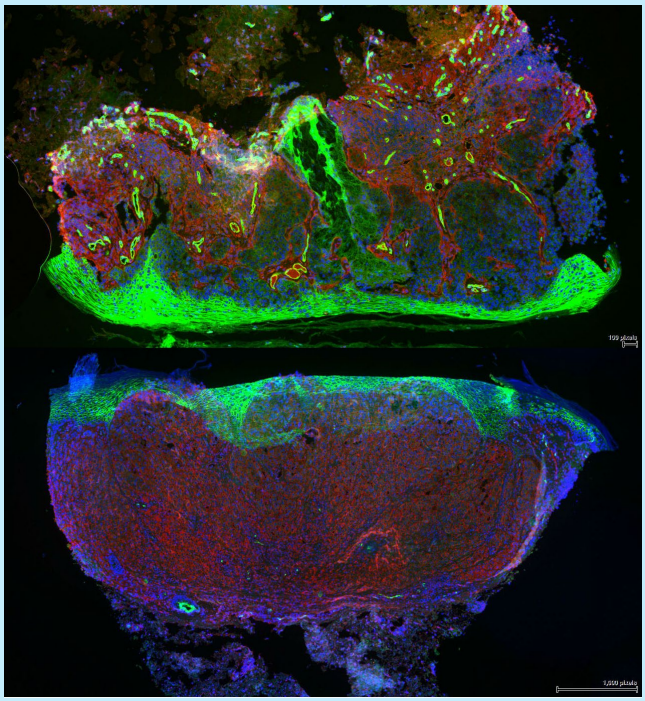
# MOLECULAR PHARMACOLOGY
# ALBERT EINSTEIN COLLEGE OF MEDICINE



Lectin fluorescence images of primary (top) and metastatic (bottom) melanoma. (Agrawal lab).

**Jonathan M. Backer, M.D., Chair**

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| **Praveen Agrawal, Ph.D.** | **Chaoyuan Kuang, Ph.D.** |
| **Michael Aschner, Ph.D.** | **Sridhar Mani, Ph.D.** |
| **Michael D. Brenowitz, Ph.D.** | **Hayley M. McDaid, Ph.D.** |
| **Dongsheng Cai, M.D., Ph.D.** | **Pabitra K. Parua, Ph.D.** |
| **Edward Chu, M.D., M.M.S.** | **Jeffrey E. Pessin, Ph.D.** |
| **Kelvin Davies, Ph.D.** | **Gaetano Santulli, M.D., Ph.D.** |
| **Eugen Dhimolea, Ph.D** | **Edward L. Schwartz, Ph.D.** |
| **Matthew J. Gamble, Ph.D.** | **David Sharp, Ph.D.** |
| **Louis Hodgson, Ph.D.** | **Kosaku Shinoda, Ph.D.** |
| **Derek M. Huffman, Ph.D.** | **Kamini Singh, Ph.D.** |
| **Young-Hwan Jo, Ph.D.** | **Sylvia O. Suadicani, Ph.D.** |
| **Marina Konopleva, M.D., Ph.D.** | **Mia M. Thi, Ph.D.** |

**2022-2023**

# The Department of Molecular Pharmacology

Pharmacology is the study of drugs and the signaling proteins that they target. Research in Molecular Pharmacology at Einstein has a strong emphasis on signal transduction and hormone action at the nuclear, cellular and organismic level; the mechanisms of drug action and the development of new therapeutics; and the disruption of normal physiology by toxicants. Work in our department targets important diseases such as cancer, diabetes and obesity, aging, as well as neurodevelopmental and neurodegenerative disorders. We have strong ties to the Cancer and Diabetes Centers as well as the Institute for Aging Research.

Graduate training in Molecular Pharmacology exposes student to state of the art methodologies that cover a wide range of approaches, including genetic studies in flies, worms and mice, genome-wide studies of chromatin organization, mRNA transcription, splicing and translation, glycobiology, advanced quantitative imaging, and biochemical studies on purified enzymes. Studies with animal models and human-derived specimens insure that our research is at the forefront of translational science.

The Department has 25 primary and secondary faculty members as well as 38 graduate students and postdoctoral fellows. The highly collaborative nature of investigators within the department, and the school as a whole, creates a broad- based and dynamic scientific environment. The Department sponsors a seminar series for visiting scientists from other institutions, as well as journal clubs and weekly work-in-progress research meetings. Monthly afternoon "happy hours" and annual departmental outings promote scientific and social interactions among the students, fellows and faculty.

Graduate students in the Department of Molecular Pharmacology have earned postdoctoral positions in outstanding laboratories and received prestigious fellowships. Our postdoctoral trainees have found positions in academia, biotechnology and pharmaceutical companies, and at the National Institutes of Health and the Food and Drug Administration. We are proud of the accomplishments of our students and postdocs and we welcome new students to join us in this exciting age of scientific advances.

## MOLECULAR PHARMACOLOGY - PRIMARY FACULTY

| Name | Title | Location | Phone | E-mail |
|---|---|---|---|---|
| Praveen Agrawal | Assistant Professor | Forchheimer 231 | 2604 | praveen.agrawal@einsteinmed.edu |
| Michael Aschner | Professor | Forchheimer 209 | 2317 | michael.aschner@einsteinmed.edu |
| Jonathan M. Backer | Professor / Chair | Forchheimer 230 | 2153 | jonathan.backer@einsteinmed.edu |
| Dongsheng Cai | Professor | Forchheimer 216 | 2426 | dongsheng.cai@einsteinmed.edu |
| Eugen Dhimolea | Assistant Professor | Forchheimer 248 | 4121 | eugen.dhimolea@einsteinmed.edu |
| Matthew J. Gamble | Associate Professor | Golding 202 | 2942 | matthew.gamble@einsteinmed.edu |
| Louis Hodgson | Professor | Price Center 217 | 1027 | louis.hodgson@einsteinmed.edu |
| Derek M. Huffman | Associate Professor | Golding 201 | 4278 | derek.huffman@einsteinmed.edu |
| Hayley McDaid | Associate Professor | Forchheimer 223 | 8829 | hayley.mcdaid@einsteinmed.edu |
| Pabitra Parua | Assistant Professor | Forchheimer 236 | 4284 | pabitra.parua@einsteinmed.edu |
| David Sharp | Professor | Ullmann 223 | 3463 | david.sharp@einsteinmed.edu |
| Kamini Singh | Assistant Professor | Golding 203 | 2466 | kamini.singh@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - SECONDARY FACULTY

| Name | Title | Location | Phone | E-mail |
|---|---|---|---|---|
| Michael D. Brenowitz | Professor | Forchheimer 311 | 3179 | michael.brenowitz@einsteinmed.edu |
| Edward Chu | Professor | Chanin 209 | 2302 | edward.chu@einsteinmed.edu |
| Kelvin Davies | Professor | Forchheimer 742 | 3201 | kelvin.davies@einsteinmed.edu |
| Young-Hwan Jo | Associate Professor | Forchheimer 511 | 2987 | young-hwan.jo@einsteinmed.edu |
| Marina Konopleva | Professor | Ullmann 915 | 4068 | marina.konopleva@einsteinmed.edu |
| Chaoyuan Kuang | Assistant Professor | Chanin 628 | 2594 | chaoyuan.kuang@einsteinmed.edu |
| Sridhar Mani | Professor | Chanin 302-D1 | 2871 | sridhar.mani@einsteinmed.edu |
| Jeffrey E. Pessin | Professor | Price Center 375 | 1029 | jeffrey.pessin@einsteinmed.edu |
| Gaetano Santulli | Associate Professor | Forchheimer 529 | 3637 | gaetano.santulli@einsteinmed.edu |
| Edward L. Schwartz | Professor | Block 614 | 8864 | edward.schwartz@einsteinmed.edu |
| Kosaku Shinoda | Assistant Professor | Price Center 355 | 1189 | kosaku.shinoda@einsteinmed.edu |
| Sylvia O. Suadicani | Associate Professor | Forchheimer 744 | 3225 | sylvia.suadicani@einsteinmed.edu |
| Mia M. Thi | Associate Professor | Golding 101 | 3460 | mia.thi@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - ADMINISTRATION

| Name | Title | Location | Phone | E-mail |
|---|---|---|---|---|
| Anna Cioffi | Administrator | Forchheimer 251 | 2911 | anna.cioffi@einsteinmed.edu |
| LaTarsha Arthur | Administrative Assistant II | Forchheimer 251 | 2911 | latarsha.arthur@einsteinmed.edu |
| Gloria Rice | Secretary VI | Forchheimer 251 | 2911 | gloria.rice@einsteinmed.edu |
| Jocelyn Santiago | Assistant Administrator | Forchheimer 251 | 2911 | jocelyn.santiago@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - INSTRUCTORS / ASSOCIATES

| Name | Title | Location | Phone | E-mail |
|---|---|---|---|---|
| Pan Chen | Research Associate Professor | Forchheimer 209 | 4047 | pan.chen@einsteinmed.edu |
| Monica Bastos Paoliello | Instructor | Forchheimer 209 | 4047 | monica.paoliello@einsteinmed.edu |
| Beatriz Ferrer Villahoz | Associate | Forchheimer 206 | 7920 | beatriz.ferrervilllahoz@einsteinmed.edu |
| Dongkyeong Kim | Associate | Forchheimer 216 | 2427 | dongkyeong.kim@einsteinmed.edu |
| Kai Mao | Research Assistant Professor | Golding 201 | 7964 | kai.mao@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - POSTDOCTORAL FELLOWS

| Name | Mentor | Location | Phone | E-mail |
|---|---|---|---|---|
| Olusiji Akinrinmade | Dhimolea | Forchheimer 248 | 4121 | olusiji.akinrinmade@einsteinmed.edu |
| Tirthankar Bandyopadhyay | Parua | Forchheimer 236 | 4556 | tirthankar.bandyopadhyay@einsteinmed.edu |
| Baidehi Basu | Parua | Forchheimer 236 | 4556 | baidehi.basu@einsteinmed.edu |
| Ahmet Caglayan | Cai | Forchheimer 216 | 2427 | ahmet.caglayan@einsteinmed.edu |
| Airton Da Cunha Martins Junior | Aschner | Forchheimer 209 | 4047 | airton.dacunhamartinsjunior@einsteinmed.edu |
| Romina Deza Ponzio | Aschner | Forchheimer 209 | 4047 | romina.dezaponzio@einsteinmed.edu |
| Gyeongyun Go | Cai | Forchheimer 216 | 2427 | gyeongyun.go@einsteinmed.edu |
| Shoeb Ikhlas | Cai | Forchheimer 216 | 2427 | shoeb.ikhlas@einsteinmed.edu |
| Hyungug Jung | Cai | Forchheimer 216 | 2427 | hyungug.jung@einsteinmed.edu |
| Minwoo Kim | Cai | Forchhemier 216 | 2427 | minwoo.kim@einsteinmed.edu |
| Maira Lima | Hodgson | Price Center 211 | 1558 | maira.lima@einsteinmed.edu |
| Sandra Pagano | Hodgson | Price Center 211 | 1558 | sandra.pagano@einsteinmed.edu |
| Colline Sanchez | Hodgson | Price Center 211 | 1558 | colline.sanchez@einsteinmed.edu |
| Afia Usman | Cai | Forchheimer 216 | 2427 | afia.usman@einsteinmed.edu |
| Salman Usmani | Cai | Forchheimer 216 | 2427 | salman.usmani@einsteinmed.edu |
| Yellamandayya Vadlamudi | Agrawal | Forchheimer 231 | 2604 | yellamandayya.vadlamudi@einsteinmed.edu |
| Marie Winter | Dhimolea | Forchheimer 248 | 4121 | marie.winter@einsteinmed.edu |
| Dongming Zhang | Cai | Forchheimer 216 | 2427 | dongming.zhang@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - PREDOCTORAL FELLOWS

| Name | Mentor | Location | Phone | E-mail |
|---|---|---|---|---|
| Kyle Aronson | Cai | Forchheimer 216 | 2427 | kyle.aronson@einsteinmed.edu |
| Rayna Birnbaum | Sharp | Ullmann 233 | 3464 | rayna.birnbaum@einsteinmed.edu |
| Matthew Engel | Huffman | Golding 201 | 7964 | mengel1@mail.einsteinmed.edu |
| Nicole Fernandez | Pessin | Price Center 375 | 1029 | nicole.fernandez@einsteinmed.edu |
| Jessica Fyodorova | Gamble | Golding 202 | 2192 | jessica.fyodorova@einsteinmed.edu |
| Ryan Graff | Backer | Forchheimer 230 | 2124 | rgraff@mail.einsteinmed.edu |
| Adam Haimowitz | Gamble | Golding 202 | 2943 | ajhaimow@mail.einsteinmed.edu |
| Gregory Hamilton | Gamble | Golding 202 | 2943 | ghamilto@mail.einsteinmed.edu |
| Nazia Jamil | McDaid | Forchheimer 223 | 2192 | nazia.jamil@einsteinmed.edu |
| Kyle Jewell | Huffman | Golding 201 | 7964 | kyle.jewell@einsteinmed.edu |
| Sofia Kylova | Pessin | Price Center 375 | 1029 | sofia.krylova@einsteinmed.edu |
| Austin Landgraf | Shinoda/Pessin | Price Center 335 | 1189 | austin.landgraf@einsteinmed.edu |
| Mahfuzur Miah | Aschner | Forchheimer 209 | 4047 | mahfuzur.miah@einsteinmed.edu |
| Sushma Narayan | Huffman | Golding 201 | 7964 | Sushma.Narayan@einsteinmed.edu |
| Megan Pirtle | Shinoda | Price Center 355 | 1189 | megan.pirtle@einsteinmed.edu |
| Andrea Ramirez | Hodgson | Price Center 211 | 1558 | andrea.ramirez@einsteinmed.edu |
| Joshua Saltzberg | Gamble | Golding 202 | 2943 | joshua.saltzberg@einsteinmed.edu |
| Karishma Smart | Sharp | Ullmann 233 | 3464 | karishma.smart@einsteinmed.edu |
| Ruixuan Wang | Huffman | Golding 201 | 7964 | gsalloum@mail.einsteinmed.edu |
| Elizabeth Yun | Gamble | Golding 202 | 2943 | elizabeth.yun@einsteinmed.edu |

## MOLECULAR PHARMACOLOGY - RESEARCH TECHNICIANS

| Name | Mentor | Location | Phone | E-mail |
|---|---|---|---|---|
| Qualia Hooker | McDaid | Forchheimer 223 | 2192 | qualia.hooker@einsteinmed.edu |
| Zunju Hu | Huffman | Golding 201 | 7964 | zunju.hu@einsteinmed.edu |
| Adriana Levine | Backer | Forchheimer 230 | 2124 | adriana.levine@einsteinmed.edu |
| Trang Uyen Nguyen | Singh | Golding 203 | 2475 | tranguyen.nguyen@einsteinmed.edu |

# DEPARTMENT OF MOLECULAR PHARMACOLOGY

**Jonathan M. Backer, M.D. – Chair** The Backer Lab studies signaling by phosphoinositide 3-kinases, which regulate cell proliferation, motility, and transformation. Experimental approaches range from biochemical analysis to in vivo studies on metastasis in animals.

