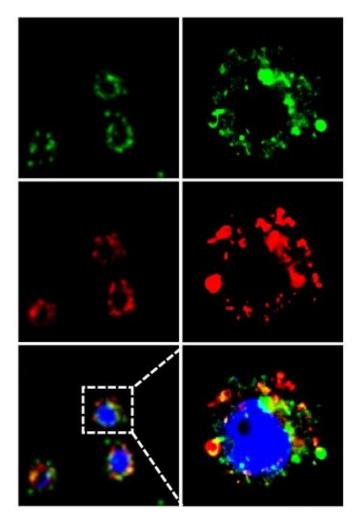


Hormone Related Cancers 2020 Retreat

Agenda Program Overview Themes HRC Members

Co-Leaders: Stuart Martin, Ph.D. and Arif Hussain, M.D.



The pH-triggered release of siRNA nanoparticles (red) from lysosomes (green).

Xu, J., Liu, Y., Li, Y. He, X. *et al.* Precise targeting of *POLR2A* as a therapeutic strategy for human triple negative breast cancer. *Nat. Nanotechnol.* **14**, 388–397 (2019).

2020 HRC Retreat Agenda

Hormone Related Cancers Program 2020 Annual Retreat September 24, 2020 9:00 AM - 1:30 PM Zoom

9:00 9:15 9:30	Introductory Remarks – Stuart Martin, PhD Breast Program Clinical Overview – Katherine Tkaczuk, MD Clinical Trials Program in Prostate Cancer – Arif Hussain, MD
Theme 1: Target Mechanisms That Regulate Cancer Stem Cells and Promote Metastasis 9:40 Giuliano Scarcelli, PhD – "Brillouin microscopy for cell mechanical analysis"	
10:00	Xiaoming (Shawn) He, PhD - "Bioinspired micro and nanoscale technologies for cancer therapy and detection"
10:20	Antonino Passaniti, PhD - "An alternative metabolic target for a novel transcriptional inhibitor of breast cancer"
10:40	BREAK
Theme 2: Identi 11:00 11:20 11:40	fy Targets in Hormone-Related Cancers That Mediate Innate and Acquired Resistance Vincent Njar, PhD, – "Update on The Development of Galeterone and Next Generation Galeterone Analogs (NGGAs or GALNEX) for Prostate and Pancreatic Cancers" Jianfei Qi, PhD- "Histone demethylase JMJD1A in prostate cancer" Ginette Serrero ScD – "GP88 studies present and future"
Theme 3: Develop Strategies to Improve Diagnosis, Inform Treatment, and Evaluate Treatment Response	
12:00	Achuth Padmanabhan, PhD - "p53 Mutations In Ovarian Cancer: Turning A Liability Into An Opportunity"
12:20 12:40	Dirk Mayer, Dr. rer. nat. - "Applications of Hyperpolarized 13C MRI in Prostate Cancer" Stuart Martin, PhD – "Rapid tumor cell phenotyping to inform treatment and minimize metastatic risk"
1:00	Wrap up - Discussion

Hormone Related Cancers (HRC) Program Overview

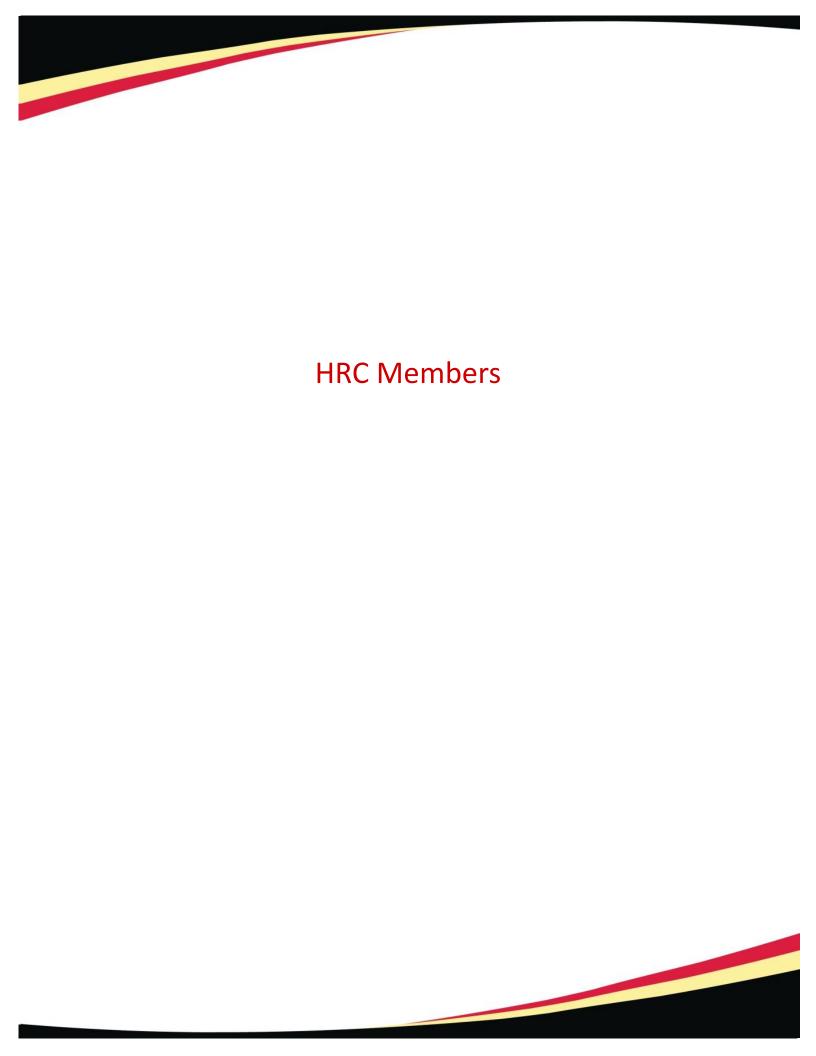
The Hormone Related Cancers (HRC) Program was established in 2004 to probe the common biology between malignancies of the breast and prostate gland. These malignancies, the most common in women and men respectively, are a major cause of morbidity and mortality. Investigators at the UM Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCCC) have made key contributions to understanding hormone-responsive cancers, and these contributions have led to practice-changing discoveries, such as the development of the first aromatase inhibitors.

As major disparities exist in the incidence and outcome of hormone-responsive cancers in different populations, an overarching goal of the HRC Program and UMGCCC is to identify and reduce these disparities. The HRC Program addresses this through the design of clinical trials that reflect the high breast and prostate cancer prevalence in UMGCCC's catchment area and through translational studies that examine cancer subtypes that contribute to overall cancer disparities.

Themes

In pursuit of its scientific goals to reduce morbidity and mortality from hormone-related cancers, the HRC Program's investigations focus on three themes:

- 1. Target Mechanisms That Regulate Cancer Stem Cells and Promote Metastasis.
- 2. Identify Targets in Hormone-Related Cancers That Mediate Innate and Acquired Resistance.
- 3. Develop Strategies to Improve Diagnosis, Inform Treatment, and Evaluate Treatment Response.



Stuart S. Martin, PhD

Professor of Physiology Co-Leader, Hormone Related Cancers University of Maryland School of Medicine ssmartin@som.umaryland.edu



Personal Statement:

The Martin lab works to improve the treatment of breast cancer metastasis by identifying novel molecular targets through interdisciplinary collaborations between tumor cell biologists, bioengineers and clinicians. Approaches include targeting the cytoskeleton of circulating tumor cells (CTCs) for drug development and rapid testing of patient tumor cell drug responses. Dr. Martin's lab discovered unique microtentacles that promote the metastatic reattachment of breast cancer CTCs in distant tissues. These microtentacles arise from an imbalance in the cytoskeletal physical forces of microtubule expansion and the contraction of the actin cortex that lies beneath the plasma membrane (Chakrabarti et al., Clin Cancer Res, 2015). Collaborating with the UMCP bioengineering lab of Jewell (TII), the Martin lab invented microfluidic cell tethering technology that captures CTCs to facilitate the study of dynamic properties of live CTCs and measure drug responses within 1 hour. Ongoing collaborations with Konstantopoulos (Johns Hopkins) also use tumor cell phenotyping for metastatic prediction in breast cancer (Yankaskas et al., Nat Biomed Eng, 2019) and glioblastoma (Wong et al., Nat Biomed End, 2020).

Projects:

1R01CA154624-01A1, NIH/NCI, Principal Investigator (Martin), 7/1/12-6/30/24. Title: <u>Targeting microtubule stabilization to reduce breast tumor metastasis</u>.

BX002746, VA BLR&D Merit, Principal Investigator (Martin), 10/1/18-9/30/23 Title: Rapid analysis of patient tumor cell drug responses to reduce metastatic risk.

1R01CA124704-10, NIH/NCI, 9/1/15-8/31/21

Title: Stabilized microtubule protrusions in detached mammary epithelial cells.

*1R01CA124704-09S1: Administrative supplement (9/1/18-8/31/21) for zebrafish metastasis model.

