# Where are Cell Biology Labs?



What do we offer?

We offer a comprehensive training program leading to a PhD In Biomedical Sciences with specialization in Cell Biology.

**Research Areas:** 

Cell Organelle Cardiovascular Biology

**Brain Injury & Repair** 

**Stem Cell Biology** 

**Cancer Biology** 

**Signal Transduction** 

**Reproductive Biology** 

**Computational Biology** 



Signaling through nanotubes in Stem Cell Niche (Dr. Mayu Inaba's Lab)



"Car Garage" stack organization of the Golgi Apparatus (by Dr. Mark Terasaki)



Embryo in the making (by Dr. Lisa Mehlmann)



Brain Vasculature by Two-Photon Imaging

#### Dr. Rindy Jaffe Professor and Chair of Cell Biology Department

In the coming year, we will continue to investigate mechanisms of intracellular communication between the luteinizing hormone receptor and the NPR2 guanylyl cyclase and other signaling molecules in the mouse ovarian follicle.

- 1. In collaborative studies with Henning Urlaub's lab (Max Planck Institute, Goettingen), we have been using mass spectroscopy to analyze which regulatory subunits of PPP family phosphatases are phosphorylated and activated by LH receptor signaling. These studies have identified PPP2R5D as a candidate phosphatase linking LH stimulation of protein kinase A (PKA) to downstream targets including NPR2 and cofilin. To investigate the functions of PPP2R5D in the preovulatory follicle, we have generated a genetically modified mouse line in which PPP2R5D cannot by phosphorylated by PKA (*Ppp2r5d*-S566A). We will investigate the consequences of preventing PPP2R5D phosphorylation on LH signaling.
- 2. We will continue our studies using light and serial section electron microscopy to examine the cellular and subcellular distribution of the LH receptor in follicles from mice expressing an HA-tagged version of the LH receptor after LH stimulation. Together with Dan Bernard (McGill University), we have found that we can precisely mimic the endogenous LH surge by intraperitoneal injection of kisspeptin, which elicits a highly synchronized and reproducible increase in serum LH with the same kinetics and amplitude as occur naturally. This method will allow us to deliver murine LH to the follicle through the circulation, under physiological conditions. Using this approach, we are finding that LH receptor stimulation causes outer mural granulosa cells to migrate inwards into the follicle, within 2 hours after the peak of the LH surge. We hypothesize that LHR stimulation causes cell migration by way of dephosphorylating and activating the actin depolymerizing protein cofilin. To test this hypothesis, we are in the process of generating a genetically modified mouse line to co-express, in the same cells as the LH receptor, a dominant negative form of cofilin that cannot be dephosphorylated (*Cof1*-S3E). We will investigate the consequences of preventing cofilin dephosphorylation for LH-induced cell migration and ovulation.



#### Daniel W. Rosenberg, Ph.D.

HealthNet, Inc. Chair in Cancer Biology and Professor of Medicine Director, Colon Cancer Prevention Program Investigator, Center for Molecular Medicine University of Connecticut Health Center 263 Farmington Avenue Farmington, CT 06030-3101

https://facultydirectory.uchc.edu/profile?profileId=Rosenberg-Daniel

My laboratory focuses in the prevention of colorectal cancer, the second-leading cause of cancer-related deaths in the U.S. We combine mouse genetic models of cancer with human clinical intervention trials to develop new strategies to harness the cancer preventive benefits of natural products and repurposed pharmaceutical agents that target specific dysregulated pathways in cancer cells. Our work is highly collaborative in nature and you will obtain experience working with governmental agencies, academic labs and biotechnology. We are currently recruiting graduate students; some of our ongoing studies are described below:

