet1 regulates H3K27 modification and embryonic stem cell biology independent of its catalytic activity, *Nucleic Acid Research*, February (2022), PMID:35150568 PMCID: PMC8989540
- Ma L, Tang Q, Gao X, Lee J, Lei R, Suzuki M, Zheng D., Ito K, Frenette PS, and Dawlaty MM., Tet-mediated DNA demethylation regulates specification of hematopoietic stem and progenitor cells during mammalian embryogenesis, *Science Advances*, March (2022), PMID:35235365 PMCID: PMC8890710
- Ito Ky*, Lee J*, (co-first), Chrysanthou S, Zhao Y, Josephs K, Sato H, Teruya-Feldstein J, Zheng D, Dawlaty M.M.**, Ito K**, Non-catalytic roles of Tet2 are essential to regulate hematopoietic stem and progenitor cell homeostasis, *Cell Reports*, September (2019), PMID: 31484061 PMCID: PMC6750732
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Our group is interested in understanding how chronic systemic inflammation changes neutrophil biology and impacts outcomes after injury, infection, liver disease, and cancer. Neutrophils are known as the first leukocyte to be recruited to inflammatory sites. They fight infection, coordinate injury repair, support regeneration, and help restore immune balance, but they can also drive tissue damage, immunopathology, immune suppression, and tumor progression. Human disease is complex, many patients do not experience injury, infection, or cancer from a healthy starting point. The challenges humans face throughout their life often occurs in the setting of obesity, diabetes, cardiovascular disease, chronic liver disease, aging, autoimmune disease, environmental exposures, or genetic susceptibility, all known to be associated with chronic systemic inflammation. We ask how these pre-existing inflammatory states and context reshape neutrophil decisions, the programs that they regulate, and the disease outcomes. Our overall goal is to define how inflammatory history rewires neutrophils and impacts their response and role in injury, infection, and cancer. We aim to improve current therapeutic approaches by identifying mechanisms that can be redirected to improve healing, restore immune balance, enhance host defense, and strengthen anti-tumor immunity in high-risk patients which experience disease in a complex inflammatory state.

Severe Injury, Polytrauma, and Neutrophil Prioritization | We discovered that after injury to multiple tissues, neutrophils do not respond randomly. Instead, they appear to prioritize inflammatory responses and resolution in crucial organs such as the liver and central nervous system. This matters because survival after severe injury may depend not only on how strongly the immune system responds, but on whether neutrophils respond to the right tissues, at the right time, and resolve inflammation appropriately. Ongoing work examines neutrophil prioritization during polytrauma and how systemic inflammatory stress disrupts this coordinated response.

Metainflammation, Burn Injury, Regeneration, and Infection Susceptibility | We study how pre-existing metabolic inflammation changes neutrophil responses to severe injury, including burn and polytrauma. Using zebrafish models of diet-induced metabolic disease, burn, tissue injury, and infection, we ask how chronic inflammatory stress alters neutrophil behavior and how these changes correlate with tissue regeneration, wound repair, susceptibility to secondary infection, sepsis-like outcomes, and survival. Ongoing work investigates burn injury, regeneration, and neutrophil responses under metabolic inflammatory stress.

Metabolic Inflammation, Liver Disease and Cancer Progression | A major focus of the lab is to understand how Western-type diets and chronic metabolic inflammation alter neutrophil biology during liver disease progression. These studies ask how diet-induced inflammation changes neutrophil recruitment, resolution, liver injury, and inflammatory mediators such as GDF15 as disease progresses from early metabolic dysfunction toward more severe liver pathology. Using zebrafish genetic and xenograft liver cancer models, we also study how metabolic disease reshapes the liver tumor microenvironment by reshaping neutrophils generating distinct tumor immune microenvironment from non-metabolic associated-HCC. We are currently investigating the GDF15–neutrophil axis as a mechanism of immune suppression and therapeutic resistance in liver cancer.

Computational Neutrophil Behavior Signatures | Across these projects, we are developing computational approaches to define how neutrophils behave in living animals under healthy and chronically inflamed conditions. Our goal is to build whole-animal neutrophil behavior signatures that distinguish protective from harmful inflammatory responses and link cell behavior to outcomes such as regeneration, infection susceptibility, tumor progression, and survival (Joaquin Canton Sandoval). Zebrafish provide a powerful platform for this work because they allow us to visualize neutrophils in living animals at whole-organism scale and single-cell resolution. We combine intravital imaging, photoconversion, genetic and pharmacologic perturbation, behavioral analysis, flow cytometry, single-cell approaches, proteomics, xenografts, and computational analysis to connect neutrophil dynamics with mechanism and outcome.



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The main focus of our laboratory is the identification, dissection and targeting of signaling pathways critical for neoplastic transformation and tumor progression. We utilize genetically engineered mouse models and relevant cell culture systems to identify and deconstruct novel signaling cascades altered during neoplastic transformation and progression to undifferentiated cancer with the goal of designing and testing in vivo innovative, rationally designed therapeutic approaches for incurable tumor types.

We utilize the thyroid gland as our main model system and have recently added Ewing sarcoma as an additional tumor model.

Current research areas:

- **Beyond AKT: additional PI3K-regulated pathways in thyrocyte transformation.**

PI3K pathway activation, via mutation/amplification of *PIK3CA*, or *PTEN* mutation/silencing, is a frequent event in thyroid cancer. However, our data suggest that the linear PI3K-PDK1-AKT pathway is not sufficient to drive thyroid transformation, and that additional PDK1-dependent pathways, including a novel one leading to activation of SGK1, are absolutely required for tumor development and thus may represent valid therapeutic targets.

- **mTOR activation as a key hub for RAS-mediated transformation.**

NRAS-mutant anaplastic thyroid cancer (ATC) often shows concomitant dysregulation of the PTEN/PI3K/AKT pathway. We have developed a novel *Nras/Pten/Tp53* mouse model that recapitulates the genetic and histological features of ATC. Interestingly, *Nras*^{Q61R} alone is not sufficient to transform thyroid epithelial cells. Concomitant *Pten* deletion (or *Pik3ca* activation) and *Tp53* inactivation lead to the development of aggressive ATC. We are defining the role of mTOR as a key signaling node that allows full RAS transforming activity.

- **Novel synthetic lethalties in ATC and Ewing sarcoma.**

We have found that mouse and human ATC, as well as Ewing sarcoma, consistently upregulate genes encoding enzymes involved in the one-carbon metabolic pathway, which uses serine and folates to generate both nucleotides and glycine. Genetic and pharmacological inhibition of one-carbon metabolism leads to significant inhibition of cell proliferation and colony forming ability, which is primarily caused by depletion of the purine pool and consequent replicative stress. Genetic depletion of one-carbon metabolism genes or pharmacological inhibition of one-carbon metabolism enzymes dramatically impair tumor growth in vivo, in mouse models of ATC and Ewing sarcoma. We are currently defining and characterizing the mechanisms through which small molecule inhibitors of additional, rationally selected pathways induce conversion of the cytostatic activity of one-carbon metabolism inhibitors into cytotoxic combinations, leading to synthetic lethality.

Selected Publications

- Orlacchio, A., Ranieri, M., Brave, M., Antico Arciuch V., Forde, T., De Martino, D., Anderson, K.E., Hawkins, P., and **Di Cristofano, A.** SGK1 is a critical component of an AKT-independent pathway essential for PI3K-mediated tumor development and maintenance. *Cancer Res.*, 77: 6914-6926, 2017.
- Sugarman A.J., Huynh L.D., Shabro A., **Di Cristofano A.** Anaplastic Thyroid Cancer Cells Upregulate Mitochondrial One-Carbon Metabolism To Meet Purine Demand, Eliciting A Critical Targetable Vulnerability. *Cancer Lett.* 568: 216304, 2023.
- Zirpoli, S., Copperman, N., Patel, S., Forrest, A., Hou, Z., Matherly, L.H., Loeb, D.M., **Di Cristofano A.** One-Carbon Metabolism Inhibition Depletes Purines and Results in Profound and Prolonged Ewing Sarcoma Growth Suppression. *Cancer Res. Commun.*, 5: 1298, 2025.