Publications

- **1.** Ju J.A., et al..., Vitolo, M.I., Jewell, C.M., **Martin, S.S.** (2020) Partial thermal imidization of polyelectrolyte multilayer cell tethering surfaces (TetherChip) enables efficient cell capture and microtentacle fixation for circulating tumor cell analysis. **Lab on a Chip** 20(16):2872-2888.
- **2.** Pratt SJP, Lee RM, et al..., Vitolo MI, Schneider MF, Stains JP, Ward CW, **Martin SS** (2020) *Mechanoactivation of NOX2-generated ROS elicits persistent TRPM8 Ca2+ signals that are inhibited by oncogenic KRas. Proc. Natl. Acad. Sci. USA* (accepted for publication).
- **3.** Yankaskas CL, et al..., Kontrogianni-Konstantopoulos A, **Martin SS**, Konstantopoulos K. (2019) *A microfluidic assay for the quantification of the metastatic propensity of breast cancer specimens. Nature Biomed Eng. 2019 May 6. doi: 10.1038/s41551-019-0400-9.*

Arif Hussain, MD

Professor, Medicine Co-Leader, Hormone Related Cancers University of Maryland School of Medicine ahussain@som.umaryland.edu



Personal Statement:

Our research interests are in prostate cancer biology, particularly as they relate to adaptive pathways to clinically relevant therapeutics, while our clinical work is focused on genitourinary malignancies, primarily prostate and kidney cancers. Regarding the former, our efforts are to identify and target relevant nodes, particularly nodes recruited via cross-talk amongst adaptive intracellular pathways, in response to treatment selection (androgen receptor axis targeting, cytotoxics, or both). We are also attempting to identify adaptive signaling nodes in pre-clinical models that may be *common* across prostate cancer cells selected for resistance to agents with different anti-cancer mechanisms of action via transcriptomic and bioinformatic approaches. We are participating in research efforts at Hopkins to understand the potential relevance of polypoid giant cancer cells in the context of treatment resistance in prostate cancer. Our clinical work includes trials ranging from phase 1 to phase 3 studies that reflect different disease states of clinical prostate cancer, including both metastatic castration sensitive and metastatic castration resistant prostate cancer.

Projects:

VA Merit Review Grant: Multi-faceted Targeting of Treatment-Sensitive and Treatment-Resistant Prostate Cancer (PI)

DoD: Polypoid Giant Cancer Cells Actuate Prostate Cancer Tumor Resistance and Lethal Phenotype (Sub-PI)

Six active investigator-initiated and sponsored clinical trials in prostate cancer (Institutional PI)

Publications:

Hussain A, Lee RJ, Graff JN, Halabi S. The evolution and understanding of skeletal complication endpoints in clinical trials of tumors with metastasis to the bone. *Critical Rev Oncolog/Hemat*. 2019; 139:108-116. PMID: 31170574.

Njar V, **Hussain A**. Male hormonal therapies: In A. Emadi & J. Karp (Eds.), *Cancer Pharmacology*. New York, NY: Springer Publishing Company [in press]

Jeon HY, **Hussain A**, Qi J. Role of H3K9 demethylases in DNA double-strand break repair. *J Cancer Biol.* 2020; 1: 10-15.

Toni M. Antalis, PhD
Professor of Physiology
Associate Director for Training and Education
University of Maryland School of Medicine, UMGCCC
tantalis@som.umaryland.edu



Research in my laboratory focuses on the pathophysiology of protease-induced signaling pathways that regulate tumor dissemination and metastasis, inflammation, and vascular biology. I have a broad background in biochemistry, cell biology, molecular biology, and animal models of disease. I was formally trained as a biochemist-molecular biologist and have had previous translational research experience in the biotechnology industry. I am interested in graduate and postgraduate research training and as associate director of training and education for the UMGCCC, I guide efforts to coordinate the expanding portfolio of cancer education and training pipeline programs that span middle school scholars through to post-doctorates. I also direct the Molecular Medicine Graduate Program in the Graduate Program in Life Sciences (GPILS) and am co-principal investigator of the NCI-funded T32 Training Grant in Cancer Biology that supports the training of PhD and physician-scientists.

Projects

My laboratory studies protease signaling pathways in ovarian cancer and molecular mechanisms associated with deep vein thrombosis and its resolution. We are internationally recognized for pioneering discoveries in the area of membrane-anchored serine proteases (*e.g.*, matriptase, testisin, TMPRSS2, hepsin), a group of multidomain proteolytic enzymes linked directly to cells that play abnormal roles in human cancers and have been suggested as biomarkers indicative of disease severity. One focus is a NCI-funded study of mechanisms underlying proteolytic activation of the G-protein coupled Protease Activated Receptor (PAR-2) signaling pathway and the contributions of this pathway to ovarian cancer dissemination and metastasis. We have patented a prodrug therapy based on the anthrax toxin that is activated by ovarian tumor-associated serine proteases. Cancer increases the risk of venous thromboembolism, and in another aspect funded by a VA Merit Award, we are studying proteolytic mechanisms that underlie pathophysiological inflammatory processes associated with adverse outcomes in venous thrombus resolution.

Publications

Conway GD, Buzza MS, Martin EW, et al. PRSS21/testisin inhibits ovarian tumor metastasis and antagonizes proangiogenic angiopoietins ANG2 and ANGPTL4. *J Mol Med (Berl)*. 2019;97(5):691-709.

Martin EW, Buzza MS, Driesbaugh KH, et al. Targeting the membrane-anchored serine protease testisin with a novel engineered anthrax toxin prodrug to kill tumor cells and reduce tumor burden. *Oncotarget*. 2015;6(32):33534-33553.

Pawar NR, Buzza MS, Antalis TM. Membrane-Anchored Serine Proteases and Protease-Activated Receptor-2-Mediated Signaling: Co-Conspirators in Cancer Progression. *Cancer Res.* 2019;79(2):301-310.

Marguerite Buzza, PhD Research Associate, Department of Physiology and CVID University of Maryland School of Medicine mbuzza@som.umaryland.edu



Personal Statement

My research career has focused on understanding the (patho) physiological functions of serine proteases, and over the past several years in collaboration with Dr. Toni Antalis, I have been investigating the role of membrane-anchored serine proteases in the metastasis and progression of ovarian cancer. Ovarian cancer remains the most deadly gynecological cancer, and despite recent advances, there has been little improvement in survival rates over the last 30 years. We have recently discovered that the GPI-anchored membrane serine protease, testisin, maintains the function of microvascular endothelial cell adherens junctions, whose absence results in vascular leak during angiogenic responses. Understanding this activity is critically important since vascular permeability both promotes tumor-induced angiogenesis and is also a factor that strongly impairs drug delivery to tumors, decreasing the efficacy of conventional therapies. It is envisioned that understanding the molecular mechanisms involved in testisin-mediated regulation of microvascular permeability during tumor-induced angiogenesis will reveal novel anti-permeability factors and alternate strategies for anti-tumor therapies.

Projects

Investigation of the molecular mechanisms by which endothelial cell GPI-anchored membrane-anchored serine protease testisin/PRSS21 mediates microvascular endothelial barrier function during tumor-induced angiogenic responses. This project was originally funded by an ACS-IRG in 2019.

Publications

Peroutka RJ, **Buzza MS**, Mukhopadhyay S, Johnson TA, Driesbaugh KH, Antalis TM. Testisin/Prss21 deficiency causes increased vascular permeability and a hemorrhagic phenotype during luteal angiogenesis. PLoS One. 2020 Jun 8;15(6):e0234407. doi: 10.1371/journal.pone.0234407. PMID: 32511276

Conway GD, **Buzza MS**, Martin EW, Duru N, Johnson TA, Peroutka RJ, Pawar NR, Antalis TM. PRSS21/testisin inhibits ovarian tumor metastasis and antagonizes proangiogenic angiopoietins ANG2 and ANGPTL4. *J Mol Med*. 2019 Mar 25. doi:10.1007/s00109-019-01763-3. PMID: 30911775.

Pawar NR, **Buzza MS**, Antalis TM. Membrane-Anchored Serine Proteases and Protease-Activated Receptor-2-Mediated Signaling: Co-Conspirators in Cancer Progression. *Cancer Res.* 2019 Jan 15;79(2):301-310. doi:10.1158/0008-5472. Review. PMID: 30610085.

Meenakshi Chellaiah PhD Professor, Oncology and Diagnostic Sciences University of Maryland School of Dentistry mchellaiah@umaryland.edu



Personal Statement

My lab projects primarily focus on the molecular mechanisms controlling actin dynamics in migration/bone resorption of osteoclasts (OC) and migration/invasion of prostate cancer cells (PC3). PC3 cells were derived from human bone metastases. Sealing ring formation is a requirement for OC bone resorption. We are the first to demonstrate that the formation of nascent sealing zones (NSZs) occurs prior to the formation of mature sealing rings in resorbing OCs. Also, we identified the role of invadopodia in the invasion of PC3 cells. Our studies on OCs and PC3 cells reveal varied types of actin dynamics. We have published comprehensively and presented orally in these areas in the form of peer-reviewed papers and scientific meeting abstracts. Publications and presentations greatly increased the importance of the research in the field of OC migration/bone resorption and PC3 prostate cancer cell invasion.

Projects

Project I: Invasion and metastasis of prostate cancer cells to bone and bone loss

Project II: Determination of the relationship of sequence-specific CD44-ICD interaction with RUNX2 in the expression of MMP-9 and metastasis of PC3 cells

Project III: L-plastin: a novel target for intervention in the treatment of osteoporosis (R01)

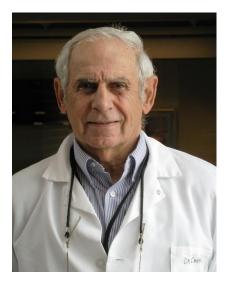
Publications

Senbanjo LT, Aljohani H, AlQranei M, Majumdar S, Ma T, and **Chellaiah MA**. Identification of sequence-specific interactions of the CD44-intracellular domain with RUNX2 in the transcription of matrix metalloprotease-9 in human prostate cancer cells. Cancer Drug Resist 2020 (July) ;3: http://dx.doi.org/10.20517/cdr.2020.21

Chellaiah MA. Osteoclast Cytoskeleton, Podosome, Motility, Attachment, and Signaling By Receptors, 2020. In: Zaidi, M (ed.) Encyclopedia of Bone Biology [Oxford: Academic Press].Vol. [1], pp. 236-250.