**Praveen Agrawal, Ph.D.** The Agrawal lab studies changes in the cellular glycosylation associated with tumor progression, metastasis and resistance to targeted therapy. Our studies utilize cutting edge glycomic techniques, glycogene data mining of clinical samples, in vitro/in vivo functional screens and metastasis models.

**Michael Aschner, Ph.D.** The focus of our laboratory is on understanding (1) gene x environment interactions in triggering neurodevelopmental and neurodegenerative disorders, (2) metal uptake and distribution in the brain and their cellular and molecular mechanisms of neurotoxicity.

**Michael D. Brenowitz, Ph.D.** Our laboratory seeks answers to questions related to the structure – function relationships that govern macromolecular function by combining quantitative analysis with innovative approaches.

**Dongsheng Cai, M.D., Ph.D.** The Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, neural epigenetics, and epigenetic reprogramming.

**Edward Chu, M.D.** The major focus of my research is to investigate the molecular mechanisms of cellular drug resistance in colorectal cancer that relate to the fluoropyrimidine class of anticancer agents and inhibitors to thymidylate synthase and to develop novel agents that can overcome and/or prevent the development of drug resistance. Our lab has worked on developing novel bifunctional siRNA molecules as well as small molecules and Chinese herbal medicine. In addition, I am actively involved in the early-phase clinical development of novel agents and/or combination regimens for the treatment of colorectal cancer, and my lab has been involved in conducting the key pre-clinical experiments and translational biomarker studies that serve as the rational basis for the first in man clinical studies.

**Kelvin Davies, Ph.D.** My laboratory investigates the molecular and biochemical determinants of benign and oncologic urogenital disease, with the goal of developing novel clinically translatable strategies for their treatment.

**Eugen Dhimolea, Ph.D.** The Dhimolea Lab studies the mechanisms through which cancer cells persist during treatment with pharmacological and immune therapies in the broader context of the tumor microenvironment. Our experimental approaches combine in vitro 3D cultures/co-cultures, and in vivo patient-derived xenografts and orthotopic tumor models, with molecular analyses and functional studies.

**Matthew J. Gamble, Ph.D.** Through the lens of chromatin biology, we explore the mechanisms which regulate transcription and splicing, and their dysregulation in cancer, using a host of cellular, computational and -omics based approaches.

**Louis Hodgson, Ph.D**. Hodgson Lab studies the mechanisms of the Rho family small GTPase coordination during cell adhesion, invasion and motility, in normal cells and diseased states including cancer and inflammation. We engineer fluorescent biosensors based on Förster Resonance Energy Transfer (FRET) to target posttranslational modification and protein activation events in living cells. We use high-resolution light microscopy, computational and direct multiplex imaging approaches to study GTPase signal cross talks in living cells.

**Derek M. Huffman, Ph.D.** The Huffman laboratory is focused on four areas: 1) Aging-metabolism interplay, 2) Aging drug synergy, 3) Role of systemic factors in aging, and 4) physiologic resilience and aging.

**Young-Hwan Jo, Ph.D.** The focus of our laboratory is to examine the roles of the central melanocortin system in the regulation of energy metabolism and glucose homeostasis.

**Marina Konopleva, M.D., Ph.D.** The focus of our laboratory is to characterize therapeutic vulnerabilities of acute leukemias, with emphasis on targeting cell death machinery, metabolism and leukemic stem cells. Our experiments utilize cell lines, primary samples and PDX models, biochemical and metabolomic assays and multi-parametric CyTOF analysis.

**Chaoyuan Kuang, M.D., Ph.D.** The Kuang Lab studies novel therapeutics for colorectal cancer. We utilize both preclinical and clinical models such as 2-D cell culture, 3-D patient derived organoids, mouse xenografts, and patient tumor specimens. Our goal is to discover the best new therapies to test in clinical trials and predictive biomarkers of colorectal cancer.

**Sridhar Mani, M.D.** Our laboratory focuses on the study of host-microbiome relationships as it relates to human and veterinary health and disease (inflammation, metabolism, and cancer).

**Hayley M. McDaid, Ph.D.** We are a senescence-centric lab whose broad goal is to understand and exploit the senescence that occurs in response to cancer therapy. Major areas include senescence biomarker identification, defining molecular dependencies of senescent cells, and developing novel cancer therapies that induce stable senescence.

**Pabitra K. Parua, Ph.D.** The research of the Parua lab is focused on dissecting the regulation of the RNA polymerase II (RNAPII) transcription cycle by kinase-phosphatase antagonisms. Our central interest is to uncover novel signaling networks governed by upstream stimuli and converge to regulate gene expression. Intriguingly, the prospective avenues are to explore how the aberrations of that critical molecular circuitry cause neoplasms.

**Jeffrey E. Pessin, Ph.D.** Our laboratory examines the molecular, cellular and integrative systems physiology of metabolism and energy expenditure focusing on the insulin signal transduction pathways regulating glucose uptake and lipogenesis.

**Gaetano Santulli, M.D., Ph.D.** In our laboratory, we study the mechanistic role of intracellular calcium and microRNAs in the pathophysiology of cardiovascular and metabolic disorders, including heart failure, hypertension, and diabetes mellitus.

**Edward L. Schwartz, Ph.D.** Our lab focuses on the identification of new targets and novel drugs to treat lung and prostate cancer, particularly tumors that have inactivating mutations in the RB1 tumor suppressor gene. This includes determining the critical signaling pathways downstream of RB1 and designing pharmacologic agents that would restore its function and cause tumor regressions.

**David Sharp, Ph.D.** Our research is focused on the roles of the microtubule cytoskeleton in basic aspects of cellular mechanics such as cell division, movement, and growth. We are also working to translate this basic research into novel therapies to promote tissue regeneration/repair.

**Kosaku Shinoda, Ph.D.** My lab is focused on the biology of adipocytes. Understanding the basic biology of adipocytes is fundamental to the treatment and prevention of type 2 diabetes and obesity. We use cutting-edge single-cell genomics and bioinformatics to map cellular lineage and the genetic program of adipocytes in disease states and under normal physiological conditions.

**Kamini Singh, Ph.D.** My laboratory investigates the gene expression and therapeutic vulnerabilities in cancer through the lens of ribosome. Using bulk and single cell ribosome footprinting approach we study the mechanism of mRNA translation, role of regulatory RNA elements, and the function of aberrant translation products in cancer progression, tumor microenvironment, and immune response.

**Sylvia O. Suadicani, Ph.D.** Research in our laboratory investigates the involvement of altered ATP and gap junction signaling in mechanisms of disease, with particular focus on urogenital dysfunction and chronic pelvic pain.

**Mia M. Thi, Ph.D.** Primary focus of our laboratory is to understand the molecular and cellular mechanisms involved in how cells sense, transduce and signal mechanical stimuli and how cells work in synchrony to propagate locally generated signals throughout the skeletal tissue and others mechanosensitive tissues such as endothelium, urothelium by means of receptor, junctional, cytoskeletal and focal adhesion proteins under healthy and pathological conditions.

**Praveen Agrawal, Ph.D., Assistant Professor**
**Forchheimer - 231**
**(718) 430-2604; Email: praveen.agrawal@einsteinmed.edu**

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Glycans (carbohydrates) can substantially influence and modulate protein structure and function in multiple ways, such as protein folding, conformation, stability, activity, etc., which directly impact key processes supporting tumor progression and metastasis, including cell adhesion, motility, invasion, signaling activation, cell-matrix interactions, immune evasion. We are specifically interested in studying the precise mechanisms by which biochemical and structural changes in glycans of a glycoprotein regulate tumor progression and metastasis, and resistance to various therapies.

**1. Glycosylation as a regulator of tropism of melanoma metastasis:** Malignant melanoma is one of the most aggressive cancers and can disseminate from a relatively small primary tumor and metastasize to multiple sites, including the lung, and liver, brain, bone, and lymph nodes. Recently, we identified that a fucosyltransferase FUT8 is a driver of melanoma metastasis (**Agrawal et al., 2017**). Further, we postulated that adaptation of tumor cells to specific secondary sites requires specific changes in cell surface glycosylation. To explore this idea and identify glycan epitopes and glycogenes involved in site-specific organ tropism of melanoma, we utilize multiple approaches such as glycomics and glycogenomics of in vivo melanoma metastasis models and clinical patient samples of melanoma. We aim to identify target glycoproteins and their mechanism of action, contributing to the site-specificity of melanoma metastasis.

**2. Investigation of the biological role of L1CAM glycosylation in melanoma brain metastasis:** Metastases to the brain are among the most clinically significant because even a single one is likely to cause severe disability. Our previous melanoma study showed that in vitro L1CAM cleavage is dependent on core fucosylation and a glycosylation site is adjacent to the L1CAM cleavage site. L1CAM is known to be expressed by metastatic cells for spreading along brain capillaries and metastatic outgrowth. Currently, we are testing if modulation of glycosylation site/s affects L1CAM cleavage, protein-protein interactions, and brain metastasis capability using various biochemical approaches and in vivo brain metastasis models.

**3. The role of glycosylation alteration in resistance to targeted therapy of Prostate cancer:** In the past years, many therapeutic advances have been achieved in castration-resistant prostate cancer (CRPC), with the approval of several new drugs such as AR inhibitors abiraterone and enzalutamide which have shown an improvement in overall survival (OS) however sooner or later acquired drug resistance appears. As glycans are active players throughout cancer development and progression, we identify specific glycosylation changes required for resistance to therapy of PCa. We utilize a multi-step systems biology approach including lectin microarray (**Agrawal et al., 2014**) and glycan mass spectrometry-based glycomics, glycogene data mining of PCa clinical datasets, in vivo high-throughput functional screen with a barcoded glycogene shRNA/sgRNA library and identification of glycoprotein targets using lectin-affinity pulldown and mass spectrometry. These glycoproteins will be further analyzed for the role of their glycosylation status, and mechanism of action in PCa targeted therapy.

**Relevant publications:**

**Agrawal P,** Fontanals-Cirera B,… Mahal L and Hernando E, A systems biology approach identify FUT8 as a driver of melanoma metastasis, Cancer Cell, June 2017;31(6):804-819.
**Agrawal P,** Tomasz Kurcon,…and Lara K, Mapping posttranscriptional regulation of the human glycome uncovers microRNA defining the glycocode, Proceedings of the National Academy of Sciences (PNAS), 111, 4338-4343, 2014.
**Song W*, Agrawal P*….** Hernando E, Zhang B, Network models of primary melanoma microenvironments identify key melanoma regulators underlying prognosis, Nat Commun. 2021; 12: 1214. *Equal co-first authors

**Michael Aschner, Ph.D., Professor**
**Forchheimer - 206 & 209**
**(718) 430-2911; michael.aschner@einsteinmed.edu**

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Research in our laboratory focuses on the interaction between genetics and the environment in triggering disease both during central nervous system (CNS) development and senescence. We are addressing metal uptake across the blood-brain barrier (BBB) and distribution in the brain (neurons and glia), specifically with methylmercury (MeHg) and manganese (Mn), as well as their cellular and molecular mechanisms of neurotoxicity. Our studies address mechanisms of transport and neurodegeneration in various experimental models (*C. elegans*, tissue cultures and rodents), as well as follow-up on the sequalae of heavy metal deposition in the brains of human neonates by means of magnetic resonance imaging (MRI).

Hypotheses presently tested include the following: *(1)* Modulation of *C. elegans* genes (*aat, skn-1, daf-16*) that are homologous to mammalian regulators of MeHg uptake and cellular resistance will modify dopaminergic neurodegeneration in response to MeHg exposure. *(2)* Under conditions of MeHg-induced oxidative stress, Nrf2 (a master regulator of antioxidant responses) coordinates the upregulation of cytoprotective genes that combat MeHg-induced oxidative injury, and that genetic and biochemical changes that negatively impact upon Nrf2 function increase MeHg's neurotoxicity. *(3)* PARK2, a strong PD genetic risk factor, alters neuronal vulnerability to modifiers of cellular Mn status, particularly at the level of mitochondrial dysfunction and oxidative stress.

Our studies are ultimately designed to *(1)* shed novel mechanistic insight into metal-induced neurodegeneration; *(2)* provide novel targets for genetic or pharmacologic modulation of neurodegenerative disorders; *(3)* increase knowledge of the pathway involved in oxidative stress, a common etiologic factor in neurodegenerative disorders; *(4)* develop improved research models for human disease using knowledge of environmental sciences.

**Representative Publications**

Manganese: Its Role in Disease and Health. Erikson KM, Aschner M. Met Ions Life Sci. (2019) Jan 14;19. pii:/books/9783110527872/9783110527872-016/9783110527872-016.xml. doi:10.1515/9783110527872-016.

Post-translational modifications in MeHg-induced neurotoxicity. Ke T, Gonçalves FM, Gonçalves CL, Dos Santos AA, Rocha JBT, Farina M, Skalny A, Tsatsakis A, Bowman AB, Aschner M. Biochim Biophys Acta Mol Basis Dis. (2019) Aug 1;1865(8):2068-2081. doi:10.1016/j.bbadis.2018.10.024.

Combined exposure to methylmercury and manganese during L1 larval stage causes motor dysfunction, cholinergic and monoaminergic up-regulation and oxidative stress in L4 Caenorhabditis elegans. Schetinger MRC, Peres TV, Arantes LP, Carvalho F, Dressler V, Heidrich G, Bowman AB, Aschner M. Toxicology. (2019) Jan 1;411:154-162. doi: 10.1016/j.tox.2018.10.006.

Hypothyroidism induced by loss of the manganese efflux transporter SLC30A10 may be explained by reduced thyroxine production. Liu C, Hutchens S, Jursa T, Shawlot W, Polishchuk EV, Polishchuk RS, Dray BK, Gore AC, Aschner M, Smith DR, Mukhopadhyay S. J Biol Chem. (2017) Oct 6;292(40):16605-16615. doi: 10.1074/jbc.M117.804989.

**Jonathan M. Backer, M.D., Professor**
**Forchheimer - 230**
**(718) 430-2153; jonathan.backer@einsteinmed.edu**

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Phosphoinositide 3-kinases (PI3Ks) are lipid kinases that mediate signaling downstream from receptor tyrosine kinases and G-protein coupled receptors (GPCRs). They are important regulators of cellular proliferation, motility, apoptosis, and vesicular trafficking. Mutational activation of PI3Ks is commonly found in human cancers. We are interested in how the altered regulation of PI3K contributes to human cancer.