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The liver has a remarkable capacity to restore mass and function following injury or surgical resection in both rodents and humans. Despite this regenerative ability, liver disease remains a growing global health burden, and transplantation –the only effective therapy for severe liver failure– is limited. Our research program focuses on the spatial regulation of messenger RNAs in the liver to better understand fundamental molecular events that allow liver cells rebuild the organ during regeneration. We develop advanced imaging technologies to visualize individual RNA molecules within the intact mouse tissue while preserving native cellular architecture. This approach enables us to investigate of how hepatocytes coordinate regeneration in space and time revealing aspects of liver biology that are masked by conventional methods.

Current Projects*Spatial regulation of ki67 mRNA in regenerating hepatocytes*

Menn'h Hasheesh

Spatiotemporal plasticity of hepatocytes in response to nutritional changes

Dr. Junichi Okada (co-mentored postdoc in Dr. Pessin lab)



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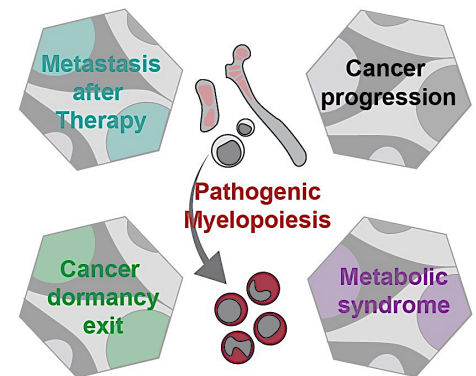
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LAB OF REACTIVE MYELOID CELL BIOLOGY – SAMARTH HEGDE, PH.D.

Our lab is passionate about understanding how development of myeloid cells - chiefly monocytes and neutrophils - is co-opted by tumor inflammation to suppress anti-tumor immune responses, and how myeloid responses are distorted after rounds of genotoxic therapies (e.g.– chemotherapy, radiation).

We have a particular interest in dissecting the early education of myeloid cell progenitors in bone marrow and/or spleen by inflammation. Combining high-dimensional longitudinal profiling of patient tissues with mechanistic studies in mouse models of cancer, our lab aims to understand how inflammatory cues alter the genetic, epigenetic, and metabolic wiring during hematopoietic development to drive myelopoiesis (myeloid-biased expansion). Our preclinical lab will work closely with clinician-scientists at Einstein and beyond, developing and testing the next generation of myeloid cell-targeted immunotherapies for solid tumors such as pancreatic cancer.



Some questions we are interested in:

- **“How does tumor-associated myelopoiesis impact BM cells epigenetically?”**

Our prior work has started revealing the impact of cancer inflammation on chromatin state of myeloid progenitors. We are now interested in understanding the mechanistic details of how tumor cues alter chromatin and/or DNA methylation at consequential gene loci, and how long-lasting these changes are. We are developing cutting-edge assays to integrate knowledge from transcriptome, epigenome, DNA architecture, with a focus on molecular pathways involved in stress regulation, RNA quality control, and proteostasis.

- **“What are the metabolic consequences of oxidative stress during tumor-associated myelopoiesis?”**

Distal tumors can reshape bone marrow homeostasis by disrupting HSPC proteostasis (quality control of protein synthesis/degradation) and escalating oxidative stress. Our research focuses on how these metabolic maladaptations in myeloid progenitors drive downstream gene dysregulation, hyperproliferation, lineage fate transitions, and spatial mislocalization. By leveraging low-input metabolomics with an emphasis on ER and mitochondrial dynamics, we aim to dissect how tumor-driven inflammation re-engineers the metabolic landscape across both the bone marrow and peripheral tissue sites.

- **“How do acute or chronic genotoxic therapies impact reactive myelopoiesis?”**

Genotoxic therapies such as chemotherapy and systemic radiation can impose severe physiological strain on the bone marrow in patients, and oxidative stress regulators such as NRF2 emerge as the primary arbiters of hematopoietic recovery and myeloid ‘rebound’. Leveraging mouse models and primary human samples, our lab is extremely interested in understanding the short-term (immunoparalysis) and long-term consequences (innate memory of immunosuppression) of such therapies on BM progenitor biology and BM niche architecture, with implications for subsequent susceptibility to secondary cancers or infections.

- **“Does myelopoiesis in response to therapies influence met dissemination and dormancy exit?”**

Post-therapy reactive myelopoiesis is important to renewing the host immune system but can also inadvertently trigger the awakening of dormant cancer cells or promote metastatic seeding. There is clear clinical evidence

that chemotherapies can result in a myeloid 'rebound', releasing a surge of immature immunosuppressive monocytic/neutrophilic cell states (often termed MDSCs). We are very excited to be working within the larger Cancer Dormancy Institute ecosystem to address the systemic interplay between myeloid rebound and subsequent metastatic/relapse risk. The ultimate goal is to develop myeloid targeting strategies that complement existing therapies to limit relapse risk while sparing homeostatic function.

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Research in the Hegde lab spans themes of hematopoietic stem cell and progenitor development, systems physiology, stress-associated proteostasis, and tumor microenvironment biology.

Selected Publications:

- **Hegde S**, Giotti B[^], Soong BY[^], Halasz L, Le Berichel J, Schaefer MM, Kloeckner B, Mattiuz R, Park MD, Magen A, Marks A, Belabed M, Hamon P, ..., Kim-Schulze S, Flores RM, Kaufman AJ, Ginhoux F, Buenrostro JD, Josefowicz SZ, Tsankov AM, Marron TU, Ma S, Brown BD, Merad M. Myeloid progenitor dysregulation fuels immunosuppressive macrophages in tumours. *Nature*. 2025 Sep 10. doi: 10.1038/s41586-025-09493-y. Epub ahead of print. PMID: 40931076.
- Park MD, Le Berichel J, Hamon P, Wilk CM, Belabed M, Yatim N, Saffon A, Boumelha J, Falcomatà C, Tepper A, **Hegde S**, ... Vabret N, Brown BD, Marron TU, Merad M. Hematopoietic aging promotes cancer by fueling IL-1 α -driven emergency myelopoiesis. *Science*. 2024 Sep 5:eadn0327. doi: 10.1126/science.adn0327. PMID: 39236155.
- LaMarche NM, **Hegde S**[^], Park MD[^], Maier BB, Troncoso L, Le Berichel J, Hamon P, Belabed M, ... Passequé E, Kim-Schulze S, Brown BD, Hirsch FR, Kim BS, Marron TU, Merad M. An IL-4 signalling axis in bone marrow drives pro-tumorigenic myelopoiesis. *Nature*. 2023 Dec 6. doi: 10.1038/s41586-023-06797-9. PMID: 38057662.
- Park MD*, Reyes-Torres I*, LeBerichel J, Hamon P, LaMarche NM, **Hegde S**, Belabed M, ... Colonna M, Marron TU, Merad M. TREM2 macrophages drive NK cell paucity and dysfunction in lung cancer. *Nature Immunology*. 2023 May;24(5):792-801. doi: 10.1038/s41590-023-01475-4. Epub 2023 Apr 20. PMID: 37081148.
- **Hegde S**, Krisnawan VE, Herzog BH, Zuo C, Breden MA, Knolhoff BL, Hogg GD, Tang JP, Baer JM, Mpyo C, Lee KB, Alexander KA, Rogers BE, Murphy KM, Hawkins WG, Fields RC, DeSelm CJ, Schwarz JK, DeNardo DG. (2020) Dendritic Cell Paucity Leads to Dysfunctional Immune Surveillance in Pancreatic Cancer. *Cancer Cell*; Mar 16 2020. PMID: 32183949
- Jiang H, **Hegde S**, Knolhoff BL, Zhu Y, Herndon JM, Meyer MA, Nywening TM, Hawkins WG, Shapiro IM, Weaver DT, Pachter JA, Wang-Gillam A, DeNardo DG. (2016). Targeting Focal Adhesion Kinase Renders Pancreatic Cancers Responsive to Checkpoint Immunotherapy. *Nature Medicine*; July 4 2016. PMID: 27376576

