UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM
COMPREHENSIVE CANCER CENTER

## FEATURES


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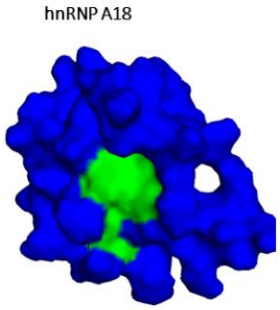
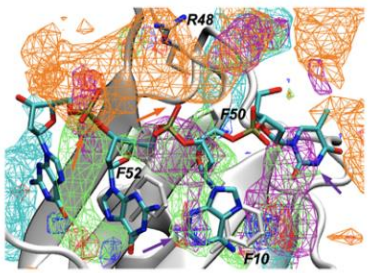
# Molecular and Structural Biology

## 2020
## Program Retreat


Co-Leaders:
David Weber, PhD
France Carrier, PhD

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# Molecular and Structural Biology Program
# 2020 Annual Retreat
## Thursday, October 22, 2020

**8:30** Introductory Remarks- **David Weber, PhD and France Carrier, PhD**

**8:40** MSB P30 sight visit overview- **David Weber, PhD and France Carrier, PhD**

**Aim 1: Define Mechanisms of Genomic Instability in Cancer**

**9:00** **A-Lien Lu-Chang**, "The Role of DNA Damage Response in DNA Repair and Cancer Treatment"

**9:20** **Alex Drohat,** "Mechanisms of BER in Preserving Genomic Integrity"

**9:40** **Scott Devine, "**Mutagenesis of human genomes by endogenous mobile elements on a population scale"

**Aim 2: Identify Changes in Gene Expression and RNA Function in Cancer**

**10:00** **Alexander MacKerell,** "Computer-Aided Drug Design at UMB"

**10:20** **Alexandros Poulpoulos**, "Novel Cas9 fusions for in vivo genome editing"

**10:40** **Jonathan Dinman**, "From too few to too many cells: solving Dameshek's Riddle"

**Aim 3: Define how Signaling Pathways in Cancer are Deregulated**

**11:00** **Charles Hong,** "Chemical Biology of Embryonic Development: Treasure Trove of Future Therapies"

**11:20** **Lai-Xi Wang,** "Glycoengineering of Antibodies to Modulate Immune Functions"

**11:40** **Nariman Balenga**, "GPR64 is a novel regulator of calcium-sensing/signaling in parathyroid tumors."

**12:00** **Richard Eckert**, "Transglutaminase 2 enhances HGF signaling to drive the mesothelioma cancer cell phenotype"

**Shared Services Overview**

**12:20** **Nick Ambulos**

**12:40** Closing Remarks - **David Weber, PhD and France Carrier, PhD**

**Upcoming MSB Meeting Dates**
**Scheduled on the 4th Thursday of the month at Noon**

January 28, 2021
March 25, 2021
April 22, 2021
May 27, 2021
June 24, 2021

## Molecular and Structural Biology Program Overview

The scientific goals of the MSB Program are to elucidate molecular mechanisms and cellular processes that are altered in cancer and to translate such basic scientific findings into the development of novel strategies for treating cancer using molecular and structural biology approaches. To achieve these goals, MSB research is organized into three scientific aims:

**Aim 1: Define Mechanisms of Genomic Instability in Cancer-** characterize how defects in DNA repair and checkpoint pathways lead to genomic instability and the initiation and/or progression of carcinogenesis

**Aim 2: Identify Changes in Gene Expression and RNA Function in Cancer-** determine how defects in transcriptional and posttranscriptional processes lead to inappropriate regulation of protein expression in cancer

**Aim 3: Define how Signaling Pathways in Cancer are Deregulated-** delineate how signaling pathways (i.e., oncogenic, tumor suppressor, etc.) are deregulated in cancer and identify specific biomolecules that can be targeted for suppressing cancer

# MSB Members
# and
# Research Highlights


# David J. Weber, PhD

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Leader, Molecular and Structural Biology Program
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## Research Interests

Basic science from the Weber lab includes studies of the structure, function, and inhibition of proteins, enzymes, and other biologically relevant complexes. The principle biophysical techniques used are nuclear magnetic resonance (NMR), X-ray crystallography and more recently single particle cryoEM, but others are used, as needed. Some of the major findings have to do with how dynamic properties affect protein-protein interactions (PPIs), including the idea that protein specificity in various biological interactions is the result of "Binding and Functional Folding (BFF)", a concept developed in the Weber lab. Of high interest are complexes involving calcium-signaling (Stra6, S100s, CaM, RyR1, RyR2, etc). Structure-based drug design and protein engineering projects are also underway. One set of ongoing projects involves examining S100 proteins, including those involved in cancer progression and metastases. As part of this project, molecules that inhibit S100 proteins involved in cancer (i.e., S100B, S100A4, others) were designed and synthesized. One such inhibitor, SBi1 (pentamidine), developed as a means to treat cancer advanced to a Phase 2 clinical trial (http://clinicaltrials.gov/ct/show/NCT00729807), and several patents for inhibiting S100 proteins are being processed and/or were issued. As the Director of the Center of Biomolecular Therapeutics (CBT), the Director of the Program of Molecular & Structural Biology, and the Co-director of the Greenebaum Cancer Center Structural Biology Shared Service, our lab also works with PI's throughout the University System of Maryland (USM) and the Greenebaum Cancer Center on numerous structural and drug design projects, as part of service activities and via collaborative efforts. Such efforts involve state-of-the-art scientific discipline-based programs necessary for the discovery and regulation of disease targets in cancer (S100B, mts1, A18, others), diabetes (grb10), heart disease (RyR1, RyR2, S100A1), and bacterial toxins (i.e. binary toxin of c. difficile) including, but not limited to, genomics/bioinformatics, target identification & validation, assay development & high-throughput screening, protein production & characterization, structural biology, computer-aided drug design, medicinal chemistry, and in vivo testing & biology. , others), diabetes (grb10), heart disease (RyR1, RyR2, S100A1), and bacterial toxins (i.e. binary toxin of c. difficile).

## Highlighted Research

1. NIH - R01 EY027405 (funded) "Structural basis of receptor-mediated cellular vitamin A uptake". This project is to determine the calcium-dependent component of vitamin A transport.

2. NIH R01 AI143107 (pending) "Structure, function, and inhibition of the binary toxin from clostridium difficile. C. difficile infection (CDI) is a major problem for cancer patients, so the inhibition of the most virulent strains of CDI is the objective here using structure-based drug design.

3. NIH R01 GM139826-01 (pending) "Activation of protein kinase A (PKA) via calcium-dependent S100A1-RIIB complex formation". How the S100A1 protein activates protein kinase A in a cAMP-independent manner is the goal of this project.

## Highlighted Publications


1. Xu, X. Godoy-Ruiz, R., Adipietro, K.A., Peralta, C., Ben-Hail, D., Varney, K.M., Cook, M.E., Roth, B.M., Wilder, P.T., Cleveland, T., Grishaev, A., New, H.M., Michel, S., Yu, W., Beckett, D., Rustandi, R.R., Lancaster, C., Loughney, J.W., Kristopeit, A., Christanti, S., Olson, J.W., MacKerell, A.D., des Georges, A., Pozharski, E., Weber, D.J. (2020) Structure of the cell-binding component of the Clostridium difficile binary toxin reveals a novel macromolecular assembly. Proc Natl Acad Sci USA, 117, 1049-1058. PMCID: PMC31896582. (Cover art was used from this manuscript; F1000Prime Recommended).

2. Kwegyir-Afful, A., Ramalingam, S., Ramamurthy, V., Purushottamachar, P., Murigi, F., Vasaitis, T., Huang, W., Kane, M., Zhang, Y., Ambulos, N., Tiwari, S., Srivastava, P., Nnane, I., Hussain, A., Qiu, Y., Weber, D.J., Njar, V. (2019) 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, 11, 1637. PMCID: PMC6895912.

3. Donohue1, E., Khorsand, S., Mercado, G., Varney, K.M., Wilder, P.T., Yu, W., MacKerell, A.D., Alexander, P., Van, Q.N., Moree, B., Stephen, A.G., Weber, D.J., Salafsky J., McCormick F. (2019) Second harmonic generation detection of Ras conformational changes and discovery of a novel small-molecule binder, Proc Natl Acad Sci USA, 116, 17290-17297. PMCID: PMC6717309.

## France Carrier, PhD

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**Research Interests**

The Carrier's lab pursues basic and translational cancer researcher. More specifically we are interested in targeted cancer therapies including the development of small molecules inhibitors for protein translation in cancer cells. Our work has established hnRNP A18CIRP as a key regulator of protein translation in cancer cells by delineating its mechanism of action through specific signature motifs located in the 3'UTR of hnRNP A18CIRP targeted transcripts. Our translational cancer research includes pioneered work on the efficiency of histone deacetylase inhibitors in combination with conventional anticancer drugs. This led to a Phase 1 clinical trial for relapsed and/or acute leukemia and myelodysplastic syndromes. We also contribute to the development of new clinical trials in radiation oncology with Low-Dose Fractionated Radiation Therapy (LDFRT) and radiation-stimulated immune response. Recently we identified the Dual Oxidase II enzyme as a key mediator of hyper-radiosensitivity in gastric cancer cells. Our lab has been continually funded by the NIH and the VA. Dr. Carrier holds four patents and her publications have been cited over 7,000 times.

**Highlighted Research**

1. VA Merit Award: I01BX003437: Role PI
   Title: Chemopotentiation by Low Dose Fractionated Radiation Therapy for disseminated intra-abdominal Cancers.
   07/01/17-06/30/21

2. NIH: NCI MPIs RO1 CA177981-01: Role Lead PI, MPI (David Weber)
   Title: Rational targeting of protein translation for cancer treatments.
   Competing renewal Pending

3. NIH: NCI R21: Role Lead PI, MPI (Pranshu Mohindra
   Title: Inducing Synthetic Lethality in Mantle Cells Lymphoma.
   Pending

**Highlighted Publications**


1. Nguyen, D.M., Parekh, P.R., Chang, E.T., Sharma, N.K., Carrier, F#. Contribution of Dual Oxidase 2 (DUOX2) to hyper radiosensitivity in human Gastric Cancer cells. Radiation Research, 184,151–160, 2015. PMID: 26207686.
2. Chang, E.T., Parekh, P.R., Yang, Q., Nguyen, D.M., and Carrier, F#. The heterogenous ribonucleoprotein A18 (hnRNP A18) promotes tumor growth by increasing protein translation of selected transcripts in cancer cells. Oncotarget, (Vol.7) No 9, p. 10578-10593, 2016 Jan 25, Epub ahead of print. PMID: 26824423.
3. Coburn, K., Melville, Z., Aligholizadeh, E., Roth, B.M., Varney, K.M., Carrier, F., Pozharski, E., and Weber, D.J. Crystal Structure of the Human Heterogeneous ribonucleoprotein A18 (hnRNP A18) RNA Recognition Motif. Acta Crystallographica Section F, Apr 1;73(Pt 4):209-214, 2017.


