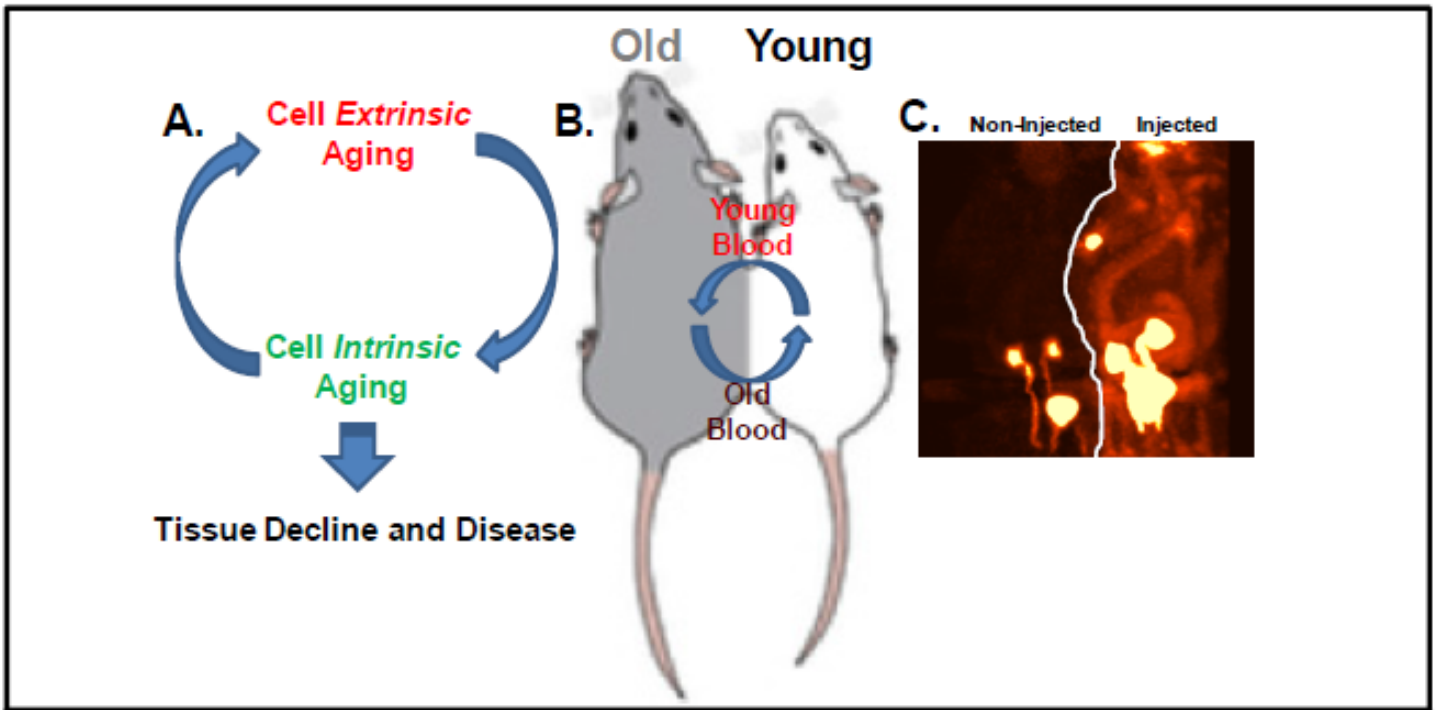
MOLECULAR PHARMACOLOGY
ALBERT EINSTEIN COLLEGE OF MEDICINE

Parabiosis: A tool to study extrinsic regulation of aging



A. *Aging is driven by a combination of events both intrinsic and extrinsic to the cell, which contributes to tissue decline and disease.* ***B.*** *Heterochronic parabiosis, which is the surgical union of a young and old animal, in order to create a shared circulation, is currently being utilized to understand systemic regulation of aging phenotypes.* ***C.*** *Evidence of blood exchange can be visualized by ^{18}FDG-PET, whereby tracer is observed in the non-injected animal within 1 hour of ^{18}FDG administration.*

Charles S. Rubin, Ph.D, Co-Chair
Susan Band Horwitz, Ph.D., Co-Chair
Michael Aschner, Ph.D.
Derek M. Huffman, Ph.D.
Jonathan M. Backer, M.D.
Young-Hwan Jo, Ph.D.
C. Fred Brewer, Ph.D.
Hayley M. McDaid, Ph.D.
Dongsheng Cai, M.D., Ph.D.
Thomas V. McDonald, M.D.
Chi-Wing Chow, Ph.D.
Roman Perez-Soler, M.D.
Lloyd D. Fricker, Ph.D.
Jeffrey E. Pessin, Ph.D.
Matthew J. Gamble, Ph.D.
Rajat Singh, M.D.
I. David Goldman, M.D.
Ji Ying Sze, Ph.D.
Richard Gorlick, M.D.

2015 - 2016

The Department of Molecular Pharmacology

Welcome to Molecular Pharmacology. The Department offers a training program that encompasses current "state of the art" research that includes investigations on protein phosphorylation, transcriptional regulation and chromatin modifying proteins, targeting intracellular signals, ion channel regulation, obesity and energy metabolism, signal transduction / cell regulation, autophagy hormone action and biogenesis, molecular basis of therapeutics, membrane transporters, cytoskeleton structure and function, and development of activators and inhibitors. Important methodologies and areas of expertise are: proteomics, RNA interference analysis, protein and phosphoinositide kinases and phosphatases, glycoproteins and lectins, signaling to the nucleus and gene regulation, structural / functional studies of membrane transporters and ion channels, differentiation and development, innate immunity, antitumor drug development and pharmacogenomics. Target diseases include: diabetes, cancer, thyroid and cardiac pathogenesis, behavioral disorders, learning and depression, as well as neurodevelopmental and neurodegenerative disorders. Mouse models are frequently used in these efforts, as are human-derived specimens so that our research is at the forefront of translational science. The research program in the department trains Ph.D. and M.D. / Ph.D. students for independent research careers. Students are key participants in our research endeavors and present their research at national meetings, conferences and symposia.

The Department has 21 faculty members and a cadre of 47 graduate students and postdoctoral fellows who participate in all departmental activities. Numerous scientific collaborations within the Department and with faculty with related interests in other Departments provide students with the opportunity for interactions with multiple faculty members, thus creating a broad-based and dynamic scientific environment. The Department sponsors a seminar series for senior visiting scientists that enables students to interact with distinguished extramural investigators. Journal clubs, work-in-progress research meetings, a weekly Department-wide seminar, a monthly Wednesday afternoon "happy hour" and scientific retreats promote scientific and social interactions among the students, fellows and faculty.

Graduates of the Department of Molecular Pharmacology have earned postdoctoral positions in outstanding laboratories and received prestigious fellowships. Our graduates have permanent positions in academia, biotechnology / pharmaceutical companies and at the National Institutes of Health and the Food and Drug Administration. We are proud of the accomplishments of our graduates and welcome new students to join us as we prepare for a future in science that has limitless potential for progress in basic biomedical knowledge and amelioration of disease.

MOLECULAR PHARMACOLOGY - PRIMARY FACULTY

Name	Title	Location	Phone	E-mail
Michael Aschner	Professor	Forchheimer 209	2317	michael.aschner@einstein.yu.edu
Jonathan Backer	Professor	Forchheimer 230	2153	jonathan.backer@einstein.yu.edu
Curtis Fred Brewer	Professor	Forchheimer 206	2227	fred.brewer@einstein.yu.edu
Dongsheng Cai	Professor	Forchheimer 216	2426	dongsheng.cai@einstein.yu.edu
Chi-Wing Chow	Associate Professor	Forchheimer 223	2715	chi-wing.chow@einstein.yu.edu
Lloyd Fricker	Professor	Forchheimer 248	4225	lloyd.fricker@einstein.yu.edu
Matthew Gamble	Associate Professor	Golding 203	2942	matthew.gamble@einstein.yu.edu
Susan Band Horwitz	Professor / Co-Chair	Golding 201	2163	susan.horwitz@einstein.yu.edu
Charles S. Rubin	Professor / Co-Chair	Forchheimer 229	2505	charles.rubin@einstein.yu.edu
Ji Ying Sze	Associate Professor	Golding 202	2084	jiying.sze@einstein.yu.edu

MOLECULAR PHARMACOLOGY - SECONDARY FACULTY

Name	Title	Location	Phone	E-mail
I. David Goldman	Professor	Chanin 209	2302	i.david.goldman@einstein.yu.edu
Richard Gorlick	Associate Professor	MMC-CHAM	741-2342	rgorlick@montefiore.org
Marina Holz	Voluntary Asst. Professor	Stern College	212-340-7883	mholz@yu.edu
Gloria Huang	Instructor / Associate Professor (OB-GYN)	Forchheimer 219	3431	gloria.huang@einstein.yu.edu
Derek Huffman	Assistant Professor	Fochheimer 236	839-7964	derek.huffman@einstein.yu.edu
Young-Hwan Jo	Assistant Professor	Forchheimer 511	2987	young-hwan.jo@einstein.yu.edu
Hayley McDaid	Assistant Professor	Forchheimer 249A	8829	hayley.mcdaid@einstein.yu.edu
Thomas McDonald	Professor	Forchheimer G39	3370	tom.mcdonald@einstein.yu.edu
Roman Perez-Soler	Professor	Hoffheimer 100	920-4001	roman.perez-soler@einstein.yu.edu
Jeffrey Pessin	Professor	Price Center 375	678-1029	jeffrey.pessin@einstein.yu.edu
Rajat Singh	Associate Professor	Forchheimer 505	4118	rajat.singh@einstein.yu.edu
Allen Spiegel	Marilyn & Stanley M. Katz Dean	Belfer 312	2801	allen.spiegel@einstein.yu.edu

MOLECULAR PHARMACOLOGY - ADMINISTRATION

Name	Title	Location	Phone	E-mail
Anna Cioffi	Administrator	Forchheimer 251	2911	anna.cioffi@einstein.yu.edu
Rhomina Carrasco	Administrative Coordinator	Forchheimer 251	2911	rhomina.carrasco@einstein.yu.edu
Gloria Rice	Secretary VI	Forchheimer 251	2911	gloria.rice@einstein.yu.edu
Thelma Valentin	Administrative Coordinator	Golding 201	2191	thelma.valentin@einstein.yu.edu