Selected Reviews:

- Park MD, Belabed M, Chen ST, Hamon P, **Hegde S**, ... Merad, M. (2023) On the Biology and Therapeutic Modulation of Macrophages and Dendritic Cells in Cancer. *Annual Reviews of Cancer Biology* Vol. 7:291-311 April 2023 [Review]
- **Hegde S**^{*}, Leader AM^{*}, Merad M. (2021) MDSC: Markers, development, states, and unaddressed complexity. *Immunity*. 2021 May 11. [Review] PMID: 33979585 *co-first author
- **Hegde S**. (2020) Pancreatic Cancer Immuno-oncology in the Era of Precision Medicine. *Indian Journal of Surgical Oncology*; Aug 2020, 1-10. [Review] PMID: 33994737
- Vabret N, Britton GJ, Gruber C, **Hegde S**, Kim J, ... Samstein RM, Sinai Immunology Review Project. Immunology of COVID-19: current state of the science. *Immunity*; May 5 2020. [Review] PMID: 32505227
- Jiang H, **Hegde S**, DeNardo DG. (2017) Tumor-associated fibrosis as a regulator of tumor immunity and response to immunotherapy. *Cancer Immunology Immunotherapy*; 1-12. [Review] PMID: 28451791



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A genetic model for Endosomal Microautophagy

Aging-associated diseases are an increasing socio-economic burden despite efforts to improve healthspan. Pathologies that cause degeneration of the nervous system are particularly devastating, and in many cases are associated with decline in proteostasis and lysosomal malfunction. Prime examples are Parkinson and Alzheimer's disease that are characterized by accumulation of insoluble protein aggregates that lead to neuronal decay. Autophagy delivers cytosolic components to lysosomes for degradation and is thus essential for cellular homeostasis and to cope with different stressors. Macroautophagy (MA) can selectively degrade organelles or aggregated proteins, but selective degradation of single proteins has only been described for Chaperone-mediated autophagy (CMA) and endosomal Microautophagy (eMI). These two autophagic pathways, described to date only in mammals, are specific for proteins containing KFERQ-related targeting motifs. In collaboration with the Cuervo lab, we have established a genetic model for eMI in *Drosophila in vivo*. We are thus for the first time able to perform genetic screens for regulatory components of eMI, this only recently identified form of autophagy about which barely anything is known.

Lysosomes are also important regulatory hubs that integrate nutritional signals and participate in lipid metabolism. We have recently characterized *Drosophila* Lamp1, a bona fide homolog of the mammalian LAMP1/2. *Lamp1* deficiency results in an increase in the number of acidic organelles in the fat body, strongly suggesting defects in the regulation of the pH of the endolysosomal system. Furthermore, *Lamp1* mutant larvae have elevated levels of sterols and diacylglycerols, indicating functions of Lamp1 in lipid transport beyond sterols. Significantly, these phenotypes are similar to loss of glucocerebrosidase, the gene causing Gaucher disease and a major risk factor for Parkinson. Indeed, *Lamp1* mutations enhance fly PD models!

Rho kinase and its effector Cmb in spermiogenesis

During development, genetic and molecular programs control the differentiation of various cell types and orchestrate their morphogenetic behaviors to form organs with specific functions. Organogenesis requires the coordination of cell polarity, cellular movement, and cell shape, driven by intercellular signaling and the tissue-specific interpretations of these signals. Traditionally, Rho kinase (Rok) functions as effector of the non-canonical Wnt/Frizzled PCP pathway during gastrulation and neural tube formation. In a systematic, genome-wide screen, we have identified the previously uncharacterized Comover, an intrinsically disordered protein as novel Rok substrate. Significantly, our follow up studies have identified a novel and unanticipated role of Rok and Cmb during spermiogenesis. We currently address how, downstream of Rok, Comover orchestrates the transition between axoneme elongation and sperm individualization by coordinating the actin and microtubule cytoskeletons with the plasma membrane, thus ensuring proper resolution of the syncytial spermatids into functional sperm that are encapsulated by their own plasma membrane. The biomedical significance of sperm individualization is further exemplified by the presence of multiciliate spermatozoa and spermatids with unresorbed cytoplasm in infertile men.

Our goal is to use *Drosophila* as model system to address fundamental questions that are relevant for development and disease.

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Selected Publications:

- Steinhauer, J. , Statman, B, Fagan, J., Borck, J., Surabhi, S., Yarikipati, P., Edelman, D., **Jenny, A.** (2019) Combover interacts with the axonemal component Rsp3 and is required for sperm individualization. **Development**, 146(17). pii: dev179275. doi: 10.1242/dev.179275
- Mukherjee, A., Koga, H., Cuervo, AM., **Jenny, A.** (2016) Selective endosomal microautophagy is starvation inducible in *Drosophila*. **Autophagy**, 12 (11), 1984-1999.
- Mesquita, A., Glenn, J., **Jenny, A.** (2020) Differential activation of eMI by distinct forms of cellular stress. **Autophagy**, doi: 10.1080/15548627.2020.1783833.
- Chaudhry, N.*, Sica, M.*, Surabhi, S.*, Sanchez Hernandez, D., Mesquita, A., Selimovic, A., Riaz, A. Lescat, L., Bai, H., Macintosh, G, C.*, **Jenny, A***. (2022) Lamp1 mediates lipid transport, but is dispensable for autophagy in *Drosophila*. **Autophagy** 10.1080/15548627.2022.2038999
- Rahmani, Z. *, Surabhi, S., Rojo-Cortés, F., Dulac, A., **Jenny, A.***, Birman, S.* (2022) Lamp1 Deficiency Enhances Sensitivity to α -Synuclein and Oxidative Stress in *Drosophila* Models of Parkinson Disease. **Int J Mol Sci**, DOI: 10.3390/ijms232113078.
- Yarikipati, P., Jonusaite, S., Pleinis, J. M., Dominicci Cotto, C., Sanchez-Hernandez, D., Morrison, D. E., Goyal, S., Schellinger, J., Penalva, C., Curtiss, J., Rodan*, A. R., **Jenny, A.*** (2023) Unanticipated domain requirements for *Drosophila* Wnk kinase in vivo. **PLoS Genet** 19, <https://doi.org/10.1371/journal.pgen.1010975>
- Dutta, D., Kanca, O., Shridharan, R., Marcogliese, P., Steger, B., Morimoto, M., Frost, G., Macnamara, E., Undiagnosed Diseases Network, Wangler, M., Yamamoto, S., **Jenny. A.**, Adams, D., C. Malicdan, M., Bellen, H. (2024) Loss of the endoplasmic reticulum protein TMEM208 affects cell polarity and multicellular development. **PNAS** <https://doi.org/10.1073/pnas.2322582121>

Selected reviews and books

- Rodan, A.R., **Jenny, A.** (2017) WNK kinases in development and disease. Edited by Jenny, A. **Curr. Top. Dev. Bio.** 123:1-47.
- Dominicci Cotto, C., **Jenny, A.** (2026) 'From Syncytium to Sperm: Coordinated Membrane and Cytoskeletal Remodeling in *Drosophila* Spermiogenesis' Edited by Qui, H. **Curr. Top. Dev. Bio.** DOI: 10.1016/bs.ctdb.2026.03.005
- Sakai, Y., Behrends, C, Debnath, J., Izumi, M., **Jenny, A.**, Molinari, M., Nakamura, S., Oku, M., Otegui, MS., Santambrogio, L., Shen, H., Taguchi, T., Thumm, M., Ushimaru, T., Xie, Z., Cuervo, AM., Reggiori, F. (2026) Microautophagy: Current understanding of its molecular mechanisms and functions. **Autophagy Reports**, DOI: 10.1080/27694127.2026.2626661



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Ionizing radiation (IR) introduces time dependent functional defects in cell-mediated immunity and elevated Reactive Oxygen Species (ROS) production is the leading cause for IR associated injury that ultimately results in cell death. Worthy of note is that the radiation damage associated ROS can be countered via ROS-initiated redox signaling ('sublethal dose' of radiation). Cells however, display different redox sensitivities and distinctive defense mechanisms, predicting that survivors need to achieve a cell type dependent fine balance between ROS/redox states. Not surprisingly, supplementation with antioxidants of cancer patients undergoing radiotherapy can be detrimental if adequate antioxidant status exists but beneficial to those with antioxidant deficiencies. A literature review revealed that details of radiation responses over time and in this context were still sparse and led us to conclude that improved understanding of cellular mechanisms would greatly facilitate the development of radiation countermeasures.