## Zubair M. Ahmed, PhD

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**Research Interests**

Dr. Ahmed long-term goal is to understand how sensory epithelia of various organs, including eye, ear and skin develop and function. His lab study various inherited human disorders like Usher syndrome (deaf-blindness), Albinism, Vitiligo, vision impairment, deafness, etc. to improve our understanding of these organs at the molecular level, to study the pathophysiology of these disorders in animal models for the purpose of developing new strategies to prevent and treat these neurosensory disorders. The studies under investigation are designed to answer the following broad questions: What are the precise mechanisms of various forms of these dysfunctions? How do the pathogenic mutations in disease-causing genes affect the ear, eye and skin structure and function? And which molecules or genetic factors can exacerbate and/or mitigate the effects of disease-causing genes? For these studies, families segregating inherited these disorders are being collected from various populations around the world. Mutant mouse and zebrafish models have been developed and his lab evaluates them to understand the function of new proteins. Functional analysis of the newly identified genes associated with these disorders promises new insights into the molecular mechanisms of vision, auditory and skin development and functions and will facilitate the rational design of potential therapies.

**Recent Publications**


1. FUT2 Variants Confer Susceptibility to Familial Otitis Media. Santos-Cortez RLP et al, Am J Hum Genet. 2018 Nov 1;103(5):679-690. doi: 10.1016/j.ajhg.2018.09.010. Epub 2018 Oct 25.

2. Delineation of Novel Compound Heterozygous Variants in LTBP2 Associated with Juvenile Open Angle Glaucoma. Saeedi O , Yousaf S, Tsai J, Palmer K, Riazuddin S, Ahmed ZM. Genes (Basel). 2018 Oct 30;9(11).

3. Inframe deletion of human ESPN is associated with deafness, vestibulopathy and vision impairment. Ahmed ZM, Jaworek TJ, Sarangdhar GN, Zheng L, Gul K, Khan SN, Friedman TB, Sisk RA, Bartles JR, Riazuddin S, Riazuddin S. J Med Genet. 2018 Jul;55(7):479-488. doi: 10.1136/jmedgenet-2017-105221. Epub 2018 Mar 23.

4. CIB2 interacts with TMC1 and TMC2 and is essential for mechanotransduction in auditory hair cells. Giese APJ, Tang YQ, Sinha GP, Bowl MR, Goldring AC, Parker A, Freeman MJ, Brown SDM, Riazuddin S, Fettiplace R, Schafer WR, Frolenkov GI, Ahmed ZM. Nat Commun. 2017 Jun 29;8(1):43. doi: 10.1038/s41467-017-00061-1.

5. Molecular outcomes, clinical consequences, and genetic diagnosis of Oculocutaneous Albinism in Pakistani population. Shahzad M, Yousaf S, Waryah YM, Gul H, Kausar T, Tariq N, Mahmood U, Ali M, Khan MA, Waryah AM, Shaikh RS, Riazuddin S, Ahmed ZM; University of Washington Center for Mendelian Genomics (UW CMG) Consortium. Sci Rep. 2017 Mar 7;7:44185. doi: 10.1038/srep44185.


## Nicholas P. Ambulos Jr., PhD

Professor, Microbiology and Immunology
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### Research Interests

Dr. Ambulos joined the faculty at the UMSOM 1992, beginning his tenure in, what was then called the Biopolymer Core Facility, taking over as director in 1993 and building it into a genomics core facility. In 2011, he played a key role in establishing a new resource, the Translational Genomics Laboratory (TGL), which is now a College of American Pathologists accredited genomics lab that provides clinical investigators and physicians a source for clinically validated genomics assays for the diagnosis, care, and treatment of a disease. This provides access to resources that permit both basic and clinical genomic tools, which ultimately offers an effective pathway that supports novel discoveries, aids in translating them into clinical applications, and applying these clinical applications into routine clinical care. He directs the UMGCCC's Genomics Shared Services, which brings together what was the Biopolymer lab, the TGL, the Cytogenetics Lab, and the Institute for Genome Science's Genomics Resource Center (GRC) to provide comprehensive basic, translational and clinical genomics applications to the UMGCCC. In addition to his leadership role in the UMGCCC, he serves on scientific advisory boards of three cancer centers across the country.
Dr. Ambulos is the associate director for shared services in the UMGCCC a position held since 2004, organizing the Shared Services through the initial P30 grant application and two subsequent 5-year renewals. In 2009, he successfully secured NIH funding to renovation 28,000 square feet of lab and office space to relocate many of our biomedical research cores into shared space.

### Recent Publications


1. Ambulos, Jr., N.P., Schumaker, L.M., Mathias, T.J., White, R., Troyer, J., Wells, D., Cullen, K.J. Next Generation Sequencing based HPV genotyping assay validated in formalin-fixed, paraffin-embedded oropharyngeal and cervical cancer specimens. J. Biomolec. Tech. 2016;27(2):46-52. PMCID: PMC4802743.

2. Luzum, J.A., Pakyz, R.E., Elsey, A.R., et al. The Pharmacogenomics Research Network Translational Pharmacogenomics Program: Outcomes and metrics of pharmacogenetic implementation across diverse healthcare systems. Clin. Pharmacol. Ther. 2017; Jan 16. Doi: 10.1002/cpt.630.

3. Nowak, R.G., Ambulos, N.P., Schumaker, L.M., Mathias, T.J., White, R.A., Troyer, J., Wells, D., Charurat, M.E., Bentzen, S.M., Cullen, K.J. Genotyping of high-risk anal human papillomavirus (HPV): ion torrent-next generation sequencing vs. linear array. Virology J. 2017; 14(1):112. PMCID:PMC5470268.

4. Griffith, K.A., Zhu, S., Johantgen, M., Kessler, M.D., Renn, C., Beutler, A.S., Kanwar, R., Ambulos, N., Cavaletti, G., Bruna, J., Briani, C., Argyriou, A.A., Kalafonos, H.P., Yerges-Armstrong, L.M., Dorsey, S.G. Oxaliplatin-induced peripheral neuropathy and identification of unique severity groups in colorectal cancer. J Pain and Sympt Mgmt. 2017; Jul 22. Pii: S0885-3924(17)30297-X. doi: 10.1016/j.jpainsymman.2017.07.033.

5. Singh, Z.N., Duong, V., Koka, R., Zou, Y., Sawhney, S., Tang, L., Ambulos, N., El Chaer, F., Emadi, A. High-risk acute promyelocytic leukemia with unusual T/Myeloid immunophenotype successfully treated with ATRA and arsenic trioxide-based regimen. J Hematopathol. 2018; 11(3):67-74.

6. Adige, S., Lapidus, R.G., Carter-Cooper, B.A., Duffy, A., Patzke, C., Law, J.Y., Baer, M.R., Ambulos, N.P., Zou, Y, Bentzen, S.M., Emadi, A. Equipotent doses of daunorubicin and idarubicin for AML: a meta-analysis of clinical trials versus in vitro estimation. Cancer Chemo. Pharmacol. 2019; 83(6):1105-1112.


## Songon An, PhD

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### Research Interests

The long-term objective of our research program is to understand how metabolic pathways and their organizations are functionally regulated in space and time as essential components of a living system. We have been at the frontline of studying "enzymology in a cell" using quantitative fluorescence live-cell microscopy in combination with conventional biochemical and cellular assays. Our pioneering approaches have allowed us to discover spatial organizations of metabolic enzymes and their pathways (i.e. metabolic condensates) in living human cells, including the glucosome for glucose metabolism and the purinosome for de novo purine biosynthesis. Such metabolic condensates are spatially independent, functionally active, and spatiofunctionally specific to each metabolic pathway. These discoveries thus set the stage for an extraordinary opportunity to explore the spatial and temporal advantages to the cell in regulating these metabolic condensates as the heart of human disease mechanisms, specifically including human cancers. Collectively, our research program has potentials to invoke a paradigm shift in our thinking about operation of metabolic enzymes and their pathways, and outcomes will be beneficial for human health.

### Highlighted Research

1. NIH R01 GM125981 (An (P.I.)): A Multienzyme Metabolic Complex for Glucose Metabolism. The research objective is to understand how a metabolic complex of human glucose metabolism regulates glucose flux in a size-dependent manner at subcellular levels. Role: P.I.

2. NIH R03 CA219609 (An (P.I.)): Functional Contribution of Metabolic Complex to Cancer Cell Metabolism. The objective of this proposal is to characterize cancer-specific alterations of a metabolic complex of human glucose metabolism, the glucosome, and its functional contribution to cancer cell metabolism. Role: P.I.

3. NIH R01 GM134086 (Kyoung (P.I.)): 4D Functional Mapping of Glucose Metabolism in Living Cells. The objective of this proposal is to elucidate how glucose metabolism (i.e. glycolysis and gluconeogenesis) and mitochondrial metabolism are spatially and functionally interconnected and dynamically orchestrated in human living cells. Role: Co-Investigator

### Highlighted Publications


1. Jeon M, Kang H-W*, An S*. A mathematical modeling of the enzyme clustering in glucose metabolism. Scientific Reports (2018) 8, 2696 [PMCID: 5807315]

2. Kohnhorst CL, Kyoung M, Jeon M, Schmitt DL, Kennedy EL, Ramirez J, Bracey SM, Luu B-T, Russell SJ, An S*. Identification of a multienzyme complex for glucose metabolism in living cells. J. Biol. Chem. (2017) 292, 9191-9203 [PMCID: 5454101]

3. An S*, Kumar R, Sheets ED*, Benkovic SJ*. Reversible compartmentalization of de novo purine biosynthetic complexes in living cells. Science (2008) 320, 103-106 [PMID: 18388293]


**Corresponding Authors*


## Nariman Balenga, PhD

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**Research Interests**

We use a multi-disciplinary approach to investigate the signaling pathways and function of orphan G protein-coupled receptors in health and disease. Currently, we are focused on the pathophysiological roles of GPR64 in endocrine system.

**Highlighted Research**

1R01GM130617-01A1, National Institute of General Medical Sciences (Balenga PI)

09/01/19-05/31/23

Mechanisms of activation, signaling and trafficking of adhesion GPCRs GPR64 and GPR56

To characterize unique pharmacological characteristics of GPR64 and GPR56, members of the adhesion G protein-coupled receptor family in vitro and in vivo.

**Highlighted Publications**


1. Spatial regulation of GPR64/ADGRG2 signaling by β-arrestins and GPCR kinases. Azimzadeh P, Talamantez-Lyburn SC, Chang KT, Inoue A, Balenga N. Ann N Y Acad Sci. 2019 Nov;1456(1):26-43.

2. Parathyroid-Targeted Overexpression of Regulator of G-Protein Signaling 5 (RGS5) Causes Hyperparathyroidism in Transgenic Mice. Balenga N, Koh J, Azimzadeh P, Hogue J, Gabr M, Stains JP, Olson JA Jr. J Bone Miner Res. 2019 May;34(5):955-963.

3. Orphan Adhesion GPCR GPR64/ADGRG2 Is Overexpressed in Parathyroid Tumors and Attenuates Calcium-Sensing Receptor-Mediated Signaling. Balenga N, Azimzadeh P, Hogue JA, Staats PN, Shi Y, Koh J, Dressman H, Olson JA Jr.J Bone Miner Res. 2017 Mar;32(3):654-666.


## Aditi Banerjee, PhD

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**Research Interests**

The Banerjee group has recently identified the inverse relationship in expression of oncogenic FoxM1 and tumor suppressor RASSF1A in various stages of colorectal cancer (CRC). This inverse correlation was also observed in mCRC cell lines (T84, Colo 205). Her group also demonstrated that inhibition of FoxM1 expression in mCRC cells as well as in ex vivo model resulted in increased RASSF1A expression. Reduced levels of RASSF1A expression were found in normal cells (RWPE-1, HBEpc, MCF10A, EC) stimulated with exogenous VEGF165. Downregulation of FoxM1 also coincided with increased YAP phosphorylation, indicative of tumor suppression. Conversely, downregulation of RASSF1A coincided with FoxM1 overexpression. Therefore her studies have identified for the first time an integrated signaling pathway between FoxM1 and RASSF1A in mCRC progression, which may facilitate the development of novel therapeutic options for advanced colorectal cancer therapy.