MOLECULAR PHARMACOLOGY - INSTRUCTORS / ASSOCIATES

Name	Title	Location	Phone	E-mail
Pan Chen	Instructor	Forchheimer 206/209	4047	pan.chen@einstein.yu.edu
Marianne Land	Vol. Visiting Associate	Forchheimer 233	2184	marianne.land@einstein.yu.edu
Chia-Ping Yang	Instructor / Asst. Prof. (OB-GYN)	Golding 201	2361	chia-ping.h.yang@einstein.yu.edu
Rongbao Zhao	Instructor / Asst. Prof. (Med.)	Chanin 628	2594	rongbao.zhao@einstein.yu.edu

MOLECULAR PHARMACOLOGY - POSTDOCTORAL FELLOWS

Name	Mentor	Location	Phone	E-mail
Clara Aicart Ramos	Rubin	Forchheimer 233	2184	clara.aicart-ramos@einstein.yu.edu
Alberto Ale Miranda	Cai	Forchheimer 216	2427	alberto.ale@einstein.yu.edu
Srinivas Aluri	Goldman	Chanin 628	2594	srinivas.aluri@einstein.yu.edu
Alessandra Antunes dos Santos	Aschner	Forchheimer 206/209	4047	alessandra.antunes@einstein.yu.edu
Christopher Barnhart	Aschner	Forchheimer 206/209	4047	christopher.barnhart@einstein.yu.edu
Sayani Dasgupta	Fricker	Forchheimer 248	2173	sayani.dasgupta@einstein.yu.edu
Zahra Erami Rud Majani	Backer	Forhheimer 230	2124	erami.zahra@gmail.com
Zhi-Chao Feng	Cai	Forchheimer 216	2427	zhichao.feng@einstein.yu.edu
Beatriz Ferrer Villahoz	Chow	Forchheimer 223	2716	beatriz.ferrervilllahoz@einstein.yu.edu
Jae Hoon Jeong	Jo	Forchheimer 511	2987	jaehoon.jeong@einstein.yu.edu
Min Soo Kim	Cai	Forchheimer 216	2427	minsoo.kim@einstein.yu.edu
Fanrong Kong	McDonald	Forchheimer G35	3370	fanrong.kong@einstein.yu.edu
Dong-Kun Lee	Jo	Forchheimer 511	2987	dong-kun.lee@einstein.yu.edu
Kai Mao	Huffman	Forchheimer 236	7964	kai.mao@einstein.yu.edu
Nuria Martinez Lopez	Singh	Forchheimer 505	3254	nuria.martinez@einstein.yu.edu
Michal Meron	Pessin	Price Center 369	1031	michal.meron@einstein.yu.edu
Brian Neel	Pessin	Price Center 369	1031	brian.neel@einstein.yu.edu
Nancy Parmalee	Aschner	Forchheimer 206/209	4047	nancy.parmalee@einstein.yu.edu
Emilie Petit	Sze	Golding 202	2093	emilie.petit@einstein.yu.edu
Adi Pinkas	Aschner	Forchheimer 206/209	4047	adi.pinkas@einstein.yu.edu
Judith Reichel	Cai	Forchheimer 216	4047	judith.reichel@einstein.yu.edu
Matthew Rice	Cai	Forchheimer 216	2427	matthew.rice@einstein.yu.edu
Joanna Ruskiewicz	Aschner	Forchheimer 206/209	4047	joanna.ruszkiewicz@einstein.yu.edu
Leleesha Samaraweera	Horwitz / McDaid	Golding 201	2164	leleesha.samaraweera@einstein.yu.edu
Jaakko Sarparanta	Singh	Forchheimer 511	3254	jaakko.sarparanta@einstein.yu.edu
Yizhe Tang	Cai	Forchheimer 216	4425	yizhe.tang@einstein.yu.edu
Elena Tarabra	Pessin	Price Center 369	1031	elena.tarabra@einstein.yu.edu
Tanara Vieira Peres	Aschner	Forchheimer 206/209	4047	Tanara.Peres-Vieira@einstein.yu.edu
Donghai Wang	Huffman	Forchheimer 236	7964	donghai.wang@einstein.yu.edu
Jingqi Yan	Cai	Forchheimer 216	4425	jingqi.yan@einstein.yu.edu
Yanhua Yao	Backer	Forhheimer 230	2124	yanhua.yao@einstein.yu.edu
Dou Yeon Youn	Pessin	Price Center 369	1031	douyeon.youn@einstein.yu.edu
Ya-Lin Zhang	Cai	Forchheimer 216	2427	yalin.zhang@einstein.yu.edu
Ziyan Zhang	Aschner	Forchheimer 206/209	4047	ziyan.zhang@einstein.yu.edu

MOLECULAR PHARMACOLOGY - PREDOCTORAL FELLOWS

Name	Mentor	Location	Phone	E-mail
Alyssa Casill	Gamble	Golding 203	2943	alyssa.casill@einstein.yu.edu
Shuonan Chen	Cai	Forchheimer 216	2427	shuonan.chen@einstein.yu.edu
Megan Culbreth	Aschner	Forchheimer 206/209	4047	meagan.culbreth@phd.einstein.yu.edu
Gabriela E. Farias Quilpildor	Huffman	Forchheimer 236	7964	gabriela.fariasquipildor@phd.einstein.yu.edu
Samantha Heitz	Backer	Forchheimer 230	2124	samantha.heitz@phd.einstein.yu.edu
Bassem Khalil	Backer	Forchheimer 230	2124	bassem.khalil@phd.einstein.yu.edu
Pratistha Koirala	Gorlick	MMC-SB 116 (Gorlick)	718-920-7977	pratistha.koirala@med.einstein.yu.edu
Deepti Mathew	Horwitz / McDaid	Golding 201	2164	deepti.mathew@phd.einstein.yu.edu
Marika Lee Osterbur	McDonald	Forchheimer G35	3370	marika.osterbur@med.einstein.yu.edu
Penelope Ruiz	Gamble	Golding 203	2943	penelope.decarolis@phd.einstein.yu.edu
Gilbert Salloum	Backer	Forchheimer 230	2124	gilbert.salloum@hotmail.com
Meagan Vogt	Horwitz / McDaid	Golding 201	2164	meagan.donaldson@phd.einstein.yu.edu
Yichen Wang	Pessin	Price Center 369	1031	yichen.wang@phd.einstein.yu.edu

MOLECULAR PHARMACOLOGY - RESEARCH TECHNICIANS

Name	Mentor	Location	Phone	E-mail
Jurriaan Brouwer	Huang	Forchheimer 219	2614	jurriaan.brouwer@einstein.yu.edu
Sophia (Dan Qing) He	Rubin	Forchheimer 233	2184	sophia.he@einstein.yu.edu
Zunju Hu	Huffman	Forchheimer 236	7964	zunju.hu@einstein.yu.edu
Adriana Levine	Backer	Forchheimer 230	2124	adriana.levine@einstein.yu.edu
Mila Losev	Pessin	Price Center 369	1031	mila.losev@einstein.yu.edu
Leonid Novikov	Gamble	Golding 203	2943	leonid.novikov@einstein.yu.edu
Marion (Myung Rang) Park	Aschner	Forchheimer 206/209	4047	marion.park@einstein.yu.edu
Alicia Rodriguez-LaRocca	Horwitz / McDaid	Golding 201	2361	alicia.rodriguez-larocca@einstein.yu.edu

MOLECULAR PHARMACOLOGY - RESEARCH TRAINEES

Name	Mentor	Location	Phone	E-mail
Leticia Arantes	Aschner	Forchheimer 206/209	4047	leticia.arantes@einstein.yu.edu
Brenda Daroz	Fricker	Forchheimer 248	2173	brenda_daroz@hotmail.com
Filipe Marques Goncalves	Aschner	Forchheimer 206/209	4047	fmarques.gon@gmail.com
Willian Goulart Salgueiro	Aschner	Forchheimer 206/209	4047	willian_cgs@hotmail.com
Mitra Najmi	Goldman	Chanin 628	2594	mitra.najmi@einstein.yu.edu
Thuy Nguyen	Aschner	Forchheimer 206/209	4047	thuy.nguyen@einstein.yu.edu
Wenhe Wu	Cai	Forchheimer 216	4425	wenhe.wu@einstein.yu.edu
Yumin Zhang	Cai	Forchheimer 216	4425	yumin.zhang@einstein.yu.edu

DEPARTMENT OF MOLECULAR PHARMACOLOGY

Susan Band Horwitz, Ph.D. - Co-Chair "The focus of our laboratory is on 1) the development of new drugs derived from natural products, such as Taxol, for the treatment of malignancies and 2) the mechanisms by which tumors become resistant to drugs."

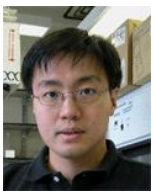
Charles S. Rubin, Ph.D. - Co-Chair "We study protein kinase D, a lipid-activated signaling protein that regulates functions of neurons and intestinal cells. Our work addresses molecular and cellular mechanisms underlying learning and innate immunity.

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.

Jonathan M. Backer, M.D. "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."

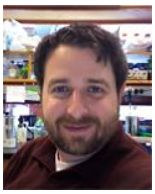
C. Fred Brewer, Ph.D. "Our work is directed at understanding the molecular basis of lectin-glycan and glycan-glycan interactions in cellular homeostasis, pathogenesis and innate immunity."

Dongsheng Cai, M.D., Ph.D. "The interest of our laboratory is to investigate the roles of stress and immunity pathways in the brain for the development of metabolic diseases (obesity, diabetes, and related cardiovascular diseases) and aging-associated disorders."



Chi-Wing Chow, Ph.D. "The long term goal of this research is to understand the molecular basis of cellular machinery and their relationships to human disease."

Lloyd D. Fricker, Ph.D. "The major focus of research in my laboratory is peptides that function in inter- and intracellular signaling, and the peptidases that produce and degrade these peptides."



Matthew J. Gamble, Ph.D. "We explore the mechanisms by which macrodomain-containing proteins (e.g. macroH2A1) couple transcriptional regulation to NAD^+-signaling. We strive to determine how these factors influence cancer progression and senescence."

I. David Goldman, M.D. "Our laboratory studies the molecular pharmacology of antifolate chemotherapeutics; in particular, the mechanisms of their membrane transport and the role of transport in drug selectivity and tumor cell drug resistance."