ROS related activation of NFE2L2 (best known as NRF2), is pivotal for regulation of an antioxidant defense. The mechanisms underlying the NRF2-antioxidant response however, is complex and includes multiple interaction points with various other molecular pathways (Anuranjani and Bala 2014). To map this cellular network effectively, we characterized ROS/NRF2 activation over time and combined quantitative mass spectrometry (MS) with bioinformatics to monitor radiation-induced changes using Jurkat cell line as a model system.

Results of our proteomics analysis coupled to an in silico-based approach identified several networks, embedded in 7 trendlines, with some outcomes underscoring the importance of radiation dose. Both protein synthesis machinery (ribosomal proteins) and clearance pathways (autophagy and proteasomes) were simultaneously downregulated, indicating a severe threat to proteostasis. Also observed was a general failure to upregulate either NRF2 or NRF2 targets in general (i.e. glutathione levels declined in proportion to radiation dose). Without functional NRF2 activation and upregulation of detoxifying enzymes (i.e. persistently low glutathione (GSH) production), this redox imbalance predicts high vulnerability to oxidative stress. To effectively map if cells could increase lysosomal biogenesis to augment autophagic clearance, we evaluated the CLEAR (Coordinated Lysosomal Expression and Regulation) gene network. TFEBexplorer was used to evaluate CLEAR gene network driven by the master gene transcription factor EB (TFEB), which regulates lysosomal biogenesis and function (Palmieri, Impey et al. 2011, De Cegli, Carrella et al. 2022). According to this web-tool, many of the genes upregulated in our proteome analysis, correspond to those that respond to TFEB induction. In parallel, aspects of mitochondrial biogenesis were also maintained or elevated. An unanticipated finding was the prediction of a complement system's activity inside cells, the complosome pathway. The long prevailing view that complement is a serum-localized danger sensor has more recently been updated to include the complosome, whose activation can boost mitochondrial and lysosomal function (Arbore, Kemper et al. 2017, Rahman, Singh et al. 2021, Afzali, Singh et al. 2025).

Thus far, the paradoxical dynamic of delayed effects of radiation exposure in our system suggest a sacrifice/modification of peak function for long-term viability. T lymphocyte survival of therapeutic sublethal doses of radiation has been documented and is known to contribute to 'exhaustion'—detail at organellar levels remains considerably less well understood (Ellsworth, Yalamanchali et al. 2022, Battistello, Hixon et al. 2023, Prades-Sagarra, Yaromina et al. 2024, Sandul, Al-Hamami et al. 2026). To fill that unmet need, our current characterizations have delineated a multimodal panel of biomarkers with connections to nucleus, ER, mitochondria and lysosomes. An anticipated outcome is that targeted evaluations of these organelles will serve as a foundation for novel functional readouts and a better design of interventions.



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The work in our laboratory is focused on bone sarcoma metastasis, with projects involving every point along the metastatic cascade.

1. Metabolic targeting of the primary tumor: In collaboration with Dr. Antonio Di Cristofano, we are leveraging our finding of a synthetic lethal relationship between the replicative stress intrinsic to Ewing sarcoma cells and their dependency on 1-carbon metabolism pathways to develop a biologically-based novel treatment for chemotherapy-resistant tumors.

2. The role of the RNA helicase, DDX3, in Ewing sarcoma: In collaboration with Dr. Evris Gavathiotis, we are exploring the synthetic lethal effect of simultaneously inhibiting DDX3 and mitofusin-2 and how this alters mitochondrial dynamics and mitochondrial function. In a related project, we have demonstrated the role of DDX3 in preventing the accumulation of cytoplasmic nucleic acids, a byproduct of replicative stress, which results in a “cold” tumor immune microenvironment and are exploring how inhibiting DDX3 might reshape the TIME and support immunotherapeutic approaches to treatment of both Ewing sarcoma and osteosarcoma.

3. Tumor microenvironment of metastasis: In collaboration with Dr. Maja Oktay, we are investigating the role of a 3-cell assembly consisting of a Menainv-expressing tumor cell, a Tie2-high expressing macrophage, and an endothelial cell (termed the Tumor Microenvironment of Metastasis) in mediating Ewing sarcoma tumor cell dissemination, and how inhibiting the function of TMEM-associated macrophages can prevent tumor cell dissemination, especially that which is promoted by the counterintuitive pro-inflammatory effects of neoadjuvant chemotherapy.

4. Preventing osteosarcoma metastasis: We found that inhibiting the canonical Wnt signaling antagonist, DKK-1, can induce osteoblastic differentiation in osteosarcoma cells and prevent metastasis. Future work will identify key signaling pathways regulated by DKK-1 and develop novel therapeutic compounds to enable therapeutic translation in high-risk patients.

5. Targeting disseminated tumor cells: We have found that disseminated Ewing sarcoma cells are uniquely vulnerable to ferroptosis, and that inhibition of polyamine biosynthesis with the ODC inhibitor, DFMO, triggers ferroptosis and limits metastatic outgrowth. Ongoing work will clarify the global metabolic changes induced by DFMO and identify mechanisms of resistance to DFMO that can be exploited clinically.



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Specialized tissue functions depend on cells building architectures that differ from generic epithelial or endothelial organization. Our research asks how cells interpret extracellular-matrix, adhesion, and mechanical cues to establish tissue-specific morphology and polarity, how these architectures are maintained during normal tissue use, and why they fail during injury, disease, and aging. We address these questions in liver sinusoidal endothelial cells, hepatocytes, and epithelial stress-response systems. Our studies use cell-biological approaches in primary cells, quantitative live- and fixed-cell imaging, and ultrastructural analysis to connect molecular signaling with membrane organization, cytoskeletal architecture, and cell function.

ECM-integrin control of liver sinusoidal endothelial fenestration: The liver sinusoidal endothelium contains transcellular pores, or fenestrae, that permit unusually efficient exchange between the blood and hepatocytes. Fenestrae are lost early in chronic liver disease and during aging, as liver sinusoidal endothelial cells acquire a capillary-like state and the normally sparse extracellular matrix becomes enriched in basement-membrane components. The central question is whether this matrix remodeling merely accompanies de-fenestration or actively instructs it. We are investigating how laminin-binding integrins and other ECM receptors regulate the membrane and cytoskeletal organization required for fenestra formation, and whether persistent ECM-integrin signaling prevents mature sinusoidal endothelial identity. Defining this relationship could explain why fenestration is difficult to restore once the sinusoidal niche has become fibrotic or aged and identify points at which the loss of endothelial specialization might be reversed.

ECM and adhesion control of hepatocyte polarity: Hepatocytes organize a branched bile-canalicular network between neighboring cells while simultaneously maintaining broad exchange surfaces facing the blood. This architecture is fundamentally different from the simple ducts and acini formed by most epithelia, yet the signals that specify it remain incompletely understood. Our work asks how the unusual ECM environment of the healthy liver cooperates with integrin and cell-cell adhesion signaling to orient hepatocyte junctions and build a continuous canalicular network. We further ask how fibrosis-associated changes in matrix composition, rigidity, and integrin expression distort this polarity program. The goal is to determine how disease converts a normally adaptive dialogue between cell-matrix and cell-cell adhesions into junctional arrangements that fragment or misdirect bile canaliculi, thereby impairing bile secretion and contributing to cholestasis and loss of liver function.