Chellaiah MA, Moorer MC, Majumdar S, Aljohani H, Morley SC, Yingling V, and Stains JP. L-Plastin deficiency produces increased trabecular bone due to attenuation of sealing ring formation and osteoclast dysfunction Bone Research (2020) 8:3 (Springer Nature) (https://doi.org/10.1038/s41413-019-0079-2

Leslie C. Costello
Professor, Oncology and Physiology
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I am included in the top 5% leading biomedical scientists in the world. I discovered the medication (3% Clioquinol Cream) that results in the termination of advanced prostate cancer; i.e. the first and only existing successful treatment for that malignancy. That treatment was based on my extensive studies, which led to my discovery that the hormone, prolactin is the major factor identification in the development of advanced prostate cancer. Those achievements are the results of my record of receiving 27 NIH research grants that total more than 100 budget years. That is a record has been achieved by very few scientists. I have about 200 published reports and book chapters. About 100 focus on zinc and cancer relationships in prostate, liver, kidney, and breast carcinomas. Those studies led to the discovery that carcinomas exhibit a marked decreased zinc compared to normal cells.; which protects the malignancy from the toxic effects of a high zinc level. My research and clinical interests are to continue and to expand studies regarding those relationships into other medical disorders. One such focus is the potential of 3% Clioquinol Cream for the treatment and prevention of COVID-19 infections.

Projects

NIH Grant, Testosterone Control of Prostate Citrate Production NIH Grant, Prolactin Regulation of Prostate Citrate Production NIH Grant, Novel Aspartate Transport in Prostate Cells

Publications

Costello LC, Franklin RB, Yu GW. A Novel Patient Case Report to Show the Successful Termination of Untreatable Androgen-independent Prostate Cancer: Treatment with Cabergoline (Dopamine agonist). Mathews J Case Rep. 2019;4(1):42.

Costello LC, Franklin. A Proposed Efficacious Treatment with Clioquinol (Zinc Ionophore) and Cabergoline (Prolactin Dopamine Agonist) for the Treatment of Terminal Androgen-independent Prostate Cancer. Why and How? J Clin Res Oncol. 2019;2(1).

Costello LC, Franklin RB. . A comprehensive review of the role of zinc in normal prostate function and metabolism; and its implications in prostate cancer. Arch Biochem Biophys. 2016 Dec 1;611:100-112.

Hancai Dan, PhD
Assistant Professor, Pathology/Oncology
University of Maryland School of Medicine
<a href="https://doi.org/10.2016/j.jc/html//ht



I study the role of the crucial signaling pathways especially, the role of EGFR/PI3K/Akt/mTOR and IKK/NF-κB pathways in the regulation of cancer cell proliferation, survival, metastasis and resistance to chemotherapy in prostate cancer and head and neck cancer. In particular, I am interested in identifying effective kinase inhibitors to inhibit cancer growth and metastasis and override chemoresistance. We use cancer cell lines, patient-derived cancer xenografts and multiple animal models for our study. In collaboration with oncologists at our cancer center, we will begin to translate our findings into new therapeutic approaches in clinic.

Projects

The role of IKK/NF-κB in regulation of castration and Docetaxel resistance in prostate cancer.

The role of PI3K and Wee1 kinases in regulation cell proliferation and chemoresistance in prostate cancer.

The role of IKK/NF-kB in regulation of cisplatin and EGFR inhibitor resistance in head and neck cancer.

Publications

Gao Y, Gartenhaus RB, Lapidus RG, Hussain A, Zhang Y, Wang X, and Dan HC. Differential IKK/NF-κB Activity is mediated by TSC2 through mTORC1 in PTEN-null Prostate Cancer and Tuberous Sclerosis Complex Tumor Cells. *Mol Cancer Res*. 2015 Dec; 13(12):1602-14.

Zhang Y, Lapidus RG, Liu P, Choi EY, Adediran S, Hussain A, Wang XH, Liu X, Dan HC. Targeting IkB kinase β /NF-kB signaling in human prostate cancer by a novel IkB kinase β inhibitor CmpdA. *Mol Cancer Ther*. 2016 Jul; 15(7):1504-14.

Li Z, Liao J, Yang Z, Choi EY, Lapidus RG, Liu X, Cullen KJ, Dan H. <u>Co-targeting EGFR and IKKβ/NF-κB signaling pathways in head and neck squamous cell carcinoma: a potential novel therapy for head and neck squamous cell cancer.</u> Br J Cancer. 2019 Feb;120(3):306-316.

Renty Franklin, PhD
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The focus of our research is the biology of the prostate gland and prostate cancer. The prostate gland normally accumulates and secretes an extraordinarily high level of citric acid. In addition, the prostate also accumulates very high levels of zinc. These physiological functions are regulated by endocrine hormones, specifically testosterone and prolactin. A major area of interest in our laboratory is the molecular mechanisms by which these hormones regulate citrate production and zinc accumulation. These differentiated functions are universally lost with the development of prostate cancer. Thus, we are interested in the metabolic alterations that account for the metabolic transformation in prostate malignancy. Our work has established that zinc plays an important role in the normal function of the prostate. Zinc inhibition of mitochondrial aconitase is the mechanism whereby the prostate is capable of accumulating citrate. The loss of zinc accumulating ability is an early change in the progression to prostate cancer. A goal of our current research is to understand the molecular mechanism and regulation of zinc uptake and whether it can be effective targets for therapy and/or diagnosis.

Projects

Prolactin receptor signaling of prolactin metabolic effects in the prostate

Publications

Costello, L. C. and R. B. Franklin (2019). "A Proposed Efficacious Treatment with Clioquinol (Zinc Ionophore) and Cabergoline (Prolactin Dopamine Agonist) for the Treatment of Terminal Androgen-independent Prostate Cancer. Why and How?" J Clin Res Oncol **2**(1).

Costello, L. C. and R. B. Franklin (2018). "Energy Dispersive X-Ray Fluorescence Zn/Fe Ratiometric Determination of Zinc Levels in Expressed Prostatic Fluid: A Direct, Non-Invasive and Highly Accurate Screening for Prostate Cancer." <u>Acta Sci Cancer Biol</u> **2**(9): 20-26.

Srinivasan, D., L. Senbanjo, S. Majumdar, R. B. Franklin and M. A. Chellaiah (2018). "Androgen receptor expression reduces stemness characteristics of prostate cancer cells (PC3) by repression of CD44 and SOX2." J Cell Biochem.

Amy M. Fulton, PhD Professor, Pathology University of Maryland School of Medicine afulton@som.umaryland.edu



Personal Statement

My laboratory is identifying inflammatory pathways that promote breast cancer growth and metastasis to develop therapeutic strategies, with a focus on Triple Negative Breast Cancer. Our goal is to understand the role of COX-2 driven inflammation in promoting tumor progression. Specific targeting of the COX-2 pathway at the level of prostaglandin E receptor EP4 avoids the potential toxicities of COX-2 inhibition while preserving anti-metastatic activity. Breast cancer stem-like cells have elevated levels of EP4 and are more sensitive to inhibition by EP4 antagonists than the non-stem cell population. Cancerassociated immune suppression is also mediated by EP4 expressed on immune effector cells. These findings have led to the design of a clinical trial to examine efficacy of an EP4 antagonist in advanced malignancy by AskAt, Inc. We have also discovered that the chemokine receptor CXCR3 promotes metastasis and that the CXCR3B isoform selectively drives breast cancer stem cells. We are examining novel allosteric CXCR3 modulators developed by our collaborators in Germany that selectively inhibit activation of CXCR3 by individual ligands. Working with Dr. Kundu, we have identified a novel and potent inhibitor of metastasis isolated from the Taro plant. We are now working with Dr. Hoag, School of Pharmacy, to encapsulate Taro Extract in preparation for first in human clinical trials in collaboration with Drs. Emadi, Hussain, Tkaczuk, Rosenblatt and Lapidus. Drs. Weber and Ruiz are employing novel approaches to identify the active moiety in TE and to discern mechanism of action to guide the development of recombinant Taro proteins with improved efficacy, stability and reduced toxicity that can be scaled up for evaluation in future clinical trials.

Projects:

Namita Kundu, Ph.D., David Weber, Ph.D., Raquel Ruiz, Ph.D. Taro recombinant proteins Arif Hussain, MD, Stephen Hoag, Ph.D., Ashkhan Emadi, M.D., Kate Tkaczuk, M.D., Paula Rosenblatt, M.D., Rena Lapidus, Ph.D.-clinical trial of Taro Extract

Jocelyn Reader, Ph.D., Dana Roque, M.D., Gautam Rao, M.D. role of EP4 in gynecologic malignancies John Laterra, M.D./Ph.D. Identification and therapeutic targeting of KCNK9 in multiple malignancies Regine Brox, Ph.D. Nuska Tschammer, Ph.D. Novel allosteric CXCR3 modulators

Publications:

Laterra J, Sun H, Luo L, Lal B, Ma X, Chen L, Hann C, Fulton A, Leahy D and Li M. A monoclonal antibody against KCNK9 K+ channel extracellular domain inhibits tumor growth and metastasis. Nature Commun., Feb. 4, 2016.

Kochel TJ, Ma X, Kundu N, Reader J, Goloubeva O and Fulton AM. MRP4 and PGT determine PGE2 levels in the microenvironment of triple negative breast cancer. Oncotarget 8:6540-6554, 2017.

Kundu N, Ma X, Brox R, Fan X, Kochel T, Reader J, Tschammer N and Fulton AM. The chemokine receptor CXCR3 isoform B drives breast cancer stem cells. Breast Cancer: Basic and Clinical Res., in press, 2019.

Olga Goloubeva, PhD

Professor, Department of Epidemiology University of Maryland School of Medicine ogoloubeva@som.umaryland.edu



Personal Statement

I have 20 years of experience in statistical design and analysis of laboratory preclinical, clinical, and epidemiological studies in medical research as a biostatistician. My statistical expertise lies in the design and analysis of preclinical studies and Phase I–III clinical trials; evaluation of diagnostic tests, biomarkers, and their combination; prognostic models of cancer and other diseases; longitudinal, clustered, and hierarchical data modeling; and integration of data from proteomics and genomics into modeling of patients' survival experience. I have been also working with large SEER-Medicare link database to assess treatment and toxicities and to estimate survival experience of the beneficiaries diagnosed with head and neck cancer as compared to healthy and matched controls. I have published over a hundred twenty peer-reviewed research papers since 2000. I have been serving as a board member and as a statistical consultant on multiple institutional, national, and international scientific and funding committees for many years and strongly believe in the importance of statistical assessment and review.