Richard Gorlick, M.D. "Our laboratory is focused upon osteosarcoma. In the context of this malignancy we study drug resistance, potential therapeutic targets and mechanisms of pathogenesis with the aim being the improved treatment of this disease."

Derek M. Huffman, Ph.D. "The Huffman laboratory is focused on four areas: 1) The IGF-1 signaling pathway and aging, 2) Mechanisms of central insulin and IGF-1 signaling on peripheral metabolism, 3) Role of systemic factors on intestinal aging, and 4) The cancer-aging interface."

Young-Hwan Jo, Ph.D. "My long-term research goal is to understand the molecular and cellular mechanisms underlying neuronal excitability, synaptic connectivity and synaptic plasticity of hypothalamic neuronal circuits involved in energy homeostasis."

Hayley M. McDaid, Ph.D. "We focus on therapeutics directed at breast, lung and ovarian cancers and defining mechanisms of resistance, in particular those related to tumor cell senescence"

Thomas V. McDonald, M.D. "The McDonald Laboratory studies the biology, genetics, and biophysics of ion channels in health and disease. Among the conditions of interest are sudden infant death syndrome, Long-QT syndrome, and malaria."

Roman Perez-Soler, M.D. "Our laboratory is designing and testing mechanism-based molecular therapies for lung cancer and other solid tumors. Novel drug delivery systems that combine anatomical and molecular targeting approaches are in development."

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."

Rajat Singh, M.D. "The focus of our laboratory is to examine the organ-specific roles of autophagy in the regulation of energy homeostasis, and the mechanisms of reduction in autophagy that lead to the metabolic syndrome of aging."

Ji Ying Sze, Ph.D. "The research in our laboratory investigates the genetic basis of the regulation of synaptic transmission of the neurotransmitter serotonin, using *C. elegans* and mouse as animal models."

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

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:

Benedetto A, Au C, **Aschner** M. Manganese-induced dopaminergic neurodegeneration: Insights into mechanisms and genetics shared with Parkinson's disease. Chem Rev 2009; 109:4862-84.

Sidoryk-Wegrzynowicz M, Lee E, **Aschner** M. Mechanism of Mn(ii)-mediated dysregulation of the glutamine–glutamate cycle: focus on glutamate turnover. J Neurochem 2012; 122:856-867.

Lee E, Sidoryk-Węgrzynowicz M, Wang N, Webbs A, Son D-S, **Aschner** M. GPR30 regulates glutamate transporter GLT-1 expression in rat primary astrocytes. J Biol Chem 2012; 287:26817-26828.

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

Phosphoinositide 3-kinases are lipid kinases that mediate signaling by receptor tyrosine kinases and G-protein coupled receptors (GPCRs). They are important regulators of cellular proliferation, motility, apoptosis, and vesicular trafficking. Mutational activation of PI 3-kinases is commonly found in human cancers. We are interested in the how the altered regulation of PI 3'-kinase contributes to human cancer. The Backer lab works collaboratively with the lab of Dr. Anne Bresnick, Dept. of Biochemistry, on all of these projects.

1. GPCR-regulated PI 3-kinases in human cancer. The Class IA PI 3'-kinase is a heterodimer composed of a catalytic subunit (p110) and a regulatory subunit (p85). Class IA PI 3-kinases are activated when p85 binds to phosphotyrosine residues in receptor tyrosine kinases and their substrates. The p85/p110β isoform of PI 3-kinase is unique in that it also directly binds to and is regulated by Gβγ subunits downstream of activated GPCRs. We have recently identified point mutants that specifically disrupt p110β binding to Gβγ, and have shown that these mutants disrupt p110β-mediated transformation, invasion, and tumorigenesis. We are studying the role of Gβγ-regulated signaling by p110β in cell culture and animal models. We are focusing of p110β signaling in breast cancer metastasis and in PTEN-null prostate cancer. These studies will be important for understanding the role of GPCR-regulated PI 3-kinase signaling in human cancer.

2. PI 3-kinase regulation by Rab GTPases. The p110β isoform of PI 3-kinase is also unique in that it specifically binds to the endosomal GTPase Rab5, which regulates vesicular trafficking in the early endosome. We have mapped the Rab5 binding site in p110β and produced mutants that are specifically defective for Rab5 binding. Cells expressing these mutants show a defect in some endocytic processes, as well as a disruption of autophagy in nutrient-starved cells. We are using knockdown/rescue methods in breast cancer and prostate cancer cells, as well as mouse knock-in models, to define the mechanisms by which Rab5-p110β binding regulates vesicular trafficking and responses to nutrient stress.

3. PI 3'-kinases in autophagy. Autophagy is a cellular response to nutrient deprivation in which cytosolic contents are engulfed and delivered to the lysosome for degradation. Autophagy is required for the viability of pancreatic beta cells, hepatocytes and neurons and for innate immune responses to pathogens. Downregulation of autophagic degradation has been implicated in neurodegenerative syndromes and in aging. The mammalian Class III PI 3-kinase, hVps34, plays essential roles in both vesicular trafficking and autophagy. We are studying the role of hVps34 in autophagy, with a focus on identifying novel regulators of Vps34 activity and targeting.

Representative Publications:

Cao, Y, Chen, Y, Abi Saab, W., Yang, F., Pessin, JE, and Backer, J.M. NRBF2 regulates autophagy as a component of Vps34 Complex 1. (2014) Biochemical J. 461:315-322.

Dbouk, HA, et al. and **Backer, JM**. Characterization of a tumor-associated activating mutation of the p110β PI 3-kinase. (2013) PLoS One 8:e63833

Dbouk HA, et al. and **Backer, JM**. G Protein–Coupled Receptor–Mediated Activation of p110β by Gβγ Is Required for Cellular Transformation and Invasiveness (2012) Science Signaling 5:ra89

Dbouk, HA, Pang, H, Fiser, A, and **Backer, JM.** A biochemical mechanism for the oncogenic potential of the p110β catalytic subunit of phosphoinositide 3-kinase. (2010) PNAS 107:19897-19902.

Curtis F. Brewer, Ph.D., Professor
Mazer - 108
(718) 430-2227; fred.brewer@einstein.yu.edu

Cell surface carbohydrates have been demonstrated to be involved in a variety of biological recognition phenomena including cellular recognition and adhesion, regulation of inflammation, control of cell growth and metastasis. Although the structures of many of these carbohydrates have been elucidated, relatively little is known about their molecular recognition properties other than their interactions with glycosylases and lectins. Lectins are carbohydrate-binding proteins that are widely found in nature including in plants, animals and pathogenic organisms. Lectins and the cell surface glycans of glycoproteins and glycolipis in metazoans play important roles in cellular homeostasis and innate and adaptive immunity. Our research includes characterizing the biophysical and biochemical properties of lectins and their interactions with multivalent glycans and glycoproteins that are cellular receptors involved in signal transduction processes including cell growth, arrest and apoptosis. Techniques used to explore these interactions include nuclear magnetic resonance spectroscopy, isothermal titration microcalorimetry, x-ray crystallography and atomic force microscopy.

Representative Publications:

Haugstad, K. E., Stokke, B. T., Gerken, T. A., **Brewer, C. F**. and Sletmoen, M., Single molecule study of heterotypic interactions between mucins possessing the Tn cancer antigen. Glycobiology 25; 524 (2015).

Brewer, C. F., Glycosylation Density in Cellular Homeostasis, Glycoscience: Biology and Medicine, (Taniguchi, N., Endo, E., Hart, G.W., Seeberger, P. and Wong, C.-H., eds.), Springer, Japan, pp. 661-666 (2015).

Dennis, J. W. and **Brewer, C. F**., Density dependent lectin-glycan interactions as a model for conditional regulation by post-translational modifications. Mol. Cell. Proteomics 12; 913 (2013).

Haugstad, K. E., Gerken, T. A., Stokke, B. T., Dam, T. K., **Brewer, C. F**. and Sletmoen, M., Enhanced self-association of mucins possessing the T and Tn-carbohydrate cancer antigens at the single-molecule level. Biomacromolecules 13; 1400 (2012).

Dam, T. K., Cavada, B. S., Nagano, C. S., Rocha, B. A. M., Benevides, R. G., Nascimento, K. S., de Sousa, L. A. G., Oscarson, S. and **Brewer, C. F**., Fine specificities of two lectins from *Cymbosema roseum* seeds: a lectin specific for high-mannose oligosaccharides and a lectin specific for blood group H type II trisaccharide. Glycobiology 21; 925 (2011).

Dam, T. K. and **Brewer, C. F**., Maintenance of cell surface glycan density by lectin-glycan interactions: a homeostatic and innate immune regulatory mechanism. Glycobiology 20; 1061 (2010).

Dam, T. K. and **Brewer, C. F**., Lectins as pattern recognition molecules: the effects of epitope density in innate immunity, Glycobiology 20; 270 (2010).

Sletmoen, M., Dam, T. K., Gerken, T. A., Stokke, B. T. and **Brewer, C. F.**, Single-molecule pair studies of the interactions of the α-GalNac (Tn-antigen) form of porcine submaxillary mucin with soybean agglutinin. Biopolymers 91; 719 (2009).

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

Obesity and diabetes represent two important epidemic and public health problems facing the nation which also facilitate aging related disorders. The research in our laboratory is to study how inflammatory pathways mediate the central nervous system dysregulation of systemic physiology to cause obesity- and aging-related disorders such as diabetes, hypertension and neurodegenerative diseases. To address these questions, (1) we aim to study metabolic challenge-induced inflammation in the brain, the connections with glial, neural and neuroendocrine pathways, and the molecular bases for obesity, diabetes and aging-related diseases. (2) We aim to analyze the neural mechanisms of aging and lifespan at both cellular and organism levels and how they are altered under inflammatory environment. (3) We aim to identify the intrinsic molecular systems that counteract metabolic inflammation and to explore why and how these systems are weakened under nutritional oversupply or aging. (4) We aim to translate the mechanistic understandings into developing interventional strategies for preventing neural dysregulation of physiology in order to control the spread of these diseases.