Borg5 control of epithelial architecture under mechanical stress: Cells in intact epithelia are continually compressed, stretched, and rearranged as tissues change density or respond to injury. We identified Cdc42EP1/Borg5, a regulator of septin and actin organization, as a candidate coordinator of the cellular response to these forces. We ask how junctional or mechanical stress controls Borg5 abundance and distribution, how Borg5 preserves apical surface organization, and why its loss compromises epithelial shape. A second, unexpected question is how Borg5 protects nuclear integrity and limits DNA damage through a mechanism that may be separable from its role in septin-actin organization. By resolving these functions, we aim to understand how epithelial cells buffer routine mechanical stress and why failure of this protective system may promote persistent injury, defective repair, and age-associated tissue decline.

Selected Publications

- Cohen D, Lázaro-Diéguez F, and Muesch A. Bile canaliculi formation in primary hepatocytes requires $\alpha 1\beta 1$ integrin-dependent adherens junction re-organization. *Journal of Cell Science* 2025;138(23):jcs264412. doi:10.1242/jcs.264412.

- Cohen D, Fernandez D, Lázaro-Diéguez F, Überheide B, and Müsch A. Borg5 restricts contractility and motility in epithelial MDCK cells. *Journal of Cell Science* 2024;137(23):jcs261705. doi:10.1242/jcs.261705.
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- Cohen D, Rodriguez-Boulan E, and Müsch A. Par1 promotes a hepatic mode of apical protein targeting in MDCK cells. *Proceedings of the National Academy of Sciences USA* 2004;101:13792-13797.

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In the Petsakou lab, we aim to understand how the crosstalk between the nervous and intestinal system restores tissue homeostasis and prevents diseases. We are interested in identifying key neuro-regulated mechanisms that help the gut heal after injury and prevent the development of chronic intestinal disorders like cancer. Our studies address three basic unanswered questions:

1) Which mechanisms tilt the scales between wound healing and tumorigenesis?

A fundamental unresolved question in regeneration is how a tissue returns to homeostasis after injury. Answering this question is vital not only for understanding how to heal tissues but also to protect against systemic effects that could worsen disease progression in complex disorders like cancer. Previously, we discovered that in the fly gut, Ca^{2+} currents across the intestinal epithelium promote homeostasis after injury, while loss of these epithelial Ca^{2+} currents promotes ISC over-proliferation and makes the gut prone to hyperplasia. By combining fly genetics and mouse intestinal organoids, together with advanced microscopy, high-resolution multiplexed immunofluorescence, and multi-omic approaches, we will unravel downstream ion channels, pumps, and exchangers that guide conserved molecular pathways towards either wound healing or tumorigenesis.

2) How do peripheral neurons impact intestinal tumor growth?

How peripheral neurons impact cancer progression is a vital unresolved question in cancer neuroscience. It is proposed that the tumor microenvironment reprograms the function of peripheral neurons, but the underlying mechanisms remain unclear. Previously, we characterized a specific small population of cholinergic enteric neurons in the fly, which we named ARCENs (Anti-inflammatory Recovery Specific Enteric Neurons), that sense inflammatory cytokines and, in response, promote rapid repair of the intestinal epithelium and transition to homeostasis after injury. We will take advantage of the direct signaling between ARCENs and the gut, using it as a simple *in vivo* bidirectional model to identify fundamental mechanisms governing neuro-gut communication during tumor development. Utilizing the powerful genetic toolkit available in *Drosophila*, we will perform sophisticated thermo- and opto-genetic perturbations and perform spatial transcriptomics to identify neuronal changes during intestinal tumor growth. Overall, we will unravel basic mechanisms used by the gut tumor microenvironment to hijack the function of peripheral neurons.

3) How do changes in feeding behavior alter cancer progression?

Cancer cachexia (CC) is a complex, lethal syndrome characterized by organ wasting. Having a comprehensive understanding of the early events before the onset of organ wasting is crucial for the etiology and diagnosis of this syndrome. Anorexia (loss of appetite) is an early sign of CC; however, early CC-linked mechanisms responsible for changes in feeding behavior remain unclear. We previously discovered that inflammation and low insulin signaling impair feeding pathways in the fly brain and cause early appetite changes, making the fly prone to protein malnutrition, which worsens organ wasting. Building on these findings, we will utilize *Drosophila*, which is a powerful system to study organ communication, tumor growth, and feeding behavior, to decipher how mechanisms driving amino-acid feeding imbalance guide early aspects of organ wasting that could be used as potential diagnostic markers and therapeutic targets.

Selected Publications

- Petsakou, A.*, Filine, E., Li, M., Chen, Y., Zheng, A., and Perrimon, N*. Tumor-induced orexigenic imbalance lowers protein appetite and drives early organ wasting symptoms. *Nature Communications* DOI:10.1038/s41467-026-70074-2 (2026). (*corresponding author)
- Petsakou, A.*, Liu, Y., Liu, Y., Comjean, A., Hu, Y., and Perrimon, N*. Cholinergic neurons trigger epithelial Ca^{2+} currents to heal the gut. *Nature* 623, 122-131. DOI: 10.1038/s41586-023-06627-y. (2023). (*corresponding author)
- Petsakou, A.*, and Perrimon, N*. Bioelectric regulation of intestinal stem cells. *Trends in Cell Biology* DOI: 10.1016/j.tcb.2022.10.003. (2023). (*corresponding author)

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Coronary artery disease is the single largest contributor to global mortality, accounting for ~9 million deaths each year. Acute coronary syndromes, commonly known as heart attacks, are typically caused by complications of non-occlusive atherosclerotic plaques in coronary arteries that lead to thrombosis. The resulting thrombus can grow and occlude the lumen of the vessel, causing ischemia that, if prolonged, leads to myocardial infarction.

The most common complication is plaque rupture, which accounts for ~60% of heart attacks and is characterized by disruption of the fibrous cap. Smooth muscle cells (SMCs) form and maintain the fibrous cap; however, the underlying molecular mechanisms governing these processes are not fully understood. The second most frequent complication is plaque erosion, which accounts for ~40% of cases and is characterized by the loss of endothelial cells (ECs) from the inner surface of the plaque while the fibrous cap remains structurally intact. Compared with plaque rupture, the pathophysiology of plaque erosion remains poorly understood. Few extrinsic factors that act on ECs and lead to EC detachment or cell death have been proposed, while mechanisms of EC repair have not yet been explored.

Our research addresses these major knowledge gaps by studying human tissue samples, genetically modified mice, and primary mouse and human vascular cells in culture. To investigate the underlying mechanisms, we employ transcriptomic, proteomic, and metabolomic analyses, together with a broad range of molecular, cellular, and biochemical approaches. Our goal is to identify novel molecular targets that will enable new strategies to prevent or treat acute coronary syndromes.

Studies relevant to plaque rupture: Because SMCs are critical for maintaining the fibrous cap, we are investigating novel regulators of SMC biology. We previously found that the atypical cadherin FAT1 limits SMC proliferation and neointimal formation following vascular injury, in part by suppressing mitochondrial respiration. We are currently studying FAT1 and a mitochondria-specific form of its intracellular domain in mouse models of atherosclerosis. Preliminary results suggest that SMC-specific deletion of FAT1 leads to thicker fibrous caps. In parallel, we are investigating the role of SMC respiration in vascular remodeling. We have found that animals lacking NDUFS4, a respiratory complex I subunit, specifically in SMCs exhibit reduced neointima formation following vascular injury. These findings provide a strong rationale for assessing the role of SMC respiration in atherosclerosis. Finally, we are exploring the role of UTY, a Y chromosome gene, as a novel regulator of SMC biology.

Studies relevant to plaque erosion: Because EC biology is central to plaque erosion, we are investigating EC-intrinsic factors that may influence the susceptibility of these cells to undergo cell death or participate in repair. Our research focuses on mitochondrial mechanisms and cytoskeletal dynamics, including the roles of mitochondrial respiratory complex I and BORG proteins. We are studying these factors in vascular homeostasis, endothelial repair following injury in normal and atherosclerotic arteries, atherosclerosis progression, and spontaneous atherosclerotic plaque erosion.

