

THE NATIONAL CONSTITUTION CENTER

12TH NOVEMBER | 2019

11 A M - 6 : 3 0 P M



The Pharmacology Graduate Group at
the University of Pennsylvania
proudly presents its

35th Annual Student Symposium

KEYNOTE SPEAKER

LISA SHIPLEY, PHD

Vice President | Global Digital
Analytics & Technologies

MERCK & CO.

Smart Trials:
Moving from
Site-centric to
Patient-centric
Clinical Trials



SCHEDULE OF EVENTS – 2019 SYMPOSIUM

KIRBY LOBBY

11:00 AM Registration and boxed lunches

KIRBY AUDITORIUM

12:00 - 12:15 PM Opening Remarks - Chair of Pharmacology Graduate Group

12:15 - 1:45 PM Student Talks – Session 1

Nathan Kendersky (Maris Lab)

Investigating the Oncogenic Role and Regulation of DLL3 in Neuroblastoma

Theresa Patten (De Biasi Lab)

Investigating the role of flavorants in nicotine reward: a mouse model to study vaping

Joseph Johnson (Lynch Lab)

Frataxin deficiency induces Drp1-dependent mitochondrial fragmentation in cellular models of Friedreich ataxia

BOGLE CHAIRMAN'S ROOM

1:45 – 2:45 PM Student Poster Session

KIRBY AUDITORIUM

2:50 – 4:10 PM Student Talks – Session 2

Laura Puentes (Mach Lab)

Beyond the nucleus: the role of poly(ADP-ribose) in promoting α -synuclein aggregation and neurotoxicity

Edward Chuang (Shorter Lab)

Small molecule enhancers of the human Hsp70/Hsp40/Hsp110 disaggregase system

Jack Jacobs (Sehgal Lab)

*Anandamide metabolites protect against seizures through the TRP channel Water witch in *Drosophila melanogaster**

KIRBY LOBBY

4:15 - 4:30 PM Coffee Break

KIRBY AUDITORIUM

4:30 PM **The John S. O'Brien Memorial Lecture**

Lisa A. Shipley, Ph.D., Vice President, Digital and Analytics Technologies
Merck Research Laboratories

Smart Trials: Moving from Site-centric to Patient-centric Clinical Trials

DELEGATES CAFE

5:45 - 6:45 PM Cocktail Reception

John S. O'Brien Memorial Lecture



Lisa A. Shipley, Ph.D.

Vice President, Digital and Analytics Technologies

Merck Research Laboratories

Dr. Shipley is Vice President of Digital and Analytics Technologies in Merck Research Laboratories. She has the overall responsibility to design, operationalize, and direct Discovery, Preclinical and Early Development's (DPED) contribution to Merck's digital vision. In partnership with key technical lines, she is responsible for the leadership, operational and strategic management of initiatives focused on advancing knowledge, experience and capabilities in digital technologies, data management and analysis to transform the use of digital health approaches in all stages of drug discovery and clinical trial management, moving from a site-centric to patient centric model of drug development. Dr. Shipley joined Merck and Company in 2008 as the Vice President of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism before moving into her current role. Prior to joining Merck, Dr. Shipley spent over 20 years at Eli Lilly and Company in roles of increasing responsibility including the positions of executive

director, Lean Six Sigma and vice president Drug Disposition, PK/PD and Trial Simulations. Dr. Shipley obtained her undergraduate degree from McDaniel College and her doctoral degree in Pharmacology and Toxicology from the University of Maryland at Baltimore. Her postdoctoral training was conducted at the Walter Reed Army Institute of Research as a National Research Council Fellow elucidating the metabolism and pharmacokinetics of antileishmanial and antimalarial drugs under development by the U.S. Army.

Dr. Shipley has authored or co-authored three book chapters, over 25 journal articles, 40 abstracts on drug metabolism, pharmacokinetics, analytical assay development, drug disposition and digital clinical trials and has been granted five patents. She has chaired sessions at the Gordon Research Conference in Drug Metabolism, the Society of Toxicology, the American Association of Pharmaceutical Sciences, International Conference on Drug Development, PhRMA workshops and the Drug Information Association. She has served as the chair of the Drug Metabolism Technical Group within the Pharmaceutical Research and Manufacturing Association (2007-09), a member of the IQ Consortium and as a member of the International Society of the Study of Xenobiotics Council (2010-12). She has also served as a reviewer for Drug Metabolism and Disposition, Journal of Clinical Pharmacology, the Journal of Chromatography and Toxicology and Applied Pharmacology, and a lecturer for the University of Indiana School of Medicine and Purdue University. She was awarded the 2000-2001 Chairman's Ovation Award for leadership in motivating and developing people, the LRL President's Award for Diversity in 2007, the Chairman's Award in Environmental Health and Safety in 2013 and was awarded the NAFE Women of Excellence Healthcare Champion in 2017.

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Special thanks to the 3rd year students
for planning and organizing this year's
Pharmacology Student Symposium



Front Row (Left to right): Jerrick To, Monica Thapaliya, Lauren Shaw, Kryshawna Beard, Khadija Wilson, Nicole Robles-Matos, Kate Webb, Laura Romano

Back Row: Ziyang Xu, Shivesh Ghura, Michael Hart, Daniel Jacome, Dan Brown, Varun Bahl, Anne Fosnocht, John Maurer, Ross Pirnie

And many thanks to **Sarah Squire**
for coordinating the PGG symposium!

The Pharmacology Graduate Group's
35th Annual Student Symposium



Student Speakers

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Investigating the Oncogenic Role and Regulation of DLL3 in Neuroblastoma

Nathan Kendserky

Advisor: John Maris, MD

Neuroblastoma is a pediatric solid tumor that arises from deregulated development of the sympathetic nervous system. The 5-year survival of patients with high-risk neuroblastoma is only 50% and survivors have life-long morbidities from intensive chemotherapy. This underscores the need to identify biologically relevant and clinically actionable targets for children with high-risk disease. A subset of neuroblastoma tumors is driven by a core regulatory circuit (CRC) that includes seven transcription factors (TF) (ASCL1, MYCN, PHOX2B, HAND2, ISL1, GATA3, TBX2) driven by a strong enhancer element. Additionally, each TF regulates expression of itself and the other CRC TFs. Here, we present an integrated epigenomics and RNA-sequencing-based approach to identify neuroblastoma tumor cell-specific surface molecules regulated by the CRC: molecules we hypothesize are amenable to immunotherapy. With CRC ChIP-sequencing data, we used the bedtools and HOMER toolkits to identify genes bound by these TFs. We performed differential expression with limma voom comparing RNA-sequencing data from neuroblastoma patients (TARGET, N=162) and 25 normal tissues (GTEx, N=1641). Our analysis identified several candidate genes that are known immunotherapeutic targets in neuroblastoma (ALK, L1CAM, DLL3). Of those genes, we prioritized Delta-like canonical notch ligand 3 (DLL3), a differentially expressed, tumor-associated protein abundant on the surface of neuroblastoma cells. We observe a strong correlation (RNA-seq) between DLL3 and ASCL1 expression in cell lines ($R=0.803$, $p=4.62e-10$) and patient samples ($R=0.711$, $p=1.56e-24$). To understand downstream signaling associated with DLL3, we performed shRNA knockdown in cell lines with high DLL3 expression and observed a dramatic reduction in cellular viability and proliferation. These data suggest components of the CRC may regulate DLL3 and cause DLL3 overexpression in neuroblastoma. Our data also support previous studies that have detailed DLL3 as an inhibitory Notch ligand, which show Notch de-repression results in a significant loss of fitness. Together, our results support DLL3 as a candidate immunotherapeutic target in neuroblastoma, which warrants further investigation into its oncogenic function. Ultimately, targeting CRC-bound cell-surface proteins represents a novel way to exploit transcriptional dependencies in neuroblastoma and should abrogate classical mechanisms of immune escape, such as selection of subclones with low or absent target expression.

Investigating the role of flavorants in nicotine reward: a mouse model to study vaping

Theresa Patten

Advisor: Mariella De Biasi, Ph.D.