**1. PI3Ks in breast cancer.** Class I PI3Ks are the sole source of the signaling lipid phosphoinositide-3,4,5-$P_3$ ($PIP_3$) in cells, which activates downstream kinases like Akt, small GTPases like Rac and Cdc42, and signaling enzymes like Phospholipase C. The PI3Kβ isoform of PI3K is unique among Class I PI3Ks in that it (a) is activated by binding to receptor tyrosine kinases, (b) is also activated by direct binding to Gβγ subunits downstream of activated GPCRs and to the small GTPase Rac1, and (c) specifically binds to the small GTPases Rab5, which regulates vesicular trafficking in the early endosome. We have identified point mutants that disrupt PI3Kβ binding to either Gβγ or Rab5, and have shown that these mutants block tumor cell invasion in cell culture and animal models of breast cancer metastasis.

Our current work focusses on the mechanisms by which PI3Kβ regulates breast cancer invasion, particularly its role in stromal cells such as macrophages and platelets. We have developed mice expressing the mutations that inhibit PI3Kβ binding to either Gβγ or Rab5, and we are studying how these mutations affect the behavior of primary macrophages and platelets. We have shown that mutations in PI3Kβ that block its binding to Gβγ inhibit the ability of both platelets and macrophages to stimulate the invasive behavior of tumor cells. Mutation of PI3Kβ in macrophages also inhibits tumor cell production of IL8, a cytokine that promotes immune cell responses in primary tumors. Finally, we have shown that PI3Kβ is essential for tumor cell macropinocytosis, a fluid-phase endocytic pathway that provides nutrients to support tumor growth. Taken together, our findings suggest that PI3Kβ could be an important drug target in the treatment of tumor growth and metastasis.

**2. S100A4 signaling in macrophages.** In collaboration with Dr. Anne Bresnick (Biochemistry), we are studying the regulation of cellular motility and invasion by the dimeric calcium-binding protein S100A4. S100A4 is prometastatic when expressed in tumor cells. We have recently found that S100A4 also regulates invasion and matrix degradation by both tumor cells and macrophages, and it is required for platelet stimulation of invasion by tumor cells. Our current work uses genomic, proteomic and cell biological methods to study how macrophage S100A4 regulates vesicular trafficking pathways that contribute to macrophage motility and invasion.

**Representative Recent Publications**

Salloum, G., Jakubik, CT, Erami, Z., Heitz, SD, Bresnick, AR, and Backer, JM. PI3Kβ is selectively required for growth factor-stimulated micropinocytosis. (2019) J. Cell Sci. 132(16). pii: jcs231639

Heitz, SD, Hamelin, DJ, Hoffmann, RM, Greenbeerg, N, Salloum, G., Eramie, Z., Khalil, B., Shymanets,A, Steidle, EA, Gong, GQ, Nurrnberg, B, Burke, JE, Flanagan, JU, Bresnick, AR, and Backer, JM. A single discrete Rab5-binding site in phosphoinositide 3-kinase β is required for tumor cell invasion (2019) J. Biol. Chem 294:4621-4633.

Erami, Z., Heitz, SD. Bresnick AR, and Backer, JM. PI3Kβ links integrin activation and $PI(3,4)P_2$ production during invadopodial maturation (2019) Molecular Biology of the Cell 15:2367-2376.

Khalil, BD, Hsueh, C., Cao, Y, Abi Saab, WF, Wang, Y, Condeelis, JS, Bresnick, AR and Backer, JM. (2016) GPCR signaling mediates tumor metastasis via PI3Kβ. Cancer Research 76:2944-2953

**Michael Brenowitz, Ph.D., Professor**
**Forchheimer – 311**
**(718) 430-3179; michael.brenowitz@einsteinmed.edu**

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Biology is a dynamic process. Among the myriad array of reversible association reactions that constitute life, small molecules bind to proteins, proteins self-associate and bind to other proteins and nucleic acids and nucleic acids fold and bind to each other in elaborate processing, signaling and regulatory cascades. What is common to these myriad processes is the physical chemistry that underlies the molecular interactions. For example, electrostatics mediate both the binding of proteins to DNA and the folding of RNA. Proteins that mimic the electrostatic character of DNA may competitively regulate DNA binding by other proteins. Our laboratory seeks answers to questions related to the structure – function relationships that govern macromolecular function by combining quantitative analysis with innovative methodological approaches.

- The longest running programmatic theme of our laboratory is the study of the mechanisms by which proteins recognize and bind specific sequences of DNA. We have turned our attention to proteins involved in epigenetic regulation exploring the biophysics of an epigenetic regulatory methyl-CpG binding protein MeCP2 whose disruption is a cause of the neurological disorder Rett Syndrome.
- Our interest in RNA structure and folding has led us to explore the packaging and delivery of RNA therapeutics. We use analytical ultracentrifugation to study the size and density of RNA delivery vehicles in support of their use as novel therapeutics. We also use this approach to analyze the assembly and purity of proteins and nucleic acids that are approved or potential therapeutics.
- We have developed and utilize a high-throughput method to map protein-protein interactions using amino acid side chain oxidation by the hydroxyl radical to measure solvent accessibility as a tool for mapping the molecular interfaces of regulatory complexes and protein therapeutics.

**Representative Publications**

Bou-Assaf, G.M., Budyak, I.L., **Brenowitz, M.**, Day, E.S., Hayes, D., Hill, J., Majumdar, R., Ringhieri, P., Schuck. P., Lin, J.C. (2022) Best Practices for Aggregate Quantitation of Antibody Therapeutics by Sedimentation Velocity Analytical Ultracentrifugation, *J Pharm Sci.* 111, 2121-2133, PMID: 34986360

Sun, Y., Stransky, S., Aguilan, J., Koul, S., Garforth, S.J., **Brenowitz, M.**, & Sidoli, S. (2021) High throughput and low bias DNA methylation and hydroxymethylation analysis by direct injection mass spectrometry, *Analytica Chimica Acta*, 1180, 338880, PMID: 34538324

Dixit, U., Bhutoria, S., Wu, X., Qiu, L., Spira, M., Mathew, S., Harris, R., Adams, L.J, Cahill, S., Pathak, R., Prakash, R., Nguyen, M., Acharya, S.A., **Brenowitz, M.**, Almo, S.C., Zou, X., Steven, A.C., Cowburn, D., Girvin, M., & Kalpana, G.V. (2021) INI1/SMARCB1 Rpt1 domain mimics TAR RNA in binding to integrase 2 to facilitate HIV-1 replication, *Nature Communications*, 2021 May 12;12(1): 2743, PMID: 33980829

Khrapunov, S., Tao, Y., Cheng, H., Padlan, C., Harris, R., Galanopoulou, A.S., Greally, J.M., Girvin, M.E., **Brenowitz, M.** (2016) MeCP2 Binding Cooperativity Inhibits DNA Modification-Specific Recognition, *Biochemistry* 55, 4275 - 85

**Dongsheng Cai, M.D., Ph.D., Professor**
**Forchheimer - 216**
**(718) 430-2426; dongsheng.cai@einsteinmed.edu**

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Aging and overnutrition are two major etiological conditions for epidemiological diseases such as Alzheimer's disease, Parkinson's disease, diabetes, stroke and heart failure. The Cai lab investigates the roles of the central nervous system, the neuroendocrine system, and the neural-peripheral connections in causing aging, metabolic syndrome and some related diseases (e.g., neurodegenerative diseases, diabetes, stroke, hypertension, and infections). Many important model systems are employed in our research, such as genetic rodent models, drosophila models, neural stem cells and iPSC models. Our research has led to a series of paradigm-shifting research breakthroughs, for example, we pioneered discovering the role of the hypothalamus in regulating whole-body aging, identifying hypothalamic neural stem cells (htNSC), and developing htNSC exosomes for anti-aging and various disease treatments. These efforts have resulted in many high-profile publications, some of which are represented below. Current highlights of our research include neuroimmunological network, neural stem cells and organoids, exosomes, epigenetics, and epigenetic reprogramming, each representing an important front of today's biomedical science.

**Representative Publications**

Zhang Y, Kim M, Jia B, Yan J, Hertz J, Han C, Cai D. Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. **Nature** (article), 548 (7665):52-57, 2017.

Zhang YL, Reichel JM, Han C, Zuniga-Hertz JP, Cai D. Astrocytic process plasticity and IKK/NF-kB in central control of blood glucose, blood pressure and body weight. **Cell Metabolism**. 25 (5); 1091-1102, 2017.

Zhang YM, Liu G, Yan J, Zhang YL, Li B, Cai D. Metabolic learning and memory formation by the brain influence systemic metabolic homeostasis. **Nature Communications**. 6: 67042015, 2015.

Kim M, Yan J, Wu W, Zhang G, Zhang Y, Cai D. Rapid linkage of innate immunological signal to adaptive immunity by the brain-fat axis. **Nature Immunology**. 16(5): 525-33, 2015.

Yan J, Zhang H, Yin Y, Li J, Purkayastha S, Tang Y, Cai D. Obesity- and aging-induced excess of central TGF-b potentiates diabetic development via an RNA stress response. **Nature Medicine**, 20 (9):1001-8, 2014.

Zhang G, Li J, Purkayastha S, Tang Y, Zhang H, Yin Y, Liu G, Cai D**.**Hypothalamic Programming of Systemic Aging Involving IKKÎ²/NF-ÎºB and GnRH. **Nature**, (article), 497 (7448): 211-6, 2013.

Li J, Tang Y, Cai D. IKKÎ²/NF-ÎºB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. **Nature Cell Biology**, 14 (10): 999-1012, 2012.

Zhang G, Bai H, Zhang H, Dean C, Wu Q**,** Li J, Guariglia S, Cai D. Neuropeptide exocytosis involving synaptotagmin-4 and oxytocin in hypothalamic programming of obesity and metabolic diseases. **Neuron**, 69 (3): 523-535, 2011.

Purkayastha S, Zhang G, Cai D. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKKÎ²/NF-ÎºB. **Nature Medicine**, 17 (7), 883-7, 2011.

Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKb/NF-kB and ER stress link overnutrition to energy imbalance and obesity. **Cell**, 135 (1): 61-73, 2008.

**Edward Chu, M.D., Professor**
**Chanin – 209**
**(718) 430-2302; edward.chu@einsteinmed.edu**

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Over the past 20+ years, my research lab has focused on developing novel agents and/or combination regimens for the treatment of colorectal cancer.

**Translational regulation of gene expression**: My lab was the first to demonstrate that the expression of the folate-dependent enzyme thymidylate synthase was controlled by a translational autoregulatory mechanism whereby the thymidylate synthase protein binds to cis-acting regulatory elements on the cognate TS mRNA and regulates translation. This was a seminal finding as this was the first description of this type of translational autoregulatory mechanism in a eukaryotic organism. Moreover, the acute induction of TS expression in response to TS inhibitor compounds represents a novel mechanism of acute cellular drug resistance. My lab then followed up on this observation to demonstrate that the expression of another folate-dependent enzyme dihydrofolate reductase is controlled in an identical translational autoregulatory manner. It has now been well-established that translation autoregulation is a common mechanism by which cellular gene expression can be controlled in a very efficient and rapid manner.

**Development of siRNAs as novel therapeutic molecules**: The Chu lab has been investigating the potential role of siRNA's as novel therapeutic molecules for the treatment of colorectal cancer. The goal of these studies is to identify novel molecules to prevent and/or overcome the development of cellular drug resistance to inhibitor compounds that target thymidylate synthase, a well- established target for cancer chemotherapy. The Chu lab observed that siRNA's were significantly more potent and specific in their ability to repress TS mRNA translation, resulting in potent inhibition of TS synthesis. Moreover, these molecules were able to completely restore chemosensitivity to anticancer agents that target TS, including the fluoropyrimidines and TS antifolate inhibitors.

**Herbal medicine:** Our lab identified bruceantinol (BOL), a natural quassinoid isolated from the plant *Brucea javanica*, as a potent inhibitor of CRC growth. BOL suppressed >90% of tumor growth in both HCT116 xenograft-bearing athymic mice and a syngeneic MC38 tumor model. However, at high doses, BOL treatment was associated with spleen and body weight loss suggesting normal host toxicities. Using multiple biochemical and molecular techniques, we demonstrated that BOL binds to STAT3 resulting in inhibition of STAT3 phosphorylation, and our data suggests that direct targeting of STAT3, by itself, has little to no effect on CRC cell growth. Previous studies have suggested that the mechanism of action of quassinoids may be mediated through inhibition of protein synthesis. A comparison between cycloheximide, a well-established inhibitor of protein synthesis, and BOL revealed similarities as well as significant differences with regard to alterations in protein expression. Newly developed BOL-resistant CRC cells were not cross resistant to cycloheximide suggesting BOL may inhibit protein synthesis in a completely different manner.

The overarching hypothesis of our research is that quassinoids inhibit cancer cell growth through suppression of protein synthesis with subsequent inhibition of cancer-dependent signaling pathways. We believe that they can be developed as novel therapeutic molecules for the treatment of mCRC. Our research has 3 main aims: Aim 1: Investigate the biological activity of BOL and its analogs on protein synthesis; Aim 2: Design and develop novel therapeutic quassinoid analogs. Preliminary data demonstrates that the C15 side chain influences the ability of BOL to inhibit protein synthesis as well as STAT3. We will synthesize novel quassinoid-based analogs to increase in vitro cytotoxicity and in vivo antitumor activity and enhance target selectivities; and Aim 3: Develop novel nanoparticle technologies for BOL delivery. Preliminary data reveal that encapsulation of BOL into nanomicelles reduced BOL toxicities without affecting antitumor activity. The ADME properties of the BOL-nanomicelles will be further characterized.

**Kelvin P. Davies, Ph.D., Professor**
**Forchheimer - 742**
**(718) 430-2914; kelvin.davies@einsteinmed.edu**

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My laboratory has a broad range of research interests in the Field of Urology, with the common goal of increasing our knowledge of the molecular mechanisms underlying urogenital pathologies in order to identify novel, clinically translatable, strategies for their treatment. In pursuit of this goal, we have consistently applied cutting edge investigative techniques to urogenital disease and have developed expertise in the application of "omic" technologies to understanding underlying mechanisms of urogenital pathology. We are adept at performing urogenital physiologic studies in small rodent animal models, such as determining bladder function by cystometry, and we are one of the few laboratories in the world that utilize animal models to scientifically document erectile function through cavernosometry.