Lab website: <https://sites.google.com/view/riascos-bernal-laboratory/home>

Selected Publications

- Oliveira-Paula GH, Liu S, Maira A, Ressa G, Ferreira GC, Quintar A, Jayakumar S, Almonte V, Parikh D, Valenta T, Basler K, Hla T, Riascos-Bernal DF*, Sibinga NES*. The β -catenin C terminus links Wnt and sphingosine-1-phosphate signaling pathways to promote vascular remodeling and atherosclerosis. *Sci Adv*. 2024 Mar 15;10(11):eadg9278. PMID: 38478616. * Co-corresponding authors.
- Becher T*, Riascos-Bernal DF*[#], Kramer DJ, Almonte VM, Chi J, Tong T, Oliveira-Paula GH, Koleilat I, Chen W, Cohen P[#], Sibinga NES. Three-dimensional imaging provides detailed atherosclerotic plaque

morphology and reveals angiogenesis after carotid artery ligation. *Circ Res.* 2020 Feb 28;126(5):619-632. PMID: 31914850. * Equal contribution, # co-corresponding authors.

Selected Reviews

- Riascos-Bernal DF*, Quinones G, Abdelaal SA, Menegus MA, Sibinga NES. Pathogenesis of plaque erosion. *Trends Cardiovasc Med.* 2026 Feb;36(2):105-112. PMID: 40935270. * Corresponding author.
- Riascos-Bernal DF*, Ressa G, Korrapati A, Sibinga NES*. The FAT1 cadherin drives vascular smooth muscle cell migration. *Cells.* 2023 Jun 14;12(12). PMID: 37371091. * Co-corresponding authors.

**Michael Ross, M.D.**

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Despite the success of antiretroviral therapy in improving mortality, persons with HIV (PWH) have shortened lifespan and increased prevalence of non-infectious diseases including chronic kidney disease (CKD). HIV-associated nephropathy (HIVAN) occurs almost exclusively in persons of African ancestry and variants of the APOL1 gene, which confer resistance to trypanosomal disease, markedly increase risk of progressive CKD. 14% of African Americans have APOL1 high risk (HR) genotypes, which confer a 29-89-fold increased risk of HIVAN among PWH, likely by predisposing kidney epithelial to HIV-induced injury. Since most persons with APOL1 HR genotypes never develop kidney disease, additional “hits”, including viral infection (HIV, SARS-coV-2), exposure to high levels of interferon, and/or additional genetic factors, are necessary to initiate progressive CKD.

Our group was the first to identify a role for the ubiquitin-like protein Ubiquitin D (UBD) in the pathogenesis of kidney disease (HIVAN). We reported roles for UBD in promoting HIV-induced kidney epithelial cell injury and innate immune activation. A role for UBD in modulating kidney injury in APOL1-mediated kidney disease is supported by recently published studies demonstrating increased UBD expression in glomeruli in humans and mice with APOL1 HR genotypes and kidney disease and a recent report that UBD increases APOL1 degradation in vitro. Our analysis of the UBD gene locus identified a haplotype comprised of four missense mutations with an allele frequency of 0.43 in African Americans but only 0.02 in Europeans. Our preliminary data demonstrate that this haplotype (UBDb) is associated with a 5.8-fold increased risk of HIVAN in persons with APOL1 HR genotypes.

Further, data from our laboratory indicate that there are important functional differences in the UBDb protein compared to UBDA (reference allele). However, the mechanism by which the UBDb variant synergizes with APOL1 risk alleles to promote kidney injury is unknown. Since UBD can covalently and non-covalently interact with cellular proteins and increase/decrease degradation or alter protein function, we will test our hypothesis that the UBDb variant increases the risk of HIVAN via changes in interactions with APOL1 and other proteins, leading to kidney cell injury.

Current projects:

Effect of Ubiquitin D variants upon APOL1-mediated kidney injury

We are determining the effects of the UBDA and UBDb alleles upon HIV-induced injury and inflammatory responses in novel human kidney lines with APOL1 HR and non-risk genotypes. We are also use high throughput proteomics and targeted in vitro assays to delineate differences in covalent and non-covalent protein-protein interactions of UBD variants and effects of UBD variants on APOL1 protein ubiquitination and degradation in human podocytes with APOL1 HR and non-risk genotypes.

**Aditi Shastri, M.B., B.S.**

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At the Shastri Translational Research Lab, we are committed to advancing the understanding and treatment of hematopoietic diseases, with a particular focus on myeloid malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). Our research encompasses several interrelated domains.

Hematopoietic Stem and Progenitor Cell (HSPC) Targeting Therapeutics

Recent research suggests that myeloid malignancies originate from leukemic stem cells, and their progression is driven by the persistence and survival of these cells. We are developing innovative therapies targeting HSPCs in myeloid malignancies, focusing on targeting Signal Transducer and Activator of Transcription 3 (STAT3) pathway. STAT3 is a key regulator that is overexpressed in hematological malignancies and is associated with reduced overall survival. In our lab, we have targeted STAT3 using several novel agents, including antisense oligonucleotides and degraders, in leukemic cell lines, generating promising preclinical data. We aim to translate these findings into early phase clinical trials.

Interactions of STAT3 in HSPCs

We are investigating how STAT3 interacts with apoptosis inhibitors such as BCL2, MCL1 in HSPCs, as well as how these interactions are influenced by inflammatory environment in the bone marrow niche. This work could reveal novel therapeutic strategies to overcome resistance in myeloid malignancies.

Aging-Related Clonal Hematopoiesis (CH)

In collaboration with Dr. Millman and her team, we are studying a longevity cohort enriched for centenarians. This research aims to uncover how centenarians resist age-related diseases, such as cancer, cardiovascular disease, and Alzheimer's. Specifically, we are examining the frequency and type of CH mutations in these individuals and investigating whether longevity provides protection against harmful CH mutations.

The Effect of Air Quality and Other Environmental Health Hazards on Myeloid Malignancies

We analyze large datasets to understand differences in the incidence, treatment, and outcomes of myeloid malignancies. By identifying social, genetic, and environmental factors, specifically differences in air quality, we aim to develop strategies to effect policy change and improve cancer patient outcomes across the world.

**Nicholas E.S. Sibinga, M.D.**

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Vascular disease, the greatest single cause of morbidity and mortality worldwide, results from interactions between circulating inflammatory cells, the endothelium that lines the vasculature, underlying vascular smooth muscle cells (SMCs) that comprise most of the arterial wall, and stem/progenitor cells found in the surrounding adventitia. The underlying pathogenesis is complex: factors that impinge on these cell types include reactivated developmental pathways, innate and acquired immune responses, and changes in cell function that result from physical stresses, perturbed blood flow, and biochemical stimuli. We seek to characterize these responses at the molecular level, in cell culture, and in mouse models that reflect specific types of vascular injury, including atherosclerosis, disturbed blood flow, mechanical trauma, and immune rejection that accompanies solid organ transplantation.

Current projects

- FAT1 cadherin processing and SMC growth regulation – Amado Quintar
- The FAT1 cadherin in endothelial cell biology and vascular repair – Oscar Bermudes
- Mitochondrial respiration in SMC biology and vascular remodeling – Alishba Maira

Ongoing work in these areas involves defining the molecular and cellular bases for these observations. By identifying such novel mechanisms, we hope to find new targets for therapeutic intervention to regulate vascular cell activities and improve related disease prevention and treatment.