E-cigarettes (e-cigs) are popular across age groups, with approximately 9 million adults and 3.6 million school-aged students using these products. A hallmark feature of e-cigs is the availability of non-traditional flavorants (e.g. fruit, candy, alcohol). Flavored e-cigarettes are commonly used to initiate nicotine use in adolescence or to attempt nicotine cessation in adulthood. We developed a longitudinal animal model that mimics the life of a “vaper”, in which mice initiate nicotine use in adolescence and continue into adulthood. Using this model, we can study the effect of a fruit-flavorant on nicotine consumption and preference introduced either in adolescence or in adulthood. Male and female C57BL/6J mice were tested in a 2-bottle choice paradigm that involves three phases: (1) mice initiate nicotine use in adolescence with either unflavored nicotine or flavored-nicotine, (2) throughout young adulthood all mice receive unflavored nicotine in the 2-bottle choice test, (3) flavor is then either introduced for the first time or re-introduced into the nicotine bottle in adulthood. Adolescent mice preferred a fruit-flavored nicotine solution over an unflavored solution during adolescence. In addition, adolescent mice with access to flavored-nicotine consumed higher daily doses of nicotine than those with access to unflavored nicotine. Adult mice exposed to flavored-nicotine for the first time in adulthood maintained their baseline nicotine consumption despite the addition of flavorants to the nicotine bottle, while mice that were re-introduced to flavored-nicotine in adulthood significantly increased their nicotine consumption. Our data in adolescent mice recapitulate clinical data which have shown (1) a higher preference for and (2) increased consumption of flavored nicotine compared to unflavored or tobacco-flavored nicotine. In addition, our data suggest that for adolescents currently using a flavored tobacco product, avoiding previously nicotine-paired flavorants could be a key element to their success in future nicotine cessation attempts.

Frataxin deficiency induces Drp1-dependent mitochondrial fragmentation in cellular models of Friedreich ataxia

Joseph Johnson

Advisor: David Lynch, MD, Ph.D.

Friedreich ataxia (FRDA) is a neurodegenerative disease leading to ataxia, dysmetria, dysarthria, and cardiomyopathy, for which no treatment is available. The disease is caused by genetically-induced deficiency in frataxin, a mitochondrial matrix protein critical for iron-sulfur cluster biosynthesis and ATP production. However, the role of frataxin in mitochondrial dynamics in FRDA pathophysiology remains largely unknown. Here, we report that frataxin deficiency induces Drp1-dependent mitochondrial fragmentation in cellular models of Friedreich ataxia. FRDA patient fibroblasts exhibit excessively fragmented mitochondrial networks, a phenotype that is reversible by overexpression of wild type frataxin or a metabolically inactive frataxin point mutant. Indeed, siRNA knockdown of frataxin in healthy fibroblasts significantly increases the percentage of cells with fragmented mitochondrial networks and increases mitochondrial network fragmentation in each cell. Furthermore, frataxin knockdown significantly increases the localization of the mitochondrial fission protein phospho-Drp1 (Ser616) to sites of mitochondrial fragmentation, suggesting that frataxin knockdown may cause mitochondrial network fragmentation through a Drp1-dependent pathway. Selective Drp1 inhibition prevents frataxin-knockdown-induced mitochondrial fragmentation, although it does not reverse mitochondrial fragmentation in FRDA patient fibroblasts. Moreover, frataxin knockdown does not alter cellular ATP levels, but inhibiting Drp1 in frataxin knockdown fibroblasts decreases ATP levels, suggesting that frataxin-knockdown-induced mitochondrial network fragmentation is critical to maintain ATP levels. Our findings thus demonstrate that frataxin deficiency causes excessive mitochondrial fragmentation through a Drp1-dependent mechanism, and that fragmentation may represent a homeostatic mechanism that initially maintains normal ATP levels in frataxin deficient cells but chronically plays a less defined role in cell viability.

Beyond the nucleus: the role of poly(ADP-ribose) in promoting α -synuclein aggregation and neurotoxicity

Laura Puentes

Advisor: Robert Mach, Ph.D.

The exact cause of Parkinson's disease (PD) remains unknown; however, a recent finding by Kam et al. is shedding new light on poly(ADP-ribose) (PAR) as a key mediator of aberrant α -synuclein neurotoxicity in PD. PAR is a polymer that is primarily biosynthesized in the nucleus by Poly(ADP-ribose) Polymerase-1 (PARP-1). In the last decade, extensive research has been done exploring the role of PAR in modulating cellular functions outside of the nucleus. In this project, our focus lies on studying the interactions between PAR and pathologic α -synuclein. Specifically, we are interested in assessing the role of PAR in promoting α -synuclein aggregation, along with elucidating PAR-binding sites on fibrillar forms of α -synuclein — in order to better inform our development of PET imaging tracers for PD. To address these research questions, we employed a wide array of in vitro and ex vivo techniques which allowed us to identify the amino acid residues that are involved in PAR-binding and study the molecular effects that arise from this interaction. Our results suggest that increased intracellular levels of PAR promote the formation of oligomeric conformations of α -synuclein and that the interaction between PAR and fibrillar α -synuclein involves positively-charged amino acid residues on the N-terminal region of the protein. Together, these results unveil important information on the availability of sites on α -synuclein for targeting with either imaging or therapeutic modalities and hints at the potential of using PARP-1 inhibitors to decrease intracellular PAR levels and possibly reduce the formation of aberrant forms of α -synuclein in PD.

Small molecule enhancers of the human Hsp70/Hsp40/Hsp110 disaggregase system

Edward Chuang

Advisor: James Shorter, Ph.D.

Proteins perform a myriad of essential and non-essential functions within the cell; however, proteins must be properly folded in order to function. During cellular stress, proteins may become misfolded and aggregate through aberrant intermolecular interactions. The 70 and 40 kDa heat shock proteins (Hsp70 and Hsp40) form one of the predominant molecular chaperone systems within the cell that unfolds and refolds misfolded proteins. However, aggregated proteins contain stable intermolecular interactions that are more difficult to break. Hsp110, a member of the Hsp70 superfamily, collaborates with Hsp70 and Hsp40 to enable disassembly of protein aggregates and restoration of native protein function. Our lab has shown that the metazoan disaggregase system (MDS) comprising of Hsp70, Hsp40, and Hsp110 family members refolds disordered aggregates such as urea-denatured luciferase and heat-denatured GFP *in vitro*. The human genome contains 12 Hsp70 genes, over 50 Hsp40 genes, and 4 Hsp110 genes, giving rise to thousands of three-component combinations of the MDS. Select combinations more effectively disassemble α -synuclein amyloid than others, suggesting that different combinations of the MDS can have drastically different efficacy against the same substrate. This combinatorial phenomenon may be the key to understanding how a disaggregase system of under a hundred genes could chaperone a proteome of tens of thousands of proteins. We have purified a number of Hsp70, Hsp40, and Hsp110 proteins that are expressed in humans and systematically assessed the disaggregase activity of each combination against aggregated substrates. We have also identified a number of small-molecule modulators of disaggregation activity. These small-molecules are promising candidates for the treatment of neurodegenerative diseases. The results presented here further our understanding of the MDS and provide crucial therapeutic leads for a devastating class of diseases.

Anandamide metabolites protect against seizures through the TRP channel Water witch in *Drosophila melanogaster*

Jack Jacobs

Advisor: Amita Sehgal, Ph.D.

Endocannabinoids are protective against seizures, but their mechanism of action is still unclear as they can have effects independent of known cannabinoid receptors. Using *Drosophila melanogaster*, which lack cannabinoid receptor 1 and 2, we report here that the endocannabinoids anandamide and 2-arachidonoylglycerol protect against seizures in multiple fly seizure models. Surprisingly, we find that inhibition of anandamide catabolism renders flies insensitive to the anticonvulsant effect of anandamide, indicating that anandamide metabolites are responsible for the observed seizure protection. Consistent with this finding, arachidonic acid, a direct metabolite of anandamide, is protective against seizures. To identify downstream effectors, we tested for a role of TRP channels and find that the TRPV1 antagonist capsazepine blocks the protective effect of anandamide. Also, a targeted genetic screen of TRP channels identifies *water witch* as a mediator of the anti-seizure action of anandamide. Through the use of a *Drosophila* model, this study reveals the unappreciated role of arachidonic acid in seizure protection and identifies a cannabinoid receptor 1/2-independent mechanism of endocannabinoid seizure protection.

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Poster Abstracts

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P1

Glycolytic Flux as the Central Mediator of Glucagon Secretion

Varun Bahl

Advisor: Klaus Kaestner, Ph.D.