Projects

Evaluation of epidemiologic trends in Major SGC and to evaluate treatment patterns including use of surgery, radiation, chemotherapy as well as treatment-related complications for these malignancies including facial nerve paralysis.

Cisplatin every three weeks versus weekly cisplatin or carboplatin with definitive radiotherapy for squamous cell carcinoma of the head and neck is associated with improved overall survival in a representative national population.

The addition of 400 cGy total body irradiation to he reduced intensity allogeneic stem cell transplantation using busulfan and fludarabine is safe and reduces relapse without increasing non-relapse mortality in hematologic diseases: A single center experience

Publications

Badros, Ashraf; Elizabeth Hyjek; Ma, Ning; Alex Lesokhin; Ahmet Dogan; Rapoport, Aaron; Kocoglu, Mehmet; Lederer, Emily; Philip, Sunita; Milliron, Todd; Dell, Cameron; **Goloubeva, Olga;** Singh, Zeba. Pembrolizumab, Pomalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma. *Blood*. 2017 Sep 7; 130 (10):1189-1197.

Dan P Zandberg, Kevin Cullen, Soren M. Bentzen, **Olga G. Goloubeva**. Definitive radiation with concurrent cetuximab vs. radiation with or without cytotoxic chemotherapy in older patients with squamous cell carcinoma of the head and neck: analysis of the SEER-Medicare linked database. 2018 September. *Oral Oncol.* 2018 Nov; 86:132-140.

Kazi A, **Goloubeva O**, Schech A, Yu S, Sabnis GJ. Efficacy of a novel orally active SERD AZD9496 against hormone dependent post-menopausal breast cancer depends on inhibition of cellular aromatase activity. *J Steroid Biochem Mol Biol*. 2020 May 24; 202: 106697.

Xiaoming (Shawn) He, PhD

Professor, Fischell Department of Bioengineering University of Maryland College Park shawnhe@umd.edu



Personal Statement

My research has been focused on developing multiscale (nano, micro, and macro) biomaterials/devices to encapsulate the whole spectrum of today's medicine for safe, effective, and controlled delivery to treat diseases. My laboratory has developed novel non-planar microfluidic, coaxial electrospray, layer-by-layer conformal coating, and micro-nano matrix technologies to encapsulate various bioactive agents in capsules/matrices with a uniform size and biomimetic structure that can be tailored for the specific applications. Specifically for cancer, we have extensive experience in developing 1), smart micro-electromechanical systems/devices for early detection of cancer; 2), biomimetic 3D vascularized tumor model for cancer drug discovery; and 3), multiscale (micro-nano-macro) technologies for delivery of cells, macromolecules, and small hydrophobic and hydrophilic molecules, to treat cancer. My laboratory also has extensive experience with enriching and characterizing breast, prostate, ovarian, colorectal, and brain CSCs/TICs, and developing nanoparticles to effectively target and eliminate the CSCs/TICs in vitro and in vivo.

Projects

NIH R01 CA243023: Nanotechnology for targeted therapy and fundamental understanding of therapeutic resistance in triple negative breast cancer (PI)

NIH R01 CA206366: Nanotechnology enabled targeting of p53 deficiency in human cancer (PI)

NIH R01 EB023632: Microfluidic encapsulation of ovarian follicles for biomimetic 3D culture and cryopreservation (PI)

Publications

Wang H, Gao Z, Liu X, Agarwal P, Zhao S, Conroy DW, Ji G, Yu J, Jaroniec CP, Liu Z, Lu X, Li X, He X. Targeted production of reactive oxygen species in mitochondria to overcome cancer drug resistance. *Nature Communications* 2018; 9 (1): 562. PMCID: 5805731.

Xu J, Liu Y, Li Y, Wang H, Stewart S, Van der Jeught K, Agarwal P, Zhang Y, Liu S, Zhao G, Wan J, Lu X, He X. Precise targeting of *POLR2A* as a therapeutic strategy for human triple negative breast cancer. *Nature Nanotechnology* 2019; 14 (4): 388-397. PMCID: 6449187.

Wang H, Agarwal P, Jiang B, Stewart S, Liu X, Liang Y, Hancioglu B, Webb A, Fisher JP, Liu Z, Lu X, Tkaczuk KHR, He X. Bioinspired culture and isolation of highly tumorigenic and metastatic cancer stem cells capable of multilineage differentiation. *Advanced Science*. 2020; 7: 2000259. PMCID: 7284220.

Huang Chiao (Joe) Huang

Assistant Professor, Fischell Dept. of Bioengineering University of Maryland College Park hchuang@umd.edu



Personal Statement

Dr. Huang's research interests include photodynamic therapy, precision cancer nanomedicine, mechanism-based combination therapy, and site-directed photochemistry and fluorescence diagnostics.

Projects

NIH/NCI, K99/R00 Award: Multifunctional, GBM-activatable Nanocarriers for Image-guided Photochemotherapy

NIH/NIBIB, R21 Trailblazer Award: Photodynamic Priming for Bidirectional Modulation of Drug Transport Across the Blood-Brain Tumor Barrier

NSF/CBET: Photosensitizing Nanoconstructs for Regulation of ATP-Binding Cassette Transporters in the Brain

Publications

Breaking the Selectivity-Uptake Trade-Off of Photoimmunoconjugates with Nanoliposomal Irinotecan for Synergistic Multi-Tier Cancer Targeting. Liang BJ, Pigula M, Baglo Y, Najafali D, Hasan T, Huang HC. Journal of Nanobiotechnology. 2020 Jan 02;18(1):1. PMID: 31898555.

Porphyrin-lipid Assemblies and Nanovesicles Overcome ABC Transporter-Mediated Photodynamic Therapy Resistance in Cancer Cells. Baglo Y, Liang BJ, Robey RW, Ambudkar SV, Gottesman MM, Huang HC. Cancer Letters. 2019 Aug 10;457:110-118. PMID: 31070369.

Photodynamic Priming Mitigates Chemotherapeutic Selection Pressures and Improves Drug Delivery. Huang HC, Rizvi I, Liu J, Anbil S, Kalra A, Lee H, Baglo Y, Paz N, Hayden D, Pereira S, Pogue BW, Fitzgerald J, Hasan T. Cancer Research. 2018 Jan 15;78(2):558-571. PMID: 29187403.

Aikaterini Kontrogianni-Konstantopoulos, PhD

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Personal Statement

My research focuses on the elucidation of the roles of cytoskeletal proteins as structural and signaling mediators. Earlier studies implicated OBSCN, encoding the giant cytoskeletal proteins obscurins (720-870 kDa), in cancer development due to its high mutational prevalence in different types of cancer, including breast cancer. In light of this observation, we began to unravel the roles of the OBSCN gene in breast cancer formation and progression. Our studies were the first to show that giant obscurins are abundantly expressed in normal breast epithelium but are virtually absent from advanced stage human breast cancer biopsies. Normal breast epithelial cells depleted of giant obscurins exhibit dramatically increased survival (when treated with common chemotherapies), stemness, motility and invasiveness. Consistent with these findings, obscurin-knockdown (KD) breast epithelial cells fail to form adherens junctions and undergo Epithelial to Mesenchymal Transition (EMT). More importantly, obscurin-KD, but not scramble control, breast epithelial cells expressing an active form of K-Ras form extensive local (primary) tumors and lung metastases in vivo. We therefore postulate that giant obscurins function as tumor suppressors in normal breast epithelial cells, and that their loss potentiates tumorigenesis and metastasis. Our current studies aim to elucidate the molecular and cellular alterations associated with loss of giant obscurins from breast epithelial cells, and to design effective approaches to restore their expression and/or functionality using genome editing and peptide therapy. Collectively, our research has important discovery science and translational implications in the establishment of obscurins as novel tumor suppressors in breast epithelim and the development of new, more effective, and targeted therapies.

Projects

Obscurins are novel tumor metastasis suppressors in breast epithelial cells acting upstream of the PI3K/AKT/NFkB pathway.

Epigenetic regulation of *OBSCN* in breast epithelial cells; **Subproject 2a**: Exploring the role of hypermethylation in silencing *OBSCN* in breast cancer cells; **Subproject 2b**: Modulation of *OBSCN* expression via long non-coding *OBSCN* antisense RNAs.

Generation of mini-obscurins and examination of their effectiveness in suppressing the tumorigenic and metastatic potential of obscurin-deficient breast cancer cells.

Publications

Perry, N.A., Shriver, M., Mameza, M.G., Grabias, B., Balzer, E., and **Kontrogianni-Konstantopoulos, A.***, "Obscurins: Giant Proteins with Tumor Suppressing Activities in Breast Cancer", *FASEB Journal*, 26(7), 2764-75, 2012.

Shriver, M., Stroka, K.M., Vitolo, M.I., Martin, S.S., Huso, D.L., Konstantopoulos, K., and **Kontrogianni-Konstantopoulos A.**# "Loss of giant obscurins from breast epithelium promotes epithelial-to-mesenchymal transition, tumorigenicity and metastasis" *Oncogene*, 2014, doi: 10.1038/onc.2014.358.

Yankasas, C.L., Thompson, K.N., Paul, C.D., Vitolo, M.I., Mistriotis, P., Mahendra, A., Shea, D.J., Manto, K.M., Chai, A., Varadarajan, N., **Kontrogianni-Konstantopoulos, A.**, Martin, S.S., and Konstantopoulos, K., "Development of a microfluidic invasion network device (MIND) for diagnosis and precision care in breast cancer", *Nat Biomed Eng*, 2019, 3(6):452-465. doi: 10.1038/s41551-019-0400-9.