Representative Publications:

Zhang, G., Li, J., Purkayastha, S., Tang, Y., Zhang, H., Yin, Y., Li, B., Liu, G., **Cai, D.** Hypothalamic programming of systemic aging involving IKKβ/NF-κB and GnRH. Nature, 497 (7748): 211-216. 2013. (*Highlighted by Nature News & Views commentary; select article in Cell; recommended as a top-10 article of Faculty 1000 Prime; featured in The Scientific American, National Geographic, The Scientist and others*)

Liu, T., **Cai, D.** Counterbalance between BAG and URX neurons via guanylate cyclases controls lifespan homeostasis in *C. elegans*. EMBO J., 32: 1529–1542, 2013. (*Highlighted as EMBO J commentary*)

Cai, D. Neuroinflammation and neurodegeneration in overnutrition-induced diseases. Trends Endocrinol. Metab., 24 (1): 40-47, 2013. (*Invited review*)

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

Purkayastha, S., Zhang, H., Zhang, G., Ahmed, Z., **Cai, D.** Neural dysregulation of peripheral insulin action and blood pressure by brain ER stress. Proc. Natl. Acad. Sci. U.S.A., 108 (7): 2939-44, 2011.

Zhang, G., Bai, H., Zhang, H., Dean, C., Wu, Q., Li, J., **Cai, D.** Neuropeptide exocytosis involving synaptotagmin-4 and oxytocin in hypothalamic programming of body weight and energy balance. Neuron, 69 (3): 523-35, 2011. (*Highlighted by Neuron featured preview; highlighted as a top-2% article by Faculty 1000*)

Purkayastha, S., Zhang, G., **Cai, D.** Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKKβ and NF-kB. Nat. Med., 17 (7): 883-7, 2011. (*Highlighted by Nature Medicine commentary, Cell Metabolism preview; editorial choice of Science Signaling; highlighted as a top-10 article by Faculty 1000*)

Zhang, H., Zhang, G., Gonzalez, F.J., Park, S.M., **Cai, D.** Hypoxia-inducible factor directs POMC gene to mediate hypothalamic glucose sensing and energy balance regulation. PLoS Biology, 9 (7): e1001112, 2011. (*Highlighted as primer report and news release by PLoS Biology*)

Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., **Cai, D.** Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. Cell, 135 (1): 61-73, 2008. (*Highlighted by preview in Cell; highlighted as a top-10 article of Faculty 1000*)

Chi-Wing Chow, Ph.D., Associate Professor
Forchheimer - 223
(718) 430-2715; chi-wing.chow@einstein.yu.edu

The long term goal of this research program is to understand the molecular basis of cellular machinery and their relationships to human diseases. A branch of the laboratory focuses on elucidating the interplays between transcription factors and signaling pathways. We ask how does extracellular stimuli communicate with intracellular effectors, and eventually modulate cellular responses in normal and diseased states. For example, we have recently demonstrated that adipokine gene expression mediated by transcription factor NFAT contributes to insulin and glucose homeostasis *via* a non-cell autonomous mechanism. We have further found that upstream regulators and downstream effectors of the NFAT transcription factor impinge on adipocyte biology at multiple levels, including novel crosstalk with G-protein coupled/cAMP signal trasduction *via* phospho-dependent protein degradation. Another branch of the laboratory examines intercellular trafficking and its role in inflammatory signaling. Thus, a range of biochemistry, molecular biology and cell biology are applied, in conjunction with primary cell culture and engineered mice, to dissect the molecular basis of cellular machinery. In sum, I strongly believe elucidating the basis of molecular pathways will provide the most benefits in understanding human diseases.

Representative Publications:

Li, W., Zhu, H., Zhao, X.,Brancho, D., Liang, Y., Zou, Y., Bennett, C., and **Chow, C.W.** (2015) Dysregulated inflammatory signaling upon Charcot-Marie-Tooth 1C mutation of protein SIMPLE. *Mol Biol Cell.* 35, 2464-2478.

Zhu, H., Li, W., Brancho, D., Wang, Z.V., Scherer, P.E., and **Chow, C.W.** (2014) Role of Extracellular Signal-Regulated Kinase 5 in Adipocyte Signaling. . *J Biol Chem.* 289, 6311-22. PMID: 24425864 PMCID:PMC3937697.

Zhu, H., Guariglia, S., Yu, R.Y.L., Li, W., Brancho, D., Peinado, H., Lyden, D., Salzer, J., Bennett, C., and **Chow, C.W.** (2013) Mutation of SIMPLE in Charcot-Marie-Tooth 1C Alters Production of Exosomes. *Mol Biol Cell.* 24, 1619-37.

Suk, H.Y., Zhou, C., Yang, T.C., Zhu, H., Yu, R.Y.L., Olabisi, O A., Yang, X.Y., Brancho, D., Kim, J.Y., Scherer, P.E., Frank, P.G., Listani, M.P., Calvert, J.W., Lefer, D.J., Molkentin, J.D., Ghigo, A., Hirsch, E., Jin, J., and **Chow, C.W.** (2013) Ablation of Calcineurin Aβ Reveals Hyperlipidemia and Signaling Cross-talks with Phosphodiesterases. *J Biol Chem.* 288, 3477-88.

Yao, J.-J., Gao, X.-F., **Chow, C.W.**, Zhan, X.-Q., and Mei, Y.-A. (2012) Neuritin Activates Insulin Receptor Pathway to Upregulate Kv4.2-mediated I_A in Rat Cerebellar Granule Neurons *J Biol Chem.* 287, 41534-45.

Biswas, A., Mukherjee, S., Das, S., Shields, D., **Chow, C.W.**, and Maitra, U. (2011) Opposing Action of Casein kinase 1 and Calcineurin in Nucleo-Cytoplasmic Shuttling of Mammalian Translation Initiation Factor eIF6. *J Biol Chem.* 286, 3129-38.

Zhu, H., Suk, H.Y., Yang, T.C., Yu, R.Y.L., Olabisi, O A., Yang, X.Y., Brancho, D., Zhang, J., Maussaif, M., Durand, J.L., Jelicks, L.A., Kim, J.Y., Scherer, P.E., Frank, P.G., Listani, M.P., Calvert, J.W., Duranski, M.R., Lefer, D.J., Huston, E., Ballie, G.S., Houslay, M.D., Miller, K.G., Molkentin, J.D., Jin, J., **Chow, C.W.** (2010) Evolutionarily Conserved Role of Calcineurin in Phospho-Dependent Degradation of Phosphodiesterase 4D. *Mol. Cell. Biol.* 30, 4379-4390.

Lloyd Fricker, Ph.D., Professor
Forchheimer - 248
(718) 430-4225; lloyd.fricker@einstein.yu.edu

Peptides play many important physiological roles in most organisms. Neuropeptides and peptide hormones function in cell-cell signaling and are involved with a wide variety of biological functions including feeding and body weight regulation, fear, anxiety, pain, circadian rhythms, memory, reward mechanisms, and many others. We have discovered a number of novel peptides using mass spectrometry-based peptidomic techniques. Some of these are neuropeptides that function in cell-cell signaling that control feeding/body weight. Many of the other novel peptides are produced from cytosolic proteins, and not from secretory pathway proteins that are the precursors of classical neuropeptides. Some of the peptides derived from cytosolic proteins are secreted and bind to extracellular receptors; these are putative "non-classical" neuropeptides, a novel class of cell-cell signaling molecule. Further studies are aimed at understanding the mechanisms by which these peptides are produced, secreted, and regulated, with the overall goal to identify the peptides' functions.

In addition to peptides, we are also interested in enzymes that modify peptides/proteins. Our laboratory has discovered a dozen different carboxypeptidases and we are currently working towards determining their functions. One carboxypeptidase, which we named carboxypeptidase E, is responsible for the formation of many peptide hormones (such as insulin) and neuropeptides (such as enkephalin). We identified a strain of mouse (named fat/fat) that does not produce active carboxypeptidase E due to a point mutation; these mice are obese, sterile, hyperglycemic, and have neurological impairments. In addition to neuropeptide processing enzymes, several other cellular peptidases are being studied in the laboratory. Current projects use peptidomics and other techniques to identify the physiological function of the peptidase. Some of the enzymes being studied are the cytosolic carboxypeptidases; these enzymes modify tubulin (and possibly other proteins) by removing amino acids from the C-terminus and/or side-chains, thereby altering the properties of tubulin. Mice lacking cytosolic carboxypeptidase 1 show abnormal movement due to neurodegeneration of cerebellar Purkinje cells. Another enzyme currently being studied is carboxypeptidase A6; humans with mutations in this enzyme develop epilepsy. We are studying the role of carboxypeptidase A6 in animal models, with a focus on understanding how mutations in the protein lead to epilepsy.

Representative Publications:

Sapio, M.R. and Fricker, L.D., Carboxypeptidases in disease: Insights from peptidomic studies. Proteomics Clin Appl., 8:327-37, 2014. (PMCID: PMC4062080)

Dasgupta, S., Castro, L.M., Dulman, R., Yang, C, Schmidt, M., Ferro, E.S., and Fricker, L.D., Proteasome inhibitors alter levels of intracellular peptides in HEK293T and SH-SY5Y cells, PLoS One. 9:e103604, 2014. (PMCID: PMC4117522)

Wardman J.H. and Fricker, L.D., ProSAAS-derived peptides are differentially processed and sorted in mouse brain and AtT-20 cells, PLoS One, 9:e104232, 2014. (PMCID: PMC4141687)

Ferro, E.S., Rioli, V., Castro, L.M., and Fricker, L.D., Intracellular peptides: From discovery to function, EuPA Open Proteomics, 3:143–151, 2014.

Schrader, M., Schulz-Knappe, P., and Fricker, L.D., Historical perspective of peptidomics, EuPA Open Proteomics, 3:171–182, 2014.

Sapio, M.R., Vessaz, M., Thomas, P., Genton, P., Fricker, L.D., and Salzmann, A., Novel carboxypeptidase A6 (CPA6) mutations identified in patients with juvenile myoclonic and generalized epilepsy, PLoS One, 10(4):e0123180, 2015. (PMCID: PMC4395397)

Matthew J. Gamble, Ph.D., Associate Professor
Golding – 203
(718) 430-2942; matthew.gamble@einstein.yu.edu

Macrodomains are found in several histone variants, chromatin remodelers, and other transcriptional coregulators (e.g. macroH2A, PARP14, CHD1L) with roles in cancer progression, senescence, innate immune responses, and viral pathogenesis. These protein modules function, in part, as ligand binding domains for NAD^+-derived poly(ADP-ribose), ADP-ribose, and O-acetyl-ADP-ribose. The ability of macrodomains to bind these ligands links the function of macrodomain-containing proteins (MDCPs) to NAD^+-dependent signaling events catalyzed by enzymes such as PARP-1, PARG and SIRT1. Our laboratory employs a variety of cell-based, genomic and biochemical techniques to explore the role of macrodomains, their ligands and the NAD^+-utilizing enzymes that produce them in transcriptional regulation and DNA damage responses.