Selected recent publications

- Oliveira-Paula GH, Liu S, Maira A, Ressa G, Ferreira GC, Quintar A, Jayakumar S, Almonte V, Parikh D, Valenta T, Basler K, Hla T, Riascos-Bernal DF, Sibinga NES. The β -catenin C-terminus links Wnt and sphingosine-1-phosphate signaling pathways to promote vascular remodeling and atherosclerosis. *Science Advances*. 2024 Mar 15;10(11):eadg9278. PMID: 38478616.
- Chinnasamy P, Casimiro I, Riascos-Bernal DF, Venkatesh S, Parikh D, Maira A, Srinivasan A, Zheng W, Tarabra E, Zong H, Jayakumar S, Jeganathan V, Pradan K, Aleman JO, Singh R, Nandi S, Pessin JE, Sibinga NES. Increased adipose catecholamine levels and protection from obesity with loss of Allograft Inflammatory Factor-1. *Nature Communications* 2023, Jan 3;14:38. PMID: 36596796.
- Riascos-Bernal DF, Ressa G, Korrapati A, Sibinga NES. The FAT1 Cadherin Drives Vascular Smooth Muscle Cell Migration. *Cells*. 2023 Jun 14;12(12):1621. doi: 10.3390/cells12121621. PMID: 37371091
- Riascos-Bernal DF, Maira A, Sibinga NES. The Atypical Cadherin FAT1 Limits Mitochondrial Respiration and Proliferation of Vascular Smooth Muscle Cells. *Front Cardiovasc Med*. 2022 May 11;9:905717. PMID: 35647082. PMCID: PMC9130956.
- Becher T, Riascos-Bernal DF, Chi J, Cohen P, Sibinga NES. Three-Dimensional Visualization of Atherosclerotic Vessels by Tissue Clearing and Light-Sheet Fluorescence Microscopy. *Methods Mol Biol*. 2022;2419:841-851. doi: 10.1007/978-1-0716-1924-7_51. PMID: 35238005. PMCID: PMC9590274.



E. Richard Stanley, Ph.D.

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We are interested in the role of growth factors and signaling in development & disease, focusing on the developmental, physiological and pathological roles of colony stimulating factor-1 receptor (CSF-1R) and its ligands CSF-1 & IL-34, using molecular, cell biological and mouse genetic approaches.

Studies of the CSF-1 R and its ligands: We have shown that CSF-1 and the CSF-1R regulate the production of macrophages, osteoclasts, microglia, Langerhans cells, Paneth cells and neural progenitor cells and play an important role in the development of leukemia, of several inflammatory diseases and in solid tumor progression. We have developed novel biochemical and genetic approaches to CSF-1R signal transduction to analyze CSF-1R structure/function, identifying and elucidating the function of several downstream signaling molecules. In macrophages, we have shown that CSF-1R activation is anti-inflammatory, through the induction of miR-21 to suppress the macrophage M1 (inflammatory) phenotype and enhance the M2 (trophic) phenotype,

Roles in the nervous system: We have shown that 1) all microglial development and maintenance is dependent on the CSF-1R, 2) interleukin-34 (IL-34), similarly activates the CSF-1R, with a more restricted tissue distribution (brain and skin) than CSF-1, 3) via the CSF-1R, CSF-1 and IL-34 directly suppress neural progenitor cell (NPC) self-renewal and enhance NPC survival and differentiation and 4) IL-34 also acts via the protein tyrosine phosphatase zeta receptor, expressed on NPC, but not on microglia.

Roles in disease: We have shown that 1) the *Csf1r*^{+/-} mouse is a model of CSF-1R related leukoencephalopathy (CRL), a dementia in man caused by dominant inactivating mutations in the kinase domain of the *CSF1R* gene or *CSF1R* haploinsufficiency, that is most often misdiagnosed as Alzheimer's disease, 2) CRL originates in microglia, 3) glucocorticoid treatment is prophylactic for CRL and 4) that a major player in development of CRL is dysregulation of CSF-1 regulated metal ion homeostasis. In studies related to myocardial infarction, we have shown that that early systemic CSF-1 administration inhibits inflammatory activation of infarct macrophages, improves repair and attenuates adverse remodeling after MI. In addition, we have developed a mouse model of a rare interferon related factor 2 binding protein like (IRF2BPL)-related disease (IRF2BPL-RD). IRF2BPL-RD is characterized by neurodevelopmental delay, seizures, loss of speech and movement disorder. It is caused by dominantly-inherited missense and truncating mutations in IRF2BPL. This model, which faithfully reproduces aspects of IRF2BPL-RD, is under active investigation.

Lab website: Currently being updated

Selected Recent Publications:

- Chitu, V., Biundo, F., Shlager, G.G.L., Park, E.S., Wang, P., Gulinello, M.E., Gokhan, S., Ketchum, H.C., Saha, K., DeTure, M. A., Dickson, D.W., Wszolek, Z.K., Zheng, D., Croxford, A.L., Becher, B., Sun, D., Mehler M.F. and Stanley E.R. (2020) Microglial homeostasis requires balanced CSF-1/CSF-2 receptor signaling. *Cell Reports*, 30:3004-3019. PMID: 32130903
- Chitu, V., Biundo, F., Oppong-Asare, J., Gökhan, Ş., Aguilan, J.T., Dulski, J., Wszolek, Z.K., Sidole, S. and Stanley E.R. (2023). Prophylactic effect of chronic immunosuppression in a mouse model of CSF-1 receptor-related leukoencephalopathy. *Glia*, 71: 2664-2678 doi: 10.1002/glia.24446. PMID: 37519044.
- Chitu, V., Alvarenga, J., Chen, W., Reynolds, D., Liu, Y., Sun, D., Sandell, A., Danylaite-Karrenbauer, V., Uvdal, P., Silva, I.A.N., Sandt, C., Klementieva, O., Johansson, U., Subramanian Vignesh, K., Wszolek, Z. K., Dickson, D.W., Aguilian, J., Sidoli, S., Zheng, D., Stanley, E.R. 2026. Disruption of CSF-1 receptor-mediated metal iron homeostasis in the murine brain promotes neurodegenerative disease development, *J. Clin. Invest.*, Feb 26:e200121. doi: 10.1172/JCI200121. PMID: 41746753.

Selected Reviews:

- Stanley, E.R. and Chitu, V. (2014). CSF-1 Receptor Signaling in Myeloid Cells. *Cold Spring Harb Perspect Biol.*, 6(6):1-21
- Chitu, V., Gokhan, S., Nandi, S., Mehler, M. and Stanley, E.R. (2016) Emerging roles for the CSF-1 receptor and its ligands in the nervous system. *Trends in Neuroscience*, 39:378-393.
- Chitu, V. and Stanley, E.R. (2017) Regulation of embryonic and postnatal development by the CSF-1 receptor. *Curr. Top. Dev. Biol.* 123:229-275.
- Stanley, E.R., Biundo, F., Gökhan, Ş. and Chitu, V. (2023) Regulation of normal and pathological microglia states by colony stimulating factors. *Frontiers in Cellular Neuroscience*, 17: 1275935. doi: 10.3389 /fncel.2023.1275935. eCollection 2023. PMID: 37964794.

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Targeting signal transduction in hematologic malignancies:

Cytokines play important roles in the regulation of normal hematopoiesis and a balance between the actions of hematopoietic growth factors and myelosuppressive factors is required for optimal production of different hematopoietic cell lineages. The myelodysplastic syndromes (MDS) are collections of heterogeneous hematologic diseases characterized by refractory cytopenias due to ineffective hematopoiesis. These preleukemic disorders are common causes of anemia in the elderly and are rapidly increasing in incidence. We have also demonstrated that the TGF-beta superfamily/smad, IRAK and MAP kinase pathways is overactivated in MDS. Our work has led to clinical trials with Luspatercept, Galunisertib, CA4948, ARRY-614 and various other promising agents in MDS. We are trying to study the molecular mechanisms that lead to the activation of these pathways in MDS and are using small molecule inhibitors in mouse models to target these pathways.

Targeting aberrant stem and progenitor cells in myelodysplastic neoplasms:

We have demonstrated that aberrant stem cells persist during morphological remissions and are involved in relapse. We have identified novel targets against MDS/AML stem cells that are being tested in various studies. We are also conducting sequencing/epigenetic analysis of highly purified human stem cells and evaluating the role of these alterations in transformation of MDS to AML.