Conventional therapies affect only proliferating and differentiated cancer cells from the tumor mass and save cancer stem cells (CSCs). These CSCs drive tumor recurrence, metastasis and resistance to chemotherapy which ultimately leads to failure in cancer therapy. Banerjee group has recently invented a combinational therapy which has a potential therapeutic effect on metastatic colon cancer cells and stem cells derived from metastatic colon cancer cells and patient derived different stages of organoids. Banerjee group is expecting this dual therapy will provide new therapeutic modalities that will reduce morbidity and increase the overall survival of CRC patients.

**Recent Publications**


1. Blanchard TG, Lapidus R, Banerjee V, Bafford AC, Czinn SJ, Ahmed H, Banerjee A. Upregulation of RASSF1A in Colon Cancer by Suppression of Angiogenesis Signaling and Akt Activation. Cell Physiol Biochem. 2018;48(3):1259-1273. doi 10.1159/000492012. Epub 2018 Jul 25.

2. Blanchard TG, Czinn SJ, Banerjee V, Sharda N, Bafford AC, Mubariz F, Morozov D, Passaniti A, Ahmed H, Banerjee A. Identification of Cross Talk between FoxM1 and RASSF1A as a Therapeutic Target of Colon Cancer. Cancers (Basel). 2019 Feb 8;11(2). pii: E199. doi: 10.3390/cancers11020199.

## John R. Basile, DDS, DMSc

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**Research Interests**

Our lab focuses on Semaphorin 4D (S4D) and its receptor, Plexin-B1 (PB1), proteins originally shown to transmit axonal guidance cues, and their participation in an expanding repertoire of cellular functions including cell adhesion and migration, bone mineralization, and induction of angiogenesis.

I am a board certified oral and maxillofacial pathologist and director of Oral Pathology Consultants, the pathology service at the dental school. My clinical research interests include HPV-induced squamous cell carcinomas

**Highlighted Research**

1. Examination of neoplastic, infectious, and inflammatory conditions of the oral cavity, looking for unique histological characteristics and biomarkers with clinical and prognostic significance.

2. The influence that semaphorins and their receptors, the plexins, have on the ability of some tumors to metastasize to bone.

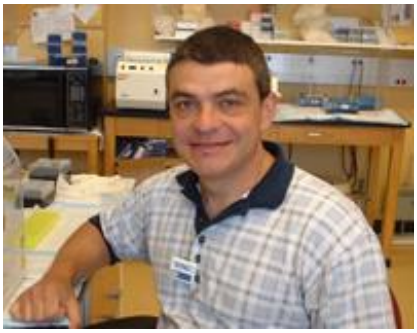
3. Expression of CD100 (Semaphorin 4D) in malignancies and its effects in tumor-induced angiogenesis.

**Highlighted Publications**


1. Immunohistochemical profile of the anti-apoptosis, apoptosis and proliferation markers Bcl-2, caspase-3, p53, and Ki-67 in botryoid odontogenic cysts compared to lateral periodontal cysts and gingival cysts of the adult. Biotech Histochem. 2020 Jul 9:1-6.

2. The use of artificial intelligence, machine learning and deep learning in oncologic histopathology. J Oral Pathol Med. 2020 May 24.

3. Combination Nivolumab/Ipilimumab Immunotherapy For Melanoma With Subsequent Unexpected Cardiac Arrest: A Case Report and Review of Literature. J Immunother. 2019 Oct;42(8):313-317.




## Jeffrey J. DeStefano, PhD

Professor, Cell Biology & Molecular Genetics
Director of MOCB Graduate Concentration Area (BISI Graduate Program)
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**Research Interests**

Our lab works on understanding the molecular basis for HIV drug resistance, focusing on drugs that inhibit reverse transcriptase (RT). We use biochemical and structural techniques to address this question. We also study the basic mechanism of polymerase fidelity using similar techniques. Recently we have been involved in making nucleic acid aptamers (nucleic acid constructs that bind with high affinity to target proteins) that target HIV viral proteins including RT and integrase (IN). Our aptamers range from those that mimic the normal substrates for these enzymes (e.g. primer-template for RT) to others made from Xenonucleic acids (XNA) which are chemically altered nucleotide analogs. Aptamers can be used like antibodies in many assays or as inhibitors, and even to help in crystallization for structural studies. Along with our collaborator Dr. Eddy Arnold (Rutgers), a primer-template mimicking aptamer was used to produce the first crystal structure of HIV RT bound to a nucleic acid without cross-linking. With our collaborators Dr. Phillip Holliger (Cambridge) and Dr. Robert Craigie (NIH) we produced an IN aptamer made from fluorarabino nucleic acid (an XNA, abbreviated FANA) that binds two orders of magnitude more strongly than previous IN aptamers. We are currently investigating this aptamer as a potential virus inhibitor and using it in structural studies with IN and IN precursor proteins.

**Recent Publications**


1. DeStefano JJ. Non-nucleoside Reverse Transcriptase Inhibitors Inhibit Reverse Transcriptase through a Mutually Exclusive Interaction with Divalent Cation-dNTP Complexes. Biochemistry. 2019 Apr 23;58(16):2176-2187. doi: 10.1021/acs.biochem.9b00028. Epub 2019 Apr 5. PubMed PMID: 30900874; PubMed Central PMCID: PMC6629025.
2. Das K, Martinez SE, DeStefano JJ, Arnold E. Structure of HIV-1 RT/dsRNA initiation complex prior to nucleotide incorporation. Proc Natl Acad Sci U S A. 2019 Apr 9;116(15):7308-7313. doi: 10.1073/pnas.1814170116. Epub 2019 Mar 22. PubMed PMID: 30902895; PubMed Central PMCID: PMC6462067.


## Scott E. Devine, PhD

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**Research Interests**

During the past year, we have continued to work on on mobile DNA and structural variation in human genomes. One focus has been to better understand the role of mobile elements in human cancers. We have been sequencing colorectal cancers and discovering mobile element insertions in these genomes using our mobile element locator tool (MELT). We also have been examining exomes from the Cancer Genome Atlas project to identify germline mobile element insertions in hematological tumors. This is a new direction that my oncology fellow is pursuing in line with his clinical interests in leukemias. We also have been working with Diane Liard at UCSC to identify mobile element insertions in teratomas.

Finally, we have been working with the Human Genome Structural Variation Consortium (which grew out of the 1000 Genomes Project structural variation group) to study human structural variation. We recently learned that our U24 grant was renewed for another four years. I am one of eight PIs on that grant, and IGS will play a significant role in the next stage of this project. In particular, IGS will sequence 1/3 of the 78 genomes that the project will sequence in the first year of the project (on our new PacBio Sequel II sequencer). We also will contribute to the analysis of these genomes and plan to develop new Pac-based MELT tools.

**Recent Publications**


1. Natarajan, P., Peloso, G.M., Zekavat, S.M., Montasser, M., Ganna, A., et al. (including Devine, S.). Deep-coverage whole genome sequences and blood lipids among 16,324 individuals. (2018). Nature Commun. 9(1):3493. Doi: 10.1038/s41467-018-05975-y. PMID: 30140-049.

2. Zekavat, S.M., Ruotsalainen, S., Handsaker, R.E., Alver, M., Bloom, J. et al. (including Devine, S.) (2018). Deep coverage whole genome sequences and plasma lipoprotein(a) in individuals of European and African ancestries. Nature Commun. 9(1):2606. Doi: 10.1038/s41467-018-04668-w. PMID: 29973585.

3. Chaisson, M.J.P., Sanders, A.D., Zhao, X., Malhotra, A., Porubsky, D., et al. (including Devine, S.E.—joint senior author). (2019). Multi-platform discovery of haplotype-resolved structural variation in human genomes. Nature Commun. 10(1):1784. Doi: 10.1038/s41467-018-08148-z. PMID: 30992455.

**Jonathan D. Dinman, Ph.D.**
Professor and Chair
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**Research Interests**

Exceptions to rules provide us with tools to understand the rules themselves. The protein synthesis dogma requires that ribosomes must maintain reading frame, and that deviations from frame maintenance is deleterious. However, the mRNAs of many viruses and a growing of list of cellular mRNAs harbor cis-acting sequence elements that program a fraction of translating ribosomes to break the canonical rules of translation by shifting from one reading frame to another. This is called programmed ribosomal frameshifting (PRF). Our studies of PRF have revealed novel insights into ribosome structure and function, how cells and viruses post-transcriptionally regulate gene expression, RNA structural dynamics, and virology.

**Highlighted Research**

1. Targeting programmed ribosomal frameshifting for antiviral applications.

2. The role of programmed ribosomal frameshifting in regulation of cellular gene expression and disease.

**Highlighted Publications**

1. Belew, A.T., Meskauskas, A., Musalgaonkar, S., Advani, V., Sulima, S.O., Kasprzak, W., Shapiro, B.A. and Dinman, J.D. 2014. Ribosomal frameshifting in the CCR5 mRNA is regulated by miRNAs and NMD. Nature 251: 265 – 269.

2. Kelly, J.A. , Olson, A.N. , Neupane, K., Munshi, S., San Emeterio, J., Pollack, L., Woodside, M.T. and Dinman, J.D. 2020. Structural and functional conservation of the programmed− 1 ribosomal frameshift signal of SARS coronavirus 2 (SARS-CoV-2). J. Biol. Chem. 295:10741-10748.

3. Sulima, S.O., Hofman, I.J., De Keersmaecker, K., and Dinman, J.D. 2017. How ribosomes translate cancer. Cancer Discovery. 7:1069-1087.

## Alexander C. Drohat, PhD

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### Research Interests

Our research centers on two broad areas, DNA repair and epigenetic regulation. The nucleobases of DNA are amenable to a broad range of chemical alterations, a feature that enables enzyme-mediated modifications but also allows for threatening DNA damage. We study enzymes that find and repair DNA lesions, thereby maintaining genomic integrity and protecting against cancer and other diseases. We also investigate enzymes that perform essential functions in epigenetic regulation, by acting on modified DNA bases. We use a broad range of biochemical, biophysical, structural, and molecular approaches, and collaborate with many other research groups at University of Maryland and groups at many other institutions.

### Highlighted Research

Our research has been supported continuously by the NIH since 2005, with the following active grants.

1 R35 GM136225 (Drohat PI)

05/01/2020 – 04/30/2025

Mechanisms of BER in Genomic Integrity and Epigenetic Regulation

The overall goal is to discover how base excision repair enzymes recognize and excise damaged or enzymatically modified forms of 5-methylcytosine and how they are regulated by PTMs including SUMO.