The histone variant macroH2A is an MDCP of particular interest to our group. MacroH2A1 incorporates into nucleosomes found in large chromatin domains that occupy a quarter of the human genome. MacroH2A1 exists as one of two splice variants, macroH2A1.1 which can bind to NAD^+-derived ligands, and macroH2A1.2 which cannot associate with these small molecules. Interestingly, while both macroH2A1 variants are present in normal adult cells, macroH2A1.1 splicing is decreased in a variety of human cancers including endometrial, lung, breast, ovarian, testicular, colon, and bladder cancer. Additionally, macroH2A1.1 can trigger an innate tumor suppressive pathway called oncogene-induced senescence. We are currently exploring the mechanisms that regulate macroH2A1 splicing, the specific roles of each macroH2A variant in transcriptional regulation and DNA damage responses, and how these processes are perturbed during oncogenesis.

Representative Publications:

Chen, H., Ruiz, P.D., McKimpson, W.M., Novikov, L., Kitsis, R.N. and **Gamble, M.J.** (2015) "MacroH2A1 and ATM play opposing roles in paracrine senescence and the senescence-associated secretory phenotype." Mol. Cell (in press).

Chen, H., Ruiz, P.D., Novikov, L., Casill, A.D., Park, J.W. and **Gamble, M.J.** (2014) "MacroH2A1.1 and PARP-1 cooperate to regulate transcription by promoting CBP-mediated H2B acetylation." Nat. Struct. Mol. Biol. 21:981-9.

Hussey, K.M., Chen, H., Yang, C., Park, E., Hah, N., Erdjument-Bromage, H., Tempst, P., **Gamble, M.J.***, Kraus, W.L.* (2014) "The histone variant macroH2A1 regulates target gene expression in part by recruiting the transcriptional coregulator PELP1." Mol Cell Biol. 34:2437-49. (*co-corresponding authors)

Gamble M.J., (2013) Expanding the functional repertoire of macrodomains. *Nat. Struct. Mol. Biol.* 20:407-8.

Novikov L., Park J.W., Chen H., Klerman H., Jalloh A.S., and **Gamble M.J.** (2011) QKI-mediated alternative splicing of the histone variant macroH2A1 regulates cancer cell proliferation. *Mol. Cell Biol.* 31:4244-55.

Zhang X.*, **Gamble M.J.***, Stadler S., Cherrington B.D., Causey C.P., Thompson P.R., Roberson M.S., Kraus, W.L., Coonrod S.A. (2011) Genome-wide analysis reveals PADI4 cooperates with Elk-1 to activate *c-Fos* expression in breast cancer cells. *PLoS Genet* 7(6): e1002112. (* equal contribution).

Gamble M.J. and Kraus W.L. (2010) Multiple facets of the unique histone variant macroH2A: From genomics to cell biology. *Cell Cycle* 9:2568-2574.

Gamble, M.J., Frizzell, K.M., Yang C., Krishnakumar, R. and Kraus, W.L. (2010) The histone variant macroH2A1 marks repressed autosomal chromatin, but protects target genes from silencing. *Genes Dev* 24:21-31.

Krishnakumar, R.*, **Gamble, M.J.***, Frizzell, K.M., Berrocal, J.G., Kininis, M. and Kraus, W.L. (2008) Reciprocal binding of PARP-1 and histone H1 at promoters specifies transcriptional outcomes. *Science* 319:819-21. (* equal contribution).

I. David Goldman, M.D., Professor
Chanin - 209
(718) 430-2302; i.david.goldman@einstein.yu.edu

This laboratory has had a long-standing interest in membrane transport processes, in particular, the mechanisms of transport of folates and antifolate cancer chemotherapeutics. Recently, this laboratory cloned the proton-coupled folate transporter (PCFT- SLC46A1), required for the intestinal absorption of folates and transport of folates across the choroid plexus into the cerebrospinal fluid, and established that there are loss-of-function mutations in this gene in the autosomal recessive disorder, hereditary folate malabsorption (Cell 127:917-928, 2006; Blood 116:5162-9, 2010;Ann Rev Physiol 76:251-74,2014)). Areas of research include: (1) PCFT structure/function: This encompasses the identification of residues and domains required for the maintenance of tertiary structure, the translocation pathway, folate and proton binding, and oscillation of the carrier between its conformational state. (2) Transport energetics: While the proton gradient drives the folate gradient at low pH, we recently established that PCFT-mediated transport at neutral pH, in the absence of a proton gradient, can be concentrative. The energetics of this process are under study. (3) Antifolates: Structural analogs of folates are employed for the treatment of cancer and autoimmune diseases. Membrane transport is a key determinant of the effectiveness and selectivity of antifolates and impaired transport is an important element in drug resistance. These studies explore the alterations in PCFT-mediated transported associated with acquired resistance to these agents. The mechanism of action and transport of the new-generation antifolate, pemetrexed, is being studied. (Curr Opin Investig Drugs. 11:1409-23, 2010). Studies employ both electrophysiological and substrate transport measurements in Xenopus oocytes and analyses of radiolabeled folate flux determinations in cell lines. A three-dimensional homology model of PCFT is being developed in conjunction with the functional studies. (4) Receptor-mediated endocytosis: Studies are exploring the role PCFT plays a role in the export of folates and antifolates from acidified endosomes during the endocytic process. There is also interest in a novel classes of agents consisting of folic acid linked to a variety of cytotoxics that enter tumor cells via folate receptor-mediated endocytosis. (5) Hereditary folate malabsorption: As families are identified world-wide with hereditary folate malabsorption, the functional consequences of causative PCFT mutations are studied along with their relationship to the clinical phenotype, and the genetics of the disorder are deciphered. Trainees emerge from this laboratory with a broad understanding of membrane transport physiology, structure-function, energetics and electrophysiology along with the cellular, biochemical and molecular pharmacology of cancer chemotherapeutics with a focus on antifolates.

Representative Publications

Visentin M, Unal ES, Najmi M, Fiser A, Zhao R, Goldman ID. Identification of Tyr residues that enhance folate substrate binding and constrain oscillation of the proton-coupled folate transporter (PCFT-SLC46A1). Am J Physiol Cell Physiol. 308:C631-41, 2015. PMCID: PMC4398847.

Zhao R, Diop-Bove N, Goldman ID, Enhanced Receptor-mediated Endocytosis and Cytotoxicity of a Folic Acid-desacetylvinblastine Monohydrazide Conjugate in a Pemetrexed-Resistant Cell Line Lacking Folate-specific Facilitative Carriers but with Increased Folate Receptor Expression. Mol. Pharmacol. 85:310-21, 2014. PMCID: PMC3913358.

Shin DS, Zhao R, Fiser A Goldman ID. The role of the fourth transmembrane domain in proton-coupled folate transporter (PCFT-SLC46A1) function as assessed by the substituted cysteine accessibility method. Am J Physiol. Cell Physiol. 304:C1159-67, 2013. PMCID:PMC3680650

Visentin M, Zhao R, Goldman ID. Augmentation of reduced folate carrier-mediated folate/antifolate transport through an antiport mechanism with 5-aminoimidazole-4-carboxamide riboside monophosphate. Mol Pharmacol. 82:209-16, 2012. PMCID:PMC3400841

Richard Gorlick M.D., Professor
Molecular Pharmacology and Pediatrics
Chanin – 302A, CHAM, Rosenthal - 300
(718) 741-2342; rgorlick@montefiore.org

Our laboratory is focused upon osteosarcoma, which is the most common bone cancer in children and adolescents. In the context of this malignancy we study drug resistance, potential therapeutic targets and mechanisms of pathogenesis with the aim being the improved treatment of this disease.

The longstanding focus of the laboratory has been the mechanisms of antifolate resistance that are observed in osteosarcoma. We have evolved from that area to more broadly identifying new therapies that may be relevant for the treatment of osteosarcoma. We are interested in defining the signal transduction pathways that are relevant to osteosarcoma as these pathways may be amenable to inhibition by targeted therapies enhancing the standard treatment with cytotoxic chemotherapy. We are investigating several immunotherapy approaches. We are interested in understanding the cell of origin of osteosarcoma, which may be a mesenchymal stem cell or a more differentiated osteoblast. We are exploring further, the genetic pathways that drive these cells towards an osteosarcoma phenotype. The laboratory performs preclinical drug studies utilizing osteosarcoma xenografts as a site for the National Cancer Institute funded Pediatric Preclinical Testing Consortium. A wide variety of functional and molecular approaches are used to study the various candidate genes as well as to address the drug resistance questions.

Representative Publications (from 2015 only):

Geller DS, Singh MY, Zhang W, Gill J, Roth ME, Kim MY, Xie X, Singh CK, Dorfman HD, Villanueva-Siles E, Park A, Piperdi S, **Gorlick R**. Development of a Model System to Evaluate Local Recurrence in Osteosarcoma and Assessment of the Effects of Bone Morphogenetic Protein-2. Clin Cancer Res. 2015 Jul 1;21(13):3003-12.

Moriarity BS, Otto GM, Rahrmann EP, Rathe SK, Wolf NK, Weg MT, Manlove LA, LaRue RS, Temiz NA, Molyneux SD, Choi K, Holly KJ, Sarver AL, Scott MC, Forster CL, Modiano JF, Khanna C, Hewitt SM, Khokha R, Yang Y, **Gorlick R**, Dyer MA, Largaespada DA. A Sleeping Beauty forward genetic screen identifies new genes and pathways driving osteosarcoma development and metastasis. Nat Genet. 2015 Jun;47(6):615-24.

Mirabello L, Yeager M, Mai PL, Gastier-Foster JM, **Gorlick R**, Khanna C, Patiño-Garcia A, Sierrasesúmaga L, Lecanda F, Andrulis IL, Wunder JS, Gokgoz N, Barkauskas DA, Zhang X, Vogt A, Jones K, Boland JF, Chanock SJ, Savage SA. Germline TP53 variants and susceptibility to osteosarcoma. J Natl Cancer Inst. 2015 Apr 20;107(7)

Smith MA, Reynolds CP, Kang MH, Kolb EA, **Gorlick R**, Carol H, Lock RB, Keir ST, Maris JM, Billups CA, Lyalin D, Kurmasheva RT, Houghton PJ. Synergistic activity of PARP inhibition by talazoparib (BMN 673) with temozolomide in pediatric cancer models in the pediatric preclinical testing program. Clin Cancer Res. 2015 Feb 15;21(4):819-32.