- We use a multi-omics approach to study the earliest cellular stages associated with colorectal cancer. We have developed a powerful combinatorial method that combines the specificity of laser-capture microdissection with genome-wide epigenetic, mutational and gene expression profiling of early human neoplasia to understand how cancer first develops. Through the use of bioinformatics, we can identify altered signaling pathways that can be targeted to reverse these early cellular changes.
- 2) Our laboratory focuses on how the gut microbiome contributes to the progression of colorectal cancer and how we can modify the microbiome through simple dietary approaches to alter the course of the disease. In a large clinical and pre-clinical study that will begin in the late Spring, we will determine how plant-based phytochemicals are metabolized by the gut microbiome, producing powerful anti-inflammatory molecules that we believe may modulate the immune response to neoplastic cells. This project will use several mouse genetic cancer models and extensive metabolomics analysis to uncover novel pathways of cancer suppression.
- 3) We have recently shown that adherent microbiota that are present within the gut epithelia are possibly responding to specific cancer-related somatic mutations (e.g. BRAF, APC). Further studies are required to characterize this important microbial-host interaction and how it may influence carcinogenesis.
- 4) We are working with the NCI to develop novel drug combinations to block colorectal cancer at the initiation and promotional stages of the disease. This work combines commonly used drugs, such as NSAIDs, with naturally occurring fatty acids to block tumor development. Thus, a key focus of our laboratory is to understand the role of diet-derived bioactive lipids in the promotion (and suppression) of colorectal cancer and to discover new lipid signaling molecules.
- 5) We are using a novel dietary intervention strategy the targets one-carbon metabolism to block colorectal cancer in a conditional mouse genetic model. This work has identified the role of mitochondria and altered metabolomics/energy generation as a key aspect of cancer promotion and suppression.
- 6) We have identified inappropriate epigenetic control of the vitamin D receptor that we believe may impair the ability of vitamin D to suppress cancer in many individuals. An important goal is to develop pharmacologic strategies to overcome this epigenetic block of VDR to restore its downstream anti-inflammatory signaling cascade.
- 7) Our laboratory has a long-standing interest in the pathogenesis of inflammatory bowel disease, specifically ulcerative colitis. We are developing an organoid-based cell culture system to study how dietary agents can be used to alter epigenetic changes we believe cause the disease.

#### Dr. Kimberley Dodge-Kefka Professor of Cell Biology, Molecular Biology and Biophysics

Pathological cardiac remodeling is due, in part, to increased sympathetic stimulation of myocyte b-adrenergic receptors (bAR) and the aberrant production of the second messenger cAMP, resulting in increased Protein Kinase A (PKA) signaling. This pathway is responsible for the increase in inotropy and chronotropy normally seen in the flight-or-fight response, but long-term stimulation of the heart results in pathological remodeling via Ca<sub>2+</sub>-stimulated gene transcription. Accordingly, bAR blockade is first line therapy for the treatment of cardiovascular disease and prevention of heart failure.<sup>1</sup> However, as bAR blockade also affects contractility, more precise targeting of the cAMP signaling that induces remodeling, including pathways that regulate Ca<sub>2+</sub>-mediated gene expression, might yield therapeutics with fewer side effects. We propose that distinct pools of cAMP and PKA exist in the cardiac myocyte, including pools localized to the nucleus that regulates Ca<sub>2+</sub>-mediated pathological gene transcription.<sup>2,3</sup> New preliminary data show that a perinuclear pool of bAR stimulates PKA localized to the nuclear envelope via binding to the scaffolding protein muscle A-kinase anchoring protein b (mAKAPb). Activation of mAKAPb-bound PKA orchestrates an increase in perinuclear Ca<sub>2+</sub> signaling to induce hypertrophic gene transcription (Fig. 1).

The central hypothesis of this proposal is that targeting mAKAPb signalosomes will inhibit the nuclear bARmediated PKA and Ca<sub>2+</sub> signaling that induces pathological gene expression, without inhibiting, and in fact maintaining, cardiac contractility.

**Specific Aim 1: Stimulation of a nuclear pool of Ca<sub>2+</sub> is required for induction of cardiac hypertrophy.** We have published that mAKAPb binding the Ca<sub>2+</sub>/calmodulin-dependent phosphatase calcineurin (CaN) is obligatory for the activation of NFAT and MEF2 transcription factors and the induction of cardiac myocyte hypertrophy.<sup>4-6</sup>. New data suggest that mAKAPb-bound PKA induces a perinuclear Ca<sub>2+</sub> transient that stimulates the associated CaN. We propose that targeting the mAKAPb signalosome-regulated pool of perinuclear Ca<sub>2+</sub> will block induction of hypertrophy without affecting excitation-contraction coupling. We will test this hypothesis by selectively buffering perinuclear Ca<sub>2+</sub> and manipulating CaN-mAKAPb association in cultured primary cardiac myocytes (Aim1a). In addition, using adeno-associated virus (AAV) to express the recombinant perinuclear Ca<sub>2+</sub> "buffer" in cardiac myocytes *in vivo*, we will demonstrate the relevance of mAKAPb-stimulated perinuclear Ca<sub>2+</sub> transients to pathological remodeling induced by pressure overload and catecholamine infusion (Aim1b).