My research takes a highly interdisciplinary approach to understand both benign and oncologic urogenital disease, and we have formed several successful collaborations with research groups that might not have otherwise applied their knowledge to the Field of Urology. This has generated several research interests, including: **i)** investigating mechanisms to facilitate cavernous/peripheral nerve regeneration as a treatment to erectile dysfunction following radical prostatectomy, **ii)** the use of nanoparticles as a dermal delivery vehicle for various agents used to treat urogenital disease, **iii)** the role of the MaxiK channel expressed in the urothelium in regulating overall bladder activity, **iv)** the molecular mechanisms underlying the development of priapism associated with sickle cell disease, **v)** the role of the microbiome in the development of kidney stone disease, **vi)** the role of opiorphin in sperm motility, **vii)** the mechanism of hyperglycemic memory in the diabetic bladder, and most recently, **viii)** the role and potential mechanism of opiorphin in development of prostate cancer.

**Representative Recent Publications (2021-2022)**

Mukherjee, A., Park, A., Wang, L. and **Davies, K.P. (2021)** The role of opiorphin genes in prostate cancer growth and progression. Future Oncol.17(17):2209-2223. PMID: 33593085

Baker, L., Tar, M., Villegas, G., Charafeddine, R.A., Kramer, A., Vafaeva, O., Nacharaju, P., Friedman, J., **Davies, K.P.** *, and Sharp, D.J*. *=co-senior authors. **(2021)** Fidgetin-like 2 is a novel negative regulator of axonal growth and can be targeted to promote functional nerve regeneration after injury. JCI Insight. 10;6(9):138484. PMID: 33872220

Andersson, K.E., Christ, G.J, **Davies, K.P.**, Rovner, E. and Melman. A. **(2021)** Gene Therapy for Overactive Bladder: A Review of BK-Channel α-Subunit Gene Transfer. Ther Clin Risk Manag.;17:589-599. doi: 10.2147/TCRM.S291798. PMID: 34113116

Liu, J.L., Chu, K.Y. Gabrielson, A.T., Wang, R., Trost, L., Broderick, G., **Davies, K.P.**, Brock, G., Mulhall, J., Ramasamy, R. and Bivalacqua, T.J. **(2021)** Restorative Therapies for Erectile Dysfunction: Position Statement from the Sexual Medicine Society of North America (SMSNA). Sex Med. 9(3):100343. doi: 10.1016/j.esxm.2021.100343. PMID: 34000480

Tar, M.T., Friedman, J.M., Draganski, A. and **Davies, K.P**. **(2021)** Topically delivered nitric oxide acts synergistically with an orally administered PDE5 inhibitor in eliciting an erectile response in a rat model of radical prostatectomy. Int J Impot Res.; doi: 10.1038/s41443-021-00451-6. PMID: 34017115. Online ahead of print.

Mukherjee, A., Park, A. and **Davies, K.P. (2022)** *PROL1* is essential for xenograft tumor development in mice injected with the human prostate cancer cell-line, LNCaP, and modulates cell migration and invasion. Journal of Men's Health 18(2):044, PMID: 35547856

Villegas, G., Tar, M.T. and **Davies, K.P. (2022)** Erectile dysfunction resulting from pelvic surgery is associated with changes in cavernosal gene expression indicative of cavernous nerve injury. Andrologia 54(1):e14247. PMID: 34514620

**Eugen Dhimolea, Ph.D., Assistant Professor**
**Forchheimer - 248**
**(718) 430-4121; eugen.dhimolea@einsteinmed.edu**

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Our laboratory is interested on the cell-autonomous and microenvironmental mechanisms that enable tumor cells to survive during treatment.

1) Despite the advances in cancer treatment, administered therapeutics often fail to eradicate the tumor cells in patients. One key focus area for our lab is the biology of the tumor cells that persist (residual tumor) after the initial acute cytotoxic effect of treatment and represent a reservoir for the eventual relapse. The goal of our research program is to functionally dissect the cancer cell state transitions that enable their persistence to multiple treatments and prevent the curative outcome. Our previous work has demonstrated that post-treatment residual cancer cells evade drug-induced cytotoxicity by adopting a distinct cellular state of reversible dormancy. This molecular program in persistent cancer cells resembles the adaptive diapause in epiblast stem cells, a dormant stage of suspended development in pre-implantation embryos triggered by stress and associated with suppressed Myc activity and overall biosynthesis. We aim to identify the molecular mechanisms that allow the tumor cells to enter, survive during and exit this diapause-like dormant state. We are also interested on the molecular similarities and unifying principles across treatment-induced adaptive dormancy and other survival states of quiescence in nature, such as the paused pluripotency during embryonic development. To this end, we combine the use of versatile in vitro (e.g. 3D monotypic and heterotypic organoid cultures) and in vivo (subcutaneous, orthotopic, or patient-derived xenografts) cancer models with molecular and functional studies.

2) Tumor cells reside in a complex 3-dimensional tissue microenvironment and interact with other, non-malignant, cell types (e.g. mesenchymal, immune cells etc.) and with extracellular matrix (ECM) molecules. Our previous work has focused on the reciprocal cross play between tumor cells and stromal cells as well as the ECM remodeling within the tissue microenvironment. We have observed that the interactions between tumor cells and the surrounding stroma (non-malignant cells and ECM) can profoundly affect the sensitivity of tumor cells to various classes of therapeutics (e.g. hormonal agents in breast and prostate cancer). Our current work focuses on dissecting the molecular interactions between tumor cells and the other elements of the microenvironment in the context of cancer therapy. Our goal is to increase the efficacy of pharmacological and immune therapies through manipulation of the tumor microenvironment.

**Recent Relevant Publications**:

- **Dhimolea E***, de Matos Simoes R, Kansara D, Al'Khafaji A, Bouyssou J, Weng X, Sharma S, Raja J, Awate P, Shirasaki R, Tang H, Glassner BJ, Liu Z, Gao D, Bryan J, Bender S, Roth J, Scheffer M, Jeselsohn R, Gray NS, Georgakoudi I, Vazquez F, Tsherniak A, Chen Y, Welm A, Duy C, Melnick A, Bartholdy B, Brown M, Culhane AC, Mitsiades CS*. An Embryonic Diapause-like Adaptation with Suppressed Myc Activity Enables Tumor Treatment Persistence. *Cancer Cell.* 2021 Feb 8;39(2):240-256. [corresponding authors]
- **Dhimolea E***, de Matos Simoes R, Kansara D, Weng X, Sharma S, Awate P, Liu Z, Gao D, Mitsiades N, Schwab JH, Chen Y, Jeselsohn R, Culhane AC, Brown M, Georgakoudi I, Mitsiades CS*. Pleiotropic Mechanisms Drive Endocrine Resistance in the Three-Dimensional Bone Microenvironment. *Cancer Res.* 2021 Jan 15;81(2):371-383. [corresponding authors]

**Matthew J. Gamble, Ph.D., Associate Professor**
**Golding – 202**
**(718) 430-2942; matthew.gamble@einsteinmed.edu**

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**MacroH2As, histone variants with diverse roles in gene expression and DNA damage responses** – The macroH2A-type histone variants (which include macroH2A1.1, macroH2A1.2 and macroH2A2) have roles in tumor suppression, cellular senescence, activation and repression of transcription, promotion of DNA repair and suppression of the reprogramming of differentiated cells into stem cells. MacroH2As are typified by a histone H2A-like region fused by a flexible linker to a C-terminal macrodomain, a ligand-binding domains whose functions is modulated by binding to poly(ADP-ribose) produced by a family of poly(ADP-ribose) polymerases. MacroH2A1 regulates the expression of genes found within its large chromatin domains which can span hundreds of kilobases. Through changes in its expression and/or alterations in its genomic localization, disruption of macroH2A1's tumor suppressive functions are common in cancer; alterations of macroH2A transcription and splicing occur in a variety of cancers including those of lung, breast, colon, ovaries, endometrium, bladder, testicles, and melanocytes. Consistently, macroH2A1 loss in primary cells is sufficient to trigger an oncogenic gene expression profile. We are interested in many aspects of macroH2A biology. 1) How are macroH2As targeted to specific regions of the genome? 2) How does macroH2A1.1 in collaboration with PARPs regulate gene expression? 3) How does macroH2A1 regulate chromatin accessibility at enhancers? 4) How does macroH2A participate in DNA repair? 5) What regulates macroH2A1's alternative splicing?

**Chromatin dynamics during oncogene-induced senescence and cancer** – Oncogene-induced senescence (OIS) is an important tumor suppressive mechanism whereby a cell harboring an oncogenic mutation enters a stable proliferative arrest. At the same time the senescent cell secretes a host of inflammatory cytokines, chemokines and metalloprotease called the senescence-associated secretory phenotype (SASP), which serves to recruit immune cells to clear the senescent cells from tissues. The histone variant macroH2A1 plays a critical role in the transcriptional regulation of SASP genes during senescence. We are currently studying the mechanism by which macroH2A regulates the SASP response. We hypothesize that changes in macroH2A1 expression, seen in many cancers, allows these cells to bypass senescence and proceed on the pathway towards transformation.

**Interplay between transcriptional elongation rates and alternative splicing** – Alternative splicing is a crucial aspect of gene expression, allowing a gene to yield functionally distinct products, the abundance of which are regulated by cellular cues. Splicing dysregulation is central to several cancers and developmental diseases. Alternative splicing can be regulated through the recruitment of splicing factors which promote or repress distinct splicing events. Splicing largely occurs co-transcriptionally, and so, splicing outcomes are also affected by aspects of the transcription process and chromatin environment. The local elongation rate of RNA polymerase II is one aspect of transcription with important consequences on splicing outcomes. A barrier to progress in the field has been the lack of a high-throughput assay to measure splicing rates in mammalian cells. To address this, we have developed SKaTER-seq (Splicing Kinetics and Transcript Elongation Rates through sequencing). With this assay, we are exploring a myriad of factors that regulate splicing, including elongation rate, gene architecture, binding sites for RNA binding factors, chromatin structure and histone modifications. With this powerful approach we will determine the underlying causes of spicing alterations in disease.

**Representative Publications:**

Ruiz, P.D., Hamilton, G.A., Park, J.W., **Gamble, M.J.** (2019) MacroH2A1 regulation of Poly(ADP-ribose) synthesis and stability prevents necrosis and promotes DNA repair. Mol Cell Biol. 40:e00230-19.

Ruiz, P.D., **Gamble, M.J.** (2018) MacroH2A1 chromatin specification requires its docking domain and acetylation of H2B lysine 20. *Nat. Commun*. 9:5143.

**Louis Hodgson, Ph.D., Professor**
**Price – 217 & 211**
**(718) 678-1027; louis.hodgson@einsteinmed.edu**

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P21 Rho family of small GTPases are critically important in normal and disease processes including cancers, developmental defects, arthrosclerosis, and autoimmune dysfunction. RhoGTPases control processes including cell polarity, motility, and invasion/migration through their actions on downstream targets important for cytoskeleton and adhesion dynamics, proliferation and vesicular transport pathways. The coordination of multiple RhoGTPases is thought to regulate a variety of cellular signaling outcomes; however, it has been difficult if not impossible to dissect the spatiotemporal dynamics of signal regulation by conventional imaging or biochemical techniques.

Our laboratory specializes in development of Förster Resonance Energy Transfer (FRET)-based fluorescent biosensors to visualize the spatiotemporal dynamics of protein activations in living cells in real time. FRET biosensors enable direct visualization signaling pathways at the resolution limits of light microscopy, previously inaccessible by traditional biochemical methods. Understanding the regulatory mechanism of GTPases is important and has potential impact in many areas including cancer metastasis and cell migration. Regulatory and coordinating effects of multiple GTPases at the leading edge of cell migration have yet not yet been fully elucidated. This is an exceptionally rich area of study in the field of cell and cancer biology.

Our laboratory has pioneered the direct-multiplex FRET visualization approach where we monitor two or more protein activities simultaneously using orthogonal pairs of FRET biosensors in living cells. These biosensors are engineered to maximize signal-to-noise ratio (SNR) and dynamic range of response and are optimized especially for simultaneous imaging in living cells using state-of-the-art high-resolution, multichannel microscope system.

**Representative Publications:**

Hülsemann, M., Donnelly, S.K., Verkhusha, P., Mao, S.H., DesMarais, V., Segall, J., and Hodgson, L. "TC10 GTPase regulates breast cancer invasion and metastasis." (2021), Communications Biology: 4: 1091.

Shcherbakova, D.M., Cox Cammer, N., Huisman, T.M., Verkhusha, V.V. and Hodgson, L. (2018) "Direct multiplex imaging and optogenetics of RhoGTPases enabled by near-infrared FRET." Nature Chemical Biology: Jun;14(6):591-600.

Donnelly, S.K., Cabrera, R., Chiang, S., Christin, J.R., Wu, B., Guo, W., Bravo-Cordero, J.J., Condeelis, J.S., Segall, J.E., and Hodgson, L. (2017) "Rac3 regulates breast cancer invasion and metastasis by controlling adhesion and matrix degradation." J. Cell Biology: Dec 4;216(12):4331-4349.

Moshfegh Y, Bravo-Cordero JJ, Miskolci V, Condeelis J and Hodgson L. "A Trio-Rac1-PAK1 signaling axis drives invadopodia disassembly". (2014) Nature Cell Biology, Vol.16, 574-86.

Bravo-Cordero, J. J., Oser, M., Chen, X., Eddy, R., Hodgson, L. and Condeelis, J. "A novel spatiotemporal RhoC activation pathway locally regulates cofilin activity at invadopodia". (2011) Current Biology: .Vol. 21(8), 635-44.

**Derek M. Huffman, Ph.D., Associate Professor**
**Golding - 201**
**(718) 430-4278; derek.huffman@einsteinmed.edu**

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1. Aging and metabolism – A major goal of my research are to understand the interplay between aging and metabolism. We have recently published that the **IGF-1R** is a viable target via IGF-1R mAb treatment to delay aging in female mice, a pattern consistent with several genetic models of low IGF-1 signaling. In related studies, we have uncovered novel mechanisms of insulin and **IGF-1 signaling in the brain**, with implications for treating age-related metabolic decline and type 2 diabetes. Studies are further investigating the potential utility of growth factors targeted to the brain via the intranasal route may harbor therapeutic potential for cognitive decline. We have also investigated the role of metabolites in aging, identifying sarcosine, which is a byproduct of **glycine-N methyltransferase (GNMT)**, is upregulated by dietary restriction, and may be a key mediator of its effects. A focus of the lab is to further understanding the role of GNMT in metabolism and aging biology.

2. A geroscience approach to identify aging drug synergy –While single drugs can improve lifespan and healthspan, there is now evidence that combinatorial strategies designed to simultaneously target multiple aging pillars can result in greater efficacy than single agents. However, given the sheer number of potential aging drug combinations, a **systems geroscience approach** that integrates multi-level data could potentially make powerful, informed predictions regarding probability of synergistic effects between seemingly unrelated compounds. We are currently leveraging this approach in a mouse model of AD to determine the ability to identify aging drug synergy.