Maintaining glucose homeostasis is central to our health, and its failure results in debilitating diseases such as diabetes. Diabetes mellitus affects over 425 million people worldwide and is a leading cause of death in many countries. The pathophysiology of type 2 diabetes (T2D) is bihormonal, with both insufficient insulin production by beta-cells and elevated glucagon release by alpha-cells. While a great deal of effort has been devoted to understanding the molecular events controlling insulin secretion from beta-cells, the exact mechanisms governing glucagon release by alpha-cells are still not completely understood, though a role for glycolytic flux was recently demonstrated by alpha-cell specific gene ablation of glucokinase (Gck). This is a critical knowledge gap, as the normal suppression of glucagon secretion by elevated glucose levels fails in T2D patients, contributing to hyperglycemia through stimulation of hepatic glucose production. Using single cell RNAseq of islets from T2D organ donors, we have made the striking discovery that G6PC2, encoding the islet-specific glucose-6-phosphatase 2, is dramatically upregulated in alpha-cells in these patients. G6PC2 limits glycolytic flux by creating a futile cycle with GCK that likely hinders glucose-mediated suppression of glucagon secretion. We hypothesize that reduced glycolytic flux is a central driver of alpha-cell dysfunction in T2D. We will address this overarching hypothesis through innovative mouse models developed in the Kaestner Lab, as well as loss- and gain-of-function ex vivo studies in mouse and human pancreatic islets.

P2

Exploring the role of the gut microbiome in COX-2 selective and nonselective NSAID-induced gastroenteropathy

Kayla Barekat

Advisor: Garret FitzGerald, M.D., FRS

Nonsteroidal anti-inflammatory drugs (NSAIDs), used to treat pain and inflammation, have been associated with cardiovascular (CV) and gastrointestinal (GI) adverse events, including myocardial infarction, stroke, intestinal bleeding, ulceration, and stenosis. Traditional NSAIDs, like naproxen and indomethacin, exert their effects by inhibiting both cyclooxygenases (COX) -1 and -2 and have long been recognized to cause GI complications in up to 30% of patients. This toxicity was attributed to inhibition of COX-1-dependent synthesis of prostaglandin (PG) E₂ and prostacyclin (PGI₂) in gastroduodenal epithelial cells, which are involved in protection of the GI mucosal barrier. Thus, the COX-2 selective NSAIDs, including celecoxib, were developed in an attempt to avoid the GI complications; however, COX-2 selective NSAIDs are also associated with GI toxicity. Moreover, inhibition or genetic deletion of COX-1 alone does not result in spontaneous GI lesions, and concomitant inactivation of COX-2 is necessary to cause GI damage in mouse models. Thus, further research is necessary to elucidate the mechanisms underlying NSAID-induced gastroenteropathy. Our previous studies have shown that there is a bidirectional interaction between NSAID treatment and the gut microbiome. Gut bacteria with β -glucuronidase activity enable enterohepatic recirculation of NSAIDs, thus prolonging systemic exposure of the parent drug and augmenting its pharmacodynamic effect. Furthermore, removal of bacteria by antibiotic treatment results in faster drug clearance and reduces the GI toxicity associated with indomethacin. Taken together, there is still a missing link between differential inhibition of the COX enzymes and subsequent impact on the gut microbiome in eliciting gastroenteropathy, and variation in gut bacterial composition may help explain the wide range in NSAID tolerance across individuals. Novel genetic and pharmacological approaches are being applied **to address the hypothesis that a differential impact on the gut microbiome contributes to a divergent incidence of gastroenteropathy following suppression of COX-1+COX-2 vs COX-2 alone**. This translational project paves the way for clinical trials examining the impact of concomitant antibiotics on NSAID efficacy and toxicity in patients.

P3

Brain-derived Exosomes as Diagnostic Biomarkers of Traumatic Brain Injury

Kryshawna Beard

Advisors: David Meaney, Ph.D. and David Issadore, Ph.D.

Traumatic brain injury (TBI) is characterized by diverse primary mechanisms of injury (closed vs open head injury, deceleration injuries, focal, and diffuse injuries) that lead to the development of secondary pathological cascades that drive neurological deficit post-TBI. These secondary injury processes include inflammation, gliosis, axonal shearing, edema, and vascular injury, and each plays distinct, patient-dependent roles in TBI pathology. Inability to separate patients based on the presence of these different endophenotypes represents a major challenge for diagnosis and treatment of TBI. The goal of the present study was to identify blood-based biomarkers that relate to the post-concussive state to improve clinical diagnosis and management of TBI. Extracellular vesicles including exosomes isolated from patient plasma have emerged as promising potential biomarkers for TBI due to their ability to cross the BBB into systemic circulation with molecular cargo (proteins, RNA, and metabolites) intact for analysis. The Issadore lab has developed a novel microfluidic platform for rapid isolation of brain-derived (GluR2-expressing) exosomes providing a tool with which the biochemical state of neurons and glia can be directly assessed post-TBI. We used the ultra-sensitive, single molecule array (SIMOA) assays to quantify concentrations of the 7 protein biomarkers, 4 brain-specific markers (Tau, UCHL-1, NFL, and GFAP) and 3 cytokines (IL6, IL10, TNF) in the plasma and brain-derived exosomes of mild TBI (mTBI) patients (N=30) and controls (N=23). We report that concentrations of plasma and exosome GFAP, NFL, Tau, and UCHL1 were elevated in mTBI patients compared to controls ($p=0.019$ and $p=0.0280$ respectively). Discrimination of mTBI patients from controls was most accurate, specific, and sensitive when machine learning algorithms on the panel of biomarkers were used compared to logistic regression models of single biomarkers. Specifically, highest accuracy and specificity was observed when exosome Tau and whole plasma GFAP levels were combined (AUC =0.93, accuracy = 0.88). This data suggests that neuron-derived exosomes contain information that characterizes the injured and recovering brain. It also suggests that analysis of a panel of biomarkers from a combination of both blood and exosomal compartments could lead to more accurate diagnosis of mTBIs.

P4

LOXHD1 as an Ewing Sarcoma Tumor Associated Antigen

Tatiana Blanchard

Advisor: Beatriz Carreno, Ph.D. and Carl June, M.D.

Ewing Sarcoma (ES) is the second most common malignant bone tumor predominantly affecting children and young adults. Standard of care high-dose chemotherapy yields a poor prognosis for patients with high-risk recurrent disease with a 5-year overall survival of < 10%. Recent successes in the field of cellular immunotherapy for the treatment of hematological malignancies have reinvigorated efforts investigating the use of adoptive cell therapies (ACT) for solid tumors including sarcomas. ACT strategies utilizing T cells redirected against tumor-associated antigens (TAA) such as NY-ESO-1 have yielded promising results for the treatment of synovial sarcoma, however highly specific targets for ES remain to be identified. The identification of appropriate antigenic targets poses a key challenge to effective immunotherapeutic strategies. The target antigen should be highly expressed in tumor cells with minimal expression in normal tissue. At the molecular level, ES is driven by t(11:22)(q24;q12) translocations resulting in EWSR1-FLI1 fusion in 85 % of ES cases. We have identified EWSR1-FLI1 fusion to result in aberrant expression of cancer testes antigen Lipoxxygenase Homology Domains 1 (LOXHD1) which has been determined to be required for ES cell growth and tumorigenesis. We hypothesize that LOXHD1 is a TAA targetable by T cell-based immunotherapies for the treatment of ES, relying on the rationale that LOXHD1 specific epitopes are processed and presented, immunogenic, and can elicit cytotoxicity from LOXHD1 specific CD8+ T cells. Using netMHC4.0 in silico epitope prediction, we identified 17 LOXHD1 epitopes with predicted strong binding affinity (<100 nM) to HLA-A*02:01. The immunogenicity of LOXHD1 epitopes was confirmed by the generation of LOXHD1-specific CD8+ T cell responses from healthy donors following in vitro stimulation and expansion of autologous CD8+ T cells using peptide-pulsed matured monocyte-derived dendritic cells and artificial antigen presenting cells. Using this methodology, we identified a total of 6 peptides (35%) to be immunogenic as determined by IFN- γ secretion. Ongoing studies include (1) utilization of a novel proteomic strategy using human ES cell lines engineered to express specific HLA alleles to further validate processed and presented epitopes and (2) isolation of TCRs to redirect T cells to LOXHD1. Isolated TCRs will be evaluated for LOXHD1 antigen-specificity as well as T cell mediated cytotoxicity ES tumor cells. This study will serve as a platform to identify and characterize LOXHD1-specific CD8+ TCRs which may have implications for ES patients in need of novel treatment strategies.