#### Specific Aim 2: Inhibition of mAKAPb-bound PKA blocks induction of cardiac hypertrophy. Our

previous work found that expression of mAKAPb is mandatory for induction of cardiac hypertrophy both in vitro and in vivo.4,6-9 PKA-mAKAPb binding is required for the induction of myocyte hypertrophy,6 implying that targeting cAMP signaling at mAKAPb signalosomes might constitute an effective therapeutic strategy for the prevention of heart failure. Recently, we have developed molecular tools that selectively inhibit, or stimulate cAMP signaling at mAKAPb signalosomes.<sup>10</sup> In Aim2a, we will investigate the impact of modulating perinuclear cAMP and mAKAPb-bound PKA on perinuclear Ca<sub>2+</sub> dynamics and the induction of myocyte hypertrophy. To demonstrate the specificity of targeting mAKAPb-cAMP signaling, effects on cell growth will be contrasted to those on SR Ca<sub>2+</sub> dynamics and myocyte contraction. In vivo experiments using AAV9 to express these tools in a myocyteautonomous manner will demonstrate the physiological impact of modulating perinuclear cAMP signaling on induction of cardiac disease induced by pressure overload and catecholamine infusion (Aim2b). Specific Aim 3: A nuclear bAR receptor is responsible for cardiac hypertrophy. Numerous past studies have identified bARs on the cardiac nuclear envelope, but the presence and significance of these internal receptors remains controversial.11-14 New preliminary data suggest an internal pool of bAR is required for activation of mAKAPb-bound PKA, consistent with a model in which this nuclear pool of bARs is responsible for induction of cardiac hypertrophy. Using pharmacological inhibitors, mAKAP-targeted nanobodies that regulate bARs in close proximity to the scaffold, and siRNA against specific bAR subtypes, we will determine the importance of nuclear bARs for mAKAPb-bound PKA activity, local Ca2+ transients and pathological hypertrophy.

While compartmentation of PKA signaling is well established, it has been generally assumed that receptors responsible for initiating cAMP signaling are located on the cell membrane at potentially great distances from individual signalosomes. Taken together, the Aims of this proposal will elucidate how mAKAPb orchestrates a signaling compartment where local perinuclear bARs activate local PKA and Ca<sub>2+</sub> transients required for pathological gene transcription and initiation of cardiac hypertrophy. This project will advance our

understanding of the extent of compartmentalized second messenger signaling in the cell, while providing proof-of-concept for novel approaches for the inhibition of pathological cardiac remodeling and the prevention of heart failure.

Fig. 1. Model for Perinuclear bAR Signaling dedicated to the regulation of pathological cardiac remodeling. NEnorepinephrine



Archana Sanjay PhD Associate Professor Dept. of Orthopaedic Surgery Email: asanjay@uchc.edu Office and Lab : MARB Building 4<sup>th</sup> floor Funding: NIDCR R01-DE030716 and NIAMS R01-DE030716

#### Novel activation of Wnt signaling to improve bone repair

**Significance:** Older individuals are much more likely to experience long bone fractures than their young and middle-aged

counterparts, and those fractures, when repaired, take longer to heal. There is an urgent clinical need to develop new

therapeutics to promote bone regeneration in aged patients. Canonical Wnt signaling is crucially important

for activation of this progenitor population during healing, and in many clinical studies activating canonical Wnt signaling increases bone regeneration. R-spondins (roof plate specific spondin) are a family of

four secreted matricellular proteins (Rspo1-4) that bind to Leucine-rich repeat-containing G-protein coupled receptors 4/5/6 (Lgrs) (Fig 1). Stem cells exist in niches surrounded by differentiated cells, which express secreted Rspo

proteins that bind to Lgrs on progenitor cells. This interaction enhances cWnt signaling and influences fate determination and proliferation. Rspo-Lgr studies have focused largely on maintenance of the progenitor cell pool and regulation of regenerative mechanisms in non-skeletal tissues, in young animals, exploring these concepts in the skeleton, with

aging, is truly unique. Rspo-Lgr interaction potentiate canonical Wnt pathway by preventing the turnover of Wnt Frizzled receptors, thereby regulating canonical Wnt signaling. Rspo2 is produced during bone healing,