3. Role of cell non-autonomous factors in aging – We use several strategies, including **heterochronic parabiosis**, to understanding the role of systemic factors in tissue and cellular aging. We are currently pursuing studies to identify the systemic factor(s) responsible for driving features of intestinal decline as well as vascular aging.

4. Physiologic resilience and aging –Resilience is the ability in which an organism can respond to a physical challenge or stress and return to homeostasis, and. the gradual loss of resilience with age may underlie the onset of chronic disease, multimorbidity, frailty and death. We are developing a battery of simple, short-term assays to characterize resilience in rodents and are now using these assays in combination with molecular approaches to better understand the **molecular mechanisms underlying physiologic resilience** in mice and its loss with age.

**Representative Publications**

Mao K, Farias Quipildor G, Tabrizian T, Guan F, Walters RO, Delahaye F, Hubbard GB, Ikeno Y, Ejima K, Li P, Allison DB, Beltran P, Cohen P, Barzilai N, **Huffman DM**. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat Commun* 2018 Jun 19;9(1):2394. PMC6008442

Walters RO, Arias E, Diaz A, Burgos ES, Guan F, Tiano S, Mao K, Green CL, Qiu Y, Shah H, Wang D, Hudgins AD, Tabrizian T, Tosti V, Shechter D, Fontana L, Kurland IJ, Barzilai N, Cuervo AM, Promislow DEL, **Huffman DM.** Sarcosine is uniquely modulated by aging and dietary restriction in rodents and humans *Cell Rep* 2018 Oct 16;25(3):663-676.e6. PMC6280974

Farias-Quipildor G, Mao K, Hu Z, Novaj A, Cui MH, Gulinello M, Branch CA, Gubbi S, Patel K, Moellering DR, Tarantini S, Kiss T, Yabluchanskiy A, Ungvari Z, Sonntag WE, **Huffman DM**. Central IGF-1 reduces depressive-like behavior and improves cognitive and physical performance with aging preferentially in male mice *Geroscience* 2019 May 10 PMC6544744

Farias-Quipildor G, Mao K, Beltran P, Barzilai N, **Huffman DM**. Modulation of Glucose Production by Central Insulin Requires IGF-1 Receptors in AgRP Neurons. *Diabetes* 2021 (*in press*)

**Young-Hwan Jo, Ph.D., Associate Professor**
**Forchheimer - 505B**
**(718) 430 -3495; young-hwan.jo@einsteinmed.edu**

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My research program focuses on studying the neurobiology of energy metabolism in general and hypothalamic neural mechanisms associated with metabolic dysregulation and obesity in particular. Accordingly, I seek to understand how distinct hypothalamic neurons differently sense, detect, and respond to circulating hormones, nutrients, and recently hypothalamic temperature. This laboratory has demonstrated that an increase in body temperature during exercise is directly transmitted to ARC POMC neurons that translates it into neuronal signaling through activation of temperature-sensitive TRPV1-like receptors. Using phenotype-specific neuronal mapping and optogenetics, my lab has also showed that cholinergic neurons in the dorsomedial hypothalamus regulate not only energy expenditure via increased brown adipose tissue thermogenesis but also energy intake through activation of ARC POMC neurons. My ongoing study focuses on the role of ARC POMC neurons in modulating hepatic glucose metabolism using neuronal mapping, optogenetics, and *in vivo* fiber photometry. I also had developed a novel noninvasive optogenetic stimulation method permitting direct transcutaneous stimulation of opsin-expressing autonomic efferent nerves. This new technology allows me to study the roles of the autonomic nervous system innervating peripheral organs such as BAT and liver.

In addition, my lab examines the role of intracellular glycolysis in nonshivering thermogenesis. Interscapular brown adipose tissue (BAT) is the principal site of nonshivering thermogenesis, resulting from the uncoupling of mitochondrial oxidative respiration from ATP production to generate heat. We recently found that BAT expresses HCAR1 (or GPR81, lactate receptor). Hence, my lab seeks to determine the role of HCAR1 in the development of hyperglycemia in diet-induced obese mice.

This laboratory uses multiple cutting-edge techniques such as conditional viral tracing, optogenetics, pharmacogenetics, *in vivo* calcium imaging, in vivo fiber photometry, CRISPR/Cas-9 gene-knockdown, and electrophysiology.

**Representative publications:**

Kwon, E., Joung H.-Y., Liu, S. M., Chua, S. C., Jr., Schwartz, G. J., and Jo, Y. H. Optogenetic stimulation of the liver-projecting melanocortinergic pathway promotes hepatic glucose production. *Nature Commun.* December (2020); 11(1):6295. doi: 10.1038/s41467-020-20160-w

Jeong JH, Lee DK, Liu SM, Chua SC Jr, Schwartz GJ, Jo YH. Activation of temperature-sensitive TRPV1-like receptors in ARC POMC neurons reduces food intake. PLoS Biol. (2018) Apr 24;16(4):e2004399: Selected as a research highlight of the week in Nature and as a feature article in PLoS Biol.

Jeong JH, Lee DK, Jo YH. Cholinergic neurons in the dorsomedial hypothalamus regulate food intake. Mol Metab. (2017) Jan 12;6(3):306-312.

Jeong JH, Lee DK, Blouet C, Ruiz HH, Buettner C, Chua S Jr, Schwartz GJ, Jo YH. Cholinergic neurons in the dorsomedial hypothalamus regulate mouse brown adipose tissue metabolism. Mol Metab. (2015) Apr 11;4(6):483-92.

Lee DK, Jeong JH, Chun SK, Chua S Jr, Jo YH. Interplay between glucose and leptin signaling determines the strength of GABAergic synapses at POMC neurons. Nat Commun. (2015) Mar 26; 6: 6618.

**Marina Konopleva, MD, PhD., Professor**
**Ullmann - 915**
**(718) 430-4068; marina.konopleva@einsteinmed.edu**

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**Targeting BCL-2 family proteins in leukemias.** Our lab has a long-standing interest in targeting BCL-2 family proteins in leukemia. Pre-clinical studies have demonstrated high activity of BCL-2 inhibitor venetoclax in acute leukemias,and have transitioned into clinical trials and eventually FDA approval of this agent used in combinations for older unfit for chemotherapy AML patients. In the laboratory, we have focused on mechanisms of resistance to venetoclax, and have identified FLT3/MCL-1 and RAS/MAPK/MCL-1 pathways (*STTT* 2022). My lab has performed pre-clinical studies indicating synergy of monoclonal antibodies and engagers of innate immunity and Azacitidine/venetoclax, and clinical trials are currently underway. In ALL and more recent in subsets of AML, we have demonstrated a role of BCL-XL in addition to BCL-2, in control of apoptotic threshold. Studies with dual Bcl-2/XL inhibitor and novel -2/XL degraders are ongoing in AML and ALL models.

**Targeting mitochondrial metabolism in leukemias.** Based on pre-clinical findings of high OxPhos dependency in AML, I led a first-in-human Phase I clinical trial of oxidative phosphorylation (OxPhos) inhibitor IACS-010759 in relapsed/refractory AML, which showed target modulation, but was discontinued due to toxicities. The ongoing studies are focusing on exploration of other OxPhos inhibitors in combination with chemotherapy and target agents. We demonstrated metabolic dependency of Notch-mutated T-ALL on OxPhos and sensitivity to IACS-010759, alone and in combination with chemotherapy (*Nature Comm* 2022) and MCT1 inhibitors. We have an ongoing collaboration on novel mitochondrial inhibitors. We continue studies aimed at understanding the role of glutamine metabolism, and targeting glutaminase in combination with BCL-2 and FLT3 inhibitors in AML.

**Biology and therapy of blastic plasmacytoid dendritic cell neoplasm (BPDCN).** My lab is studying combined BCL-2 and anti-CD123 targeting in BPDCN, a rare hematologic malignancy with poor outcomes. Studies in my lab have shown pre-clinical activity of allogeneic UCARTCD123 CAR-T cells (*Nature Comm 2022*) and CD123 ADC IMGN123 in models of BPDCN. Both strategies have translated into ongoing clinical trials. We are developing CART targeting novel antigens in BPDCN.

**Studying the role of CD200 as a novel AML LSC marker** conveying immune-suppressive properties of ASML cells. We identified CD200 as a highly expressed marker on AML LSC, and demonstrated that overexpression reduced cytokine production and metabolism of T-, NK-cells and macrophages (*JITC 2021*). Targeting CD200 using a tool anti-CD200 IgG1-antibody induced single agent activity and eliminated AML in immune-reconstituted AML in vivo models, and potentiated efficacy of Azacitidine/venetoclax in immune-deficient AML PDX models. We are currently developing a novel anti-CD200 antibody.

**Immuno-oncology.** My lab is performing pre-clinical studies to determine efficacy and feasibility of proceeding towards clinical trials of several immune conjugates and CARTs against AML stem cell antigens. Using proteomics, we have several novel testis-specific antigens expressed in AML and are developing targeting antibodies.

**Representative Recent Publications**

Pan R.et al. Selective BCL-2 Inhibition by ABT-199 Causes On Target Cell Death in Acute Myeloid Leukemia. Cancer Discov 4(3):362-75, 3/2014.

Zhang Q. et al. Activation of RAS/MAPK pathway confers MCL-1 mediated acquired resistance to BCL-2 inhibitor venetoclax in acute myeloid leukemia. Signal Transduct Target Ther 7(1):51, 2/2022.

DiNardo CD, Konopleva MY. A venetoclax bench-to-bedside story. Nat Cancer 2(1):3-5, 1/2021.

Baran N. et al. Inhibition of mitochondrial complex I reverses NOTCH1-driven metabolic reprogramming in T-cell acute lymphoblastic leukemia. Nat Commun. 13(1):2801, 5/2022.

Cai T. et al. Targeting CD123 in blastic plasmacytoid dendritic cell neoplasm using allogeneic anti-CD123 CAR T cells. Nat Commun 13(1):2228, 4/2022.

Pemmaraju N. et al. Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm. N Engl J Med 380(17):1628-1637, 4/2019.

Herbrich S. et al. Overexpression of CD200 is a Stem Cell-Specific Mechanism of Immune Evasion in AML. J Immunother Cancer 9(7):e002968, 7/2021.

**Chaoyuan (Charlie) Kuang, M.D., Ph.D., Assistant Professor**
**Chanin – 628**
**(718) 430-2594; chaoyuan.kuang@einsteinmed.edu**

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Our lab is interested in novel molecular targets for the treatment of colorectal cancer (CRC) and other gastrointestinal cancers. We investigate novel drugs and drug combinations in different preclinical models for CRC. Our techniques can be applied to mechanistic discovery as well as therapeutic validation of drugs. We will then apply our most promising drug combinations to novel cancer clinical trials.

**Cell death modulation in solid tumors**: Our prior work in treatment of CRC has demonstrated the importance of inducing programmed cell death as a therapeutic mechanism. The majority of chemotherapies utilized in the clinic induce apoptosis as a major terminal mechanism of action. We frequently measure the efficacy of cancer drugs by how potently they induce CRC cell death. We are developing tools to screen for and investigate drugs that will specifically enhance the likelihood of CRC to undergo cell death. We plan to utilize the dynamic BH3-profiling assay as a method for CRC drug discovery. We will use both established CRC cell lines as well as novel patient-derived models such as CRC organoids as the target of drug screen.

**Inhibition of CDK9 for the treatment of CRC**: We previously validated the anti-apoptosis protein MCL-1 as a key regulator of CRC sensitivity to drug treatment. MCL-1 acts as a tumor suppressor by preventing the execution of mitochondrial apoptosis in CRC cells. Stabilization of MCL-1 causes resistance to treatment by the clinically approved CRC drug regorafenib. We are engaged in an ongoing effort to use novel MCL-1 inhibitors in combination with regorafenib in clinical trials. We are also investigating novel, specific small molecule inhibitors of the transcription factor CDK9. MCL-1 expression is tightly controlled by CDK9. Blockade of CDK9 can indirectly inhibit MCL-1, to great therapeutic effect. We are currently investigating the activity and the mechanism of action of CDK9 inhibitors in CRC.

**Development of novel patient derived models for drug discovery**: Preclinical discovery and validation of cancer drugs is typically conducted using well-established cancer cell lines and xenograft models. These models are often monocultures devoid of clinically important features such as intra-tumoral heterogeneity and microenvironment. Further, the majority of established cancer models are derived from a homogeneous segment of the U.S. population. We are collecting cancer specimens from patients in the Montefiore Einstein Cancer Center to establish novel preclinical cancer models that will be used for cancer drug experiments. We will combine this biobank with rigorous clinical annotation to facilitate personalized drug discovery.

**Representative Publications**

Song X, Shen L, Tong J, et al. Mcl-1 inhibition overcomes intrinsic and acquired regorafenib resistance in colorectal cancer. Theranostics. 2020 ;10(18):8098-8110. DOI: 10.7150/thno.45363. PMID: 32724460; PMCID: PMC7381732.

Lizardo DY, Kuang C, Hao S, et al. Immunotherapy efficacy on mismatch repair-deficient colorectal cancer: From bench to bedside. Biochimica et Biophysica acta. Reviews on Cancer. 2020 Dec;1874(2):188447. DOI: 10.1016/j.bbcan.2020.188447. PMID: 33035640; PMCID: PMC7886024.

Kuang, C., Park, Y., Augustin, R.C. et al. Pembrolizumab plus azacitidine in patients with chemotherapy refractory metastatic colorectal cancer: a single-arm phase 2 trial and correlative biomarker analysis. Clin Epigenet 14, 3 (2022). https://doi.org/10.1186/s13148-021-01226-y

Ruan H, Leibowitz BJ, Peng Y, et al. Targeting Myc-driven stress vulnerability in mutant KRAS colorectal cancer. Molecular Biomedicine. 2022 Mar;3(1):10. DOI: 10.1186/s43556-022-00070-7. PMID: 35307764; PMCID: PMC8934835.

**Sridhar Mani, M.D., Professor**
**Chanin - 302D**
**(718) 430-2871; sridhar.mani@einsteinmed.edu**

Pregnane X Receptor (PXR) [a.k.a the Steroid and Xenobiotic Receptor (SXR)] is a master nuclear receptor regulator of host xenobiotic/endobiotic metabolism, detoxification and inflammation. More recently, we have shown that the receptor plays a major role in relaying host microbial signals in the intestines with innate immunity. Specifically, we have shown that microbial metabolites of L-tryptophan, indoles and indole propionates, activate PXR in intestinal epithelial cells to promote intestinal immune homeostasis via a TLR4 specific pathway*. This discovery has led our laboratory into new directions primarily focused on molecular mechanisms governing host-microbial and microbial-microbial relationships in the intestines (similar approaches could be used elsewhere or for other physiologic-pathophysiologic conditions).