P5

Nanoparticle-Mediated CRISPR/Cas Delivery for Targeting Driver Oncogenes

Dan Brown

Advisor: Saar Gill, MD, Ph.D.

Chronic myeloid leukemia (CML) is a hematological malignancy driven by the BCR-ABL fusion oncogene. BCR-ABL, formed via a chromosomal translocation t(9;22), yields a constitutively active tyrosine kinase that promotes unregulated myeloid cell proliferation. The current standard of care for CML involves administering tyrosine kinase inhibitors (TKIs) such as Imatinib (Gleevec). However, TKI therapy is not curative and prolonged administration may select for point mutations within the kinase active site that confer TKI resistance, necessitating the development of novel therapeutics that provide complete and persistent eradication of this disease. A potential approach toward this goal involves genomic modulation via a BCR-ABL-targeted CRISPR/Cas9 system. This system will consist of spCas9 mRNA and BCR-ABL breakpoint-specific single guide RNA (sgRNA), which will introduce single base pair insertions and deletions (indels) selectively within the fusion oncogene while sparing endogenous BCR and ABL genes. spCas9 mRNA and the sgRNA will be encapsulated in novel lipid nanoparticles (provided through a collaboration with Dr. Michael Mitchell at the Penn School of Bioengineering) to facilitate delivery and reduce degradation of the nucleic acids in vitro and vivo. Additional approaches involve targeting other components of the BCR and ABL genes, such as the N-terminal oligomerization domain in BCR and the kinase domain of ABL.

P6

Mechanical strain activates microglia through the P2X7 receptor in a model of glaucoma

Keith Campagno

Advisor: Claire Mitchell, Ph.D.

The interaction between mechanical strain, activation of innate immunity, purinergic receptor signaling, and neuronal loss may provide a mechanism by which elevated intraocular pressure (IOP) may lead to retinal ganglion cell (RGC) loss. We found that RGC distribution was similar in the central and middle areas of the retina, but sparser in the periphery. Elevated IOP correlated with microglia morphology emblematic of activation and an increase of gene expression of TNF α , iNOS, ARG1, YM1, and decrease of TMEM119. Increased ATP concentration in the vitreous humor after IOP elevation, and decreased morphological changes in retinas from P2X7^{-/-} implicate purinergic signaling as a contributing factor. The addition of P2X7R agonist BzATP to ex vivo retinal wholemounts from Cx3CR1-GFP^{+/+} resulted in increased fluorescence, consistent with responses from resident microglial cells. Isolated microglia express P2X7R and respond to BzATP with Ca²⁺ spikes and rapid process retraction that are abolished with P2X7R inhibitor A 839977. ATP and the P2X7R agonist BzATP increased the expression of some of the same activation genes as observed in vivo with elevated IOP. Finally, RGC loss was correlated with microglia morphological alteration in C57 but not P2X7^{-/-} retinas. In summary, this study links mechanical strain and the P2X7 receptor to microglia activation and inflammation, and implicates purinergic signaling in microglia with neuronal loss.

P7

Nr4a1 activation suppresses cocaine-induced behavior via epigenetic regulation of homeostatic target genes.

Marco Carpenter

Advisor: Elizabeth Heller, Ph.D.

Endogenous homeostatic mechanisms can restore normal neuronal function following cocaine-induced neurotoxicity. Such mechanisms may be exploited in developing novel therapies for cocaine addiction, but a molecular target has not yet been identified. Here we profiled mouse gene expression during early and late cocaine abstinence to identify putative regulators of neural homeostasis. Cocaine regulated expression of the transcription factor, Nr4a1, and its target gene, Cartpt, a key molecule in mitigating dopamine metabolism. Given that chromatin modifications confer long-lasting changes in gene expression necessary for stable cellular and behavioral phenotypes, histone modifications acquired during abstinence may cause individual genes to “remember” prior drug exposure. We found that the sustained activation of Cartpt at late abstinence was coupled with depletion of the repressive histone modification, H3K27me3, and enrichment of activating marks, H3K27ac and H3K4me3. Using CRISPR-mediated Nr4a1 activation, we demonstrate the direct causal role of Nr4a1 in this epigenetic mechanism of sustained gene expression and in repression of cocaine-evoked behavior. Further we show the preclinical efficacy of Csn-B, a small-molecule agonist of Nr4a1, in activating Nr4a1 expression in NAc, attenuating cocaine behavioral responses, and enhancing homeostatic gene transcription. Our findings provide evidence that targeting endogenous changes in homeostatic gene expression across abstinence is a potential strategy to combat cocaine addiction. Herein, we establish Nr4a1 as a key regulator of persistent gene transcription during cocaine abstinence and as a promising therapeutic target for reversing cocaine-mediated behaviors.

P8

Disruption of H19/Igf2 imprinting causes lethality in a mouse model with a humanized H19 paternal allele

Suhee Chang

Advisor: Marisa Bartolomei, Ph.D.

In mammals, a small number of genes are expressed in a parent-of-origin-specific manner. Aberrant expression of these genes is associated with human imprinting disorders such as Beckwith-Wiedemann syndrome (BWS) and Silver-Russell syndrome (SRS). Cis-regulatory elements, called imprinting control regions (ICRs), mediate this allele-specific gene regulation. The *H19/Insulin-like growth factor 2 (Igf2)* ICR [**IC1**] interacts with the zinc-finger protein CTCF. CTCF binds to unmethylated maternal IC1 and acts as an insulator to block shared enhancers from interacting with the *Igf2* promoter, allowing the enhancers to interact with the *H19* promoter. Paternal IC1 is DNA methylated, preventing binding of CTCF and letting the enhancers interact with the *Igf2* promoter. In human, various mutations of IC1 have been reported to be associated with BWS and SRS cases.

Although the mechanism of *H19/Igf2* imprinting is conserved in mouse and human, mouse IC1 (mIC1) differs from human IC1 (hIC1) in several aspects. This complicates studying human genetic mutations of IC1 using mouse models. To better model human BWS/SRS mutations in mouse, we have generated a mouse model with hIC1 replacing the endogenous mIC1 [**H19hIC1**]. The paternal transmission of hIC1 resulted in loss of DNA methylation which led to increased *H19* expression and ablated *Igf2* expression, and perinatal lethality and decreased embryonic weights. To examine if increased *H19* expression is responsible for this lethality, we have generated *H19* null mice [**H19 Δ H19**]. Lethality and decreased weight were not rescued in H19 Δ H19/hIC1 mice. Although the previously increased *H19* expression was mostly reduced, the *Igf2* expression remained very low in H19 Δ H19/hIC1 embryos. To test if low *Igf2* expression is causing the lethality, we used another mouse model with IC1 deletion [**H19 Δ 3.8**]. Surprisingly, H19 Δ 3.8/hIC1 neonates were rescued from lethality and decreased weight. *Igf2* and *H19* expression was comparable between H19 Δ 3.8/hIC1 neonates and their wild-type littermates depending on tissues.

P9

Function of Skd3, a mitochondrial AAA+ protein

Ryan Cupo

Advisor: James Shorter, Ph.D.

Skd3 is a HCLR-clade mitochondrial AAA+ protein, consisting of an N-terminal mitochondrial targeting signal, a short unstructured domain of unknown function, four ankyrin repeats, and a nucleotide-binding domain. Mutations in Skd3 result in a subtype of the severe mitochondrial disorder, 3-methylglutaconic aciduria (3MGA). 3MGA mutations in Skd3 cluster in the nucleotide binding domain. Little is known about Skd3, its function, or the effect of 3MGA mutations on its activity. Using cell biology, yeast genetics, and biochemistry we have explored the function of Skd3.

P10

Charting Hydroxymethylcytosine at Single-Base and Single-Cell Resolution

Emily Fabyanic

Advisor: Hao Wu, Ph.D.