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My research interests include study of mechanisms by which breast cancers progress and metastasize and identifying novel targets for therapy. I have been working in Dr. Amy Fulton's research team. We showed that COX-2 upregulation is associated with more aggressive disease and COX inhibitors can control tumor metastasis in a murine model of breast cancer. Another area of work is to study prostaglandin E2 (PGE2) receptors to identify more specific targets. Our work is the first to report that EP4 antagonists inhibit metastasis in vivo. Our studies showed EP1 receptor which suppresses metastasis is low in African-American women which may contribute to breast cancer disparities. We also investigated the role of cytokines and chemokines and their receptors in controlling breast cancer and showed two CXCR3 isoforms play opposing roles in breast cancer. Our work with natural product demonstrated for the first time that a water soluble extract of Taro corm (TE) has potent anti-metastatic activity in a mouse model of metastatic breast cancer. Dr. Fulton and I hold a US patent on this work. Working with Dr. David Weber we are now characterizing the recombinant taro protein showing antimetastatic activity similar to TE.

Projects

The cyclooxygenase-2 product PGE2 Promotes Tumor Progression, Metastasis and Cancer Stem Cells Through PGE2 Receptors: Our work is the first to show that treatment with EP4 antagonists significantly reduces both the size of tumors and phenotypic markers of stem cells and inhibit metastasis in vivo.

Cytokine and Chemokine Receptors Function in Malignancy: We have shown that two CXCR3 isoforms play opposing roles in breast cancer. CXCR3-A promotes metastasis in the non-stem cell population but CXCR3-B promotes the survival of tumor cells with cancer stem-like properties.

Antimetastatic Activity in Taro: We are the first to report that a water-soluble extract of the taro corm (TE) has potent anti-metastatic activity in a mouse model of metastatic breast cancer. TE significantly inhibits (98%) lung as well as (85%) spontaneous metastasis (US patent # 8,865,642). We are now characterizing recombinant taro protein which showed significant inhibition of lung metastasis like TE.

Publications

<u>Kundu, N.</u>, Campbell, P., Hampton, B., Lin, C-Y., Ma, X., Ambulos, N., Zhao, X.F., Goloubeva, O., Holt, D., Fulton, A.M. Antimetastatic activity isolated from Colocasia esculenta (taro). Anticancer Drugs. 23(2):200-11, 2012. PMID: 21934603; PMCID: PMC3769987.

Kundu N, Ma X, Kochel T, Goloubeva O, Staats P, Thompson K, Martin S, Reader J, Take Y, Collin P, Fulton A. <u>Prostaglandin E receptor EP4 is a therapeutic target in breast cancer cells with stem-like properties.</u> Breast Cancer Res Treat. 2014 Jan;143(1):19-31. doi: 10.1007/s10549-013-2779-4. Epub 2013 Nov 27. PubMed PMID: 24281828; PubMed Central PMCID: PMC3889836.

Kundu N, Ma X, Brox R, Fan X, Kochel T, Reader J, Tschammer N, Fulton A. The Chemokine Receptor CXCR3 Isoform B Drives Breast Cancer Stem Cells. Breast Cancer (Auckl). 2019;13:1178223419873628. doi: 10.1177/1178223419873628. eCollection 2019. PubMed PMID: 31619923; PubMed Central PMCID: PMC6777055.

Wolfgang Losert, PhD

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Personal Statement

My research centers on elucidating the physical and statistical properties of living systems from an excitable systems perspective. Using a combination of imaging, analysis and modeling my group develops new paradigms on how physical and statistical laws impact the functioning of living systems. My group also develops holographic optogenetics approaches to stimulate electrical depolarization of groups of neuronal cells as part of a BRAIN initiative project in collaboration with in vivo neuroscientists. The main thrust of my group is to investigate the dynamics of the cytoskeleton and of signaling pathways from an excitable systems perspective. I focus on waves of polymerization and depolymerization which provide a characteristic rhythm for many cell types.

Projects

NIH Brain Inititative U19 Center grant – co-PI Readout and control of spatiotemporal neuronal codes. The goal of the project is to develop and deploy holographic optical stimulation approaches for readout and control of neuronal sensory systems. I am the lead of the data science core and participate in the technology core

AFOSR MURI - Understanding and Controlling the Coupled Electrical, Chemical & Mechanical Excitable Networks of Living Systems

I lead a MURI team that developed an excitable systems paradigm that covers biochemical, biomechanical, and electrical excitability. The underlying hypothesis is that biomechanical and biochemical waves and rhythms in cells carry information and thus are a target for sensing and for control of cell behavior and cell fate.

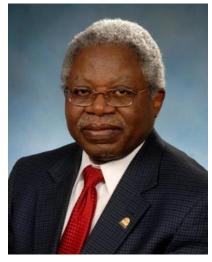
Publications

O. Ilina, L. Campanello, P.G. Gritsenko, M. Vullings, C. Wang, P. Bult, **W. Losert** and P. Friedl, "Intravital microscopy of collective invasion plasticity in breast cancer." *Disease Models & Mechanisms* **11**, dmm034330 (2018).

C. H. Stuelten, R.M. Lee, **W. Losert** and C.A. Parent, "Lysophosphatidic acid regulates the motility of MCF10CA1a breast cancer cell sheets via two opposing signaling pathways," *Cellular Signalling* **45**, 1-11 (2018).

E. C. Ory, D.Chen, K.R. Chakrabarti, P.Zhang, J.I. Andorko, C.M. Jewell, **W.Losert** and S.S. Martin, "Extracting microtentacle dynamics of tumor cells in a non-adherent environment," *Oncotarget* **8**, 111567-111580 (2017).

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Dr. Vincent Njar has a long-standing interest in the rational design, discovery and development of small molecules as anti-cancer agents. These unique agents also have potential use in treating dermatological conditions. He is the lead inventor, medicinal chemist and oncopharmacologist who has made significant discoveries in the development of novel small molecules with potential for the treatment of a variety of cancers – in particular, breast, prostate, and pancreatic cancers. Dr. Njar invented novel chemical reactions for the synthesis of novel inhibitors of several important anti-cancer targets. He is perhaps best known for his discovery and development of the unique molecule, Galeterone (originally code named VN/124-1), shown to be a potent AR/AR-V7 antagonist/degrader and Mnk1/2 degrader. Galeterone is currently in phases III and II clinical trial in prostate and pancreatic cancers, respectively. Galeterone is commercially available as a unique research reagent. His other invention, the retinoic acid metabolism blocking agents (RAMBAs) which also degrade AR/AR-V7 and Mnk1/2 proteins are currently in advanced preclinical development in view of clinical trials in a variety of cancers and dermatological diseases.

Projects

Development of Next Generation Galeterone Analogs (NGGAs or GALNEX) for Prostate and Pancreatic Cancers. The prostate cancer project is currently funded by an NIH/NCI award (R01CA224696) focusing on the development of lead agent, VNPP433-3β. This project was recently selected to be included in the "Stepping Stones Program" at the NCI Division of Cancer Treatment and Diagnosis for the program in-kind assistance. Specifically, the NCI Program will directly carry out Investigational New Drug (IND) studies to support an IND application to the US Food and Drug Administration (FDA) for a Phase I clinical trial in men with castration-resistant prostate cancer (CRPC).

Development of Novel Retinamides for the treatments of Breast and Prostate Cancers and Dermatological Diseases. In addition to ongoing laboratory investigations, the cancer projects are the basis of a UMB New Ventures Initiative start-up company, Isoprene Pharmaceuticals, Inc. (IPI) founded by lead inventor, Vincent Njar and UMB New Ventures Initiative Management Team. Through a sub-license agreement, the lead agent VNLG-152 is being developed by Hoth Therapeutics Inc. New York for the treatment of dermatological diseases.

Publications

Njar VCO, Brodie AMH. Discovery and Development of Galeterone (TOK-001 or VN/124-1) for the Treatment of All Stages of Prostate Cancer" in the *J. Med Chem.*, 2015, 58: 2077-2087. PMID: 25591066.

Ramalingam, S.; Ramamurthy, V.P.; Gediya, L.K.; Murigi, F.N.; Purushottamachar, P.; Huang, W.; Choi, E.Y.; Zhang, Y.; Vasaitis, T.S.; Kane, M.A., Lapidus RG, **Njar VCO**. The Novel Mnk1/2 Degrader and Apoptosis Inducer VNLG-152 Potently Inhibits TNBC Tumor Growth and Metastasis. *Cancers (Basel)* 2019, 11, doi:10.3390/cancers11030299. PMID: 30832411

Kwegyir-Afful AK, Ramalingam S, Ramamurthy VP, Purushottamachar P, Murigi FN, Vasaitis TS, Huang W, Kane MA, Zhang Y, Ambulos N, Tiwari S, Srivastava P, Nnane IP, Hussain A, Qiu Y, Weber DJ, **Njar VCO**. Galeterone and The Next Generation Galeterone Analogs, VNPP414 and VNPP433-3β Exert Potent Therapeutic Effects in Castration-/Drug-Resistant Prostate Cancer Preclinical Models *In Vitro* and *In Vivo*. *Cancers (Basel)*. 2019 Oct 24;11(11). pii: E1637. doi: 10.3390/cancers11111637. PMID: 31653008

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Personal Statement

Research in my laboratory focuses on understanding how tumors arise and how they progress to a lethal metastatic disease. In particular, we focus on (1) understanding the molecular mechanisms underlying the progression of metastatic ovarian cancer, (2) identifying new therapeutic targets and (3) developing novel strategies to treat this deadly disease.

Projects

Rivkin Center for Ovarian Cancer - Scientific Scholar Award. 2019 – 2021. PROTAC-mediated degradation of oncogenic gain-of-function p53 mutants: A personalized therapeutic strategy for ovarian cancer.

University of Maryland Greenebaum Comprehensive Cancer Center - American Cancer Society Institutional Research Grant. P.I. (sub-award). 01/2020 – 12/2020 Impact of steroid hormones on mutant p53 driven metastatic ovarian cancer.