**1. Discovery of endobiotic PXR ligands and use of microbial metabolite mimicry to design drugs combating intestinal inflammation and cancer**. Here we are investigating how different microbial metabolites bind and activate and/or antagonize PXR function in the intestines with the hopes of establishing a physiologic role for microbial metabolites in mammals. In parallel, we have embarked on chemical biological approaches to discovery of indole propionate analogs as potent PXR ligand agonists, with the eventual hope of designing small molecule drugs (microbial metabolite mimicry) combating intestinal inflammation and inflammation-induced cancer**. More recently, the role for indole metabolites connect the gut microbes to neuronal function partly via PXR***. We are also interested in covering all other human receptors in regards to microbial metabolite effects.

**2. Discovery of new (novel) microbes and mechanisms governing its regulation of innate immunity.** Here we are interested in deciphering molecular mechanisms of indole metabolites as well as small molecule indole mimics as they interact with the host microbiome (e.g., biofilms, drug resistance etc.) in conditions of homeostasis and intestinal stress. These types of investigations have led to the identification of a novel bacterial strain with a unique community phenotype that alters intestinal inflammation. We have diversified our interests to the study of how and why these novel bacterial strains arise during inflammation, what regulates their swarming behavior, and how they execute a phenotype in mice$. Finally, our goal is to derive probiotic approaches, harnessing our internal microbiome, for the treatment of a variety of health conditions. These projects have led to multidisciplinary approaches of designing probiotic drug delivery systems using physics of bacterial spreading, molecular microbiology and host biology$$. We are also interested in bar coded recording of transcriptional events in probiotics and pathogens.

**Representative Publications**

* Venkatesh M, Mukherjee S, Wang H, Li H, Sun K, Benechet AP, Qiu Z, Maher L, Redinbo MR, Phillips RS, Fleet JC, Kortagere S, Mukherjee P, Fasano A, Le Ven J, Nicholson JK, Dumas ME, Khanna KM, Mani S. Symbiotic Bacterial Metabolites Regulate Gastrointestinal Barrier Function via the Xenobiotic Sensor PXR and Toll-like Receptor 4. Immunity 41(2): 296-310 (2014**)**

** Dvorak Z et al (40 authors), Mani S*. Targeting the Pregnane X Receptor Using Microbial Metabolite Mimicry. EMBO Molecular Medicine (Cover Page Citation) 12(4):e11621(2020)

** Dvorak Z, Sokol H, Mani S. Drug Mimicry: Promiscuous Receptors PXR and AhR, and Microbial Metabolite Interactions in the Intestine. Trends Pharm Sci (Cover Page Citation) 41(12): 900-908 (2020)

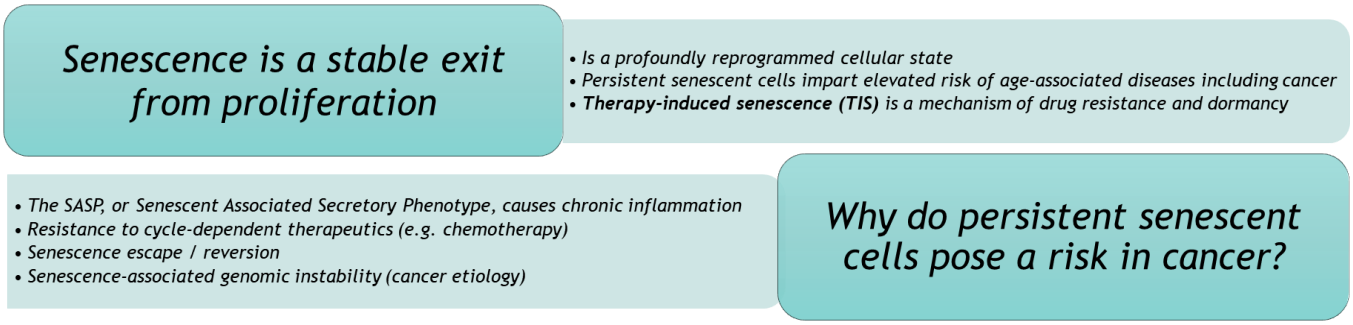
*** Serger E et al (primary work from the Giovanni lab, Imperial College, London). The gut metabolite indole-3 propionate promotes nerve regeneration and repair. Nature Jun 22 doi:10.1038/s41586-022-04884-x (online ahead of print 2022)

$ De A, Chen W, Li H, Wright JR, Lamendella R, Lukin DJ, Szymczak WA, Sun K, Kelly L, Ghosh S, Kearns DB, He Z, Jobin C, Luo X, Byju A, Chatterjee S, San Yeoh B, Vijay-Kumar M, Tang JX, Prajapati M, Bartnikas TB, Mani S. Bacterial Swarmers Enriched During Intestinal Stress Ameliorate Damage. Gastroenterology 161(1):211-224. doi: 10.1053/j.gastro.2021.03.017 ( 2021)

$$ Chen W, Mani N, Karani H, Li H, Mani S, Tang JX. Confinement discerns swarmers from planktonic bacteria. Elife 10:e64176 (2021)

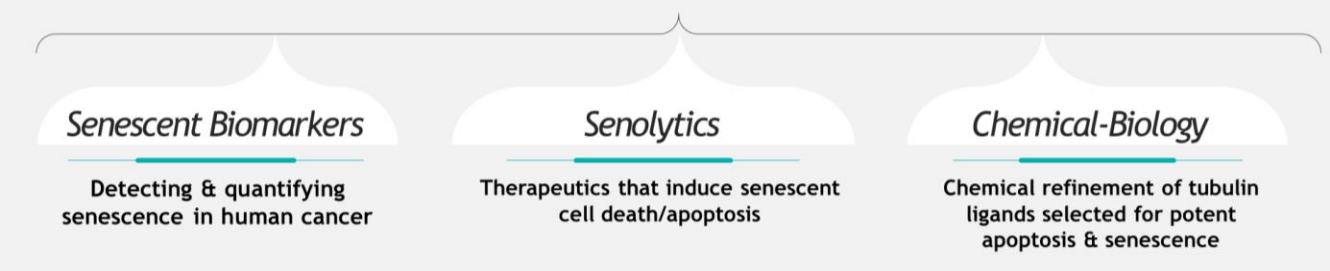
**Hayley M. McDaid, Ph.D., Associate Professor**
**Forchheimer 223**
**(718) 430-8829; hayley.mcdaid@einsteinmed.edu**

## *WE ARE A SENESCENCE-CENTRIC LAB WHOSE BROAD GOAL IS TO UNDERSTAND AND EXPLOIT THE SENESCENCE THAT OCCURS IN RESPONSE TO CANCER THERAPY*




- *We were one of the first groups to propose that chemotherapy-induced senescence (CIS) is an underappreciated mechanism of drug resistance and cause of tumor dormancy.*
- *Our interests in senescence date back to studies with the tubulin ligand, discodermolide and the discovery that it is a potent inducer of senescence. We have now developed analogs with potent dual apoptosis and senescence-inducing attributes that are being evaluated for in vivo efficacy and toxicity.*
- *We challenged the dogma that senescence was a 'permanent state,' in cancer, and showed that escape from senescence requires defective cell cycle checkpoint function and enhanced DNA-damage repair.*
- *We are an interdisciplinary group and use biochemical, genetic, and pharmacologic approaches using cell and mouse models of breast, lung and ovarian cancer.*

## *THESE STUDIES BRIDGE THE FIELDS OF CANCER PHARMACOLOGY, AGING, TUMOR DORMANCY AND BIOMARKER DISCOVERY*




-Chao SK, Lin J, Brouwer-Visser J, Smith AB 3rd, Horwitz SB, **McDaid HM** (2010). Resistance to discodermolide, a microtubule-stabilizing agent and senescence inducer, is 4E-BP1-dependent. Proc Natl Acad Sci U S A.;108(1):391-6. PMCID: PMC3017154

-Chao SK, Horwitz SB, **McDaid HM** (2011). Insights into 4E-BP1 and p53 mediated regulation of accelerated cell senescence. Insights into 4E-BP1 and p53 mediated regulation of accelerated cell senescence. Oncotarget. Jan-Feb;2(1-2):89-98. PMCID: PMC3248149

-Samaraweera L, Adomako A, Rodriguez-Gabin A and **McDaid HM**. (2017) A Novel Indication for Panobinostat as a Senolytic in NSCLC and HNSCC. Sci Rep;7(1):1900. PMID: 28507307

-Guo B, Rodriguez-Gabin A, Zhang N, Ye K, Atsaoylu O, Horwitz SB, Smith AB III, and **McDaid HM** (2020). Structural Refinement of the Tubulin Ligand Discodermolide to Attenuate Chemotherapy-Mediated Senescence. Molecular Pharmacology. August 2020, 98 (2) 156-167. PMID: 32591477

-Yang CH, Horwitz SB and **McDaid HM** (2022). Utilization of Photoaffinity Labeling to Investigate Binding of Microtubule Stabilizing Agents to P-glycoprotein and -Tubulin. Journal of natural products. Nat Prod. 2022 Mar 25;85(3):720-728. PMID: 35240035

**Pabitra K. Parua, Ph.D., Assistant Professor**
**Forchheimer - 236**
**(718) 430-4284; pabitra.parua@einsteinmed.edu**

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**Area of Research:** Regulation of gene expression; Control of RNA polymerase II transcription cycle; Kinase-phosphatase antagonism in regulating chromatin structure, antisense transcription, and transcription elongation; Unraveling the molecular mechanisms of dependencies of cancer cells on the dysregulated transcription.

**Professional Interests**

The proper regulation of RNA Polymerase II (Pol II)-dependent transcription—that normally maintains appropriate expression levels of protein-coding genes and non-coding RNAs—is crucial to keep cells healthy and prevent diseases. Pol II transcription is strictly regulated at three main stages: initiation, elongation, and termination by numerous regulatory factors, including kinases and phosphatases, chromatin structure, and antisense transcripts. Dysregulation of Pol II elongation and the production of antisense transcripts are associated with various diseases, including cancer, diabetes, cardiac and neurodegenerative disorders. Therefore, a better understanding of the fundamentals of the regulation of these processes is of paramount importance for improved diagnostic markers and therapeutic treatments. We investigate Pol II transcription regulation in the fission yeast *Schizosaccharomyces pombe* and human cells. Our research leverages integrated approaches, including biochemistry, cellular and molecular biology, classical genetics, and chemical genetics—a technique to sensitize a kinase to unnatural ATP analogs—combined with genomics and proteomics.

***To obtain mechanistic insights into promoter-proximal pausing*** **–** Most of the genes in metazoan (and ~20% genes in fission yeast) are regulated by an early regulatory event, known as promoter-proximal pausing—Pol II is paused shortly after initiation around 20-80 nucleotides downstream of the transcription start site (TSS). Properly regulated release of stalled Pol II from the promoter-proximal pause site results in the synthesis of full-length transcripts. Mis-regulation of pausing or its release can result in abnormal gene expression. Given this early regulatory event's decisive role in tuning Pol II transcription, dissecting the underlying molecular mechanisms is of utmost importance for understanding transcriptional homeostasis and its disruption in human diseases. Emerging studies suggest that the distinct kinase-phosphatase switch mechanisms control the phosphorylation of effector proteins, modulating the pause establishment, maintenance, and release. These critical kinase-phosphatase networks are mostly unknown and need to be identified and characterized precisely. We seek to investigate the regulation of promoter-proximal pausing in fission yeast and human cells to understand how the coordination between kinases and phosphatases ensures the pause establishment and synchronized release beneficial for healthy cells.

***To investigate the coupling of transcription elongation and co-transcriptional processes*** **–** The variations in the rate of Pol II elongation have been implicated in controlling co-transcriptional processes such as 5'- and 3'-end processing, antisense transcription, alternative polyadenylation (APA), and splicing of pre-mRNA. However, much is still unknown, how the elongation rate is controlled and, consequently, the coupled process. The current hypothesis is that normal speeds of Pol II elongation favor the recruitment of factors necessary to execute a particular step, whereas slower Pol II promotes aberrant recruitment of factors, resulting in premature outcomes; conversely, faster rates impair the timely execution of exact steps. The primary objective here is to examine unidentified and uncharacterized connections among kinase-phosphatase antagonisms, rate of elongation, post-translational modifications (PTMs) of histones, pre-mRNA splicing, and transcription polarity.

***To uncover how spatial and temporal phosphorylation events influence termination*** **–** The elongation to termination transition, a crucial step near the end of transcription, prepares Pol II for efficient and accurate termination following a series of sequential events: (1) deacceleration of elongating Pol II while crosses the cleavage and polyadenylation signal (CPS), leading to (2) accumulation of Ser2 phosphorylation of Pol II carboxy-terminal domain (CTD), which in turn facilitates (3) the recruitment of factors involved in pre-mRNA 3'-end formation and termination. A long-standing puzzle was how the transition from elongation to termination is initiated. Recently we identified a novel bistable switch mechanism comprising cyclin-dependent kinase 9 (Cdk9) and protein phosphatase 1 (PP1) that rapidly reverses phosphorylation at the CTD of an essential elongation factor, Spt5 (and possibly other Cdk9 substrates) during the traversal of the elongation machinery through the CPS, leading to Pol II slowing. The Spt5 CTD phosphorylation is inversely correlated with Pol II CTD Ser2 and Thr4 phosphorylation at the 3'-end of genes. However, how their reciprocal relations functionally link to influence the termination remains less understood. We will assess the spatial and temporal connections of various phosphorylation events and characterize their molecular roles in transcription termination.

**Jeffrey E. Pessin, Ph.D., Professor and Diabetes Center Director**
**Price Center - 375**
**(718) 678-1029; jeffrey.pessin@einsteinmed.edu**

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One major project in our laboratory is to understand the basis for the dysregulation of glucose and lipid metabolisms in the liver. It is well established that in insulin resistant states the regulation of gluconeogenesis is altered such that hepatic glucose production is enhanced in the fasted state with reduced suppression in the fed state. In parallel, hepatic *de novo* lipogenesis is elevated in fasted state and further increased in the fed state. Numerous studies have examined the regulation of DNA binding transcription factors, transcription factor co-activators and co-repressors in the control of liver lipogenic gene expression. Despite the intensive investigation of these trans-factors, none of these proteins directly interacts with DNA-dependent RNA polymerase II. One critical complex termed the Mediator connects multiple trans-factors to the DNA-dependent RNA polymerase II. In mammalians Mediator is composed of at least 30 individual subunits that are assembled from four sub-complexes, head, middle, tail and kinase sub-modules. In yeast, it was originally suggested that the Mediator is a constitutive component of the expression machinery. However, we recently demonstrated that the CDK8/CycC complex a component of the kinase sub-module (CDK8/CycC, Med12 and Med13) undergoes dynamic regulation by insulin and nutritional states. We are currently studying the molecular pathways and functional consequences of the Mediator structural reorganization in both rodent models and in human liver biopsy speciments. In parallel, to these efforts we are also performing comprehensive time-dependent nutritional, developmental/age, circadian cycle, and sex dependent changes in genome-wide chromosomal (Hi-C, Histone/Mediator ChIP-seq, ATAC-seq, DNA methylation) and expression (PRO-seq, RNA-seq) from normal C57BL6/J mouse livers.