DNA cytosine methylation has a profound impact on genome stability, transcription, and development. The recent discovery that ten-eleven translocation (TET) enzymes iteratively oxidize methylcytosine (mC) has triggered a paradigm shift in our understanding of how changes in DNA methylation are coupled to normal mammalian development and human disease.¹ Hydroxymethylcytosine (hmC), otherwise referred to as “the sixth base,” is the most prevalent oxidized form of methylcytosine (ox-mC). Genetic and functional studies indicate that TET enzymes and ox-mCs may play important roles in cellular differentiation, organismal development, and carcinogenesis.² The potential function of hmC in mature mammalian neurons is of particular interest as it accumulates during peak synaptogenesis and critical periods of synaptic pruning in maturing, early postnatal neurons and in adult neurons can comprise as much as 40% of modified cytosine bases.³ As the function of single neurons depends on their unique context (e.g. position, circuitry, state), it is important to study underlying epigenetic regulatory systems at the single-cell level in order to successfully probe the implications of this epigenetic modification, *in vivo*.⁴ Here, I report the development of a novel hmC-mapping method for application to single cells to study heterogeneous tissues, like the brain. Our technique has the potential to allow for the study of epigenetic heterogeneity among neuronal subtypes and will also be a powerful tool enabling systematic analysis of hmC at non-coding, gene regulatory regions in the brain in a subtype-specific manner, without requiring cellular sorting.

P11

Characterizing the protein tyrosine phosphatase SHP2 as an oncoprotein and therapeutic target in neuroblastoma

Mark Gerelus

Advisor: Yael Mossé, M.D.

Significant advances have been made over the past several years in understanding the genetic landscape and heterogeneity of neuroblastoma (NB), an extra-cranial solid tumor of neural crest origin. Our lab's discovery that heritable and somatic activating mutations in the receptor tyrosine kinase (RTK)-encoding anaplastic lymphoma kinase (ALK) oncogene in NB has positioned ALK as the major tractable oncogene product for targeted therapy in NB. An ongoing clinical trial being conducted by our lab with the next generation ALK inhibitor lorlatinib reveals potent anti-tumor activity followed by eventual resistance to the compound and rebound of tumor growth for which there is no other option for treatment. This reveals a crucial need to determine combination treatments targeting downstream of ALK to combat relapse. A potential downstream effector, the Src homology region 2-containing protein tyrosine phosphatase (SHP2), has been implicated in RTK-driven cancers. Recently, a novel allosteric small molecule inhibitor targeting SHP2, called SHP099, has been developed and studied in the context of RTK-driven cancers. While SHP2 inhibition alone is not sufficient to result in durable anti-tumor activity, studies have shown that combining an RTK-targeting inhibitor with SHP099 can resensitize RTK inhibitor-resistant cancer models. Therefore, I hypothesize that combining SHP099 with lorlatinib will resensitize ALK inhibitor-resistant NB models to small molecule inhibition. Studies testing this hypothesis will provide evidence for which patient populations would benefit from this combination for future clinical trial design and translation to the clinic. In addition to defining the therapeutic effect of inhibiting SHP2 activity via SHP099, preliminary studies suggest that there are differences in protein-protein interactions with SHP2 and nuclear localization of proteins when comparing SHP099-treated cells to cells depleted of SHP2 via shRNA. Most of the published studies investigating SHP2 thus far focus on the phosphatase activity of SHP2. However, my preliminary data suggest that SHP2 may contribute to NB independent of its phosphatase activity. Therefore, I hypothesize that there is a phosphatase-independent oncogenic role of SHP2 in ALK-driven high-risk NB. Studies testing this hypothesis will shed light on this overlooked potential role of SHP2 and allow for more rational drug development targeting SHP2 to result in a clinically impactful treatment option.

P12

Interactions between HIV, cigarette smoking and antiretrovirals in an in vitro model of HIV-induced neurotoxicity

Shivesh Ghura

Advisor: Kelly Jordan-Sciutto, PhD

Even though the mortality of HIV has decreased due to antiretrovirals (ARVs), HIV-associated neurocognitive disorders (HAND) remain prevalent, affecting 50% of HIV+ patients. HAND is a spectrum of cognitive, memory, and motor dysfunction that can present with mood and addictive disorders. Specifically, 50-70% of HIV patients abuse nicotine, emphasizing the importance of studying the effects of nicotine on antiretroviral-mediated suppression of HIV-replication and its associated toxicity. Previously, in vitro experiments indicate that HIV-replication in macrophages and microglia can be altered in the presence of nicotine or cigarette smoke extract. However, these studies were not conducted in the presence of antiretroviral treatments, which have been shown to cause direct toxicity to neurons. Importantly, indirect toxicity of antiretrovirals on neurons via their effect on macrophages remains unknown. We hypothesize that nicotine and certain ARVs interact to alter HIV replication in macrophages and subsequent cytokine and/or neurotoxin release. Specifically, nicotine increases HIV replication rate and neurotoxicity associated with antiretrovirals while decreasing the efficacy of antiretrovirals. Mock and HIV-infected monocyte-derived macrophages (HIV-MDM) were treated with nicotine and/or lopinavir. Supernatants were sampled to track HIV-replication and HIV-MDM-induced neurotoxicity. Understanding the interaction of nicotine and ARVs will aid in development of therapeutics that alleviate neurotoxicity and reduce the rate of substance abuse in people living with HIV.

Platinum drug-mediated secretion of the danger-associated molecular pattern (DAMP) high mobility group-1 (HMGB1)

Kevin Gillespie

Advisor: Ian Blair, Ph.D.

High mobility group-1 (HMGB1) is a chromatin-associated protein that also acts as a critical mediator of inflammation, thrombosis, and the innate immune response. Although post-translational modifications (PTMs) to HMGB1 have been studied in multiple models and cell types, there is no identified consistent pattern of HMGB1 PTMs that regulate HMGB1 transport between the nucleus and cytosol as well as release to the extracellular space. We have discovered that upon treatment with platinum drugs, there is a dose-dependent release of HMGB1 from HepG2 human hepatocellular carcinoma cells and A549 human adenocarcinoma lung cancer cells, with cisplatin as the most potent. We have also observed indications of differences in HMGB1 among nuclear, cytosol, and media fractions. Expanding our ultrahigh performance-liquid chromatography-high resolution mass spectrometry (UHPLC-HRMS) methodology, we have sufficiently increased our coverage to characterize PTMs throughout the entire HMGB1 protein in these fractions. Platinum chemotherapeutic agents are often used in combination with other cancer treatments like immunotherapy, especially in non-small cell lung cancer (NSCLC), and multiple studies suggest these drugs may have immune-potentiating effects. We hypothesize that platinum drug damage to nuclear DNA induces structural changes to HMGB1 that mediate its translocation and secretion.

P14

Development of pH sensitive probes for in vivo Cerenkov imaging

Andrea Guzman

Advisor: Jim Delikatny, Ph.D.

Increased acidity in the tumor microenvironment (TME) plays a role in the invasion and metastasis of cancer cells and contributes to chemotherapeutic resistance. This metabolic hallmark has sparked interest in the exploration of extracellular tumor pH measurement and imaging in vivo. The decrease in tumor microenvironment pH is due to a deregulated metabolism predominantly arising from increased glycolytic flux in cancer cells. Cerenkov radiation emitted by β -particles is a potential tool for pH imaging in vivo. pH-sensitive fluorophores can selectively attenuate Cerenkov radiation's continuous and multispectral emission through selective bandwidth quenching (SBQ) and produce Cerenkov Radiation Energy Transfer (CRET). SBQ and CRET provides a quantitative readout that can be correlated with a pH value, resulting in a non-invasive technique for pH imaging in vivo. We hypothesize that selective absorption of the Cerenkov multispectral emission by pH sensitive fluorophores will provide accurate pH measurements of the TME through Cerenkov imaging. In the current project, 5,6-carboxynaphthofluorescein succinimidyl ester was conjugated to 4-aminobutyl DOTA in a 1:1 molar ratio to produce a pH-sensitive probe suitable for chelation with ^{68}Ga . The Cerenkov emission of ^{68}Ga is 10-fold greater than ^{18}F , the radioemitter previously studied in our lab, thus creating a pH sensor with increased signal to noise. The conjugated product (NFbD) was successfully chelated with $^{69,71}\text{Ga}$ and ^{68}Ga and the complex (NFbD-Ga) maintained its pH indicator capability after chelation ($\text{pK}_a = 7.7$, $\lambda_{\text{ex}} = 600 \text{ nm}$, $\lambda_{\text{em}} = 669 \text{ nm}$ at pH 9). Cerenkov imaging of NFbD-Ga showed marked pH-dependent differences in attenuation, measured at 600 nm and standardized to 840 nm. Cerenkov radiation energy transfer (CRET) was observed at 680 nm. Cerenkov imaging with NFbD-Ga is sensitive and can detect pH changes as low as 0.2 pH units. To assess whether Cerenkov radiation could be observed in tumors, the radiolabeled complex was injected into athymic nude mice bearing MDA-MB-231 and 4175-Luc+ breast cancer tumors. Average radiance readout corresponding to Cerenkov imaging showed detectable CRET signals for each tumor, which is favorable for in vivo imaging due to decreased tissue scattering and absorption. Reasonable pH values have been obtained by interpolation, fitting average radiance signal of tumors to a Cerenkov pH titration curve. The development and characterization of this novel probe for Cerenkov imaging of the tumor microenvironment pH expands the realm of optical imaging and validates the potential of Cerenkov radiation for critical biomedical applications.