and its expression is reduced in aging periosteum and in isolated progenitor cells. We hypothesize that reduced Rspo2-Lar6 signaling contributes to reduced bone healing with age, and that activation of this pathway can restore youthful healing to aged mice. Our preliminary data showed reduced mineralization in Lgr6 null periosteal cultures; no significant differences in chondrocytic cultures or expression of Sox 9 and Col2a1 (Fig.2 A). Analysis of femoral fractures in 12week-old Lgr6 null mice versus wild-type controls, and at 14 and 28 days post-fracture by mCT and histology were done (Fig.2C). Lgr6-null mice had significant delays in mineralization during repair. Lgr6-null calluses have significantly reduced bone volume relative to controls. These calluses are characterized by large unmineralized voids shown by mCT scanning, and notably retain significant amounts of cartilage, as shown by safranin O staining, suggesting a delay in endochondral bone healing. These preliminary data indicate that Lgr6 expression in periosteal progenitors is required for proper skeletal regeneration potential. We also found that from 25-week-old male and female mice, show that Lgr6 null mouse-derived stem cells form significantly fewer percentage of ALP+ osteoblastic colonies (98% reduction in ALP+ colonies formed). µCT analysis showed that there is significantly reduced bone volume in 25-week-old Lgr6 null femurs compared to age- and sex -match controls (59% reduction in BV/TV). Combined these data suggest that Lqr6 is required for maximal osteochondral progenitor activity during homeostatic bone formation/remodeling. We have defined two specific aims to address this goal. First, in aim 1, Lgr6 role in geriatric bone healing will be assessed by examining bone healing in Lgr6 overexpressing and knockout mice; and Rspo2-Lgr6 binding will be blocked using a small molecule.

Bone healing will be assessed using microCT, histology, molecular analysis, Wnt signaling, proliferation and mechanical testing. In aim 2, Rspo2 will be delivered to fractures locally and the requirement for Lgr6 in the Rspo2 mediated effects evaluated. *Completion of this work will establish* 

the role of Rspo2-Lgr6 in geriatric fracture healing and establish whether targeting the pathway can promote bone healing in aging.

### Goal: Defining the role of adult stem cell marker Lgr6 in bone healing

1) Lgr6+ adult stem cells are responsible for bone regeneration.

2) Examine the contributions of Lgr6+ cells in bone healing in aged and diabetic mice.

3) Examine differential roles of adult Lgr6+ adult stem cells in distinct bone compartments.

4) Determine whether direct delivery of R-spondin (ligand for Lgr6) to bone injury site promotes healing.

5) Define signaling mechanism(s) related the Lgr6-mediated healing.

## Fig 1. Rspo-Lgr6 Signaling



**Fig.2.** Decreased mineralization of periosteal culture and delayed fracture healing in Lgr6 null mice **A**. Periosteal cultures from +/+ (control) and Lgr6 null mice were assessed by staining with Alizarin red S. or Alcian blue **B**. mCT and **C**. Safranin O staining



**Fig. 3** Decreased osteoprogenitors and bone volume in 5 month old Lgr6 null mice **A and B**. Colony forming units from (control) and Lgr6 null mice were assessed by staining with Giemsa or ALP. Each dot or square represents one mouse **B**. mCT images and BV/TV.



Dr. Pat Murphy Assistant Professor of Cell Biology Center for Vascular Biology

I will be accepting students.

I attached an image here to display work in our lab.

I can participate in all three sessions at this point.

Projects could range from

- 1) CRISPR KO screens to define RNAbp protein function
- 2) rescue experiments in cell lines to determine effects of RBP or splice isoform variants
- 3) single cell analysis to examine responses in vivo
- 4) informatics projects to examine splicing in human datasets
- 5) adoptive transfers and flow cytometry to track immune cell behavior in animal models
- 6) imaging studies of atherosclerotic plaque or neurodegeneration phenotypes



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**American Heart Association Predoctoral Awards** 2019 (Jess Hensel & Sarah-Anne Nicholas





## UNDERSTANDING THE MECHANISM OF ASYMMETRIC CELL DIVISION



Tissue stem cells continuously supply new cells to replace short-lived but highly differentiated cell types, such as blood, skin, and sperm. Asymmetric stem cell division balances the self-renewal and differentiation of stem cells, thus essential for the tissue homeostasis. Using Drosophila germline stem cell system, we investigate the mechanism of how one cell becomes two different cells, combining developmental- and cell-biological approaches.