5 R01 GM072711 14 (Drohat PI)

02/01/2005 – 04/30/2021

Mechanism of Glycosylase Enzymes in DNA Repair and Demethylation

This grant is being replaced by the R35 above and is in a no cost extension. Two administrative supplements (2019, 2020) have supported procurement of a new 19F-capable cryoprobe for the 600 MHz NMR spectrometer in the UMB NMR Facility, and an Oryx8-SpectroLight 610 system

### Highlighted Publications


1. Pidugu LS, Dai Q, Malik SS, Pozharski E, Drohat AC (2019) Excision of 5-carboxylcytosine by Thymine DNA Glycosylase, J Am Chem Soc 141, 18851-61

2. Dow BJ, Malik SS, Drohat AC (2019) Defining the Role of Nucleotide Flipping in Enzyme Specificity Using 19F NMR, J Am Chem Soc 141, 4952-62

3. Drohat AC and Coey CT (2016) Role of Base Excision "Repair" Enzymes in Erasing Epigenetic Marks from DNA, Chem Rev 116, 12711-29


## Richard L. Eckert, PhD

John F.B. Weaver Distinguished Professor
Chair - Biochemistry and Molecular Biology
Deputy Director - UMGCCC
Associate Director of Basic Science – UMGCCC
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**Research Interests:**

Cancer Stem Cell Survival and Function

The Eckert laboratory studies control of cancer stem cell survival in epidermal squamous cell carcinoma, melanoma and mesothelioma. Cancer stem cells comprise small subpopulation of tumor cells that are highly aggressive cells that form highly vascularized and rapidly growing tumors. These cells are responsible for tumor survival and regrowth, and resistance to chemotherapy. The laboratory has shown that key signaling systems are selectively overexpressed and activated in these cells and promote cancer stem cell survival. We have shown that epigenetic factors, including the polycomb (Ezh2/Bmi) and arginine methyltransferase (PRMT5/MEP50) genes, are overexpressed and drive cancer stem cell survival. Recent studies demonstrate a key role for the transglutaminase 2 (TG2) cancer stem cell survival protein in maintaining cancer stem cell survival and facilitating cancer stem cell invasion and migration via activation of YAP1/TAZ, VEGFA/VEGFR and MAPK/ROCK/Rho signaling. The laboratory also works on mechanisms of cancer prevention mediated by sulforaphane, a diet derived agent that is effective in suppressing tumor formation. Sulforaphane is a promising candidate cancer prevention and therapy agent that inactivate overexpressed proteins that drive cancer stem cell survival.


Keywords: Tumor Suppressors, Polycomb Genes, Arginine Methyltransferase, Transglutaminase 2, Cancer Prevention, Hippo YAP/TAZ Signaling, Angiogenesis, VEGF signaling, HGF/c-Met signaling, Mouse Cancer Models, Oncogenes, Cancer Stem Cell Survival Factors.


**Highlighted Publications**


1. Shrestha S, Adhikary G, Xu W, Kandasamy S, Eckert RL (2020) ACTL6A suppresses p21Cip1 expression to enhance the epidermal squamous cell carcinoma phenotype. Oncogene [Epub 2020].
2. Kandasamy S, Adhikary G, Rorke EA, Friedberg JS, Mickle MB, Alexander HR, Eckert RL (2020) The YAP1 signaling inhibitors, verteporfin and CA3, suppress the mesothelioma cancer stem cell phenotype. Mol Cancer Res 18, 343-351
3. Wang Y, Leonard MK, Snyder DE, Fisher ML, Eckert RL, Kaetzel DM (2019) NME1 drives expansion of melanoma cells with enhanced tumor growth and metastatic properties. Mol Cancer Res 17(8):1665-1674. PMID: 31123173; PMCID: PMC6677611
4. Grun D, Adhikary G, Eckert RL (2018) NRP-1 interacts with GIPC1 and α6/β4-integrins to increase YAP1/ΔNP63α-dependent epidermal cancer stem cell survival. Oncogene 37(34):4711-4722. PMID: 29755126; PMCID: PMC6381998


## Xiaoxuan Fan, PhD

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### Research Interests

Flow Cytometry Shared Service provides analytical and cell sorting services to the UMGCCC members. Services and value-added support include instructional lectures, hands on training, assistance with experimental design, sample acquisition, data analysis, and troubleshooting. The recently installed 3 laser and 4 laser Cytek Aurora spectral cytometers are capable of analyzing 23 and 30 color immunophenotyping panels from a single tube. MACSQuant analyzer 10 is in compliance with FDA 21 CFR Part 11, ideal for clinical studies. Its Express Modes automate analysis of flow experiments via predefined experiment settings. It is being set up for quality control for CART cell production.

### Highlighted Research

1. CRF Shared Service Pilot Award. 8/1/2018-7/31/2019 PIs: Gregory Szeto, Xiaoxuan Fan
   Development of new multiplexed panels for mouse and human cellular phenotyping using spectral flow cytometry for the Flow Cytometry Shared Service
2. Detailed immunophenotypic profiling of peripheral blood immune cells in patients with hematologic malignacies after SARS-COV-2 Infection.
3. Working with new Fannie Angelos GMP Laboratory for Cellular Therapeutics to provide quality control for CAR-T cell therapy.

### Highlighted Publications


1. Persistence of Drug-Resistant Leukemic Stem Cells and Impaired NK Cell Immunity in CML Patients Depend on MIR300 Antiproliferative and PP2A-Activating Functions. Silvestri G, Trotta R, Stramucci L, Ellis JJ, Harb JG, Neviani P, Wang S, Eisfeld AK, Walker CJ, Zhang B, Srutova K, Gambacorti-Passerini C, Pineda G, Jamieson CHM, Stagno F, Vigneri P, Nteliopoulos G, May PC, Reid AG, Garzon R, Roy DC, Moutuou MM, Guimond M, Hokland P, Deininger MW, Fitzgerald G, Harman C, Dazzi F, Milojkovic D, Apperley JF, Marcucci G, Qi J, Polakova KM, Zou Y, Fan X, Baer MR, Calabretta B, Perrotti D. Blood Cancer Discov. 2020 Jul;1(1):48-67. PMID: 32974613
2. Monocyte Subsets With High Osteoclastogenic Potential and Their Epigenetic Regulation Orchestrated by IRF8. Das A, Wang X, Kang J, Coulter A, Shetty AC, Bachu M, Brooks SR, Dell'Orso S, Foster BL, Fan X, Ozato K, Somerman MJ, Thumbigere-Math V. J Bone Miner Res. 2020 Aug 17. PMID: 32804442
3. Loss of Protease-Activated Receptor 4 Prevents Inflammation Resolution and Predisposes the Heart to Cardiac Rupture After Myocardial Infarction. Kolpakov MA, Guo X, Rafiq K, Vlasenko L, Hooshdaran B, Seqqat R, Wang T, Fan X, Tilley DG, Kostyak JC, Kunapuli SP, Houser SR, Sabri A. Circulation. 2020 Aug 25;142(8):758-775. Epub 2020 Jun 3. PMID: 32489148


## Shengyun Fang, MD, PhD

Associate Professor
University of Maryland School of Medicine
BioMET/Cancer Biology


**Research Interests**

Our lab focuses on understanding how protein homeostasis (proteostasis) in the endoplasmic reticulum and the nucleus is regulated and developing drugs to harness this regulation to treat human diseases, such as cancer, neurodegenerative diseases, and cystic fibrosis.

**Highlighted Research**

R01GM117175: High-Content Screening to identify small molecules for refolding SOD1 mutants

**Highlighted Publications**


1. Zhong Y, Fang S. Live cell imaging of protein dislocation from the endoplasmic reticulum. J Biol Chem. 2012 Aug 10;287(33):28057-66. doi: 10.1074/jbc.M112.381798. PMCID: PMC3431711.

2. Zhong Y, Wang J, Henderson MJ, Yang P, Hagen B, Siddique T, Deng HX, Fang S. Nuclear export of misfolded SOD1 mediated by a normally buried NES-like sequence reduces proteotoxicity in the nucleus. eLife. 2017 May 2;6. pii: e23759. PMCID: PMC5449186.

3. Ruan J, Rothan HA, Zhong Y, Yan W, Henderson MJ, Chen F, Fang S. A small molecule inhibitor of ER-to-cytosol protein dislocation exhibits anti-dengue and anti-Zika virus activity. Sci Rep. 2019 Jul 29;9(1):10901.

## Syed Saif Hasan, PhD

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### Research Interests

Protein secretion provides antibodies, growth factors, and hormones to accomplish cellular communication. Homeostasis in eukaryotic protein secretion depends on inter-organelle communication between endoplasmic reticulum, Golgi, and plasma membrane. Dysfunction in inter-organelle communication generates secretory stress, which affects the production of nearly one-third of the entire human proteome leading to cardiomyopathies, aggressive cancers, and viral infections. With a focus on KDEL receptors, which are crucial for biomolecule and information trafficking between Golgi and endoplasmic reticulum during secretion, my laboratory is interested in elucidating the structural basis of secretory communication. Our investigations will reveal the molecular language employed for communication between secretory organelles and the architectural details of KDEL receptors, which decrypt this molecular language to maintain secretory homeostasis. Results from our research will have broad implications for fundamental protein trafficking between organelles and for the development of therapeutics in secretory diseases.

### Highlighted Research

1. University of Maryland MPower Grant: Structural Investigations of KDEL Receptors
   Hasan SS, Hudgens JW, Pierce BP (MPI): 09/20-07/21

2. UMaryland MPower COVID19 Response Fund Award: Molecular Investigations of SARS-CoV-2 Spike Protein
   Hasan SS, MacKerell AD, Orban J (MPI): 08/20-08/21

3. University of Maryland MPower Grant: Molecular Architecture of KDELR-Gq, an Oncogenic Trans-Membrane Signalling Complex
   Hasan SS, Hudgens JW, Pierce BP (MPI): 08/19-06/20

### Highlighted Publications

1. Rehman, A, Hasan SS. KDEL receptors form a complex with Gα subunits in secretory protein trafficking. 9th Annual Biochemistry and Molecular Biology Retreat (Poster presentation), University of Maryland School of Medicine, Baltimore MD, USA. 10th January 2020.

2. Hasan, SS. Investigations of ZIKV and EEEV entry and host machinery for inter-organelle trafficking. Invited talk at Department of Microbiology and Immunology, Georgetown University, Washington DC, USA. 25th February 2020.

3. Hasan, SS. Insights into protein secretion. Invited talk at Basic Chairs' Meeting, University of Maryland School of Medicine, Baltimore MD, USA. 26th February 2020.


## Ronna P. Hertzano, MD, PhD

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**Research Interests**

I am an otolaryngologist surgeon-scientist. My clinical practice focuses on the diagnosis and treatment of diseases of the ear and hearing restoration. The goals of my research are to make significant contributions towards the treatment of congenital and acquired auditory and vestibular dysfunction. Towards hearing restoration, I work to unravel the regulatory signaling cascades that lead to the proper development of the ear and specifically the hair cells. I lead a collaborative team that develops and applies a variety of approaches for cell type-specific multi-omic analyses of the ear. We couple the results of these studies with state-of-the-art informatics analyses to identify key regulators of gene expression in hair cell development, and cell type-specific signaling cascades in acquired hearing loss. We then validate these results using a broad range of studies from auditory and vestibular physiology (ABR, DPAOE, VsEP) to molecular and biochemical assays and to imaging – both in murine and zebrafish models. To facilitate dissemination, sharing and analysis of multi-omic data I incepted and spearheaded the development of the gEAR portal –gene Expression Analysis Resource (UMgEAR.org).

**Highlighted Research**

1. NIH R01, DC013817 - "Cell Type Specific Transcriptional Cascades in Inner Ear Development"
   This project is to studies the roles of RFX and GFI1 in hair cell development and survival.
2. Hearing Health Foundation, Hearing Restoration Project (HRP) - "Implementing the gEAR for data sharing within the HRP"
   This project supports development of the gEAR for the hearing research community.
3. NIMH, R24MH114815 - "Illuminating Neurodevelopment through Integrated Analysis and Visualization" This project develops a visualization and analysis environment for brain related data.