P15

Characterization of DDAO-arachidonate for imaging cytosolic phospholipase A2 activity in non-small cell lung carcinomas

Michael C. Hart

Advisor: Jim Delikatny, Ph.D.

Lung cancer is the leading cause of cancer related death. Non-small cell lung carcinoma (NSCLC) is the most commonly diagnosed lung cancer in the United States with a five-year survival rate of approximately twenty percent. The primary treatment for NSCLC is tumor resection with adjuvant chemotherapy. Surgery to remove lesions currently relies on preoperative imaging and intraoperative tissue palpation. In order to improve complete tumor resections, our lab has designed a caged fluorophore, DDAO-arachidonate (DDAO-AA), that is activated by cytosolic phospholipase A2 (cPLA2). cPLA2 has been reported to be upregulated in a variety of cancer types including NSCLC. When cPLA2 is present, DDAO-AA is activated by the cleavage of arachidonic acid resulting in free DDAO which can be excited at 600 nm and fluorescence measured at 660 nm. This project focuses on the preclinical validation of DDAO-AA for intraoperative imaging of tumor margins. Testing of different liposomal formulations showed the optimal formulation used egg phosphatidylcholine resulting in a consistent size of 106 nm and PDI of approximately 0.1 with a zeta potential of 16.2 mV. In an assay using 0-100 units of isolated secretory phospholipase A2 (sPLA2), DDAO-AA showed a significant increase in activation with the concentration of enzyme. In KLN 205-Luc+ cells treated with DDAO-AA, the probe showed a minor increase in activation compared to when no cells were present. Finally, ex vivo studies incubating DDAO-AA with human lung tumor or normal human lung tissue showed significantly higher fluorescence of the tumor tissue. These data suggest that DDAO-AA could be a promising agent for measuring cPLA2 activity for imaging lung tumor margins.

P16

A cell non-autonomous mechanism of versican proteolysis contributes to cerebral cavernous malformations

Courtney Hong

Advisor: Mark Kahn, M.D.

Cerebral cavernous malformations (CCMs) are thin-walled, dilated vascular abnormalities that occur predominantly in the CNS and are a major cause of hemorrhagic strokes and seizures. Currently, there are no medical therapies for this progressive disease other than invasive neurosurgery. CCMs are caused by genetic mutations that result in the loss of a heterotrimeric adaptor complex required to negatively regulate MEKK3 signaling and the expression of the KLF2 and KLF4 transcription factors in brain endothelial cells (BECs). Recently, we have identified endothelial Toll-like receptor 4 (TLR4) and the gut microbiome as critical upstream stimulators of MEKK3 signaling. However, the downstream effectors relevant to disease pathogenesis remain unknown. The aim of this study is to evaluate the role of ADAMTS proteases and their substrate, the extracellular matrix proteoglycan versican, as candidate downstream targets of this causal MEKK3 pathway. Using a neonatal model of CCM disease and a combinatorial rescue approach, we have demonstrated that endothelial deletion of ADAMTS5 can significantly reduce lesion volume, while overexpression of ADAMTS5 is sufficient to recapitulate key morphological and molecular features associated with early CCMs. Rather than exacerbating the phenotype, we also found that genetic reduction of versican prevents CCMs, suggesting that cleavage of versican and not the loss of the protein is critical for lesion formation. Taken together, these studies identify a requirement for ADAMTS5 and versican proteolysis and further define the molecular mechanism through which MEKK3-KLF2/4 signaling drives CCM disease.

P17

Small Molecule Sensing of Cell-Cell Interactions

Daniel Jacome

Advisor: Mark Sellmyer, M.D., Ph.D.

Cell-cell interactions are integral to the proper function of multi-cellular organisms. In vivo monitoring of cell-cell interactions has been challenging, especially deep within an animal. Current approaches have significant limitations. For example, intravital microscopy requires a predetermined area for imaging, lacks a signal capable penetrating through tissues for detection of deep interactions, and insertion of the window/microscope can perturb the local biology. The need for improved imaging technologies has been highlighted as cell-based therapies have entered the clinic and have demonstrated great efficacy against hematologic cancers. Despite this success, targeting of solid tumors has not yielded the same results and many questions regarding T cell-solid tumor engagement, the tumor microenvironment, and T-cell persistence have arisen. Thus, it is increasingly important to study these phenomena in situ and with quantitative measures. We report the development a cell proximity sensing system with the following orthogonal components: (1) a sterically “caged” trimethoprim (TMP) with significantly reduced binding affinity to its protein target, bacterial dihydrofolate reductase (DHFR); (2) an bacterial “uncaging” enzyme (*nfsA*), nitroreductase (NTR), that liberates TMP; (3) a destabilized bacterial DHFR (dd-DHFR) that is degraded without the TMP ligand; (4) and an optical reporter fused to the destabilized protein. Dose response studies show a 20-fold shift in EC50 of TMP versus caged TMP with signal induction being rescued upon culture with nitroreductase expressing cells. Additionally, in vivo studies show 49-fold bioluminescent signal induction. In summary, we believe this platform can aid researchers assess cell-cell interactions on a whole animal scale.

P18

Investigating ALCAM as an immunotherapeutic target in neuroblastoma

Jarrett Lindsay

Advisor: John Maris, M.D.

Neuroblastoma is a cancer arising from the developing sympathetic nervous system. Only half of children diagnosed with high-risk neuroblastoma will survive five years, and those that do survive face significant therapy-induced morbidity. Because neuroblastomas arise from developing tissues, they maintain expression of cell-surface proteins not found in normal tissues, which underscores the potential of immunotherapy to improve upon current treatment. Furthermore, many of these cell-surface proteins are regulated by lineage-restricted transcription factors, which we hypothesize may hinder antigen downregulation as a mechanism of resistance to immunotherapy. Using our primary tumor RNA-sequencing data, our lab found the cell adhesion molecule ALCAM is highly expressed in high-risk neuroblastoma. To understand the role of ALCAM overexpression in neuroblastoma, we generated Pearson correlations between ALCAM and all expressed genes in two primary tumor RNA-seq datasets. Gene ontology analysis of the 70 genes most correlated with high ALCAM expression returned enrichment in processes associated with neuronal signaling and development. These data are consistent with the role of ALCAM in development of retinal ganglia, which are derived from the same neural crest progenitors as neuroblastoma. Thus, we hypothesized ALCAM expression may be driven by a network of transcription factors termed the neuroblastoma core regulatory circuit (CRC). The CRC is a feed-forward transcriptional regulatory loop in which each member drives the expression of itself and the others, together defining a noradrenergic phenotype. This phenotype is characterized by high expression of genes associated with neuronal function, such as tyrosine hydroxylase and dopamine beta hydroxylase. We investigated the ALCAM locus using ChIP-seq data (from two neuroblastoma cell lines) targeting all seven transcription factors of the CRC. The ALCAM locus showed binding of every CRC transcription factor, as well as the presence of an upstream enhancer (H3K27ac). Finally, an anti-ALCAM antibody-drug conjugate (CX-090) demonstrated low- to sub-nanomolar IC50 concentrations in five neuroblastoma cell lines. Together, these data suggest ALCAM expression may be driven by critical transcription factor networks in neuroblastoma, highlighting ALCAM as an attractive target for immunotherapy development

P19

Deciphering Chronometabolic Dysfunction in Drosophila Short Sleep Models

Dania Malik

Advisor: Aalim Weljie, Ph.D.