# 1. INVESTIGATE THE NICHE-STEM CELL SIGNALING DYNAMICS.

Niche ligands have been believed to travel only within a short distance so that they only activate adjacent stem cells but not surrounding differentiating cells. We previously demonstrated that the microtubule-rich cellular protrusions (MT-nanotubes) project from stem cells into the niche cell cluster and help stem cells to engage in adequate level of signaling. We are investigating/testing; 1) dynamics of signal activation on MT-nanotubes using BiFC (Bimolecular fluorescent complementation) technique and live cell imaging, 2) optogenetic induction of nanotube formation, 3) molecular mechanism of local cytoskeleton rearrangement for nanotube formation.



GSC; Germline stem cell GB: Gonialblast

#### Funding; NIGMS 1R35GM128678

Related publications Nature.2015;523(7560):329-332, PLoS Biol.2020;18(12):e3001003

#### 2. MECHANISM OF BREAKING SYMMETRY AT CHROMATIN LEVEL.

Transvection is an epigenetic phenomenon that results from a pairing (physical interaction) of homologous chromosomes. Transvection influences gene expression either positively or negatively. We recently found that the local chromatin pairing status of certain gene loci become different during asymmetric cell division. We are characterizing the behavior of several gene loci and determining the relationship of locus pairing status and gene expression level by combining oligopaint DNA FISH, single molecule RNA FISH and live imaging techniques. Although much has been studied about how cells maintain epigenetic information during/after the cell division, the process that alters such information during the differentiation is poorly understood. We are expecting that our finding will open a new venue for understanding this fundamental question of biology.

# 3. MECHANISM OF BREAKING SYMMETRY OF CELL CYCLE PROGRAM.

We previously demonstrated that phosphorylated Mad protein levels (pMad, a downstream effector of niche signaling) become different during asymmetric division before the completion of cytokinesis when cells are still fully sharing their cytoplasm. At that phase, two daughter cells always synchronously enter S-phase. However, soon after the cytokinesis, each cell starts a different cell cycle program (i.e, stem cell enters longer G2 phase than the other daughter cell). The mechanism of how they acquire different lengths of G2 phases is unclear. As we identified multiple cell cycle regulators as target genes of Mad, we hypothesize that different level of pMad may contribute to reprogram G2 length, whereas elongated cell connectivity enables equalization of factors for S phase synchronization. We are currently investigating the mechanism of this intriguing regulation.



Related publications https://www.biorxiv.org/content/10.1101/798116v1

#### Oguro Laboratory

#### Contact: Hideyuki Oguro Ph.D., oguro@uchc.edu

Hematopoietic stem cells (HSCs) are capable of both self-renewal and differentiation to maintain the entire blood/immune system throughout life. The Oguro laboratory investigates mechanisms that regulate HSC development, self-renewal, and malignant transformation using mouse models, human tissues, and human induced pluripotent stem cells (hiPSCs).

**Project 1: Estrogen Receptor Signaling in Hematopoietic Stem Cell Proliferation and Mobilization.** Our primary focus is to investigate how HSCs are activated for proliferation and mobilization to generate more blood cells in response to acute hematopoietic demands. We previously found that HSCs divide more often in female mice as compared to male mice, and HSC proliferation is regulated by estrogen receptor  $\alpha$  (ER $\alpha$ ) signaling (Nakada, Oguro et al., *Nature*. 2014, 505:555). In a recent paper (Oguro et al., *J. Clin. Invest.* 2017, 127:3392), we demonstrated that two endogenous ER $\alpha$  ligands, estradiol and 27-hydroxycholesterol (27HC), differentially induce proliferation and mobilization of HSCs, respectively. This hormonal regulation is particularly important during pregnancy when maternal blood expands rapidly (**Figure 1**).

Mobilization of HSCs into the peripheral blood is widely used in clinical transplantation to treat blood disorders. However, the HSC supply is not sufficient and a considerable number of donors and patients fail to mobilize HSCs via the standard mobilization protocol. With recently awarded NIH R01 grant, we are testing a hypothesis