Mirabello L, Koster R, Moriarity BS, Spector LG, Meltzer PS, Gary J, Machiela MJ, Pankratz N, Panagiotou OA, Largaespada D, Wang Z, Gastier-Foster JM, **Gorlick R**, Khanna C, Caminada de Toledo SR, Petrilli AS, Patino-Garcia A, Sierrasesumaga L, Lecanda F, Andrulis IL, Wunder JS, Gokgoz N, Serra M, Hattinger C, Picci P, Scotlandi K, Flanagan AM, Tirabosco R, Fernanda Amary M, Halai D, Ballinger ML, Thomas DM, Davis S, Barkauskas DA, Marina N, Helman L, Otto GM, Becklin KL, Wolf NK, Weg MT, Tucker M, Wacholder S, Fraumeni JF Jr, Caporaso NE, Boland JF, Hicks BD, Vogt A, Burdett L, Yeager M, Hoover RN, Chanock SJ, Savage SA. A genome-wide scan identifies variants in NFIB associated with metastasis in patients with osteosarcoma. Cancer Discov. 2015 Jun 17.

Susan Band Horwitz, Ph.D., Distinguished Professor and Co-Chair
Golding - 201
(718) 430-2163; susan.horwitz@einstein.yu.edu

The research program in this laboratory focuses on small molecules of natural product origin, such as Taxol®, which interact with the microtubule cytoskeleton. One goal is to understand, at a molecular level, the interaction of such drugs with the tubulin/microtubule system and the mechanisms by which these drugs induce growth arrest and cell death. An important part of the program is to study the mechanisms by which tumors become resistant, and drug-resistant cell lines have been developed as model systems. These have diverse mechanisms of resistance that include alterations in tubulin isotype expression, mutations in α-and β-tubulin, and changes in endogenous proteins such as MAPs that modulate drug resistance through their interactions with microtubules. Quantitative mass spectrophotometric-based methods are used to analyze the expression of tubulin isotypes and their posttranslational modifications in model systems and human tumors. In addition, hydrogen/deuterium exchange coupled to liquid-chromatography-electrospray ionization mass spectrometry is being used to study conformational effects induced by drugs on microtubules.

A second theme is focused on the seven β-tubulin isotypes present in distinct quantities in mammalian cells of different origin. The expression of β-tubulin istoypes is altered in drug resistant cell lines and human tumors from different organs. The laboratory is presently measuring the quantity of drug that binds to each isotype with the idea that β-tubulin isotype content could be related to drug response and resistance.

Representative Publications:

Brian O'Rourke, B., et.al (2014) Eribulin Disrupts EB1-Microtubule Plus-Tip Complex Formation. Cell Cycle 13:20; 3218-3221.

Albrethsen J., et.al (2014) Proteomics of cancer cell lines resistant to microtubule-stabilizing agents. Mol Cancer Ther. 13(1):260-9.

Chao, S. K., et. al. (2012) Characterization of a human βV-tubulin antibody and expression of this isotype in normal and malignant human tissue, Cytoskeleton, 69: 566–576.

Khrapunovich-Baine, M., et. al. (2011) Hallmarks of Molecular Action of Microtubule Stabilizing Agents (MSAs): Effects of Epothilone B, Ixabepilone, Peloruside A, and Laulimalide on Microtubule Conformation. J. Biol. Chem. 286, 13, 11765-11778.

Chao, S.K., et. al. (2011) Resistance to discodermolide, a microtubule stabilizing agent and senescence inducer, is 4E-BP1 dependent. PNAS, 107, 391-396.

Derek M. Huffman, Ph.D., Assistant Professor
Forchheimer - 236
(718) 430-4278; derek.huffman@einstein.yu.edu

1) IGF-1 axis and aging – Our lab is interested in the insulin/ insulin-like growth factor-1 (IGF-1) signaling axis and aging. A reduction in signal via this pathway has been consistently linked to lifespan, from model organisms to humans. Interestingly, in humans, high IGF-1 levels are associated with increased cancer risk, but are **paradoxically** linked with protection from other age-related diseases. Relevant to this paradox, we have uncovered novel, beneficial effects of centrally-acting IGF-1 on peripheral metabolism. This has led us to hypothesize that optimally modulating IGF-1 signaling to promote healthy aging and longevity in humans may require shifting the balance of IGF-1 from the periphery to the brain, in order to maximize the 'good' effects of IGF-1, while minimizing its 'bad' effects on cancer in the periphery. We are currently testing this hypothesis in animal models using a combination of genetic and pharmacologic approaches, including clinical-grade IGF-1 receptor (IGF-1R) antibodies.

2) Central insulin and IGF-1 signaling – A second area involves understanding the mechanism(s) whereby insulin and IGF-1 signaling in the brain control peripheral metabolism. We utilize the "gold standard" hyperinsulinemic-euglycemic clamp to evaluate insulin sensitivity in normal and genetically-engineered rodents with tandem central infusions of peptides/inhibitors, along with state-of-the-art fMRI techniques. Ongoing studies 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.

3) Role of systemic factors on intestinal aging – Functional decline is a hallmark of aging in multiple tissues, a process thought to be driven in part by deterioration in resident stem cell function. Intestinal stem cells and their niche have been well characterized and are responsible for maintaining the integrity of the intestinal epithelium, but we have found that intestinal stem cell function deteriorates with aging, and may perpetuate the overall decline in intestinal and whole organismal aging. Remarkably, utilizing **heterochronic parabiosis**, we have determined that intestinal stem cell and tissue homeostasis are markedly impaired in young mice exposed to old blood, suggesting that intestinal aging is modulated by circulating factors in the old systemic milieu. We are currently pursuing studies to identify the systemic factor(s) responsible for driving features of intestinal decline with aging, including (i) aberrations in intestinal stem cells and niche cells, and (ii) intestinal barrier dysfunction, inflammation and stress.

4) Studies at the cancer-aging interface – A forth area of investigation is the role of aging on cancer risk. Aging is the major underlying risk factor for most cancers, yet tremendous gaps remain in our understanding of why cancer incidence markedly increases with age, in part because pre-clinical cancer studies are almost exclusively conducted in young models. Indeed, prevention strategies proven successful in young animals often prove less effective in older humans. Thus, we are evaluating the efficacy of various dietary and pharmacologic strategies to prevent stem-cell derived intestinal tumorigenesis and improve survival in a young versus aged mouse models. Evidence of diminished efficacy in old animals could profoundly influence how future cancer prevention studies are designed and interpreted.

Representative Publications

Huffman DM, Johnson MS, Watts A, Elgavish A, Eltoum IA, and Nagy TR. Cancer progression in the transgenic adenocarcinoma of mouse prostate mouse is related to energy balance, body mass, and body composition, but not food intake. *Cancer Res* 2007 67: 417-24. (Included in "Research Highlights" on issue cover)

Muzumdar RH, Allison DB, **Huffman DM**, Ma X, Atzmon G, Einstein F, Fishman S, McVei T, Keith SW, and Barzilai N. Visceral adipose tissue modulates mammalian longevity. *Aging Cell* 2008 7(3): 438-40.

Barzilai N, **Huffman DM**, Muzumdar RH, and Bartke A. *Perspectives in Diabetes:* The Critical Role of Metabolic Pathways in Aging. *Diabetes* 2012 61(6): 1315-22.

Huffman DM, Augenlicht LH, Zhang XY, Lofrese JJ, Atzmon G, Chamberland JP and Mantzoros CS. Abdominal obesity, independently from caloric intake, accounts for the development of intestinal tumors in *Apc1638N/+* female mice *Cancer Prev Res* 2013 Mar;6(3): 177-87. (featured press release by AACR)

Milman S, Atzmon G, **Huffman DM**, Wan J, Crandall JP, Cohen P and Barzilai N. Low Insulin-like Growth Factor-1 Level Predicts Survival in Humans with Exceptional Longevity. Aging Cell 2014 Aug;13(4):769-71.

Young-Hwan Jo, Ph.D., Assistant Professor
Forchheimer - 505B
(718) 430 -3495; young-hwan.jo@einstein.yu.edu

Obesity is a chronic metabolic disorder characterized by an excess of body fat. Obesity results from prolonged positive energy balance (i.e. energy intake exceeding energy expenditure). Because obesity may develop over many years in humans, only small imbalances in energy intake and expenditure are required. The cause of excessive positive energy balance in obesity has not been clearly defined. Nevertheless, key regulatory components reside in the hypothalamus, specifically in the arcuate nucleus (ARC).

The central melanocortin system within the ARC is made up of two distinct subsets of neurons that express either pro-opiomelanocortin (POMC) or agouti-related peptide (AgRP). These peptides regulate their downstream target sites via modulation of melanocortin receptor type 3 (MC3R) and melanocortin receptor type 4 (MC4R) activity. Although POMC neurons were long considered to be a single homogeneous entity, recent studies, including our own, support considerable heterogeneity among POMC neurons. In particular, there are at least two phenotypically distinct populations of POMC neurons in the ARC. We hypothesize that these phenotypic distinctions reflect important functional differences and that the interplay between the phenotypically distinct populations of POMC neurons is required for integration of peripheral and central signaling molecules, thus controlling the anorexigenic outcome of POMC neurons. Thus we are currently determining how novel interactions between distinct populations of POMC neurons contribute to the control of hypothalamic neurophysiology and the regulation of energy homeostasis. Our laboratory employs optogenetics, electrophysiology and transgenic animal models to explore the physiological functions of these novel interactions at the cellular and whole body levels. Understanding POMC-POMC neuronal interactions will help elucidate the elementary hypothalamic microcircuits controlling feeding and energy expenditure. Hence, this understanding will be crucial as we seek to determine the underlying cellular pathogenesis of the ongoing epidemic of obesity.