Epigenomic analysis of tumors:

We are using high throughput assays to analyze DNA methylation across the genome and have optimized these assays to work with low amounts of DNA. We have successfully used these assays in conducting an integrative analysis of epigenetic and genetic alterations in various tumor models, including MDS, esophageal cancer, pancreatic cancer and renal cell cancer.

Clinical studies in Myelodysplastic syndromes:

We have a "center of excellence" clinic for patients with Myelodysplastic syndromes. We offer a variety of clinical trials for these patients.



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Herpes simplex virus (HSV) is a pathogen of the human nervous system. The virus establishes life-long latency in our sensory neurons, then periodically reactivates and travels to peripheral epithelia or the brain. Delivery to the periphery can result in painful oral and genital lesions, keratitis, blindness and neonatal infections with risk of serious birth defects and high fatality rates. Transport into the brain can cause life-threatening encephalitis, and is increasingly thought to play a major role in the development of Alzheimer's Disease. Viral transmission and the progression of disease require these viruses travel distances greater than a million times their own diameter within the nervous system. We are studying the molecular details of how these viruses accomplish this remarkable feat.

Negotiating passage - transport from the neuronal cell body into the axon

In human sensory neurons, the natural home of HSV, a high concentration of microtubule associated protein 2 (MAP2) in the proximal axon disrupts microtubule-binding by kinesin-1 motors. This provides a selective filter, ensuring that only cargo able to bind the kinesin-3 motor KIF1A can enter axons. Neurotropic herpesviruses like HSV recruit KIF1A for axonal entry using a small, virally-encoded membrane protein termed US9p. US9p resembles no other known KIF1A receptor in all of biology, and its mechanism of KIF1A binding is unknown. For most cellular axonal cargo (such as synaptic vesicles) phosphatidylinositol-(4,5)-bisphosphate [PI-(4,5)-P₂] lipids in the cargo bilayer bind to a pleckstrin homology (PH) domain at the C-terminus of KIF1A, and play a critical role in stabilizing recruitment of this motor. We are deleting, and introducing specific inactivating point mutations into, the KIF1A PH domain to test whether US9p-KIF1A interaction requires PI-(4,5)-P₂, or is by a completely different mechanism to normal cellular cargo.

The long haul - transport along the axon to the nerve terminal

Once in the axon, viral transport along the length of the axon to the nerve terminus is accomplished using the workhorse high load-capacity motor kinesin-1. Neurons express three closely related kinesin-1 isoforms: KIF5A and KIF5C, which are found only in neurons, and KIF5B which is found in all cell types. These isoforms can have distinct transport functions, for reasons that are poorly understood. For example, the axonal transport of mitochondria in zebrafish sensory neurons depends exclusively upon KIF5A, and in rodents KIF5B, not KIF5A, is involved in the development of excitatory synapses in postsynaptic neurons. Similarly, we have found that alphaherpesviruses use their gE/gI complex to recruit only neuronal-specific KIF5A and KIF5C isoforms for axonal transport, and not KIF5B. We are using fluorescently tagged versions of KIF5C/KIF5B motors, and mutant KIF5B/C hybrid motors to attempt to understand how and why these viruses discriminate so carefully between available forms of kinesin-1.

Selected Publications

- Diwaker D., Murray J., Barnes J., Wolkoff A. and **Wilson D.W.** (2020). Deletion of the Pseudorabies Virus gE/gI-US9p complex disrupts kinesin KIF1A and KIF5C recruitment during egress, and alters the properties of microtubule-dependent transport *in vitro*. *PLOS Pathogens* 16, e1008597.
- Pegg C.E., Zaichick S.V., Bomba-Warczak E., Jovasevic V., Kim D., Kharkwal H., **Wilson D.W.**, Walsh D., Sollars P.J., Pickard G.E., Savas J.N. and Smith G.A. (2021). Herpesviruses assimilate kinesin to produce motorized viral particles. *Nature* 599, 662-666
- Barnes J., Jordan B.A. and **Wilson D.W.** (2022). An ESCRT/VPS4 envelopment trap to examine the mechanism of alphaherpesvirus assembly and transport in neurons. *J. Virology* 96, e02178-21.
- Diwaker D., Kim D., Jordan B., Smith G.A. and **Wilson D.W.** (2025). The gE/gI-US9p complex is necessary for kinesin-1 recruitment during alphaherpesvirus egress from neurons. *J. Virology* 99, e0165024.

Selected Reviews

- Ahmad I. and **Wilson D.W.** (2020). HSV-1 cytoplasmic envelopment and egress. *International Journal of Molecular Sciences*. 21, 5969-6001
- **Wilson D.W.** (2021). Motor skills: Recruitment of kinesins, myosins and dynein during assembly and egress of alphaherpesviruses. *Viruses* 13, 1622-1644

**Allan W. Wolkoff, M.D.**

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Dr. Allan Wolkoff's interest in research was sparked when he worked in a biochemistry lab to help pay college bills. He began his medical studies at Dartmouth Medical College and transferred to the Albert Einstein College of Medicine where he obtained his M.D. degree. With the exception of a two year period when he was Clinical Associate in Gastroenterology-Hepatology in the Digestive Disease Branch, National Institute of Arthritis, Metabolism and Digestive Disease, he has remained at Albert Einstein. His early mentor, Irwin M. Arias, M.D. of the National Institutes of Health said of Wolkoff's work, "He built an exemplary global reputation in hepatology research, education, training and scholarship. A major participant in the creation of the Marion Bessin Liver Research Center at Albert Einstein, Dr. Wolkoff has taken advantage of the strong, interactive basic science departments and is a leader in bridging understanding of hepatocyte biology with the pathogenesis of acquired and inheritable liver diseases."

Dr. Wolkoff is a pioneer in the combining of disciplines that inform basic understanding of hepatocyte function and relation to disease and is recognized worldwide for providing new windows into physiology and pathophysiology. He has had articles published in over 100 peer-reviewed publications, given many invited lectures and has had continuous NIH-supported research. In addition, he has served on advisory committees of several NIH-supported liver research centers. In 2006, he was presented the AASLD Distinguished Service Award. In 2012, he received the highly prestigious 2012 Distinguished Scientific Achievement Award from the American Liver Foundation.

**Fajun Yang, Ph.D.**

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Dysregulation of lipid metabolism is a common feature of major human diseases, including obesity, type 2 diabetes, and metabolic dysfunction–associated steatotic liver disease (MASLD). The goal of our research is to elucidate the molecular mechanisms governing gene expression under normal physiological and pathophysiological conditions, with a particular focus on lipid and glucose metabolism. We employ biochemical and genetic approaches to investigate the function and regulation of networks of transcription factors and their cofactors in key metabolic tissues, including the liver (hepatocytes), adipose tissue (white, brown, and beige adipocytes), and skeletal muscle. In addition to DNA-binding transcription factors, eukaryotic gene expression requires a series of transcriptional cofactors. One such cofactor is the Mediator complex, an evolutionarily conserved, multi-subunit assembly organized into four distinct modules. The largest of these is the kinase module, which comprises MED13 (or MED13L), MED12 (or MED12L), CCNC, and CDK8 (or CDK19). Our current research focuses on the dynamic regulation of the Mediator complex and its tissue-specific functions in major metabolic organs, including the liver, adipose tissue, and skeletal muscle. We have previously shown that the kinase module of the hepatic Mediator complex is selectively lost in models of metabolic disease and that Mediator subunits regulate lipid metabolism in a context-dependent manner. This dynamic remodeling of the Mediator complex enables metabolic signals to be transmitted to transcriptional outputs, providing an additional layer of gene regulatory control in metabolism. For example, deletion of the MED13 subunit abolishes the plasticity of inducible gene expression in the liver but protects against the progression of metabolic dysfunction–associated steatohepatitis (MASH), an advanced form of MASLD. In contrast, deletion of the CCNC subunit disrupts hepatocyte homeostasis in the liver, causing liver cysts, while inducing white adipose tissue browning. Ultimately, our research aims to identify novel therapeutic targets for the prevention and treatment of metabolic diseases.