that administration of ER $\alpha$  ligands and modulation of specific genes downstream of ER $\alpha$  signaling could be used to improve collection of mobilized HSCs for transplantation as well as hematopoietic repopulation after transplantation. We are testing this hypothesis by following approaches. 1) Determine the potential of 27HC-ER $\alpha$  signaling to improve current HSC-mobilizing methods by the co-administration of 27HC with clinically used drugs. 2) Determine the potential of estradiol-ER $\alpha$  signaling to enhance hematopoietic repopulation after transplantation by the administration of estradiol. 3) Identify ER $\alpha$  target genes that mediate the differential effects of estradiol and 27HC on HSC proliferation and mobilization by RNA-seq and cut&run assay. We are testing functions of candidate genes by gene overexpression, knockdown, or knockout in HSCs. We use genetically engineered mouse models as well as humanized mice (i.e. immunodeficient mice transplanted with human HSCs). This study could shed light on molecular mechanisms of HSC proliferation and mobilization, and will lay the groundwork for developing novel interventions to harvest more mobilized HSCs for clinical transplantation and promote hematopoietic repopulation, such as after transplantation or blood loss.

**Project 2: Generation of HSCs from hiPSCs.** An additional focus of my research is to generate HSCs from hiPSCs by mimicking their developmental process (reviewed in Oguro, *Methods Mol Biol.* 2019, 2048:245). In vitro differentiation of hiPSCs could be a promising source for a virtually unlimited supply of HSCs for transplantation (**Figure 2**). Moreover, hiPSCs could be used to correct gene mutations in HSCs of patients with genetic blood disorders. However, fully functional HSCs have not yet been derived from hiPSCs using current differentiation protocols. To overcome current challenges, we are testing two approaches. Approach 1 is to develop a novel 'autologous' co-culture system in which human HSCs can be robustly generated from hiPSC-

cells derived co-cultured with HSC precursor hematopoietic niche cells derived from the same hiPSC line. This co-culture system is safe for clinical use because it contains only autologous human cells in serum-free, defined media, and it is a transgene-free method. Approach 2 is to examine effects of modulating specific signaling pathways by adding cell culture supplements, such as small molecules, proteins, and lipids, on hematopoietic differentiation of hiPSCs. To assess the functionality of hiPSC-derived HSCs, we examine their long-term engraftment capacity by transplanting into immunodeficient recipient mice.



# **Henry Smilowitz**

Associate Professor



Department of Cell Biology

#### Contact

Phone: 860-679-2710 Email: <u>smilowitz@.uchc.edu</u> Office: E2037 UConn Health 263 Farmington Avenue Farmington, CT 06030

#### **Research Interests**

a. Use of heavy-atom nanoparticles for tumor imaging, vascular imaging and as a radiation enhancer for tumor therapy.

b. Use of iron and gold nanoparticles for tumor hyperthermia

**c.** Development of novel brain tumor therapies for experimental, advanced, imminently lethal intracerebral malignant gliomas and melanomas in rats and mice using a combination of radiation therapy and immunotherapy.

- d. Tumor dormancy
- e. Novel biomarkers in human breast cancer.

f. Use of heavy atom nanoparticles to study vulnerable plaque in mouse models of atherosclerosis

Recent virtual talk at the 2020 Society for NeuroOncology meeting, November 18, 2020

https://www.dropbox.com/s/hrxqzdsf3hqngno/Henery%2011.01.2020.mp4?dl=0

Our laboratory is involved in a number of research projects in the fields of cancer, cancer immunotherapy, cancer therapy, tumor and vascular imaging, as can be seen by the following publications. Please contact the Smilowitz Lab for specific projects.

**1. Experimental Therapeutics of Brain Tumors:** We introduce glioma or melanoma cells into rat or mouse brains and allow the tumors to occupy about 2% of the brain (analogous to human brain tumors at the time of diagnosis) before therapy is started. We first treat with a form of radiation therapy followed by a form of experimental immunotherapy under development. A variety of immunological assays are performed in addition to survival studies.

#### **Selected Publications**

**Smilowitz HM**, Micca PL, Sasso D, Wu Q, Dyment N, Kuo L. 2016. Increasing radiation dose greatly improves the efficacy of immunotherapy in a subgroup of mice. Both Radiation and immunotherapy promote intracerebral melanoma dormancy. *Cancer Immunology Immunotherapy* 65:127-139.