University of Maryland Institute for Clinical & Translational Research (ICTR) Accelerated Translational Incubator Pilot (ATIP) Grant Program – ICTR Innovative Collaboration Pilot Grant. 2020 – 2021. High-throughput screen to identify novel selective regulators of mutant p53 in ovarian cancer cells.

Publications

<u>USP15-dependent lysosomal pathway controls p53-R175H turnover in ovarian cancer cells.</u> **Padmanabhan A***, Candelaria N, Wong KK, Nikolai BC, Lonard DM, O'Malley BW, Richards JS. Nature Communications. 2018 Mar 28;9(1):1270. *Corresponding author

Zinc Oxide nanoparticles induce oxidative and proteotoxic stress in ovarian cancer cells and trigger apoptosis Independent of p53-mutation status. Padmanabhan A*, Kaushik M, Niranjan R, Richards JS, Ebright B, Venkatasubbu GD*. Applied Surface Sciences. 2019 Sep; 487:807-818. *Co-corresponding authors

<u>Assembly of an Evolutionarily Conserved Alternative Proteasome Isoform in Human Cells.</u> **Padmanabhan A**, Vuong SA, Hochstrasser M. Cell Reports. 2016 Mar 29;14(12):2962-74.

Tony Passaniti, PhD
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The Passaniti lab focuses on developing new therapeutics for women diagnosed with breast cancer by targeting a specific protein (RUNX2) that is found to increase cancer spread to other organs (metastasis). The laboratory has discovered that RUNX2 is activated through an autocrine IGF1-growth factor pathway, which results in metabolic switching of the cancer cells from oxidative phosphorylation to aerobic glycolysis. These particular transcriptional and metabolic dysfunctions are very common in women with triple negative breast cancers and African-American women. Effective therapies in these populations of patients is a largely unmet need in breast cancer treatment. The laboratory has used computer-assisted drug design to identify new medications that prevent RUNX2 binding to its gene targets. In this way, it is expected that blocking some of these cancer-causing events will result in better patient survival. The laboratory has established novel DNA-binding assays and high-throughput screening to facilitate the discovery of inhibitors of RUNX2 that reverse the tumor's dependence on glycolysis and allow the discovery of new compounds with increased specificity and low toxicity.

Projects

UM Ventures Fund (active). Innovative medicinal chemistry approaches for pre-commercial development of new drugs for breast cancer prevention and treatment. Biochemical and biological assays combined with structure-activity relationship studies will define the potency, specificity, and biosafety of select compounds. **VA Merit (active).** Mitochondrial metabolism as a target of breast cancer therapy. The goals of this project are

to determine the significance and requirement for mitochondrial oxidative phosphorylation in metabolic regulation of breast cancer and to use novel mitochondrial-targeted approaches that alter mitochondrial function for cancer therapeutics.

NIHR01 (pending). Transcriptional targeting to prevent metabolic dysfunction and breast cancer. Goals of this study are to validate RUNX2 targeting drugs with metabolic activity and to define the mechanisms and efficacy of regulating RUNX2-mediated glycolytic function in breast cancer prevention.

Publications

M.S. Kim, R. Gernapudi, Y. Cedeño-Cedeño³, B.M. Polster⁵, R. Martinez⁶, P. Shapiro⁶, S. Kesari⁷, E. Nurmemmedov⁷ and **A. Passaniti** (2020) Targeting breast cancer metabolism with a novel inhibitor of mitochondrial ATP synthesis. **Oncotarget**, *in press (August 24, 2020)*.

Kim, M.S., Gernapudi, R., Choi, E.Y., Lapidus, R.G., and **Passaniti, A**. (2017) Characterization of CADD522, a small molecule that inhibits RUNX2-DNA binding and exhibits antitumor activity. **Oncotarget**, 8:70916-40. PMCID: PMC5642608

Jeffrey Twum-Ampofo, Dexue Fu, **Antonino Passaniti**, Arif Hussain, and M. Minhaj Siddiqui (2016) Metabolic Targets for Potential Prostate Cancer Therapeutics. **Curr Opinion in Oncology**, 28(3):241-7. PMCID: PMC7306925

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Personal Statement

My research interests are centered on the design, synthesis and evaluation of novel photonic materials with unprecedented optical properties, for a variety of diagnostic and therapeutic applications. We are focusing on the synthesis, characterization and understanding of photophysical properties of complex multichromophoric arrays and metal-chromophore conjugates, in order to develop new generations of fluorophores for anticancer fluorescene-guided surgery and photosensitizers for anticancer photodynamic therapy.

Projects

Currently, our efforts are focused on two big projects. (1) Development of activatable fluorescent probes for multicolor, fluorescence guided surgery. In this project we are developing fluorescence probes, with multiple excitation wavelengths, tunable near infrared emission, which fluorescence is activated in the target tumor cells. (2) Metal-chromophore conjugates as dual-mode photodynamic and chemotheraputic anticancer agents. In this project we are developing anticancer agents which combines photodynamic anticancer activity and chemotherapeutic functions.

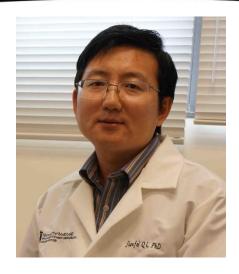
Publications

Fuyuki F.; Inagaki, F. F.; Fujimura D.; Ansteatt[,] S.; Okada, R.; Furusawa, A.; Choyke[,] P. L.; Ptaszek, M.; Kobayashi, H. Effect of short PEG-linkers on near-infrared BODIPY based activatable optical probe *ACS Omega*, **2020**, *5*, 15657-15665.

Ogata, F.; Nagaya, T.; Maruoka, Y.; Akhigbe, J.; Meares, A.; Lucero, M.; Satraitis, A.; Fujimura, D.; Okada, R.; Inagaki, F.; Choyke, P.; Ptaszek, M.; Kobayashi, H. Activatable Near-Infrared Fluorescence Imaging Using PEGylated Bacteriochlorin-Based Chlorin and BODIPY-Dyads as Probes for Detecting Cancer. *Bioconjugate Chem.* **2019**, *30*, 169-183.

Meares, A.; Satraitis, A.; Akhigbe, J.; Santhanam, N.; Swaminathan, S.; Ehudin, M.; Ptaszek, M. Amphiphilic BODIPY-Hydroporphyrin Energy Transfer Arrays with Broadly Tunable Absorption and Deep Red/Near-Infrared Emission in Aqueous Micelles. *J. Org. Chem.* **2017**, *82*, 6054-6070.

Jianfei Qi, PhDAssistant Professor, Biochemistry and Molecular Biology University of Maryland School of Medicine jqi@som.umaryland.edu



Personal Statement

My research interests aim to understand the molecular mechanisms of ubiquitin ligases and histone demethylases in the development and progression of human prostate cancer. I have a strong background in prostate cancer biology, ubiquitination and transcriptional gene regulation. I have the expertise and training in various experiment approaches including molecular cell biology, biochemistry, and mouse prostate cancer models. I have also established stable collaboration with the experts in prostate cancer pathology or system biology, who can complement our research with the immunohistochemistry analyses of human prostate cancer tissues, the profiling array or ChIP-seq analyses of the global gene regulation. Our previous study revealed a key tumor-promoting role for histone demethylase JMJD1A in prostate cancer, and further understanding the molecular mechanisms of JMJD1A underlying the prostate cancer progression and therapeutic resistance is critical towards identifying new targets and developing new rationale therapies for the advanced prostate cancer.

Projects

"Role of JMJD1A modifications in castration resistance of prostate cancer" (R01)

"Role of histone demethylase JMJD1A in the DNA damage response of prostate cancer cells" (R01) National Cancer Institute, R01CA207118

"Role of Jmjd1a in prostate cancer biology" (R00)

Publications

Xu S, Fan L, Jeon HY, Zhang F, Cui X, Mickle M, Peng G, Hussain A, Fazli L, Gleave M, Dong X, and Qi J. (2020). p300-mediated acetylation of histone demethylase JMJD1A prevents its degradation by ubiquitin ligase STUB1 and enhances its activity in prostate cancer. Cancer Research. 80, 3074-3087.

Fan L, Zhang F, Xu S, Cui X, Hussain A, Fazli L, Gleave M, Dong X, and Qi J. (2018). Histone demethylase JMJD1A promotes alternative splicing of AR-V7 in prostate cancer cells. PNAS. 115, E4584-E4593.

Fan L, Peng G, Sahgal N, Fazli L, Gleave M, Zhang Y, Hussain A, and Qi J. (2016). Regulation of c-Myc expression by the histone demethylase JMJD1A is essential for prostate cancer cell growth and survival. Oncogene. 35, 2441-2452.

Jocelyn Reader, PhD

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Personal Statement

My research interests are centered on the role of inflammation in ovarian cancer response to treatment, the COX/PGE2 pathway in ovarian cancer biology and the role of COX/PGE2 pathway in breast cancer metastasis and disparities.

Projects

The role of EP4 in ovarian cancer biology and response to treatment.

The role of microtentacles in ovarian cancer progression and response to treatment.

Nanotechnology-assisted, mechanism-based combination therapy for ovarian cancer peritoneal carcinomatosis.