Representative publications:

Lee DK, Jeong JH, Oh SH and **Jo YH*** Apelin-13 enhances arcuate POMC neuron activity via inhibiting M-current. ***PLOS One***, Mar 17;10 (3):e0119457 **(2015)**

Lee, D.K., Jeong, J.H., Chun, S.-K., Chua, S.C. Jr. and **Jo, Y.H*** Interplay between glucose and leptin signaling determines the strength of GABAergic synapses at POMC neurons. ***Nature Commun.*** 26; 6:6618. doi: 10.1038/ncomms7618 **(2015)**

Jeong J.H., Lee DK, Blouet C, Ruiz H.H., Buettner C, Chua S.C., Schwartz G.J., and **Jo YH*** Cholinergic neurons in the dorsomedial hypothalamus regulate mouse brown adipose tissue metabolism. **Molecular Metabolism**, 4:483-492 **(2015)**

Jo, YH and Buettner, C., Why leptin keeps you warm. ***Molecular metabolism***, Oct 1; 3(8):779-80 **(2014)**

Groessl F, Jeong JH, Talmage DA, Role LW and **Jo YH* (2013)**, Overnight fasting regulates inhibitory tone to cholinergic neurons of the dorsomedial nucleus of the hypothalamus. ***PLOS One***, Vol. 8 (4), e60828

Jo, YH*, Endogenous BDNF regulates inhibitory synaptic transmission in the ventromedial nucleus of the hypothalamus. ***J. Neurophysiol***. Jan; 107: 42-49 **(2012)**

Hayley M. McDaid, Ph.D., Assistant Professor
Forcheimer 249B
(718) 430-8829; hayley.mcdaid@einstein.yu.edu

Our research is broadly concerned with investigating molecular mechanisms of action and resistance to standard and novel therapeutics; specifically focused on accurately defining the fate of cells within a tumor population following therapy, especially fates that confer drug-tolerance. Drug-tolerant tumor cells often manifest as dormant phenotypes that evade cell death and are a source for re-population of a primary tumor mass and development of metastatic disease that eventually culminates in mortality.

Senescence is a form of growth arrest that can result from anti-cancer therapy. Senescence is largely perceived to be a permanent state in 'normal' cells; however recent data now indicate that in the context of cancer, senescence is transient. Persistent senescent tumor cells within the tumor microenvironment are detrimental due to pro-inflammatory secretions that promote migration and disease progression. Moreover, senescent cells often revert to a proliferative state and retain this pro-inflammatory signaling milieu that drives chemoresistance. Certain anti-cancer drugs with reactive moieties can preferentially induce senescence not only in tumor cells, but also in organs such as the heart and lung, resulting in unacceptable toxicity that can be fatal. These often irreversible toxicities also prevent patients with progressive cancer from receiving subsequent therapy.

The study of dormant phenotypes in cancer biology is challenging; however to truly evolve anti-cancer therapeutics to improve long-term survival and quality of life for patients, we need to adopt a more rigorous pre-clinical evaluation program. One important aspect of this research is the design and selection of novel anti-cancer drugs that have potent tumor cell death-inducing capabilities in both asynchronous and dormant-type cells, including senescent and tumor-initiating cancer cells. Coupled with that, new therapeutics must be efficacious in limiting the development of senescence in non-tumor tissue to lessen the risk of therapy-induced toxicity.
Areas of current research focus include:

1. Therapy-mediated senescence in cancer as a cause of intrinsic and acquired resistance associated with residual disease, and/or progressive disease leading to metastasis.
2. Biomarker development to accurately detect senescent cells from solid or liquid biopsies both at diagnosis, and during the course of therapy.
3. Drug-discovery:
(i) In collaboration with Drs. Susan Horwitz and Amos B. Smith - design, synthesis and testing of novel chemotherapeutics, screening primarily for high tumor cell kill and low senescence induction, and
(ii) Testing existing and novel drugs for the ability to kill senescent tumor cells, or inhibit the inflammatory secretions of senescent cells.

Representative Publications:

Andreopoulou E, Schweber SJ, Sparano JA, McDaid HM. (2015). Therapies for triple negative breast cancer. Expert Opin Pharmacother. 2015 May;16(7):983-98.

Hou JY, Rodriguez-Gabin A, Samaweera L, Hazan R, Goldberg GL, Horwitz SB, McDaid HM. (2013). Exploiting MEK inhibitor-mediated activation of ERα for therapeutic intervention in ER-positive ovarian carcinoma.PLoS One. 2013;8(2):e54103. doi: 10.1371/journal.pone.0054103. Epub 2013 Feb 4.

Chao, S. K., et. al. (2012) Characterization of a human βV-tubulin antibody and expression of this isotype in normal and malignant human tissue, Cytoskeleton, 69: 566–576.

Chao, S.K., et. al. (2011) Resistance to discodermolide, a microtubule stabilizing agent and senescence inducer, is 4E-BP1 dependent. PNAS, 107, 391-396.

Thomas McDonald, M.D., Professor
Forchheimer - G-35
(718) 430-3370; tom.mcdonald@einstein.yu.edu

The research interests of our lab center on investigating the role of ion channel function in normal and disease processes. Ion channels are involved in cellular excitability and signal transduction processes in every type of cell. Mutations of channel genes that alter their function play a prominent role in a wide variety of genetic diseases. We use a multi-disciplinary approach to investigate the normal function of channels and mechanisms of disease-producing mutations.

Specific projects of the lab include:

1) Mutations in several cardiac ion channel subunits cause sudden death in the inherited disease Long QT Syndrome (LQT) and Sudden Infant Death Syndrome (SIDS). These channels also play important roles in the nervous system, intestine, kidneys and in cancer. We are using a combined approach of cellular electrophysiology, proteomics, protein biochemistry, and structural chemistry to understand how these channels are regulated by protein kinases, and through interactions with other cardiac proteins. Of particular interest is:
   a) How mutations alter channel function.
   b) Structural investigation of channel subunit interaction actions.
   c) Signal transduction pathways that control channel expression and activity.
   d) Epigentic and extra-coding RNA factors regulating channel expression and function.
2) All cells express evolutionarily conserved ion channels. Channels control permeability of membranes and are essential for normal cell function and viability. We are investigating ion channel candidate genes from human parasites (Malaria, Leshmania, Toxoplasma, Trypanasoma) for their roles as determinants of viability, infectivity and virulence. The long-term goal of this research is to identify essential functional proteins that may serve as pharmacological targets.

Representative Publications:

Osterbur M, Zheng R, Marion RW, Walsh CA & McDonald TV. An interdomain hERG mutation produces an intermediate Long QT phenotype. Human Mutation Aug;36(8):764-73 2015. PMID: 25914329

Wang D, Shah KR, Um SY, Eng LS, Zhou B, Lin Y, Mitchell AA, Nicaj L, Prinz M, McDonald TV, Sampson BA, Tang Y. Cardiac channelopathy testing in 274 ethnically diverse sudden unexplained deaths. Forensic Sci Int. 2014 Apr;237:90-9. PMID: 24631775

Sroubek J, Krishnan Y, **McDonald TV**. Sequence and structure-specific elements of HERG mRNA regulate channel synthesis and trafficking. FASEB J (Epub) 2013 April 22. PMID: 23608144

Krishnan Y, Li Y, Zheng R, Kanda V, **McDonald TV**. Mechanisms underlying the protein-kinase mediated regulation of the HERG potassium channel synthesis. Biochimica et Biophysica Acta - Molecular Cell Research 1823:1273-1284. 2012. PMID: 22613764

Sroubek J & **McDonald TV**. Protein Kinase A Activity at the Endoplasmic Reticulum Surface Is Responsible for Augmentation of Human ether-a-go-go-related Gene Product (HERG). ***J Biol Chem***. 286:21927-21936. 2011. PMID: 21536683.

Chen, J., Chen, K., Sroubek, J., Wu, Z.Y., Thomas, D., Bian, J.S. and **McDonald, T.V.** Post-transcriptional control of human ether-a-go-go-related gene potassium channel protein by alpha-adrenergic receptor stimulation. *Molecular Pharmacology*. 78:186-97. 2010. PMID: 20463060

Zheng R., Thompson, K., Obeng-Gyimah, E., Alessi, D., Chen, J., Cheng, H. and **McDonald, T.V.** Analysis of the interactions between the C-terminal cytoplasmic domains of KCNQ1 and KCNE1 channel subunits. *Biochem J* 428:75-84. 2010. PMID: 20196769

Waller, K., McBride, S.M.J., Kim, K. and **McDonald, T.V.** Differential Expression and Localization of Two Potassium Channels in *Plasmodium falciparum*. *Malaria Journal* 7:19. 2008. PMID: 18218136

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

Recently, we have identified a novel crosstalk between insulin receptor signaling and a member of the Src family of non-receptor tyrosine kinases, called Fyn. Fyn null mice are lean and display markedly enhanced insulin sensitivity, glucose tolerance and improved lipid profiles. This results from increased peripheral tissue (skeletal muscle and adipocyte) fatty acid oxidation due to activation of the AMP-dependent protein kinase. In contrast, over expression of Fyn selectively in skeletal muscle results in reduced AMP-dependent protein kinase activity and surprisingly, marked muscle atrophy. The degeneration of skeletal muscle fibers occurs through defects in both mTORC1 and macroautophagy signals. We are currently investigating the signaling cross talk between metabolism and muscle maintenance that has important implications for both aging induced insulin resistance and muscle wasting (sarcopenia)

A second major laboratory program is identification and characterization of adipose tissue inflammation, adipocyte cell death and fibrosis. We have found that following high fat diet, adipocytes secrete an important pro-fibrotic cytokine (IL-13) that induces the differentiation of local adipose tissue macrophages into a TGF-□1 secreting population. In turn, local TGF-□1 production induces the secretion of extracellular matrix proteins such as collagens create a fibrotic state. Current, studies are examining the expression profiles of this unique macrophage subpopulation and determining the cellular interactions by using tissue-specific knockout mice.

Representative Publications:

Yamada, E., Bastie, C.C., Koga, H., Wang, Y., Cuervo, A.M and **Pessin, J.E.** Mouse skeletal muscle fiber-type specific macroautophagy and muscle wasting is regulated by a Fyn/STAT3/Vps34 signaling pathway. Cell Reports, 1:557-569, 2012.

Zhao, X., Feng, D., Wang, Q., Abdulla, A., Xie, X-J., Zhou, J., Sun, Y., Yang, E.S., Liu, L-P., Vaitheesvaran, B., Bridges, L., Kurland, I.J., Strich, R., Ni, J-Q., Wang, C., Ericsson, J., **Pessin, J.E.**, Ji, J-Y., and Yang, F. Conserved regulation of lipid homeostasis by CDK8-mediated control of nuclear SREBP-1 stability. J. Clin. Invest., 122:2417-2427, 2012.