Qiu Z, Huang H, Greiner J, Perez OA, **Smilowitz HM**, Adler B, Khanna KM. 2015. Cytomegalovirus-Based Vaccine Expressing a Modified Tumor Antigen Induces Potent Tumor-Specific CD8(+) T-cell Response and Protects Mice from Melanoma. *Cancer Immunology Research* 3:0F1-0F11. pdf

Smilowitz, H.M., Sasso, D., Lee, E., Goh, G., Micca, P.L., Dilmanian, F.A. 2013. Therapy model for advanced intracerebral B16 mouse melanoma using radiation therapy combined with immunotherapy. *Cancer Immunology Immunotherapy* 62:1187-1197 pdf

Smilowitz, H.M., Slatkin, D.N., Micca, P.L., Miura, M. 2013. Microlocalization of lipophilic porphyrins, nontoxic enhancers of boron neutron capture therapy. *International Journal of Radiation Biology* 89:611-617.pdf

Stoklasek, T., Colpitts, SL, **Smilowitz, H.M.** and Lefrancois, L 2010. MHC Class I and TCR avidity control the CD8 T cell response to IL15/IL15Ra complex *J. Immunol.* 185: 6857-6865. pdf

**Smilowitz, H.M.,** Weissenberger, J.,O'Neill, R.,Brown, J., Weis, J. and Laissue, J.A. 2007. Orthotopic transplantation of v-src expressing glioma cell lines into immunocompetent mice: establishment of a new transplantable in vivo model for malignant gliomas. *J. Neurosurgery* 106: 1-8 (PMID 18644191). pdf

Smilowitz, H.M., D.N. Slatkin, N. Lubimova, H. Blattman, E. Brauer-Krisch, A. Bravin, M. Di Michiel, J. Stepanek, G. Le Duc, J.-O. Gebbers, J.A. Laissue. 2006. Synergy of gene mediated immunoprophylaxis and microbeam radiation therapy (MRT) for advanced intracerebral rat 9L gliosarcomas. *J. Neuro-Oncology* 78:135-143 (PMID 16598429). pdf

Smilowitz, H.M., J.A. Coderre, M.M. Nawrocky, A. Pinkerton, W. Tu and D.N. Slatkin. 2002. The combination of X-ray-mediated radiosurgery and gene-mediated immunoprophylaxis of an advanced intracerebral gliosarcoma in rats. J. Neuro-Oncology. 57: 9-18 (PMID12125969). <u>pdf</u>

Laissue, J.A., H. Blattmann, M. Di Michiel, D.N. Slatkin, N. Lyubimova, R. Guzman, W. Zimmermann, T. Bley, P. Kircher, R. Stettler, R. Fatzer, A. Jaggy, **H.M. Smilowitz**, E. Brauer, A. Bravin, G. Le Duc, C. Nemoz, M. Renier, W. Thomlinson, J. Stepanek and H.P. Wagner.2001. Weanling piglet cerebellum: a surrogate for tolerance to MRT (Microbeam Radiation Therapy) in pediatric neuro-oncology. In. Penetrating Radiation Systems and Applications III, H. Roehrig, F. P. Doty, R. C. Schirato, E.J. Morton, Editors. Proceedings of SPIE, 4508: 65-73 (PMID N/A).

Miura, M., D.D. Joel, **H.M. Smilowitz**, M.M. Nawrocky, P.L. Micca, D.A. Hoch, J.A. Coderre and D.N. Slatkin. 2001. Biodistribution of copper carboranyltetraphenylporphyrins in rodents bearing human or isogeneic neoplasms. *J. Neuro-Oncology*, 52: 111-117 (PMID11508810). pdf

Weiner, R.E., D.E. Sasso, M.A. Gionfriddo, R.S. Thrall, S.S. Syrbu, **H.M. Smilowitz**, and J.Vento. 2001. Early detection of oleic acid-induced acute lung injury in rats using <sup>111</sup>In labeled antibody directed against intracellular adhesion molecule-1. *J. Nuclear Medicine*, 42: 1109-1115 (PMID 11438635). pdf

Smilowitz, H.M., D.D. Joel, D.N. Slatkin, P.L. Micca, M.M. Nawrocky, K. Youngs, W. Tu and J.A. Coderre. 2000. Long-term immunological memory in the resistance of rats to transplantable intracerebral 9L gliosarcoma (9LGS) following subcutaneous immunization with unmodified and X-irradiated 9LGS. J. Neuro-Oncology, 43:193-203 (PMID 10902851). pdf

**Smilowitz, H.M.**, P.L. Micca, M.M. Nawrocky, D.N. Slatkin, W. Tu and J.A. Coderre. 2000. The combination of boron neutron-capture therapy and immunoprophylaxis for advanced intracerebral gliosarcomas in rats. J. Neuro-Oncology, 43:231-240 (109032854). <u>pdf</u>