Publications

Reader, J., Harper, A., Legesse, T., Staats, P., Goloubeva, O., Rao, G., Fulton, A., Roque, D. 2019. EP4 and Class III Beta-Tubulin Expression in Uterine Smooth Muscle Tumors: Implications for Prognosis and Treatment. Cancers 2019, 11(10), 1590; https://doi.org/10.3390/cancers11101590

Smith, P., Roque, D., Ching, MM., Fulton, A., Rao, G., Reader, J. 2020. The Role of Eicosanoids in Gynecological Malignancies. Front. Pharmacol. 11:1233. Doi: 10.3389/fphar.2020.01233

Ching, MM., Reader, J., Fulton, A. 2020. Eicosanoids in Cancer: Prostaglandin E2 Receptor 4 (EP4) in Cancer Therapeutics and Immunotherapy. Front. Pharmacol. 11:819. Doi: 10.3389/fpphar.2020.00819

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Giuliano Scarcelli obtained his PhD in physics with a EU funded graduate fellowship between the University of Bari, Italy and UMBC, USA under quantum-optics pioneer Prof. Yanhua Shih. Giuliano then was at the Wellman Center for Photomedicine of Harvard Medical School for eight years, first as a postdoc in Prof. Yun's Lab, then as an instructor and assistant professor. He joined University of Maryland in 2015. Giuliano has been the recipient of several awards such as the "Exceptional by example" award for outstanding PhD studies, the Tosteson Postdoctoral Fellowship at Harvard, the Human Frontier Science Program Young Investigator Award, the NIH Quantitative Career Award, the NSF CAREER award and "Teaching excellence" awards from both Harvard University and University of Maryland.

Projects

NIH- R33; Brillouin confocal microscopy for biomechanical studies of metastatic cascade in 3D microenvironments

NIH- U01: Quantitative analyses of tumor cell extravasation (Roger Kamm PI at MIT)

NSF CAREER: Light-sheet Brillouin microscopy for mechanical analysis of tissue morphogenesis

Publications

Dorsoventral polarity directs cell responses to migration track geometries Wisniewski et al. **Science Advances** 6, eaba6505 (2020)

Nuclear Mechanics within Intact Cells Is Regulated by Cytoskeletal Network and Internal Nanostructures, Zhang, Alisafei, Nikolic, Nou, Kim and Scarcelli, **Small** 16, 1907688 (2020)

Noncontact 3D mapping of intracellular hydromechanical properties by Brillouin microscopy; Scarcelli, Polacheck, Nia, Patel, Grodzinski, Kamm and Yun, *Nature Methods* 12, 1132 (2015)

Ginette Serrero, PhDAdjunct Professor, Pharmaceutical Sciences
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Development of targeted therapy with companion diagnostic in Cancer. More specifically, my laboratory has developed a therapeutic antibody to GP88 (progranulin) and two diagnostic tests: a tissue test hat measures GP88 expression in tumor tissues and an ELISA test that measures GP88 in biological fluids. GP88 in tumor tissues has been shown to be an independent prognostic factor for several cancers including breast, lung, and prostate. Serum GP88 level is elevated in cancer when compared to control subjects. In metastatic breast cancer patients, serum GP88 level has been associated with survival and can be used to monitor response to therapy and progression of disease. We have completed IND enabling activities for the therapeutic antibody AG01. GMP manufacturing and fill finish activities are on-going for the clinical drug product with projected IND filing and start of human phase 1 at UMGCCC in early 2021. In addition, my laboratory is initiating a new pipeline for cell surface target overexpressed and internalized in solid tumors with the goal of developing of antibody drug conjugates as therapeutic approach.

Projects

Circulating GP88 in metastatic breast cancer patients, a prospective study.

GMP manufacturing of anti-GP88 antibody AG01 and human safety and dose escalation in lung and breast cancer patients

Characterization of PTGFRN as an internalizing cell surface protein as a potential therapeutic target for antibody drug conjugate approach in solid tumors.

Publications

Association of Serum Progranulin Levels with Disease Progression, Therapy Response and Survival in Patients with Metastatic Breast Cancer. Tkaczuk KHR, Hawkins D, Yue B, Hicks D, Tait N, Serrero G. Clin Breast Cancer. 2020 Jun;20(3):220-227. doi: 10.1016/j.clbc.2019.11.010. Epub 2019 Dec 5.PMID: 31928925

Expression of GP88 (Progranulin) Protein Is an Independent Prognostic Factor in Prostate Cancer Patients. Abdulrahman A, Eckstein M, Jung R, Guzman J, Weigelt K, **Serrero G**, Yue B, Geppert C, Stöhr R, Hartmann A, Wullich B, Wach S, Taubert H, Lieb V.Cancers (Basel). 2019 Dec 16;11(12):2029. doi: 10.3390/cancers11122029.

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Personal Statement

My practice is in Urologic oncology with a particular interest in prostate and bladder cancer. I split my time between my clinical practice in caring for patients with these diseases, translational research projects related to improved management and risk stratification of these tumors, and basic bench research on elucidating metabolic pathways related to these tumors and tumor progression. I have in particular developed extensive collaborative projects with radiology and school of pharmacy on translational projects related to MRI, as well as PCOR projects on improving access to prostate cancer treatments.

Projects

"Diagnosing clinically-significant prostate cancer in african american men: systematic random versus mr-image-fusion guided biopsy NIH-R01 NCI CA205058-01

"Using Metabolic Pathways to Improve Diagnosis and Risk Stratification of Prostate Cancer" Department of Defense-Prostate Cancer Idea Development Award PC150408

"The effects of a ketogenic diet intervention on overweight and obese men undergoing active surveillance for prostate cancer" Nutrition Obesity Research Center (NORC)

Publications

Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, Bloom J, Gurram S, Siddiqui MM, Pinsky P, Parnes H, Linehan WM, Merino M, Choyke PL, Shih JH, Turkbey B, Wood BJ, Pinto PA. MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. N Engl J Med. 2020 Mar 5;382(10):917-928.

Huang H, Muscatelli S, Naslund M, Badiyan SN, Kaiser A, Siddiqui MM. Evaluation of Cancer-Specific Mortality with Surgery Versus Radiation as Primary Therapy for Localized High-Grade Prostate Cancer in Men Younger than 60 Years Old. J Urol. 2018 Jul 27.

Tooker GM, Truong H, Pinto PA, **Siddiqui MM**. National Survey of Patterns Employing Targeted MRI/US Guided Prostate Biopsy in the Diagnosis and Staging of Prostate Cancer. Curr Urol. 2019 Mar 8;12(2):97-103

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My lab focuses on the intersection of metabolism, oncogenic signaling and molecular imaging. Metabolic adaptations in cancer are dependent on both nutrient availability and growth factor signaling. Therefore, molecular imaging methods that can detect nutrient uptake can inform on cancer growth, treatment and drug resistance.

Projects

We were recently awarded an R21 from the National Cancer Institute to study fructose metabolism as a biomarker for liver cancer. Fructose is broken down by ketohexokinase (KHK) and we observed reduced levels of KHK in liver cancer. We are developing blood biomarkers and imaging techniques based on magnetic resonance imaging (MRI) to detect loss of fructolysis for early detection of cancer.

Publications

Tee, S.S., Suster, I., Truong, S., Digialleonardo, V., Eskandari, R., Jeong, S., Alvarez, J.A., Aldeborgh, H., Keshari, K.R., Targeted AKT inhibition in prostate cancer cells and spheroids reduces aerobic glycolysis and conversion of hyperpolarized [1-¹³C] pyruvate to [1-¹³C] lactate. *Mol. Cancer Res.* (2018)

Granlund KL*, **Tee SS***, Vargas HA, Lyashchenko SK, Reznik E, Fine S, Laudone V, Eastham JA, Touijer KA, Reuter VE, Gonen M, Sosa RE, Nicholson D, Guo YW, Chen AP, Tropp J, Robb F, Hricak H, Keshari KR.Hyperpolarized MRI of Human Prostate Cancer Reveals Increased Lactate with Tumor Grade Driven by Monocarboxylate Transporter 1. *Cell Metab.* (2019)

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My research interests are focused on clinical drug development in breast cancer. From 1992 to present, I have been involved in 100+ Phase 1-3 clinical trials and have served as the institutional principal investigator on the majority of the University of Maryland Greenebaum Comprehensive Cancer Center (UMGCCC) BC-specific clinical trials. The UMGCCC "Hormonal Sensitive Program" (BREAST and PROSTATE) was instrumental in the UMGCCC receiving the P30 grant funding and the NCI Comprehensive Cancer Center designation in 2016. Our Clinical Breast Cancer Program contributes substantial numbers of patients to institutional and national/cooperative group clinical trials with rates of accrual much higher than the national average. In addition, we also have excellent participation and accrual of minorities to our clinical trials (many of our trials have 40-50% AAF accruals). As the Director of UMGCCC Breast Evaluation and Treatment Program (BETP), a multidisciplinary program with commitment to comprehensive, multidisciplinary breast cancer care, I have been overseeing the clinical and research aspects of the program for several years.

Projects

We continue to collaborate internally and externally on various translational research projects with the focus on endocrine resistance, the role of microtentacles in breast cancer metastasis, the role of NKT cells in breast cancer patients and healthy volunteers and many others. The glycoprotein 88 (GP-88) tissue and circulating biomarker project in collaboration with Dr Ginette Serrero continues to thrive, and we are planning to continue our collaborations with 2 new clinical trials (GCC1949) as circulating blood maker and as target for therapy (GCC1950).

Publications

Tkaczuk, KR. Yue B, Zhan M, Tait N, Yarlagadda L, Dai H and Serrero G. (2011). Increased circulating level of the survival factor GP88 (progranulin) in the serum of breast cancer patients. Breast Cancer (Auckl.) 5, 155-162. (PMCID: 3140268)

Serrero, G Hawkins DM, Yue B, Ioffe, O, Bejarano P, Phillips JT, Head JF, Elliott RL, Tkaczuk KR, Godwin AK, Weaver J and Kim WE. (2012). Progranulin (GP88) tumor tissue expression is associated with increased risk of recurrence in breast cancer patients diagnosed with estrogen receptor positive invasive ductal carcinoma. Breast Cancer Research 14, R26. (PMCID: 3496144)

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PTEN loss and the acquisition of PIK3CA mutations are often assumed to be reciprocal and mutually exclusive mutations; each resulting in the unregulated activation of PI3K/Akt signaling pathway. However, we have reported differences in cytoskeletal structure and signaling between PTEN loss and PI3K activation. A major focus of my lab is defining the role of PTEN in cytoskeleton regulation beyond that of its regulation of PI3K pathway. Highly metastatic cells are more deformable than non-malignant cells and increased deformability promotes circulating tumor cells (CTCs) survival, allowing the CTCs to squeeze through capillaries and avoid death due to fragmentation. Increased deformability can also enhance CTC reattachment efficiency. A major focus of my lab is to improve understanding of the biochemical signals which modulate cytoskeletal alterations, specifically in suspended cells and CTCs, to provide new insight for future development of pharmacologic approaches for inhibiting metastasis by chemically targeting cytoskeletal structures that regulate cell stiffness and deformability.