Sleep and circadian disruption independently have been shown to alter metabolism and are associated with adverse health risks. Circadian rhythms impose a form of regulation on various metabolic and biological processes, including sleep-wake cycles, thus understanding the interactions between the two is of high importance. To this end, untargeted liquid chromatography-mass spectrometry was utilized to assess lipidome level differences in a sleep and circadian paradigm. Discriminant analyses indicate overall lipid-level differences between circadian and sleep groups with conserved changes observed in two short sleep mutants, fumin and sleepless, compared to wild type *Drosophila*. However, assessing metabolite usage and synthesis is difficult to discern from steady state analyses. Here, an in vivo metabolic labelling platform utilizing stable isotope tracers has been adapted to enable rhythmicity of lipid biosynthesis and consumption in sleep and circadian paradigms to be assessed in a comprehensive manner. Wild type *Drosophila* were challenged with uniformly labelled glucose at 2-hour resolution for 48 hours. The metabolic fate of glucose carbons into lipids was monitored via 2-D Nuclear Magnetic Resonance Spectroscopic experiments. Initial analyses of glucose metabolic fate into lipids in wild type *Drosophila* indicates robust rhythmicity in lipid biosynthesis with potential overlap with feeding rhythms. Future experiments will incorporate short sleep and clock mutants to enable sleep and circadian driven differences in lipid biosynthesis to be separated.

P20

Epiproteomic analysis of archival formalin-fixed paraffin-embedded tumor tissue for interrogating oncogenic mechanisms in endometrial stromal sarcoma

Dylan Marchione

Advisor: Benjamin A. Garcia

Abstract:

Endometrial stromal sarcoma (ESS) is a rare uterine tumor with frequent alterations in genes encoding subunits of polycomb repressive complex 2 (PRC2), a master epigenetic regulator. Rather than causing loss-of-function, these mutations fuse a poorly characterized zinc-finger protein, JAZF1, to the N-terminus of either SUZ12 or PHF1. While prior studies suggest that JAZF1-SUZ12 fusion renders PRC2 inactive, the function of the JAZF1-PHF1 protein has not been studied mechanistically. We sought to leverage archival pathology samples in order to determine how these mutations affect the epigenome and global protein expression. We also established a cell model for further mechanistic interrogation. Contrary to several prior reports, we observe high levels of H3K27 methylation in both JAZF1-SUZ12 and JAZF1-PHF-expressing ESS, suggesting that the fusion proteins do not cause PRC2 loss-of-function. Moreover, in add-back experiments, JAZF1-SUZ12 can partially compensate for SUZ12 deletion, restoring methylation levels to near wild-type levels. Affinity proteomic characterization suggests that JAZF1-SUZ12 is assembled into a PRC2-like complex. GSEA of whole proteome data from ESS tumors revealed aberrant expression of PRC2 target genes. We hypothesize that JAZF1-SUZ12 and related fusions may hijack the repressive chromatin machinery in overlapping, but distinct, ways in order to drive cell transformation.

P21

Circuit level analysis of the preoptic area and tuberomammillary nucleus in sleep regulation

John Maurer

Advisor: Shinjae Chung, Ph.D.

Sleep is evolutionarily conserved across all mammals, yet the precise function of sleep remains unknown. In mammals, sleep is characterized by transitions between rapid eye movement (REM) and non-REM (NREM) sleep states, which are regulated through interactions between numerous neuronal populations. Sleep is negatively regulated by wake-promoting nuclei, resulting in the mutually exclusive states of sleep and wakefulness. Numerous sleep-active and wake-active brain regions have been identified, but it remains unclear how these different neuronal populations coordinate their actions to regulate sleep and wakefulness. The preoptic area (POA) of the hypothalamus contains sleep-active GABAergic neurons, and work from our lab has shown that activation of POA GABAergic axons projecting to the tuberomammillary nucleus (TMN) promotes sleep. Conversely, lesions to the TMN, the sole source of the neurotransmitter histamine in the brain, have been known to cause profound somnolence, suggesting this brain region is a prominent wake center. In addition to histamine, the TMN also contains populations of GABAergic and glutamatergic neurons. However, it is unclear which of these neuronal populations are crucial for wakefulness and if their innervation of the POA promotes arousal. The present experiments use transgenic mice to target three neuronal populations (histaminergic, GABAergic, and glutamatergic) to determine neuronal *in vivo* activity and if activation promotes wakefulness. Parallel studies are investigating if activation of the axon terminals innervating the POA promotes wakefulness. Preliminary findings suggest that optogenetic activation of glutamatergic cell bodies within the TMN and axon terminals projecting to the POA strongly promotes wakefulness. Furthermore, fiber photometry in the TMN revealed glutamatergic neurons that are wake-active and REM-active and involved in wake- and REM-transitions. While, optogenetic activation of histaminergic cell bodies and axon terminals to the POA had no effect in promoting wakefulness, *in vivo* activity of histaminergic neurons within the TMN are wake-active and involved with sleep to wake transitions. Taken together, these results provide novel evidence that glutamatergic neurons in the TMN and axon terminals to the POA are a prominent neuronal population that promotes wakefulness. Considering the crucial roles of sleep in physiological function and detrimental effects of sleep deprivation, it is vital to understand circuit-specific mechanisms underlying sleep regulation.

P22

Development and validation of a new mouse model to investigate the therapeutic potential of neuron-specific E2F1 knockout for neurodegenerative disease

Claire Meurice

Advisor: Kelly Jordan-Sciutto

The transcription factor E2F1 modulates the G1-S phase transition of the cell cycle, DNA damage response, and apoptosis. Abrogating E2F1 prevents apoptosis caused by excitotoxic and amyloid-beta treatments of primary neurons, and rescues memory impairment in APP/PS1 double transgenic mice. There is strong evidence for E2F1's involvement in neurodegenerative disease by promoting apoptosis, or de novo-generated neuronal tetraploidy that causes neuronal dysfunction/death. Previous reports of age-dependent memory impairment, anxiety, and systemic pathology in adult E2F1 mutant mice lacking the DNA binding domain (E2F1^{tm/tm}) impede the development of E2F1 targeted therapeutics. Given E2F1's detrimental role in neurons, we hypothesized that neuronal E2F1 deletion was not driving this phenotype. To test this hypothesis, we developed a neuron-specific E2F1 knockout by designing and breeding E2F1 mice with conditional alleles carrying LoxP sites flanking exon 2 and 7 (E2F1^{fx/fx}) with neuron-specific Syn1-cre (Syn⁺) mice. In parallel, constitutive E2F1 knockout mice (E2F1^{-/-}) were generated from E2F1^{fx/fx}. Middle-aged (12-13mth old) E2F1^{+/+}, E2F1^{+/-} and E2F1^{-/-}, E2F1^{+/+}, Syn⁺, E2F1^{fx/fx}, E2F1^{fx/fx};Syn⁺ mice were tested in novel object recognition, light/dark box, and open field assays to confirm the development of age-associated phenotypes (previously reported in E2F1^{tm/tm} mice) and to determine if these impairments were absent in neuron-specific E2F1 knockout mice. Context fear conditioning was added to determine if hippocampal memory was impaired by global and neuron-specific E2F1 loss. Results indicate that neuronal E2F1 loss does not produce the impairments observed in E2F1^{-/-}. In fact, E2F1^{-/-} mice do not exhibit hippocampal memory impairment. However, the LoxP insertion site in the E2F1^{fx/fx} mouse may cause an unintended systemic phenotype. Future studies will aim to identify the cell types in which E2F1 loss produces memory-impairment. This research highlights the value of developing a cell-type specific E2F1 therapy for neurodegenerative disease treatment.

P23

APC Regulation of GSK-3

Rebecca Myers

Advisor: Peter S. Klein

Mutations in Adenomatous Polyposis Coli (APC), a tumor suppressor gene, are implicated in over 80% of human colorectal cancers, and germline mutations in APC cause Familial Adenomatous Polyposis (FAP), an inherited condition that predisposes to colon cancer. APC is a component of a complex that suppresses canonical Wnt signaling by directing the degradation of β -catenin, an activator of Wnt target genes. In the absence of Wnt ligands, β -catenin is marked for degradation by phosphorylation by Glycogen Synthase Kinase-3 (GSK-3). This phosphorylation occurs within a complex formed by the scaffolding protein Axin and APC. When APC is mutated β -catenin is protected from phosphorylation, allowing for accumulation, nuclear translocation, and over-activation of Wnt pathway target genes, leading to colorectal cancer. APC and GSK-3 have been found to play similar, possibly related roles in other signaling pathways such as mTORC1 signaling. Our lab found that APC directly activates GSK-3 and that genetic loss of APC reduces GSK-3 activity, therefore leading to increased Wnt signaling in colon cancer and mTORC1 activation in tumors from FAP patients. We hypothesize that APC regulates GSK-3 through a specific motif within APC, shown previously to be necessary for β -catenin degradation, and that this regulation applies to other pathways where APC and GSK-3 are both active. The objective of this study is to define the region of APC that regulates GSK-3 activity and test whether APC regulates other signaling pathways downstream of GSK-3 in both in vivo and in vitro model systems. We will also investigate the use of mTORC1 inhibitors in the treatment of recurrent polyps in FAP.