A second major project is based upon our observations that deficiency of a specific SNARE protein responsible for intracellular membrane trafficking (SNAP23) functions to control macroautophagy and cell death in adipocytes. For example, adipocyte-specific SNAP23 knockout mice display a temporal development of severe general lipodystrophy associated with adipose tissue inflammation, insulin resistance, hyperglycemia, liver steatosis and early death. We have found that this loss of adipocytes results from an adipocyte specific apoptosis process resulting from increased levels of the pro-apoptotic protein Bax due to impaired lysosome-mediated degradation. Moreover, SNAP23 deficiency altered the trafficking of ATG9 and knockdown of ATG9 phenocopied the same increase and activation of Bax protein and apoptotic cell death. These events were specific for Bax, as the induction of apoptotic cell death was blocked by BAX knockdown in the context of either SNAP23 or ATG9 deficiency. We are now examining the SNAP23/ATG9 selective versus canonical macroautophagy pathway responsible for Bax activation by using the BAX activation specific antibody 6A7 in combination with shRNA knockdown and/or sgRNA knockout to identify other autophagy family members and SNARE proteins mediating BAX degradation/activation and apoptotic cell death.

**Representative Publications**

Song Z, Xiaoli AM, Li Y, Siqin G, Wu T, Strich R, Pessin JE, Yang F. The onserved Mediator subunit Cyclin C (CCNC) is required for brown adipocyte development and lipid accumulation. Mol Metab, In Press, 2022.

Picarda E, Galbo PM Jr, Zong H, Rajan MR, Wallenius V, Zheng D, Börgeson E, Singh R, Pessin J, Zang X. The immune checkpoint B7-H3 (CD276) regulates adipocyte progenitor metabolism and obesity development. Sci Adv. 2022 Apr 29;8(17):eabm7012.

Tang Y, Zong H, Kwon H, Qiu Y, Pessin JB, Wu L, Buddo KA, Boykov I, Schmidt CA, Lin CT, Neufer PD, Schwartz GJ, Kurland IJ, Pessin JE. TIGAR deficiency enhances skeletal muscle thermogenesis by increasing neuromuscular junction cholinergic signaling. Elife. 2022 Mar 7;11:e73360. doi: 10.7554/eLife.73360.

Youn DY, Xiaoli AM, Zong H, Okada J, Liu L, Pessin JB, Pessin JE, Yang F. The Mediator complex kinase module is necessary for fructose regulation of liver glycogen levels through induction of glucose-6-phosphatase catalytic subunit (G6pc). Mol Metab. 2021 Jun;48:101227. doi: 10.1016/j.molmet.2021.101227. Epub 2021 Mar 31.PMID: 33812059

**Gaetano Santulli, M.D., Ph.D., Associate Professor**
**Forchheimer – G35**
**(718) 430-3377; gaetano.santulli@einsteinmed.edu**

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The Santulli Lab studies the functional role of intracellular calcium fluxes and microRNAs in the pathophysiology of cardiovascular and metabolic disorders. The Lab is well funded by the National Institute of Health (NIH): indeed, the PI has 5 R01 (3 NHLBI, 2 NIDDK) and 1 T32 Grants. The lab is also supported by the American Heart Association, the Weill-Caulier and Hirschl Trusts, and the Diabetes Research Foundation. ***Website***: https://www.einsteinmed.edu/labs/gaetano-santulli/labs/

The main current projects, focusing on translational research, are:

- **Mechanistic role of intracellular calcium in mediating mitochondrial function in pancreatic beta cells.** We are studying the fundamental mechanisms underlying the key role of intracellular calcium release channels in beta cells, both in humans (including human islets) and murine models of diabetes mellitus and obesity.
- **Role of non-coding RNAs in the regulation of endothelial dysfunction in COVID-19.** We have been the first group to propose that COVID-19 is an endothelial disease (*J Clin Med*. 2020;9:1417) and we are dissecting the functional role of non-coding RNAs and microRNAs in the regulation of endothelial cells in the setting of COVID-19.
- **Intracellular calcium modulates cardiomyocyte function and fibroblast activation in myocardial infarction and heart failure.** We are investigating the functional contribution of intracellular calcium release channels in the regulation of cardiomyocyte fitness and in the phenoconversion of fibroblasts to myofibroblast following cardiac ischemia.

**Representative Recent Publications:**

Empagliflozin improves cognitive impairment in frail older adults with type 2 diabetes and HFpEF. ***Diabetes Care***. 2022 (Impact Factor: 19.11)

IP3 receptor orchestrates maladaptive vascular responses in heart failure. ***Journal of Clinical Investigation***. 2022 (Impact Factor: 19.46)

In permanent AF with narrow QRS, AV junction ablation + CRT vs. rate-control drug therapy reduced mortality. ***Ann Intern Med***. 2022 (Impact Factor: 51.6)

SGLT2 Inhibition via Empagliflozin Improves Endothelial Function and Reduces Mitochondrial Oxidative Stress: Insights from Frail Hypertensive and Diabetic Patients. ***Hypertension*** 2022 (Impact Factor: 10.19)

Tirzepatide versus Semaglutide once weekly in Type 2 Diabetes. ***New England Journal of Medicine***. 2022 (Impact Factor: 176.1)

Glycation of Ryanodine Receptor in circulating lymphocytes predicts the response to cardiac resynchronization therapy. ***Journal of Heart and Lung Transplantation***. 2022 (Impact Factor: 13.6)

Effects of adding L-arginine orally to standard therapy in patients with COVID-19: A randomized, double-blind, placebo-controlled, parallel-group trial. Results of the first interim analysis. ***The Lancet - eClinicalMedicine***. 2021 (Impact Factor: 17.03)

Role of endothelial miR-24 in COVID-19 cerebrovascular events. ***Critical Care***. 2021 (Impact Factor: 19.33).

**Edward L. Schwartz, Ph.D., Professor**
**Block - 614**
**(718) 430-8864; edward.schwartz@einsteinmed.edu**

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Small cell lung cancer (SCLC) is characterized by aggressive growth, frequent metastases, the rapid development of chemotherapy resistance, and an overall five-year survival of less than 5%. Dozens of drugs have been tested for clinical activity in SCLC, including more than 40 agents that have failed in phase III trials. The identification of driver mutations and their corresponding targeted drugs have led to significant improvements in the treatment of other solid tumors; however, similar advances have not been made in the treatment of SCLC. A unique feature of SCLC is the near uniform (>95%) bi-allelic inactivation of tumor suppressor genes RB1 and TP53 to drive tumorigenesis. This defining feature of the disease has not led to a targeted therapy, however, since genetically inactivated RB1 and TP53 cannot be reactivated, nor is it feasible to clinically reintroduce the wild-type genes into tumor cells in vivo. Our lab identifies key signaling pathways that are activated in RB1-deficient cells, and then to design and test pharmacologic agents that inhibit these pathways, restoring the lost function(s) of RB1, and causing tumor regressions.

1. pRb regulates the E3 ubiquitin ligase SCF-Skp2/Cks1 (Skp2). While the ability of pRB to bind to the E2F transcription factors has been the focus of much research, there are more than 300 cellular proteins that might also interact with pRB. pRB has been shown to exert significant cell cycle control that is transcription-independent, and this is due to pRB's regulation of protein stability by direct effects on the ubiquitin-ligase proteasomal degradation pathway. One repression target of pRB is the SCF E3 ligase, SCFSkp2/Cks1, and the knockout of the Skp2 substrate-recruiting subunit of SCFSkp2/Cks1 effectively blocked pituitary, lung, and prostate tumorigenesis in Rb1-deficient mice. Protein targets of Skp2 include the cyclin-dependent kinase inhibitor p27 (CDKN1b), a key cell cycle regulator which inhibits progression from G1 phase into S phase of the cell cycle. We are using a series of genetically- modified mouse models to determine the molecular role of Skp2, p27, and related proteins in SCLC tumorigenesis.

2. While not as common as in SCLC, prostate cancers can also have mutations that inactivate the RB1 gene, and these are often aggressive, metastatic, and drug-resistant tumors. Using similar strategies as in our lung cancer studies, we are studying Skp2 inhibitors as potential treatments of advanced prostate cancer.

3. A challenge in the identification of inhibitors of Skp2 is that the ubiquitin ligases have biochemically distinct active sites, and lack the tight, well-defined pockets of traditional enzymes or receptors. Instead, studies have targeted the coordinated series of protein-protein interactions (PPIs) that are required for ligase activity. Using in silico modeling, virtual library screening, and medicinal chemistry syntheses, we are identifying and testing small molecule inhibitors of Skp2 activity for their antitumor effects in mouse and human cancer models.

**Recent Publications**

Zhao H, Iqbal N, Sukrithan V, Nicholas C, Xue Y, Yu C, Locker J, Zou J, Schwartz EL and Zhu L. Targeted inhibition of the E3 ligase SCFSkp2/Cks1 has antitumor activity in RB1-deficient human and mouse small cell lung cancer (SCLC). Cancer Research, 2020; 80:2355-2367.

Wang J, Aldahamsheh O, Ferrena A, Borjihan H, Singla A, Yaguare S, Singh S, Viscarret V, Tingling J, Zi X, Lo Y, Gorlick R, Zheng D, Schwartz EL, Zhao H, Yang DS, Geller DS and Hoang BH. The interaction of Skp2 with p27 enhances the progression and stemness of osteosarcoma. Annals NY Acad Sci, 2021; 1490:90-104.

Gupta P, Zhou H, Hoang B, Schwartz EL. Targeting the untargetable: RB1-deficient tumors are vulnerable to Skp2 ubiquitin ligase inhibition. Brit J Cancer, 2022: in press.

**David Sharp, Ph.D., Professor**
**Ullmann – 223**
**(718) 430-3463; david.sharp@einsteinmed.edu**

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My career-long research objective has been to elucidate the molecular machinery that assembles and regulates the functions of the microtubule cytoskeleton. Work in my laboratory is presently focused on understanding the roles and regulation of microtubules in cellular motility and modifications thereof such as neuronal axon growth and guidance. We have identified new and unique functions in this process for a number of microtubule severing and depolymerizing enzymes and are currently testing the hypothesis that the differential localization and regulation of these allows the microtubule cytoskeleton to selectively tune and coordinate different parameters of cell movement. Additionally, we have found that these enzymes can be targeted in vivo using nanoparticle encapsulated siRNA to predictably alter cellular motility in a variety of clinical contexts related to tissue regeneration and repair. Tested applications include cutaneous wound healing, cardiovascular repair after myocardial infarction, and neural regeneration in both the CNS and PNS. This has led to the formation of the biotech startup, MicroCures Inc., as a commercialization vehicle for our technology.

**Selected Publications**

a. Rogers, G.C., Rogers, S.L., Schwimmer, T.A., Ems-McClung, S.C., Walczak, C.E., Vale, R.D., Scholey, J.M., and Sharp, D.J. (2004). Two mitotic kinesins cooperate to drive sister chromatid separation during anaphase. Nature 427, 364-370. http://www.ncbi.nlm.nih.gov/pubmed/14681690

b. Mennella, V., Rogers, G.C., Rogers, S.L., Buster, D.W., Vale, R.D., and Sharp, D.J. (2005). Functionally distinct kinesin-13 family members cooperate to regulate microtubule dynamics during interphase. Nature Cell Biology 7, 235-245. http://www.ncbi.nlm.nih.gov/pubmed/15723056

c. Zhang, D., Grode, K.D., Stewman, S.F., Diaz-Valencia, J.D., Liebling, E., Rath, U., Riera, T., Currie, J.D., Buster, D.W., Asenjo, A.B., Sosa, H.J., Ross, J.L., Ma, A., Rogers, S.L. and Sharp, D.J. (2011). Drosophila katanin is a microtubule depolymerase that regulates cortical-microtubule plus-end interactions and cell migration. Nature Cell Biology 13, 361-370.

d. Charafeddine, R.A., Makdisi, J., Schairer, D., O'Rourke, B.P., Diaz-Valencia, J.D., Chouake, J., Kutner, A., Krausz, A., Adler, B., Nacharaju, P., Liang, H., Mukherjee, S., Friedman, J.M., Friedman, A., Nosanchuk, J.D. and Sharp, D.J. (2015). Fidgetin-like 2: A novel microtubule-based regulator of wound healing. J Invest Dermatol. Sep;135(9):2309-18. doi: 10.1038/jid.2015.94. PubMed PMID: 25756798; PubMed Central PMCID: PMC4537388.

e. Baker, L., Tar, M., Villegas, G., Charafeddine, RA., Kramer, A., Vafaeva, O., Nacharaju, P., Friedman, J., Davies, KP, and Sharp, DJ. Fidgetin-like 2 is a novel negative regulator of axonal growth and can be targeted to promote functional nerve regeneration after injury. *Journal of Clinical Investigation Insight*.

**Kosaku Shinoda, Ph.D., Assistant Professor**
**Price - 355**
**(718) 678-1189; kosaku.shinoda@einsteinmed.edu**

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**1.** ***Single Cell Genomics of Beige Adipose Tissue.*** Brown adipose tissue (BAT) is specialized adipose tissue that dissipates energy for thermogenesis through UCP1 (Uncoupling Protein-1), whereas the function white adipose tissue (WAT) is storage of excess energy. Studies suggest that loss of BAT is linked to obesity and insulin resistance in humans. Thus, increasing energy expenditure through regeneration of BAT could be effective to counteract obesity and type 2 diabetes. Certain physiological cues, such as cold exposure, convert WAT into UCP1-positive, mitochondria-rich, energy consuming BAT-like adipocyte. This "browned" adipocyte is referred to as a "beige adipocyte" and recent studies indicate that predetermined progenitor cells exist as a source of beige adipocytes. We are working to determine the marker genes and functional characteristics of beige progenitor cells by single cell RNA sequencing.