Projects

We are currently focused on studies that will test the hypothesis that PTEN loss weakens the actin cortex which enhances disseminated tumor cell deformability to promote metastatic efficiency, a project funded by a four-year American Cancer Society Research Scholars Grant (132153-RSG-18-028-01-CSM).

Publications

Yankaskas, C.L., et. al. (2019) Development of a Microfluidic Invasion Network Device (MIND) for Diagnosis and Precision Care in Breast Cancer. **Nat Biomed Eng**. Jun;3(6):452-465. PMCID: PMC6563615.

Mathias, T.J., Chang, K.T., Martin, S.S., and **Vitolo, M.I.** (2020) Gauging the impact of cancer treatment modalities on circulating tumor cells (CTCs). **Cancers (Basel)** Mar 21;12(3). PMCID:PMC7140032.

Ju, J.A., et. al. (2020) Partial thermal imidization of polyelectrolyte multilayer cell tethering surfaces (TetherChip) enables efficient cell capture and microtentacle fixation for circulating tumor cell analysis. **Lab on a Chip.** Aug 21;20(16):2872-2888.

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Personal Statement

Dr. Wang's research work focuses on integrative genomics in cancer development/progression and cancer health disparities. He utilized approaches of molecular and cell biology, genomic (array- and sequencing-based), biochemistry, histology and pharmacology to study the molecular mechanisms underlying prostate cancer disparities. Dr. Wang is also interested in identification of molecular signatures, microRNA-mRNA pairings, aberrant splicing variations and epigenetic profiles in aggressive prostate, colon, and breast cancers. His research works have been supported by funding from NIH, DoD and American Cancer Society.

Projects

Aberrant Splice Variants as Potential Precision Biomarkers for Aggressive Prostate Cancers in African American Patients (NIH 1SC1GM127256) PI

Consequences and Mechanism of aberrant splicing in African American prostate cancer disparities (NCI R01 CA204806, PIs: Garcia-Blanco, Lee), Sub-award PI

Publications

<u>Wang, B.-D.</u>, Ceniccola, K., Hwang, S., Andrawis, R., Horvath, A., Freeman, J.A., Olender, J., Knapp, S., Ching, T., Garmire, L., Patel, V., Garcia-Blanco, M.A., S.R., and Lee, N.H. (2017) Alternative Splicing Promotes Tumour Aggressiveness and Drug Resistance in African American Prostate Cancer. *Nature Communications* 8:15921.

Wang, B.-D., and Lee, N.H. (2018) Aberrant RNA Splicing in Cancer and Drug Resistance. *Cancers* (Basel). 2018 10:458.

Olender, J., <u>Wang, B.-D.</u>, Ching, T., Garmire, L.X., Garofano, K., Ji, Y., Knox, T., Latham, P., Nguyen, K., Rhim, J., Lee, N.H. A Novel FGFR3 Splice Variant Preferentially Expressed in African American Prostate Cancer Drives Aggressive Phenotypes and Docetaxel Resistance. *Mol Cancer Res.* 2019, 10.1158/1541-7786.MCR-19-0415.

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I am working with Anthony Kim, PhD and Graeme Woodworth, MD from the Department of Neurosurgery on several projects focused on nanoparticle-mediated drug delivery for treatment of breast cancer, brain cancer and brain metastases. In addition, we have developed a transgenic rat model of brain cancer that produces tumors exhibiting many of the pathological features of the human disease. This model is being used to both study the role of specific proteins in tumor initiation and progression and to test brain drug delivery approaches such as focused ultrasound-mediated blood brain barrier disruption.

Projects

Impact of Fn14-targeted nanoparticles for triple-negative breast cancer, Co-Investigator (PI: Kim) The major goal of this project is to develop tumor-penetrating drug delivery systems that can target Fn14-positive breast cancer cells for treatment of metastatic triple-negative breast cancer.

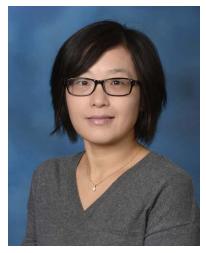
Nanotherapeutic treatment of the invasive glioblastoma microenvironment, Co-Investigator (PI: Woodworth) The major goal of this project is to investigate the therapeutic effects and cellular distribution of Fn14-targeted nanoparticles and Fn14-related tumor-host cell interplay in the invasive brain tumor microenvironment

Publications

Connolly, N.P., Stokum, J.A., Schneider, C.S., Ozawa, T., Xu, S., Galisteo, R. Castellani, R.J., Kim, A.J., Simard, M., Winkles, J.A., Holland, E.C. and Woodworth, G.F. (2017) Genetically engineered rat gliomas: PDGF-driven tumor initiation and progression in *tv-a* transgenic rats recreate key features of human brain cancer. <u>PLoS</u> One 12:e0174557.

Wadajkar, A.S., Dancy, J.G., Roberts, N.B., Connolly, N.P., Strickland, D.K., Winkles, J.A., Woodworth, G.F. and Kim, A.J. (2017). Decreased non-specific adhesivity, receptor-targeted (DART) nanoparticles exhibit improved dispersion, cellular uptake, and tumor retention in invasive gliomas. <u>Journal of Controlled Release</u> 267:144-153.

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Dr. Zhang's research focuses on developing translational biostatistics and informatics approaches to reveal novel human disease mechanisms. She has solid interdisciplinary trainings in bioinformatics and Computer Engineering. Dr. Zhang has over 20 years of research experience in integrative analysis of multi-source high-dimensional biological data for novel association discovery between different biological entities under different biological states. She has extensive collaborative research experience in medical informatics, ontology, software engineering, biomedical and basic science fields. Her current research mission is to leverage the gap between the analytical needs of arising from multi-source biological "big" data in biomedical research and advanced informatics approaches. As the lead of the bioinformatics core at University of Maryland Greenebaum Comprehensive Cancer Center and University of Maryland School of Medicine, Dr. Zhang has been serving as coprincipal investigator/co-investigator leading the bioinformatics and statistical analyses in numerous federal funded research projects including the International Consortium for Prostate Cancer Genetics (ICPCG), the consortium of Extracellular non-coding RNA biomarker discovery of hepatocellular cancer, and NHLBI Progenitor Cell Translational Consortium (PCTC). She has over 60 peer-reviewed publications involving analysis of various types of omics data such as DNA/mRNA/miRNA sequencing and methylation sequencing. She has also been organizing/co-organizing several international workshops in the informatics field since 2012.

Projects

Development of next generation galeterone analogs for prostate cancer therapy (R01, Njar) Goal: to produce a more efficacious novel agent against all forms of prostate cancer, including metastatic and drug-resistant diseases for eventual clinical evaluation. Co-Investigator

Early life exposures and breast density in young women (R01, Dorgan)

Goal: to identify early life metabolic influences on adult breast density, one of the strongest known breast cancer risk factors. Co-Investigator

Discovering cardiomyopathy modifiers and therapies via zebrafish genetics (Xu)

Goal: to identify genes that modify progression and severity of an inherited cardiomyopathy, and to develop therapies based on genes that exert therapeutic modifying effects. Site PI.

Publications

Zhang Y, Zhu Q, Liu H. Next generation informatics for big data in precision medicine era. BioData Min. 2015;8(1):1-3. PMID: 26539249.

Wang L, Ma X, Xu X, <u>Zhang Y</u>. Systematic identification and characterization of cardiac long intergenic noncoding RNAs in zebrafish. Scientific Reports. 2017 Apr 28;7(1):1250. PMID: 28455512.

Wang L, Felts SJ, Van Keulen VP, Scheid AD, Block MS, Markovic SN, Pease LR, <u>Zhang Y</u>. Integrative genome-wide analysis of long noncoding RNAs in diverse immune cell types of melanoma patients. Cancer Research. 2018 Aug 1;78(15):4411-4423. PMID: 29895674.

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Basal-like breast cancer accounts for 15-20% of all diagnosed breast cancer depending on patient population. The absence of PR, ER, and HER-2 commonly found in basal-like breast cancer leads to these patients unlikely to respond to hormone therapies or HER-2 targeted therapies. Thus, basal-like breast cancer is highly aggressive, and often results in lung and brain metastasis. Understanding risk factors for basal-like breast cancer invasion and metastasis is urgently needed for identification of novel and specific molecular targets. Our current studies will investigate the transition from early-stage basal-like breast cancer to invasive breast cancer.

Projects

Palmitic Acid and Basal-like Breast Cancer Progression Metastatic Latency and Immune Evasion through LIPG Signaling Development of Novel LIPG inhibitors

Publications

Wolfson B, Lo PK, Yao Y, Li L, Wang H, **Zhou Q**.(2018) Impact of miR-140 Deficiency on Non-Alcoholic Fatty Liver Disease. Mol Nutr Food Res. 62(13):e1800189. doi: 10.1002/mnfr.201800189. PMID:29701903

Lo PK, Yao Y, **Zhou Q** (2020) <u>Single-Cell RNA-seq Reveals Obesity-Induced Alterations in the *Brca1*-Mutated Mammary Gland Microenvironment.</u> Cancers (Basel). 12(8):E2235. doi: 10.3390/cancers12082235.PMID: 32785175

Lo PK, Yao Y, **Zhou Q** (2020) <u>Inhibition of LIPG phospholipase activity suppresses tumor formation of human basal-like triple-negative breast cancer.</u> Sci Rep. 10(1):8911. doi: 10.1038/s41598-020-65400-7. PMID: **32488004**

Additional HRC Members

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