**Highlighted Publications**


1. Chessum L*, Matern M*, Kelly MC, Johnson SL, Ogawa Y, Milon B, McMurray M, Driver EC, Parker A, Song Y, Codner G, Esapa CT, Prescott J, Trent G, Wells S, Dragich AK, Frolenkov GI, Kelley MW, Marcotti W, Brown SDM, Elkon R, Bowl MR, and Hertzano R (2018) Ikzf2/helios is a key transcriptional regulator of outer hair cell maturation. Nature. Nov;563(7733):696-700.
2. Elkon R, Milon B, Morrison L, Shah M, Vijayakumar S, Racherla M, Leitch CC, Silipino L, Hadi S, Weiss-Gayet M, Barras E, Schmid CD, Ait-Lounis A, Barnes A, Song Y, Eisenman DJ, Eliyahu E, Frolenkov GI, Strome SE, Durand B, Zaghloul NA, Jones SM, Reith W and Hertzano R. (2015) RFX transcription factors are essential for hearing in mice. Nat Commun. Oct 15;6:8549. doi: 10.1038/ncomms9549


## Charles C. Hong, MD, PhD

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**Research Interests:**

Hong Lab carries out high-throughput phenotypic screens for small molecules that modulate vertebrate embryonic development. The overarching therapeutic hypothesis of this effort is that cellular pathways and mechanisms that regulate embryonic development are important untapped source of future transformative therapies for devastating illnesses, such as cancers. Using this approach, we discovered the first small molecule inhibitor of the bone morphogenetic protein (BMP) signaling, which was successfully licensed to a biopharma for clinical development. This work has provided chemical tools that revealed potential therapies for gliomas, breast cancers, lung cancers and leukemias, in doing so spawning a number of pharmaceutical development programs to treat various cancers. In addition, we have identified novel small molecule inhibitors of Hedgehog and Wnt signaling pathways, both of which are known to be important therapeutic targets for human cancers. Lastly, we developed first-in-class extracellular proton sensing receptor inhibitors, which also show promise as anti-cancer therapeutic leads.

**Highlighted Research**

1. Explore the role of BMP inhibitors as cancer therapeutics, particularly in cancer immunotherapy.

2. Role of proton-sensing receptor in embryonic development and cancer pathogenesis.

3. Chemical genetic screens of zebrafish embryonic development as a route to novel therapies.

**Highlighted Publications**


1. Hao J, Ao A, Zhou L, Murphy CK, Frist AY, Keel JJ, Thorne CA, Kim K, Lee E, Hong CC. Selective Small Molecule Targeting ß-Catenin Function Discovered by In Vivo Chemical Genetic Screen. Cell Reports 2013; 4:898-904. PMID: 24012757. PMCID: PMC3923627.

2. Williams CH, Hempel JE, Hao J, Frist AY, Williams MM, Fleming JT, Sulikowski GA, Cooper MK, Chiang C, Hong CC. An in vivo chemical genetic screen identified phosphodiesterase 4 as a pharmacological target for hedgehog inhibition. Cell Reports 2015; 11:1-8. PMID: 25818300. PMCID: PMC4394042. PMCID: PMC4394042.

3. Owens P, Pickup MW, Novitskiy SV, Giltnane JM, Gorska AE, Hopkins CR, Hong CC*, Moses HL*. Inhibition of BMP signaling suppresses metastasis in mammary cancer. Oncogene 2015; 34:2437-49. *co-senior authors. PMID: 24998846. PMCID: PMC4689138.


## David M. Kaetzel, PhD

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**Research Interests**

I have a long-standing interest in the mechanisms that drive cancer metastasis, and have acquired a broad spectrum of molecular and cancer biological approaches are being brought to bear against this problem. Our laboratory is focused on how tumor and metastasis suppressor genes carry out their functions through the regulation of genomic stability and transcriptional programs in cancer cells. We have recently developed a genetically-engineered mouse model that exhibits UV-induced melanoma in a highly metastatic form, by virtue of a combination of genetic manipulations (HGF transgene, knockouts in the tumor suppressor p16 and the metastasis suppressor genes NME1 and/or NME2). This model has enabled a comprehensive dissection of mechanisms that underlie the progression of melanoma to its lethal and therapy-resistant forms. We have recently applied state-of-the-art NextGen sequencing technologies to identity genomic and transcriptomic alterations in melanoma tissues associated with melanoma metastasis in our mouse model, and have found significant parallels with the human disease. Our ultimate goal is to exploit that knowledge to identify new targets for diagnosis, prognosis, and treatment of advanced melanoma, all of which are poorly addressed by current clinical approaches.

**Highlighted Research**

1. Molecular profiling of mutational and transcriptomic alterations by NextGen-sequencing in a novel mouse model of metastatic melanoma, and application of those profiles for discovery of novel metastasis-regulating genes in human melanoma.

2. Analysis of a rare and highly metastatic subpopulation of melanoma cells that exhibit low expression of the metastasis suppressor genes NME1 and NME2, and potential of these cells for driving progression in human melanoma patients.

**Highlighted Publications**


1. Wang, Y., Leonard, M.K., Snyder, D., Fisher, M., Eckert, R.L. and Kaetzel, D.M. (2019) NME1 drives expansion of melanoma cells with enhanced tumor growth and metastatic properties. Mol. Cancer Res. 17:1665-1674. PMCID: PMC6677611

2. Snyder, D., Wang, Y. and Kaetzel, D.M. (2020) A rare subpopulation of melanoma cells with low expression of metastasis suppressor NME1 is highly metastatic in vivo. Sci. Rep. 10:1971-1983. PMCID: PMC7005181

3. Pamidimukkala, N., Puts, G.C., Leonard, M.K., Snyder, D., Novak, M., Dabernat, S., DeFabo, E.C., Noonan, F.P., Slominski, A., Merlino, G. and Kaetzel, D.M. Nme1 and Nme2 exert metastasis suppressor activities in a mouse model of UV-induced melanoma. Br. J. Cancer. in press.


## Tami J. Kingsbury, PhD

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**Research Interests**

Improper expression of developmental transcriptional networks, such as the PAX-SIX-EYA-DACH (network PSEDN), contributes to cancer cell survival, proliferation and metastasis. We have identified novel functional and physical interactions between PSEDN members and the GATA transcriptional network and demonstrated that the manipulation of SIX1 regulates erythroleukemia cell growth and differentiation. Briefly, overexpression of SIX1, SIX2 or their co-regulator EYA1 enhances, whereas SIX1 knockout impairs, erythroid differentiation in the human TF1 cell model of erythropoiesis. Similar results were observed for SIX1 in primary human hematopoietic stem-progenitor cells. Using co-immunoprecipitation, proximal biotin labeling assays and proximal ligation assays, we demonstrated that SIX1 interacts with GATA1, a central transcription factor in erythropoiesis. SIX1 can stimulate GATA1 activation of a GATA reporter gene and when overexpressed in TF1 cells, triggers expression of many GATA1 target genes. Our data suggest SIX1 Further studies have revealed that multiple SIX family members can modulate diverse GATA family members, suggesting the interaction of these two pathways may exert additional roles in normal and malignant development. Using BioID, we further defined the hematopoietic SIX1/SIX2 proximal interactome, which contains multiple factors previously shown to play central roles in cancer biology, including SWI/SNF and NURD complex members. Ongoing work is focused on understanding the role of SIX-GATA interaction in multiple cancers and testing the functional role of additional SIX1 proximal interactome members.

**Recent Publications**


1. Creed M, Baldeosingh R, Eberly CL, Schlee CS, Kim M, Cutler J, Pandey A, Civin CI, Fossett NG, Kingsbury TJ. PAX-SIX-EYA-DACH Network modulates GATA-FOG function in fly hematopoiesis and human erythropoiesis. Development. 2020 Jan 3;147(1). PMID: 31806659

2. Kingsbury TJ, Kim M,Civin CI. Regulation of cancer stem cell properties by SIX1, a member of the PAX-SIX-EYA-DACH network. Adv Cancer Res. 2019;141:1-42.

3. Kim M.J., Civin C.I., Kingsbury T.J. MicroRNAs as regulators and effectors of hematopoietic transcription factors. WIREs RNA e1537, 2019. PMID: 31007002

4. Weston S., Matthews K.L., Lent R., Vik A., Haupt R., Kingsbury T., Frieman M.B. A yeast suppressor screen used to identify mammalian SIRT1 as a proviral factor for Middle East Respiratory Syndrome Coronavirus replication. J Virol 93:300197-19, 2019. PMID: 31142674 PMCID: PMC6675885

## Jiayuh Lin, PhD

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**Research Interests**

The Lin lab is working on the signaling pathways of IL-6, IL-8, HuR, BRCA, and CDK4/6 in human cancer cells. We are studying the mechanisms of IL-6, IL-8, and CDK4/6 signaling in promoting triple-negative breast, ovarian cancer, and medulloblastoma progression, survival, proliferation, anti-cancer immunosuppressive, and tumorigenesis. The laboratory is also developing new drug candidates to target IL-6, IL-8, HuR, and STAT3 signaling in cancer cells as novel cancer therapeutic approaches.

**Highlighted Research**

1. Title: A novel STAT3-selective inhibitor for medulloblastoma therapy
   Funding Agency: NIH/NINDS/R01. PI: Jiayuh Lin

2. Title: IL-6/GP130 signaling as a novel chemoprevention target for triple- negative breast cancer
   Funding Agency: CDMRP (Breast Cancer Research Program). PI: Jiayuh Lin

3. Title: Simultaneously targeting IL-6 and CDK4/6 pathways as a novel therapeutic approach for triple-negative breast cancer.

**Highlighted Publications**


1. Fu S, Chen X, Lo HW, Lin J. Combined bazedoxifene and paclitaxel treatments inhibit cell viability, cell migration, colony formation, and tumor growth and induce apoptosis in breast cancer. Cancer Lett. 2019 448:11-19.

2. Pan L, Chen X, Fu S, Yu W, Li C, Wang T, Lo HW, Lin J. LLY17, a novel small molecule STAT3 inhibitor induces apoptosis and suppresses cell migration and tumor growth in triple-negative breast cancer. Breast Cancer Research and Treatment 181:31-41. 2020.

3. Sirkisoon S, Carpenter R, Rimkus T, Doheny D, Zhu D, Aguayo N, Xing F, Chan M, Ruiz J, Metheny Barlow L, Strowd R, Lin J, Regua A, Arrigo A, Anguelov M, Pasche B, Debinski W, Watabe K, and Lo H-W. TGLI1 transcription factor mediates breast cancer brain metastasis via activating metastasis-initiating cancer stem cells and astrocytes in the tumor microenvironment. Oncogene 39: 64-78, 2020


## Daniel Lobo, PhD

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**Research Interests**

At the Lobo Lab we reverse engineer the mechanisms regulating biological growth and form with an integrated systems approach. We focus on understanding, controlling, and designing the dynamic regulation and signaling that control how organisms grow, metabolize their components, and coordinate the formation of patterns and shapes. We closely integrate new computational methods, mathematical models, and bioinformatics approaches with molecular assays at the bench. We seek a mechanistic understanding of development and regeneration, find therapies for cancer and other diseases, and streamline the application of systems and synthetic biology.