**2.** ***The Molecular Mechanisms of Adipose Tissue Aging.*** We are studying the molecular mechanism of the decline in brown fat's mass and function during normal aging and whether preserving brown adipocytes can improve energy balance, insulin sensitivity, and metabolic homeostasis. We have recently found evidence suggesting that mitochondrial fission, also called fragmentation, in brown adipocytes is diminished during aging. It has been hypothesized that mitochondrial fission gives mitochondria better access to energy substrates. This research could lead to strategies to prevent brown fat's decline with age or even to increase the number of brown fat cells and boost their ability to improve glucose metabolism, burn more calories, and prevent weight gain.

**3.** ***Nanopore Sequencing of Human Adipose Tissues.*** Sequencing RNA in a biological sample can determine the transcriptional state of cells and tissues. However, current methods have limitations due to short read lengths and PCR amplification biases. We utilize nanopore direct RNA sequencing, a highly parallel, real-time, single-molecule method that circumvents these biases and identifies novel gene isoforms and alternative splicing events specific to developing human adipose tissues.

**Representative Publications:**

1) Deutsch, A. and **Shinoda, K***. (2021) The genesis of brown fat-a smooth muscle origin story revisited. ***Nature Metabolism***, 3, 449-450. *corresponding author

2) Oguri, Y*., **Shinoda, K***., Kim, H*., Alba, DL., Bolus, RW., ... Spiegelman, B.M. and Kajimura, S. (2020) CD81 controls beige fat progenitor cell growth and energy balance via FAK signaling. ***Cell***, 182, 563-577. *co-first author

3) Deutsch, A., Feng, D., Pessin J.E. and **Shinoda, K***. (2020) The Impact of Single-Cell Genomics on Adipose Tissue Research. ***Int J Mol Sci.***, 21, 4773 *corresponding author

4) Benitez, G.J. and **Shinoda, K***. (2020) Isolation of adipose tissue nuclei for single-cell genomic applications. ***Journal of Visualized Experiments***, 12, 160. *corresponding author

5) Deutsch, A., McLellan B.N. and **Shinoda, K***. (2020) Single-cell transcriptomics in dermatology. ***JAAD International***, 1, 182-188. *corresponding author

6) **Shinoda, K.**, Ohyama, K., Hasegawa, Y., Chang, H.Y., Ogura, M., Sato, A., Hong, H., Hosono, T., Sharp, L.Z., Scheel, D.W., Graham, M., Ishihama, Y. and Kajimura, S. Phosphoproteomics identifies CK2 as a negative regulator of beige adipocyte thermogenesis and energy expenditure. (2015) ***Cell Metabolism*** 22, 997-1008.

7) **Shinoda, K.**, Luijten, IHN., Hasegawa, Y., Hong, H., Sonne, S.B., Xue, R., Chondronikola, M., Kim, M., Cypess, A.M., Tseng, Y., Nedergaard, J., Sidossis, L.S. and Kajimura, S. (2015). Genetic and functional characterization of clonally-derived adult human brown adipocytes. ***Nature Medicine*** 21, 389-394.

**Kamini Singh, Ph.D., Assistant Professor**
**Location: Golding 203**
**(718) 430-2466; kamini.singh@einsteinmed.edu**

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Activation of mRNA translation is a common feature of cancer cell. However, it is not clear to what extent increased mRNA translation contributes to cancer progression, shaping the tumor microenvironment and immune response. Through the lens of ribosomes, we explore the mechanistic underpinnings of translation reprogramming in MYC and KRAS driven cancer model, the tumor microenvironment, and immune response to cancer.

**1. Differential translation control by different KRAS alleles.** Mutant KRAS is the key driver of pancreatic, lung, and colon cancer. KRAS is frequently mutated at the three missense mutation hotspots (G12, G13 and Q61) and a growing body of evidence suggests that each mutation can have specific structural, biochemical, and biological effects on KRAS function. Intriguingly, different KRAS mutant allele has differential effect on cancer growth, metabolism, and mRNA translation. Our current work focusses on investigating the differential effect of mutant KRAS allele on mRNA expression, translation, and cancer phenotypes.

**2. Explore aberrant translation in pancreatic cancer and microenvironment.**
We have identified that RNA helicase eIF4A regulates the translation of key oncogenes such as MYC, KRAS, and this can be readily targeted by using eIF4A inhibitors. KRAS and MYC activation feeds to mRNA translation programs conducive to cancer progression and shaping the tumor microenvironment. My research group investigate the mechanism of mRNA translation and its contribution in the gene expression outputs and functional proteome due to alternate translation start site selection in cancer and microenvironment.

**3. Role of aberrant translation products in cancer immunity.** My work has shown that aberrant translation products are frequently generated upon oncogene activation and alters the protein form of key immune receptors such as CD19. Interestingly, we observed that a significant fraction of translation is activated from upstream open reading frames upon oncogene activation resulting in the generation of "new short peptides of unknown function". We study the role of these short peptides and aberrant translation products in cancer signaling and cancer immunity.

**Representative Recent Publications**

**K. Singh**, J. Lin, N. Lecomte, P. Mohan, A. Gokce, V. R. Sanghvi, M. Jiang, O. Grbovic-Huezo, A. Burčul, S. G. Stark, P. B. Romesser, Q. Chang, J. P. Melchor, R. K. Beyer, M. Duggan, Y. Fukase, G. Yang, O. Ouerfelli, A. Viale, E. de Stanchina, A. W. Stamford, P. T. Meinke, G. Ratsch, S. D. Leach, Z. Ouyang, and H. G. Wendel, "Targeting eIF4A Dependent Translation of KRAS Signaling Molecules". Cancer Research, 2021, 81, 8.

**K. Singh**, J. Lin, Y. Zhong, A. Burčul, P. Mohan, M. Jiang, A. Viale, J. R. Cross, L. Sun, V. Yong, R. Hendrickson, G. R.tsch, Z. Ouyang, and H. G. Wendel, "c-MYC regulates mRNA translation efficiency and start site selection in lymphoma". Journal of Experimental Medicine, 2019, 216 (7): 1509.

**K. Singh*,**A. L. Wolfe*, Y. Zhong, P. Drewe, V. K. Rajasekhar, V. R. Sanghvi, K. J. Mavrakis, J. E. Roderick, J. V. Meulen, J. H. Schatz, C. M. Rodrigo, M. Jiang, C. Zhao, P. Rondou, E. de Stanchina, J. Teruya-Feldstein, M. A. Kelliher, F. Speleman, J. A. Porco Jr., J. Pelletier, G. R.tsch, and H. G. Wendel, "RNA G-quadruplexes cause eIF4A dependent oncogene translation in cancer". Nature, 2014, 513 p. 65–70. [*Equal Contribution].

**Sylvia O. Suadicani, Ph.D., Associate Professor**
**Forchheimer 744**
**(718) 430-3225; sylvia.suadicani@einsteinmed.edu**

Cellular communication is essential for proper coordination of organ function. It involves release of signaling molecules, activation of receptors and channels, and direct signaling through gap junctions. Among these key players is ATP and its receptors, pannexin 1 channels and connexin43 (Cx43) gap junction channels. We are interested in determining the role played by ATP (purinergic) and Cx43 signaling in disease conditions. **The Suadicani lab works collaboratively with the labs of Dr. Mia Thi, Department of Orthopaedic Surgery, Dr. Kelvin Davies, Department of Urology, and Dr. David Spray, Department of Neuroscience.**

**1. Urothelial ATP signaling in diabetic bladder dysfunction and in IC/BPS.** Urothelial cells line the interior of the urinary bladder and serve both as a protective barrier against urine contents and sensors of bladder distension. Urothelial cells release ATP in response to bladder distension, and ATP signaling from the bladder to the central nervous system regulate micturition. We have shown that the mechanosensitive pannexin 1 (Panx1) channels, which also provide a direct pathway for cellular ATP release, play essential roles in urothelial mechanosensation and ATP signaling. Panx1 has also been shown to mediate inflammasome activation. We are now investigating extent to which dysregulation of Panx1 contributes to development of bladder dysfunction in type 1 diabetes and emergence of pelvic pain and urinary symptoms in Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS).

**2. Pannexin 1 and ATP signaling in female sexual dysfunction.** The mechanosensitivity of female genital organs and its importance for perception and response to penetrative sexual stimulation are well recognized. However, little in known regarding the molecular mediators and mechanisms involved in vaginal mechanosensory transduction. We show that Panx1 is expressed in the vaginal epithelium and mediates ATP release in response to vaginal stimulation, a response that was altered in animal models of diabetes and menopause, conditions known to be associated with female genital arousal dysfunction. We are now investigating the mechanisms that lead to Panx1 dysregulation in the vaginal epithelium and whether Panx1 channels may provide novel therapeutic targets to manage this condition.

**3. Pannexin 1 and Cx43 channels in sensory neuron and glia signaling.** Neuronal activity is modulated by glial cells. We have shown that glial communication involves Panx1-mediated ATP signaling and that bidirectional satellite glial cell-neuron signaling in sensory ganglia is altered in animal models of inflammatory pain. We are currently investigating the involvement of altered glial Panx1 and Cx43 signaling in chronic pelvic pain and in mechanisms underlying development of urogenital complications (i.e. erectile dysfunction, bladder overactivity and urinary incontinence) from pelvic surgeries.

**4. ATP signaling in the diabetic bone.** Diabetes affects the skeletal system, leading to reduced bone density and increase risk for bone fractures. ATP signaling plays a central role in bone homeostasis. We have shown that Panx1 and the purinergic P2X7 receptor form a mechanosignaling complex, and that altered expression of this complex in diabetic bone results in impaired ATP release and response to mechanical loading, which might be implicated in the diabetic skeletal complications. Our studies are now focusing on investigating mechanisms that regulate Panx1-P2X7R expression in the healthy and diabetic bone.

**Representative Publications:**

Harroche J., Urban-Maldonado, M., Thi, M.M., Suadicani, S.O. (2020) - Mechanosensitive Vaginal Epithelial Adenosine Triphosphate Release and Pannexin 1 Channels in Healthy, in Type 1 Diabetic, and in Surgically Castrated Female Mice. J Sex Med; 17: 870-880.

Spray, D.C., Iglesias, R., Shraer, N., Suadicani, S.O., Belzer, V., Hanstein, R., Hananai, M. (2019) - Gap junction mediated signaling between satellite glia and neurons in trigeminal ganglia. Glia; 67: 791-801.Seref-Ferlengez, Z., Urban-Maldonado, M.; Sun, H.B. Schaffler, M.B.; Suadicani, S.O. and Thi, M.M. (2019) - Role of pannexin 1 channels in load-induced skeletal response. Ann N Y Acad Sci. 1442(1):79-90.

Negoro, H., Urban-Maldonado, M., Liou, L.S., Spray, D.C., Thi, M.M. and Suadicani, S.O. (2014) - Pannexin 1 channels play essential roles in urothelial mechanotransduction and intercellular signaling. PLoS ONE 9(8): e106269.

**Mia M. Thi, Ph.D., Associate Professor**
**Golding Building – 101**
**(718) 430-3460; mia.thi@einsteinmed.edu**

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Identifying the "mechanosomes", which is the complex responsible for sensing, transduction and signaling in response to mechanical stimuli, is essential to elucidate molecular and cellular machinery in mechanosensitive tissue. Some of the mechanosome components identified until now includes Panx1 hemichannel, purinergic receptor P2X7R, and integrin αVβ3. We are interested in how the altered mechanosome complex contributes to pathological conditions in mechanosensitive tissues such as bone and bladder. **The Thi lab works collaboratively with the labs of Dr. Sylvia Suadicani, Dept. of Urology and Dr. David Spray, Dept. of Neuroscience at Einstein and Dr. Mitchell Schaffler, Dept. of Biomedical Engineering at City College of New York, on projects listed below.**

**1. Mechanosomes in sugar coated bone.** We have recently shown that type 1 diabetes (T1D) alters Panx1-P2X7R mechanosignaling complex in osteocytes, key mechanosensing cells in bone, and disrupts proper load-induced bone adaptation and thereby likely contributes to bone loss in T1D. We further hypothesized that load-induced regulation of bone mass occurs not only at the local bone level but remotely involving direct signaling between the bone and the nervous system. Diabetes affects the nervous system, particularly sensory nerves and yet, the extent to which diabetes impairs neural regulation of load-induced bone responses is still unknown. Our studies also indicate that besides its role in osteocytic mechanosignaling, Panx1-P2X7R also participates in bone neuro-mechanosensory signaling and mediates load-induced inflammasome activation. Our current work focuses on this two new functions that are also targeted by diabetes.

**2. Structural, molecular and functional specialization of osteocyte mechanosomes.** As the key mechanosensing cells of bone, osteocytes orchestrate a wide range of bone functions including bone modeling, remodeling and loss. However, the precise mechanisms through which they accomplish this sensing task remain unclear. We have discovered that the osteocyte cell processes function as uniquely sensitive mechanosensory elements through specialized mechanosome complex (Panx1, P2X7R, αVβ3 and CaV3.2 T-type calcium channel). We are currently exploring how osteocytes function as mechanosensors in healthy and diseased bone.

**3. Mechanosomes in diabetic bladder dysfunction (DBD).** Along the course of T1D mellitus, the bladder undergoes a progressive transition from a normal to an overactive and then to an underactive state. The factors and mechanisms that regulate these temporal changes in bladder function are still unclear. We have shown that Panx1 plays an essential role in the urothelial mechanosensory, transduction and signaling system. Thus changes in Panx1 expression could alter the bladder sensitivity to distention. We are currently investigating the role of urothelial Panx1 channels in the emergence and temporal progression of DBD.

**Representative Publications**

Lewis KJ, Cabahug-Zuckerman P, Louie J, Stephen S, Spray DC, Thi MM, Seref-Ferlengez Z, Boorman-Padgett JF, Majeska RJ, Weinbaum S, Schaffler MB. E2 Depletion blunts Osteocyte Calcium Signaling Responses to Mechanical Loading In vivo and remodels mechanosome complexes. Bone. DOI: 10.1016/j.bone.2021.116072

Lewis KJ, Frikha-Benayed D, Louie J, Stephen S, Spray DC, Thi MM, Seref-Ferlengez Z, Majeska RJ, Weinbaum S, Schaffler MB. Osteocyte calcium signals encode strain magnitude and loading frequency in vivo. Proc Natl Acad Sci U S A. 114(44):11775-11780, 2017.

Seref-Ferlengez Z, Maung S, Schaffler MB, Spray DC, Suadicani SO, Thi MM. P2X7R-Panx1 Complex Impairs Bone Mechanosignaling under High Glucose Levels Associated with Type-1 Diabetes. PLoS One. 2016 May 9;11(5):e0155107.

Negoro H, Urban-Maldonado M, Liou LS, Spray DC, Thi MM, Suadicani SO. Pannexin 1 channels play essential roles in urothelial mechanotransduction and intercellular signaling. PLoS One. 2014 Aug 29;9(8):e106269.