2. Gold and Iodine Nanoparticle Enhanced Radiation Therapy; Vascular and Tumor Imaging; Gold and Iron Nanoparticle Hyperthermia. We are working collaboratively with a company on Long Island that has developed novel preparations of heavy-atom nanoparticles. These non-toxic particles can be injected iv at very high doses. Larger particles circulate for extended periods, while smaller particles are excreted by the kidney. We are working on several projects to develop novel therapies and diagnostic tests that can be performed with these agents:

• Gold and Iodine Nanoparticle Enhanced Radiation Therapy: We have shown that gold nanoparticles can greatly increase the radiation dose a tumor receives and are therefore useful as radiation enhancers. We are currently working on breast cancer, bladder cancer, squamous cell carcinoma and glioma models using gold and other heavy-atom nanoparticles.

• Gold and Iodine Nanoparticle Enhanced Imaging: We are working on several imaging projects including the development of virtual colonoscopy, breast cancer imaging, gold-based angiography, and kidney imaging.

• Iron and Gold Nanoparticle Mediated Hyperthermia: We are developing novel therapies whereby gold and iron nanoparticles can be used to treat tumors with hyperthermia.

#### **Selected Publications**

Hainfeld JF and Smilowitz HM. 2021. Gold nanoparticles and infrared heating: Use of the Hydrosun wIRA- Irradiator In: Water filtered infrared-A radiation: From basics to practice. Peter Vaupel, Editor. Accepted for Publication.

Ridwan SM Hainfeld JF, Ross V, StanishevskiyY, **Smilowitz HM**. 2021. Novel Iodine Nanoparticles Target Vascular Mimicry in Intracerebral Triple Negative Human MDA-MB-231 Breast Tumors. Scientific Reports. Accepted. Being Published Jan 13, 2021.

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**3. Novel Biomarkers in human breast cancer.** Blood samples from women with breast cancer are being screened for the presence of novel biomarkers that may be linked to more aggressive disease.

**4. Heavy Atom Nanoparticles to Image Vulnerable Plaque:** Gold and iodine nanoparticles and gold and iodine nanoparticle laden macrophage are being used to study vulnerable plaque in atherosclerotic mice.

## Dr. Lisa Mehlman

# **Department of Cell Biology**

# **Accepting Rotation Students**

Lisa Mehlmann, PhD – Associate Professor of Cell Biology

# Lab Interests:

1. Cytoplasmic changes that occur during mammalian oocyte maturation that are necessary to make a fertilizable egg



2. Molecular mechanisms by which oocytes undergo endocytosis and exocytosis



3. Effects of puberty blockers and androgens on female reproduction, using mouse as a model

# **UCONN** THE GRADUATE SCHOOL

Dr. Leslie Caromile, PhD, is an assistant professor in the Department of Cell Biology and the Center for Vascular Biology at UCONN Health where she investigates the role of prostate specific membrane antigen (PSMA) in prostate cancer tumor growth and metastasis. The Caromile Lab currently has two federally funded projects: <u>Project 1</u>: Investigation of PSMA at the prostate cancer tumor-vasculature interface. Recently, her lab has developed a novel multi-cell type, scaffold free, 3D bioprinted prostatic tumor model that accurately represents the human PSMA (+) primary tumor vasculature as well as the primary tumor microenvironment. This model provides the laboratory with a unique system for the interrogation of novel PSMA small molecule inhibitors on multiple tumorigenic endpoints.



**Project 2:** According to published data, African American (AA) men AA men are 1.6 times more susceptible to develop prostate cancer, and about 2 times more likely to die from this disease than men of European (EUR) decent. In fact, even when environmental factors are corrected for, the disparity in mortality rate between AA and EUR men is higher for prostate cancer than that for any other malignancy thus suggesting a molecular component. The Caromile lab is investigating if germ line single nucleotide polymorphisms, or SNPS, within certain components of the PSMA signaling pathway might contribute to the increased risk of prostate cancer in AA men vs that of EUR men. Investigation into these molecular mechanisms not only has the potential to improve the outcomes of all men with lethal prostate cancer but also has the capability to reduce prostate cancer disparities by improving detection, morbidity and mortality of lethal prostate cancer in AA and other at-risk populations through the identification of unique, tailored treatment and prevention strategies for each patient.

Contact Information: Leslie Caromile, PhD Email: caromile@uchc.edu Office: L-5007 Lab: L-5008