**Highlighted Research**

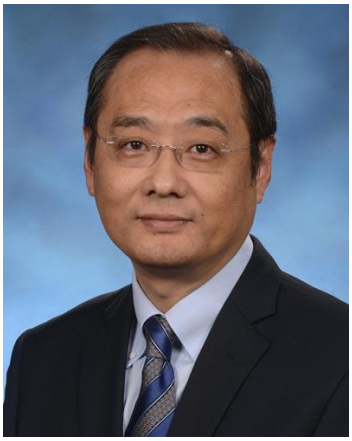
Systems Biology Of Shape And Size Regulation - R35GM137953
The genetic regulation of the shape and size of internal organs and whole body is crucial during development, regeneration, and homeostasis. This project will develop a novel integrated systems biology approach to elucidate mechanistically the molecular pathways and their coordination that control large-scale tissue growth dynamics in living organisms. These advancements will have a broad impact on our understanding of human development and regeneration towards novel therapeutic interventions for treating birth defects, traumatic injuries, and cancer.

**Highlighted Publications**


1. A. Hari, D. Lobo. Fluxer: a web application to compute, analyze, and visualize genome-scale metabolic flux networks. Nucleic Acids Research 48, pp. 427-435, 2020

2. J.M. Ko, D. Lobo. Continuous dynamic modeling of regulated cell adhesion: sorting, intercalation, and involution. Biophysical Journal 117(11), pp. 2166-2179, 2019.

3. S. Herath, D. Lobo. Cross-inhibition of Turing patterns explains the self-organized regulatory mechanism of planarian fission. Journal of Theoretical Biology 485, 110042, 2019.




## Wuyuan Lu, PhD

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**Research Interests**

The tumor suppressor protein p53 is functionally inhibited and degraded in many tumors by the action of its negative regulators MDM2 and MDMX, contributing to tumor development and progression. Using chemically synthesized MDM2 and MDMX for phage display, our laboratory discovered several high-affinity dodecameric peptide antagonists of MDM2 and MDMX, termed PMIs. However, PMIs are inactive against tumor cells harboring wild type p53 and elevated levels of MDM2 and MDMX due to their susceptibility to proteolytic degradation and inability to traverse cell membrane – two major pharmacological barriers to peptide therapeutics in general. We use mirror-image phage display, epitope grafting, sidechain stapling and nanoengineering techniques to resurrect PMIs for cancer therapy.

**Recent Publications**


1. Ma B, Niu F, Qu X, He W, Feng C, Wang S, et al. A tetrameric protein scaffold as a nano-carrier of antitumor peptides for cancer therapy. Biomaterials. 2019; 204:1-12.

2. Li X, Tolbert WD, Hu HG, Gohain N, Zou Y, Niu F, et al. Dithiocarbamate-inspired side chain stapling chemistry for peptide drug design. Chem Sci. 2019; 10(5):1522-30.

3. He W, Yan J, Wang L, Lei B, Hou P, Lu W, et al. A lanthanide-peptide-derived bacterium-like nanotheranostic with high tumor-targeting, -imaging and -killing properties. Biomaterials. 2019; 206:13-24.

4. He W, Wang S, Yan J, Qu Y, Jin L, Sui F, et al. Self-assembly of therapeutic peptide into stimuli-responsive clustered nanohybrids for cancer-targeted therapy. Adv Funct Mater. 2019; 0(0):1807736.

5. Yan J, He W, Yan S, Niu F, Liu T, Ma B, et al. Self-assembled peptide-lanthanide nanoclusters for safe tumor therapy: overcoming and utilizing biological barriers to peptide drug delivery. ACS Nano. 2018; 12(2):2017-26.

6. Niu F, Yan J, Ma B, Li S, Shao Y, He P, et al. Lanthanide-doped nanoparticles conjugated with an anti-CD33 antibody and a p53-activating peptide for acute myeloid leukemia therapy. Biomaterials. 2018; 167:132-42.

7. He W, Yan J, Sui F, Wang S, Su X, Qu Y, et al. Turning a luffa protein into a self-assembled biodegradable nanoplatform for multitargeted cancer therapy. ACS Nano. 2018; 12(11):11664-77.

8. He W, Yan J, Jiang W, Li S, Qu Y, Niu F, et al. Peptide-induced self-assembly of therapeutics into a well-defined nanoshell with tumor-triggered shape and charge switch. Chem Mater. 2018; 30(20):7034-46.


## A-Lien Lu-Chang, PhD

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**Research Interests**

At the Lobo Lab we reverse engineer the mechanisms regulating biological growth and form with an integrated systems approach. We focus on understanding, controlling, and designing the dynamic regulation and signaling that control how organisms grow, metabolize their components, and coordinate the formation of patterns and shapes. We closely integrate new computational methods, mathematical models, and bioinformatics approaches with molecular assays at the bench. We seek a mechanistic understanding of development and regeneration, find therapies for cancer and other diseases, and streamline the application of systems and synthetic biology.

**Highlighted Research**

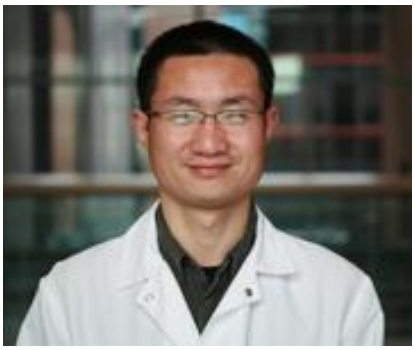
Systems Biology Of Shape And Size Regulation - R35GM137953
The genetic regulation of the shape and size of internal organs and whole body is crucial during development, regeneration, and homeostasis. This project will develop a novel integrated systems biology approach to elucidate mechanistically the molecular pathways and their coordination that control large-scale tissue growth dynamics in living organisms. These advancements will have a broad impact on our understanding of human development and regeneration towards novel therapeutic interventions for treating birth defects, traumatic injuries, and cancer.

**Highlighted Publications**


1. A. Hari, D. Lobo. Fluxer: a web application to compute, analyze, and visualize genome-scale metabolic flux networks. Nucleic Acids Research 48, pp. 427-435, 2020

2. J.M. Ko, D. Lobo. Continuous dynamic modeling of regulated cell adhesion: sorting, intercalation, and involution. Biophysical Journal 117(11), pp. 2166-2179, 2019.

3. S. Herath, D. Lobo. Cross-inhibition of Turing patterns explains the self-organized regulatory mechanism of planarian fission. Journal of Theoretical Biology 485, 110042, 2019.




## Tao Ma, PhD

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**Research Interests**

Diabetes mellitus, an alarmingly prevalent metabolic disorder affecting millions of individuals worldwide, is known to contribute to oral carcinogenesis. The knowledge of hyperglycemia effect on pre-existing Oral Potentially Malignant Disorders (OPMDs), however, is missing. In clinic, there is an urgent need to identify susceptibility of OPMDs to hyperglycemia for their malignant progression. Disturbed glucose metabolism not only change energy homeostasis but also inevitably trigger other significant phenotype changes. Our preliminary data demonstrated that high glucose treatment (20 mM) in human-derived oral dysplastic keratinocytes with a high level of basal aerobic glycolysis (DOK cells) not only increased aerobic glycolysis but also promoted proliferative, migratory and invasive responses when compared to physiological glucose levels (5 mM). These effects were not evident in oral dysplastic keratinocytes with low level of basal aerobic glycolysis (LEUK1 cells). Cetuximab, a anti-epidermal growth factor receptor (EGFR) monoclonal antibody, markedly blunted the mitogenic and motogenic responses induced by high glucose in DOK pointing to an active involvement of the EGFR signal pathway. Among seven different cognate EGFR ligands, amphiregulin (AREG) was the one highly expressed and secreted in DOK cells under high glucose treatment. AREG treatment not only mimicked high glucose induced DOK proliferation and migration, but also promoted aerobic glycolysis. We will elucidate whether the AREG/EGFR pathway could be used as a valuable biomarker and chemopreventive target in diabetes-associated oral carcinogenesis.

**Recent Publications**


1. Al Jofi FE, Ma T, Guo D, Schneider MP, Shu Y, Xu HHK, Schneider A. Functional organic cation transporters mediate osteogenic response to metformin in human umbilical cord mesenchymal stromal cells. Cytotherapy. 2018 May;20(5):650-659. doi: 10.1016/j.jcyt.2018.02.369. Epub 2018 Mar 16. PubMed PMID: 29555409; PubMed Central PMCID: PMC5948160. (Co-first author)

2. Wang S, Xia Y, Ma T, Weir MD, Ren K, Reynolds MA, Shu Y, Cheng L, Schneider A, Xu HHK. Novel metformin-containing resin promotes odontogenic differentiation and mineral synthesis of dental pulp stem cells. Drug Deliv Transl Res. 2019 Feb;9(1):85-96. doi: 10.1007/s13346-018-00600-3. PubMed PMID: 30465181


## Alexander D. MacKerell Jr., Ph.D.

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### Research Interests

Current research involves the development of empirical force fields and enhanced sampling methods for use in the simulation of biological macromolecules used in a number of simulation packages including the program CHARMM (Chemistry at HARvard Macromolecular Mechanics). Such simulations are important in advancing the understanding of how intrinsic characteristics and environmental conditions contribute to the conformational properties of proteins, nucleic acids, lipids, carbohydrates, and small molecules. These efforts involve development of a polarizable force field for biomolecules, based on a classical Drude oscillator model.

Computer-aided drug design (CADD) is a powerful tool that must contend with both the large conformational space of flexible macromolecular drug targets like proteins and the large chemical space of potential drug-like molecules to be screened against the target. Work in the MacKerell lab seeks to address these challenges with the development of new methodologies. For example, the SILCS (Site Identification by Ligand Competitive Saturation) methodology may be used for lead compound identification and optimization, evaluation of protein-protein interactions, and optimization of formulation via rational selection of excipients and buffer (see www.silcsbio.com).