McKimpson, W.M., Weinberger, J., Czerski, L., Zheng, M., Crow, M.T., **Pessin, J.E.**, Chua, S.C. Jr., and Kitsis, R.N. ARC is a novel apoptosis repressor in islets that inhibits the ER stress response to promote β-cell survival. Diabetes, In press, 2012.

Kaushik, S., Arias, E., Kwon, H., Martinez-Lopez, H., Sahu, S., Schwartz, G.J., **Pessin, J.E.** and Singh, R. Loss of autophagy in hypothalamic POMC neurons impairs lipolysis. EMBO Reports, 13:258-265, 2012.

Feng, D., Tang, Y., Kwon, H.J, Zong, H., Hawkins, M., Kitsis, R.N. and **Pessin, J.E.** High Fat Diet Induced Adipocyte Cell Death Occurs Through a Cyclophilin D Intrinsic Signaling Pathway Independent of Adipose Tissue Inflammation. Diabetes, 60:2134-2143, 2011.

Charles S. Rubin, Ph.D., Professor and Co-Chair
Forchheimer –229
(718) 430-2505; charles.rubin@einstein.yu.edu

Protein kinase D (PKD) is a protein kinase C (PKC) substrate and effector in diacylglycerol (DAG)-regulated signaling cascades. PKDs are activated by Gq-coupled hormone receptors in cultured cells. However, little is known about physiological functions, upstream regulators and downstream effectors of PKDs in normal differentiated cells *in vivo*.

We are addressing central problems in DAG signaling by studying *C. elegans* PKDs named DKF-2A and DKF-2B, which are differentially expressed in intestinal cells and neurons. Strains of DKF-2 deficient (null) *C. elegans* and transgenic (TG) animals expressing wild type (WT) and mutant DKF-2A or 2B proteins (null background) were created. The hypotheses that (a) C1a and C1b domains are essential for DAG-binding, translocation and activation of DKF-2A/2B *in vivo* and (b) two P-serines (phosphorylated by PKCs) in the activation loop (A-loop) differentially regulate catalytic activity and degradation of PKDs are being tested. Studies employing fluorescence microscopy and IgGs that bind A-loop P-serines will elucidate relationships among DKF-2A/2B activation, translocation and stability in individual cells *in vivo*.

Phenotypes of DKF-2 deficient and TG *C. elegans* are characterized to discover physiological functions of PKDs. Microarray and qRT-PCR analyses indicate that DKF-2A controls expression of ~85 proteins that protect intestinal cells against pathogenic bacteria (inducible innate immunity). Neuronal DKF-2B mediates salt-induced chemotaxis and learning. Measurements of DKF-2 regulated mRNAs and proteins, salt-sensing and learning, and resistance to bacterial infection can quantify and allow visualization of DKF-2A/2B activity *in vivo*. These assays enable 4 lines of investigation. (1) *In vivo* activation assays, in combination with genetics, will determine which receptors, heterotrimeric G proteins, PLCs and PKCs are upstream regulators that control PKD activity in intestinal cells and specific neurons. (2) Abilities of DKF-2 isoforms to phosphorylate and regulate (a) a global transcriptional regulator, HDA-4 (a histone deacetylase) and (b) a member of a p38 MAP kinase cascade, NSY-1, will be tested *in vivo*. (3) Mechanisms by which DKF-2A/2B potently induces accumulation of a large constellation of immune effector proteins will be elucidated. (4) We discovered that signals transmitted by activation of neuronal DKF-2B and intestinal DKF-2A are integrated to generate crucial neurophysiological processes: learning and behavioral plasticity. The molecular basis for gut-nervous system interactions and cooperation in learning and behavior will be elucidated. Overall, studies on the *C. elegans* model will reveal molecules, mechanisms and pathways that couple external stimuli to PKD-controlled physiological processes in normal differentiated cells and guide examination of these unexplored areas in mammalian systems.

Representative Publications:

Fu, Y. and **Rubin, C.S**., "Protein Kinase D: Coupling Extracellular Stimuli to the Regulation of Cell Physiology", *EMBO Reports*, 12, 785-796 (2011).

Chen, L., Fu,Y., Ren,M., Xiao, B. and **Rubin, C.S.** "A RasGRP, *C. elegans* RGEF-1b, Couples External Stimuli to Behavior by Activating LET-60 (Ras) in Sensory Neurons", *Neuron* 70, 51-65 (2011).

Fu, Y., Ren, M., Feng, H., Chen, L., Altun, Z. F., and **Rubin, C.S. "**Neuronal and intestinal protein kinase D isoforms mediate Na^+ (Salt Taste)-induced learning", *Science Signaling* 2 (83), ra42. [DOI: 10.1126/scisignal.2000224] (2009).

Ren, M., Feng, H., Fu, Y., Land, M. and **Rubin, C.S.** "Protein Kinase D (PKD) Is an Essential Regulator of *C. elegans* Innate Immunity", *Immunity* 30, 521-532 (2009).

Feng, H., Ren, M., Chen, L. and **Rubin, C.S.** "Properties, Regulation and *In Vivo* Functions of a Novel Protein Kinase D: *C. elegans* DKF-2 Links Diacylglycerol Second Messenger to the Regulation of Stress Responses and Lifespan", *J. Biol. Chem.* 282, 31273-31288 (2007).

Rajat Singh, M.D., Associate Professor
Forchheimer - 505
(718) 430-4118; rajat.singh@einstein.yu.edu

Autophagy or "self-eating" is an in-bulk lysosomal degradative pathway that plays a crucial role in cellular homeostasis through protein and organelle turnover. Autophagy occurs at basal levels in all cells and is induced following conditions such as stress or nutrient-deprivation. Briefly, the process of autophagy requires the de novo formation of a double-walled limiting membrane that engulfs cellular cargo destined for degradation and then seals upon itself to form an autophagosome. The delivery of the engulfed cargo to the lysosome occurs by fusion of the autophagosome with the lysosome leading to degradation of the cargo. We have recently demonstrated a novel role of autophagy in the mobilization and degradation of intracellular lipid stores in the liver, thus pointing to a possible function of autophagy in energy homeostasis. We have also recently shown that this lipophagic role of autophagy functions in hypothalamic neurons to generate neuron-intrinsic free acids that, in turn, drive neuronal feeding mechanisms.

The primary focus of the lab is to examine the organ-specific roles of autophagy in the regulation of lipid metabolism and energy homeostasis using biochemical, immunochemical, radiochemical and image-based approaches in vitro and in conditional knockout mouse models. Our efforts are currently focused on the function of autophagy in discrete neurons of the hypothalamus and in the white and brown adipose tissues. We are interested in:

1. Elucidating the role of hypothalamic neuronal autophagy in the regulation of food intake and energy homeostasis.
2. Dissecting the upstream nutrient sensing signal cascades that regulate the induction or shut down of hypothalamic autophagy in response to circulating nutrients.
3. Examining the metabolic and regulatory functions of autophagy in white and brown adipose tissue biology.

Aging is considered to reduce autophagic activity. The second focus of the laboratory is to examine the effect of aging-induced reduction of hypothalamic and adipose autophagy on the development of the metabolic syndrome of aging.

Representative Publications:

Kaushik S, Arias E, Kwon H, Martinez Lopez N, Sahu S, Schwartz GJ, Pessin JE, **Singh R**. Loss of autophagy in hypothalamic POMC neurons impairs lipolysis. EMBO Reports. 2012 Jan 17. doi: 10.1038/embor.2011.260.

Singh R, Cuervo AM. Autophagy in the cellular energetic balance. Cell Metabolism. 2011; 13: 495-504.

Kaushik S, Rodriguez-Navarro JA, Arias E, Kiffin R, Sahu S, Schwartz GJ, Cuervo AM, **Singh R**. Autophagy in Hypothalamic AgRP Neurons Regulates Food Intake and Energy Balance. Cell Metabolism. 2011 August 3. doi:10.1016/j.cmet.2011.06.008

Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. Nature 458; 1131-5: 2009

Ji Ying Sze, Ph.D., Associate Professor
Golding –202
(718) 430-2084; jiying.sze@einstein.yu.edu

This research program investigates the genetic basis of the regulation of synaptic transmission of the neurotransmitter serotonin. Drugs that target the serotonergic system are the most commonly prescribed therapeutic agents for the treatment of a wide spectrum of behavioral and neurological disorders, from depression to eating disorders, autism, schizophrenia and Parkinson's disease. Using mouse and C. elegans as animal models, our laboratory is undertaking genetic dissection of the genes and biochemical pathways in serotonin signaling and characterizing therapeutics that can alter them.

One project is to identify serotonin deficient mutants in C. elegans. We have isolated a set of neuron-specific serotonin deficient (nss) mutants through unbiased genetic screens. The nss mutants offer us a unique opportunity to elucidate genetic pathways and biochemical mechanisms that regulate the development and function of specific serotonergic neurons.

A second project is to identify and characterize antidepressant-resistant genes. Using chemical mutagenesis and RNA-interference (RNAi) technology, ongoing experiments search genome-wide for mutations that confer resistance or hypersensitivity to selective serotonin reuptake inhibitors (SSRIs) in C. elegans. This screen will broadly explore SSRIs targets distinct from the known serotonin transporter and reveal downstream pathways regulated by serotonin signaling. We will translate genetic leads from C. elegans into functional analysis in mouse models.

Representative Publications:

Gholamali, J., Xie, Y., Kullyev, A., Liang, B., and **Sze, J.Y.** (2011) Regulation of extrasynaptic 5-HT by SERT function in 5-HT-absorbing neurons underscores adaptation behavior in C. elegans. J. Neurosci. 31, 8948-57.

Kullyev, A., Dempsey, C.M., Miller, S., Kuan, C.J., Hapiak, V.M., Komuniecki, R.W., Griffin, C.T., and **Sze, J.Y.** (2010) A Genetic Survey of Fluoxetine Action on Synaptic Transmission in Caenorhabditis elegans. Genetics 186(3):929-41.

Govorunova, E.G., Moussaif, M., Kullyev, A., Nguyen, K.C., McDonald, T.V., Hall, D.H., **Sze, J.Y.** (2010) A homolog of FHM2 is involved in modulation of excitatory neurotransmission by serotonin in C. elegans. PLoS One. 28;5(4):e10368.

Moussaif, M. and **Sze, J. Y.** (2009) Intraflagellar transport/Hedgehog-related signaling components couple sensory cilium morphology and serotonin biosynthesis in C. elegans. J. Neurosci. 29, 4065-75.