### Highlighted Research

NIGMS R35 GM131710 05/01/2019-04/30/2024
Macromolecular Conformational Heterogeneity

SWCRF Investigator award (MacKerell) 07/01/19-06/30/21
Samuel Waxman Cancer Research Program for Therapeutic Targeting of Transcriptional Repression

NIH R01AI123820 (Ernst, Goodlett, MPI) 09/01/2016-08/31/2020
Protection Against Gram-Negative Sepsis Conferred by Lipid A-Based Structural Variants

### Highlighted Publication


1. Cheng, H., Linhares, B., Yu, W., Cardenas, M., Ai, Y., Jiang, W., Melnick, A., MacKerell, A.D., Jr., Cierpicki, T., Xue, F., "Identification of Thiourea-Based Inhibitors of the BCL6 BTB Domain via NMR-Based Fragment Screening and Computer-Aided Drug Design," Journal of Medicinal Chemistry, 61: 7573–7588, 2018, 10.1021/acs.jmedchem.8b00040, PMC6334293

2. Ustach, V.D., Lakkaraju, S.K., Jo, S., Yu, W., Jiang, W., and MacKerell, A.D., Jr. "Optimization and Evaluation of the Site-Identification by Ligand Competitive Saturation (SILCS) as a Tool for Target- Based Ligand Optimization," Journal of Chemical Information and Modeling, 59: 3018-3035, 2019. 10.1021/acs.jcim.9b00210, PMC6597307

3. Kognole, A.A. and MacKerell, A.D., Jr., "Mg2+ Impacts the Twister Ribozyme through Push-Pull Stabilization of Non-Sequential Phosphate Pairs," Biophysical Journal, 6: 1424-1437, 2020, 10.1016/j.bpj.2020.01.021, PMC7091459


## Silvia V. Montaner, PhD, MPH

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### Research Interests

My laboratory examines the molecular mechanisms regulating pathological angiogenesis and vessel hyperpermeability. We are focused on two human diseases: head and neck cancer and ischemic retinal disease. In cancer, angiogenesis promotes tumor growth and dissemination of cancer cells to distal organs. In ischemic retinal disease, damage to the retinal microvasculature triggers the expression of angiogenic factors that promote the formation of new immature and leaky blood vessels (as it happens in solid tumors). By studying the molecular mechanism(s) of pathological angiogenesis, our goal is to identify novel molecular targets for the treatment of these diseases. We have recently identified Angiopoietin-like 4 (ANGPTL4) as a vasoactive molecule that promotes neovascularization and vascular leakage in both cancer and ischemic retinal disease. ANGPTL4 is a hypoxia-inducible factor (HIF)-regulated factor with close homology to Angiopoietin 1 and Angiopoetin 2. ANGPTL4 is a multifunctional cytokine found in tissues as well as circulating in the bloodstream. Once the protein is translated, it is secreted and then cleaved into two major domains. Our laboratory has described a role for ANGPTL4 (and its C-terminal domain, in particular) as an angiogenic and hyperpermeability factor by inducing endothelial cell migration and endothelial cell junction instability. We have also found two novel binding partners of ANGPTL4, the membrane receptors, Neuropilin 1 and Neuropilin 2. Our investigations are focused on the elucidation of the molecular mechanisms by which ANGPTL4/NRPs trigger endothelial cell migration and the destabilization of the endothelial cell barrier.

### Recent Publications


1. Sodhi, A., Ma, T, Menon, D., Deshpande, M., Jee, K., Dinabandhu, A., Vancel, J., Lu, D. and Silvia Montaner. Angiopoietin-like 4 binds Neuropilins and cooperates with VEGF to induce diabetic macular edema. Journal of Clinical Investigation, in press.
2. Meng Q, Qin Y, Deshpande M, Kashiwabuchi F, Rodrigues M, Lu Q, Ren H, Elisseeff JH, Semenza GL, Montaner SV, Sodhi A. Hypoxia-Inducible Factor-Dependent Expression of Angiopoietin-Like 4 by Conjunctival Epithelial Cells Promotes the Angiogenic Phenotype of Pterygia. Invest Ophthalmol Vis Sci. 2017 Sep 1;58(11):4514-4523.
3. Jee K, Rodrigues M, Kashiwabuchi F, Applewhite BP, Han I, Lutty G, Goldberg MF, Semenza GL, Montaner S, Sodhi A. Expression of the angiogenic mediator, angiopoietin-like 4, in the eyes of patients with proliferative sickle retinopathy. PLoS One. 2017 Aug 23;12(8):e0183320.
4. Rodrigues M, Kashiwabuchi F, Deshpande M, Jee K, Goldberg MF, Lutty G, Semenza GL, Montaner S, Sodhi A. Expression Pattern of HIF-1α and VEGF Supports Circumferential Application of Scatter Laser for Proliferative Sickle Retinopathy. Invest Ophthalmol Vis Sci. 2016 Dec 1;57(15):6739-6746.
5. Hu K, Babapoor-Farrokhran S, Rodrigues M, Deshpande M, Puchner B, Kashiwabuchi F, Hassan SJ, Asnaghi L, Handa JT, Merbs S, Eberhart CG, Semenza GL, Montaner S, Sodhi A. Hypoxia-inducible factor 1 upregulation of both VEGF and ANGPTL4 is required to promote the angiogenic phenotype in uveal melanoma. Oncotarget. 2016 Feb 16;7(7):7816-28.
6. Babapoor-Farrokhran S, Jee K, Puchner B, Hassan SJ, Xin X, Rodrigues M, Kashiwabuchi F, Ma T, Hu K, Deshpande M, Daoud Y, Solomon S, Wenick A, Lutty GA, Semenza GL, Montaner S, Sodhi A. Angiopoietin-like 4 is a potent angiogenic factor and a novel therapeutic target for patients with proliferative diabetic retinopathy. Proc Natl Acad Sci U S A. 2015 Jun 9;112(23):E3030-9.
7. Ma T, Patel H, Babapoor-Farrokhran S, Franklin R, Semenza GL, Sodhi A, Montaner S. KSHV induces aerobic glycolysis and angiogenesis through HIF-1-dependent upregulation of pyruvate kinase 2 in Kaposi's sarcoma. Angiogenesis. 2015. Oct;18(4):477-88.


## Andrew F. Neuwald, PhD

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**Research Interests**

Development and application of statistically-based approaches for protein sequence-structural analysis, including machine learning methods for concurrent identification of residue direct couplings, of protein subgroup-specific patterns, and of correlations between subgroup patterns and structure, between subgroup patterns and direct couplings, and between direct couplings and structure. Assessment of the biological relevance of such features using measures of statistical significance and by visualizing correlated features within sequence alignments and within 3D structures. These approaches have been applied to DNA clamp loader ATPases, in conjunction with mutagenesis experiments validating this approach (manuscript under review for Scientific Reports), and are being applied to other AAA+ ATPases, protein kinases, and glycosyltransferases in conjunction with experimental analyses and molecular dynamics simulations. Development and application of a search procedure for analysis of residue correlations that ranks a data set of proteins of known structure based on measures of their biological relevance. Application of artificial intelligence methods based on deep neural networks to protein sequence-structural analysis. Other statistical applications to various biomedical systems in collaboration with researchers working on those systems.

**Recent Publications**


1. S. F. Altschul and Neuwald, A.F. 2018. Initial Cluster Analysis. Journal of Computational Biology 25(2):121-129.

2. Neuwald, A.F , Aravind, L. and S. F. Altschul. 2018. Inferring Joint Sequence-Structure Determinants of Protein Functional Specificity. eLife 7: e29880. doi: 10.7554/eLife.29880.

3. Neuwald, A.F. and S. F. Altschul. 2018. Statistical Investigations of Protein Residue Direct Couplings. PLoS Computational Biology 14(12): e100623. doi: 10.1371/journal.pcbi.1006237.

4. Tondnevis, F., Dudenhausen, E.E., Miller, A.M., McKenna, R., Altschu,l S.F., Bloom L.B. and A. F. Neuwald. 2019. Deep Analysis of Residue Constraints (DARC): identifying determinants of protein functional specificity. Scientific Reports. Under review.

## Alexandros Poulopoulos, PhD

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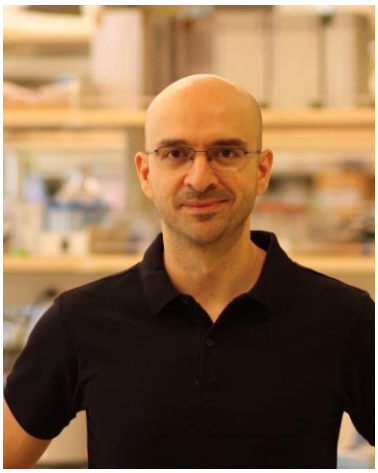

**Research Interests**

My lab develops in vivo genome editing technologies for the delivery of new CRISPR variants in the brain. Using these technologies to locally edit the genome of brain cells, we investigate mechanisms that underlie brain wiring pathologies including epilepsy, autism, and schizophrenia, as well as mechanisms of cancer metastasis. We collaborate within the School of Medicine to use our evolving in vivo CRISPR capabilities toward the development of genome therapeutics.

**Highlighted Research**

DP2 MH122398 NIH Director's New Innovator Award:
"Untangling the biology of brain wiring: high-throughput innovations for molecular screening and functional targeting of circuit development in vivo"

**Highlighted Publications**


1. Poulopoulos A, Murphy AJ, Ozkan A, Davis P, Hatch J, Kirchner R, Macklis JD. Subcellular transcriptomes and proteomes of developing axon projections in the cerebral cortex. 2019, Nature, 565(7739):356-360.

2. Richardson RR, Steyert M, Inen J, Khim S, Romanowski AJ, Altas B, Poulopoulos A. Cas9 fusions for precision in vivo editing. 2020, bioRxiv [preprint] doi: 10.1101/2020.07.15.199620


## Jean-Pierre Raufman, MD

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### Research Interests

Our lab explores the role of muscarinic receptor signaling in colon cancer. In colon cancer cells, which overexpress muscarinic receptor subtype 3 (M3R; gene name CHRM3) and express lower levels of M1R (coded by CHRM1), muscarinic agonists, like acetylcholine and selected bile acids, stimulate colon cancer cell proliferation, survival and invasion by activating M3R, and stimulating post-receptor signaling via the EGFR/ERK/PI3K-AKT and PKCα/p38 MAPK cascades. In mouse models of colon cancer, treatment with a non-selective muscarinic receptor agonist, bethanechol, promotes colon neoplasia, whereas reduced expression and activation of M3R attenuates colon neoplasia. The work in our lab currently focuses on: (a) Elucidating the functional interaction between M1R and M3R levels in progressive neoplasia; pilot studies suggest M1R expression may retard whereas M3R expression promotes cancer progression. In this context, we are exploring the role of non-coding micro and circular RNAs in epigenetic regulation of muscarinic receptor expression colon cancer stem cells. (b) Elucidating the role of a Cdc42/Rac nucleotide exchange factor, βPix, as a pivotal molecule mediating interaction between muscarinic receptor and β-catenin signaling in intestinal physiology and pathophysiology. To accomplish this goal, we created mice with conditional intestine-selective βPix deletion. Our long-term goal is to apply resulting advances in knowledge to prevent and treat disorders of the gastrointestinal tract.

### Highlighted Research

1. VA Merit Award; 1BX002129
   M3R, MMP1 and Colon Cancer Dissemination (PI; J-P. Raufman)
   January 1, 2015 – March 16, 2021 (Supplemental Funding proposal for VA IDs 14-015 and 2020-028 for Paramagnetic Bile Acid Analogues – funded March 16, 2020 @ $100,000.)
   PI (30% effort)
2. NIH, NIDDK 2R01DK068491
   Surgical Studies of Gut Permeability (PI; J-Y. Wang)
   October 1, 2015 – September 30, 2020 NCE 9/30/21
   Co-Investigator (0.3 calendar months)
3. NIH, NIDDK 2R01DK061972
   Mucosal Repair in Gut Surgical Disorders (PI; J-Y. Wang)
   July 1, 2019 – June 30, 2024
   Co-Investigator (0.3 calendar months)

### Recent Publications


1. Peng Z, Chen J, Drachenberg CB, Raufman J-P, Xie G. Farnesoid X receptor represses matrix metalloproteinase 7 expression, revealing this regulatory axis as a promising therapeutic target in colon cancer. J. Biol. Chem. 294:8529-8542, 2019.
2. Yu T, Chung HK, Xiao L, Piao J, Lan S, Rao JN, Turner DJ, Raufman J-P, Gorospe M, Wang J-Y. Long noncoding RNA H19 impairs the intestinal barrier by suppressing autophagy and lowering Paneth and goblet cell function. Cellular and Molecular Gastroenterology and Hepatology. 9:611-25; 2020.
3. Garzel B, Hu T, Li L, Lu Y, Heyward S, Polli J, Zhang L, Huang S, Raufman J-P, Wang H. Metformin disrupts bile acid efflux by repressing bile salt export pump expression. Pharmaceutical Research 37: 26; 2020. https://doi.org/10.1007/s11095-019-2753-x.


## Paul Shapiro, PhD

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**Research Interests**

Dr. Shapiro's research focuses on protein kinases and their role in regulating signaling pathways that control cellular functions and dysregulation of protein kinases during disease. Specific areas of research focus on the discovery and development of novel small molecules that inhibit the extracellular signal-regulated kinases (ERK1/2) and p38 MAP kinases and provide the rationale for clinical applications of these molecules in treating cancer or inflammatory disease.

**Highlighted Research**

1. Preclinical development of function-selective p38alpha inhibitors
   Gen1E Life Sciences (MPI: Shapiro/Hasday)

2. Non-catalytic substrate-selective p38α-Specific MAPK Inhibitors with Endothelial Stabilizing and Anti-Inflammatory Activity and Methods of Use Thereof and Non-ATP Dependent Inhibitors of Extracellular Signal-Regulated Kinase (ERK).
   Center for Maryland Advanced Ventures (CMAV)
   Life Sciences Fund (LSF) Project. (MPI: Shapiro/Hasday)

3. Evaluation of novel substrate specific inhibitors of ERK1/2 in the treatment of asthma.
   NIH-R21AI126492 (MPI: Shapiro/Deshpande)

**Highlighted Publiations**


1. Ramon Martinez III, et al. (2020) Mechanistic analysis of an ERK2-interacting compound that inhibits mutant-BRAF expressing melanoma cells by inducing oxidative stress, Journal of Pharmacology and Experimental Therapeutics. Accepted for publication.

2. Amy E. Defnet, et al., (2019) Effects of ATP-Competitive and Function-Selective ERK Inhibitors on Airway Smooth Muscle Cell Proliferation. (2019) FASEB J. Oct;33(10):10833-10843, PMID:31266368

3. Nirav G. Shah, et al, (2017) Novel Non-catalytic Substrate-selective p38α-specific MAPK Inhibitors with Endothelial-Stabilizing and Anti-inflammatory Activity. The Journal of Immunology, Vol.198(8):3296-3306. PMID:28298524

**Michael F Summers, PhD**
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**Research Interests**

We utilize nuclear magnetic resonance and biophysical methods to study the macromolecular structures and mechanisms of retroviral assembly, maturation, and genome packaging. Efforts are also underway to develop methodologies that enable NMR studies of large RNAs and protein-RNA complexes.

**Highlighted Research**

1. NIH/NIAID, 9/1/2014-12/31/22, 8 R01 AI150498, “NMR Studies of Retroviral Nucleocapsid Proteins”

2. NIH/NIAID, 9/1/17-8/31/22, U54 AI150470, “The Center for HIV RNA Studies” (CRNA)

3. HHMI, 06/01/94 – present, provides salary support for myself, computer specialist, postdoctoral fellow and an administrative assistant as well as supply money to carry out research being conducted in the lab.

**Highlighted Publications**

1. Brown, JD, et al., Structural Basis for Transcriptional Start Site Control of HIV-1 RNA Fate, Science, 368 (6489), 413-317, 2020.

2. Ding, P., et al., Identification of the initial nucleocapsid recognition element in the HIV-1 RNA packaging signal, PNAS, 117(30), 17737-17746, 2020.

3. Keane, S. C., Van, V., Frank, H. M., Sciandra, C. A., McCowin, S., Santos, J., Heng, X., Summers, M. F., “NMR detection of intermolecular interaction sites in the dimeric 5´-leader of the HIV-1 genome,” Proc. Natl. Acad. Sci. U.S.A. 113, 13033-13038 (2010).


## Lai-Xi Wang, PhD

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**Research Interests**

Research in the Wang Lab is centered on developing chemoenzymatic methods for glycoengineering of therapeutic antibodies for improving their anti-cancer, anti-inflammatory, and/or anti-viral activities. We also design and synthesize molecular probes for modulating glycan cellular functions.

**Highlighted Research**

1. Chemical biology of protein glycosylation and development of small molecule probes in modulating cellular glycan functions (R01GM080374)

2. Development of site-specific chemoenzymatic conjugation methods for making homogeneous antibody-drug conjugates for treatment of cancer (R01GM096973)

3. Glycoengineering of antibodies to modulate immune functions, aiming at generating novel glycoforms for probing the effects of glycosylation on the ADCC, CDC, and anti-inflammatory activities of antibodies. The long-term goal is to discover more effective glycoengineered antibodies for the treatment of human diseases (R01AI155716)

**Highlighted Publications**


1. Dai, Y., Hartke, R., Li, C., Yang, Q., Liu, J. O., Wang, L. X., “Synthetic fluorinated L-fucose analogs inhibit proliferation of cancer cells and primary endothelial cells”, ACS Chem. Biol., in press. 2020 Sep 15. doi: 10.1021/acschembio.0c00228.

2. Chen, X., Shi, M., Tong, X., Kim, H. K., Wang, L. X., Schneewind, O., Missiakas, D., “Glycosylation-dependent opsonophagocytic activity of Staphylococcal protein A antibodies”, Proc. Natl. Acad. Sci. USA., 117, 22992-23000 (2020).

3. Wang, L.X., Tong, X., Li, C., Giddens, J.P., Li, T., “Glycoengineering of antibodies for modulating functions”, Annu. Rev. Biochem., 88, 433-459 (2019).


## Gerald M. Wilson, PhD

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### Research Interests

My principal research foci are the characterization of ribonucleoprotein (RNP) complexes and the mechanisms by which they post-transcriptionally regulate mRNA targets in mammalian cells. I was trained in this field both as a graduate student studying LDL receptor mRNA decay in hepatic cell models (under Dr. Roger Deeley) and as a post-doc under Dr. Gary Brewer, who discovered AUF1, the first RNA-binding factor shown to selectively control decay of cytokine and proto-oncogene mRNAs. From this background I have developed a diverse research program, ranging from highly quantitative studies of RNA-protein recognition and RNP structure to assessing the consequences of these RNA-protein interactions on the turnover or translation kinetics of specific mRNA targets in living cells. Our key research interests are the cellular mechanisms that regulate the production of many important gene products, including oncoproteins, inflammatory mediators, and lipoprotein receptors. Experimental approaches vary from cell and molecular biology (cultured cell systems, transfection, RNA interference) to biochemical (gel mobility shift, protein-protein and protein-RNA cross-linking) and biophysical systems (fluorescence anisotropy, resonance energy transfer).

### Highlighted Research

Our recent efforts have revealed several exciting findings:

1. The mRNA-destabilizing protein tristetraprolin (TTP) suppresses tumor development in breast cancer cells by suppressing transcriptional signaling through the AP-1 and NF-κB pathways.

2. The pro-oncogenic heat shock protein Hsp70 can bind and stabilize select mRNAs containing AU-rich elements (AREs), including several that encode tumor-promoting factors. This activity of Hsp70 is completely independent of its well-known protein chaperone functions, and may have non-pathogenic roles in targeting Hsp70 to nascent polypeptides and/or recovering sequestered RNAs from stress granules.

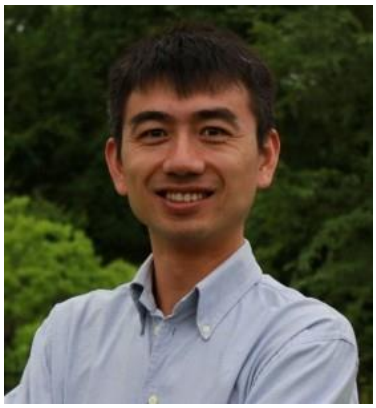
3. We have validated cytotoxic and potentially anti-oncogenic activities for a new class of substituted pyrrolo-pyrimidine compounds.

### Highlighted Publications


1. Li X, Ning H, Gu L, Ying B, Wang Q, Lu W, Peng H, Cui W, Ross CR, Wilson GM, Wold WSM, Liu J. (2015) Tristetraprolin induces cell cycle arrest in breast tumor cells through targeting AP-1/c-Jun and NF-κB pathway. Oncotarget 6, 41679-41691.

2. Kishor A, White EJF, Matsangos AE, Yan Z, Tandukar B, Wilson GM. (2017) Hsp70's RNA-binding and mRNA-stabilizing activities are independent of its protein chaperone functions. J. Biol. Chem. 292, 14122-14133.

3. Cawrse BM, Robinson NM, Lee NC, Wilson GM, Seley-Radtke KL. (2019) Structural and biological investigations for a series of N-5 substituted pyrrolo[3,2-d]pyrimidines as potential anti-cancer therapeutics. Molecules 24, E2656.




## Fengtian Xue, PhD

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**Research Interests**

Dr. Xue is currently using experimental methods from high throughput screening, medicinal chemistry and various biological assays, to develop small molecule therapeutic agents for various diseases including cancer, bacterial/parasitic infections, and nonalcoholic fatty liver disease (NAFLD).

**Recent Publications**


1. Liang D, Li L, Lynch C, Mackowiak B, Hedrich WD, Ai Y, Yin Y, Heyward S, Xia M, Wang H, Xue F. 2019. Human constitutive androstane receptor agonist DL5016: a novel sensitizer for cyclophosphamide-based chemotherapies. Eur. J. Med. Chem. 179:84-99. PMID: 31247375.

2. Liang, D.; Li, L.; Lynch, C.; Xia, M.; Wang, H.; Xue, F. 2019. DL5050: a selective agonist for the human constitutive androstane receptor. ACS Med. Chem. Lett. 10(7):1039-1044. PMID 31312405.

3. Zhao, J.; Liang, D.; Robinson, E.; Xue, F. 2019. The effects of novel heme oxygenase inhibitors on the growth of Pseudomonas aeruginosa. Microbial Pathogenesis 129:64-67.

4. Ai, Y.; Obianom, O. N.; Kuser, M.; Li, Y.; Shu, Y.; Xue, F. 2019. Enhanced tumor-selectivity of 5-fluorouracil using a reactive oxygen species-activated prodrug approach. ACS Med. Chem. Lett. 10:127-131. PMID: 30655959.

5. Obianom, O. N.; Ai, Y.; Li, Y.; Yang, W.; Guo, D.; Yang, H.; Sakamuru, S.; Xia, M.; Xue, F.; Shu, Y. 2019. Triazole-based inhibitors of the Wnt/β-catenin signaling pathway improves glucose and lipid metabolism in diet-induced obese mice. J. Med. Chem. 62(2):724-741. PMID: 30605343.


## Michal Zalzman, PhD

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### Research Interests

The Zalzman laboratory studies a mechanism trigged by the gene ZSCAN4, controlling replicative lifespan and chromatin remodeling in two major systems: stem cells and cancer stem cells. Our research focus on the telomeres, DNA structures at the end of each chromosome, that shorten with each cell replication, thereby, limiting the cell lifespan to 40-60 cell divisions. As long as this biological clock is intact, cells undergo cellular aging and eventually die. Our goal is to harness this apparatus to develop novel stem cell therapies using 3D-printed implants for bone reconstruction. Further, our team develops stem cell derived neuron cells as new therapies for Parkinson's disease.

In additional projects in the lab, our goal is to characterize the components and activities of this apparatus on chromatin remodeling that confers cancer and cancer stem cells to bypass aging and maintain stemness potency in order to allow the development of a new class of agents designed to target cancer stem cells and replicative lifespan.

### Recent Publications


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