P24

Novel targeted NIR fluorophore for intraoperative detection of choline kinase α -overexpressing lung cancer in mice

Sofya Osharovich

Advisor: Jim Delikatny, Ph.D.

Choline kinase α (ChoK α) is a lipid kinase that catalyzes the phosphorylation of choline to produce phosphocholine (PC) in the Kennedy pathway of phospholipid biosynthesis. ChoK α is an established cancer biomarker associated with aggressive phenotype, high histological tumor grade, and poor clinical outcome in many human cancers. ChoK α is overexpressed in 60% of human lung tumors. Our lab has constructed a near-infrared (NIR) ChoK α inhibitor, JAS239, that can be employed to assess ChoK α levels in tumor models using fluorescence optical imaging. JAS239 competitively binds to the active site of ChoK α , attenuates PC production, and accumulates in tumors in proportion to enzyme expression. JAS239 is fluorescent in the near- infrared region (λ_{ex} = 745 nm, λ_{em} = 775 nm), which is ideal for optical imaging, as light absorption and scattering is decreased in this range. In this study, we evaluate JAS239 for detection of tumor margins and lung metastases in mice and measure ChoK α expression in spontaneous canine adenocarcinomas. We have identified a highly metastatic murine lung cancer cell line, KLN 205, that over-expresses ChoK α . When administered to mice, JAS239 does not accumulate in normal lung tissue and is able to illuminate lung metastases. KLN 205 cells transformed with a luciferase vector (KLN 205 Luc+) were used to track metastasis from the flank to the lungs by bioluminescence imaging. The JAS239 fluorescent signal colocalized with the bioluminescent signal in the lungs, indicating that JAS239 would be useful for identification of primary tumor margins and metastases intraoperatively in mice. Toxicity studies in mice showed that JAS239 is non-toxic at doses up to 50 fold higher than the imaging dose, which is critical to establish prior to translation. Our long-term goal is to translate JAS239 into the veterinary clinic to be used as an intraoperative guide for resection of spontaneously occurring lung tumors in canine patients. Canines with spontaneous lung tumors are an excellent model of the human disease, as they are genetically diverse, are exposed to the same environmental factors, and express similar levels of ChoK α as humans. Immunohistochemistry and Western blots show elevated ChoK α levels and clear tumor delineation in spontaneous canine lung tumors compared to normal lung tissue. Further ChoK α expression profiling of lung cancer will aid in the translational application of intraoperative molecular imaging with JAS239 for detection and margin delineation of lung tumors in a real-time clinical setting.

P25

The Androgenic Impact of AKR1C3 and 11-Ketoandrogens on Polycystic Ovarian Syndrome (PCOS)

Ryan Paulukinas

Advisor: Trevor Penning, Ph.D.

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women of reproductive age affecting 10% of all women and at least 30% of all infertile women. PCOS is characterized by hyperandrogenism and leads to obesity and type 2 diabetes. Our goal is to identify targets for endocrine disrupting chemicals (EDCs) that could influence this disease. Aldo-keto reductase family 1 member C3 (AKR1C3; type 5 17 β -hydroxysteroid dehydrogenase (HSD) and prostaglandin F synthase) is the prominent peripheral enzyme involved in androgen biosynthesis and the production of prostaglandins of the F series. AKR1C3 overexpression in adipocytes in response to insulin could lead to increased androgen receptor (AR) signaling, increased de novo lipogenesis, and decreased PPAR γ signaling leading to reduce adipogenesis. This lipid overflow could exacerbate insulin resistance through a feedforward mechanism and promote the lipotoxic profile seen in PCOS. In adipocytes, the 11-oxygenated androgens of adrenal origin may be a potential source of peripheral androgens leading to the androgen excess. Serum samples from PCOS patients have increased levels of 11 β -hydroxyandrostenedione (11 β OH-A4), 11-ketoandrostene-3,17-dione (11K-A4), and 11-ketotestosterone (11K-T). 11K-T and 11-ketodihydrotestosterone (11K-5 α -DHT) have the same potency as testosterone and dihydrotestosterone in AR reporter gene assays. To determine whether AKR1C3 can convert 11K-A4 to 11K-T and 11-keto-5 α -androstane-3,17-dione (11K-5 α -dione) to 11K-5 α -DHT, kinetic parameters for these reactions catalyzed by recombinant AKR1C3 were estimated using discontinuous UV RP-HPLC enzymatic assays. Detection of UV transparent compounds was accomplished by dinitrophenylhydrazine derivatization. AKR1C3 was found to have catalytic efficiencies for 11K-A4 and 11K-5 α -dione that were 5 times greater than its normal substrate A4. By contrast 11 β OH-A4 was found to be a poor substrate indicating that it must be converted to 11K-A4 first by 11 β -HSD2. The kinetic analysis helps to elucidate the involvement of AKR1C3 and 11 β -HSD2 in the formation of the 11-oxygenated androgens. The study identifies AKR1C3, 11 β -HSD2, AR and PPAR γ as targets for EDCs that may affect PCOS onset.

P26

Investigating Protein PTMs As Liver-Injury Specific Biomarkers

Ross Pirnie

Advisor: Ian Blair, Ph.D.

Drug-induced liver injury (DILI) is a common clinical concern as well as a major barrier for the development of new therapeutics. Despite its frequency and severity, there are no specific and predictive diagnostic biomarkers for DILI. Post-translational modifications (PTM) to secreted proteins have potential to meet the increasing need for specific biomarkers. The highly conserved DNA-binding protein and cytokine high mobility group box 1 (HMGB1) is actively secreted from immune cells following PTM. Using HPLC-HRMS/MS and live cell immunostaining, we show that HMGB1 is also passively released from necrotic, drug-injured hepatocytes. Due to the unique presence of concentrated ROS and RNS, the intracellular environment of drug-injured hepatocytes has the potential to uniquely modify HMGB1. We show that in vitro, HMGB1 exposure to RNS peroxynitrite results in a unique pattern of oxidation and nitration detectable by HR LC/MS. These modifications interfere with antibody binding, which may have prevented previous detection in biological samples. The modification state and biological function of hepatocyte-released HMGB1 has not been fully elucidated, warranting further study.

P27

A blood vessel-on-a-chip that models hemostasis in humans after a puncture injury

Izmarie Poventud-Fuentes

Advisor: Lawrence Brass

Studies in mice have shown that during the hemostatic response to penetrating injuries, a hemostatic plug is characterized by a heterogeneous architecture that has highly activated platelets and fibrin restricted to the injury boundaries and the extravascular space. Bridging these studies with hemostasis in humans has been challenging, as it would require invasive surgical procedures. The goal of our study was to develop a microfluidic system that mimics a blood vessel and can recapitulate the dynamic microenvironments to which blood is exposed after a blood vessel breach to better understand hemostasis in humans. This novel microfluidic platform incorporates essential components of hemostasis in a 3-compartment design through which human blood is perfused: (1) an endothelialized “intravascular” channel, (2) a deformable “vessel wall” made of a collagen 3D matrix that contains tissue factor, and (3) an “extravascular” channel to establish a pressure drop across the vessel wall after a puncture injury. Kinetics of platelet accumulation and fibrin formation in the device can be recorded in real time. Afterwards, we study the structure of the resulting hemostatic plug using confocal and scanning electron microscopy. We find that this system recapitulates key features of hemostatic plug formation in vivo, including platelets as the main cellular component, the spatial distribution of activated P-selectin(+) platelets, sensitivity to the presence of tissue factor embedded in the collagen matrix, inhibition of platelet accumulation and contractile forces by an integrin $\alpha\text{IIb}\beta\text{3}$ antagonist, fibrin as essential scaffold for platelets to achieve a stable hemostatic plug, and a functional endothelium that localizes the response to the injury site. The result is a versatile tool that can be used in studies of human blood and to characterize emerging therapeutic approaches in the field of hemostasis and thrombosis.

Investigating the Efficacy of GluK1-containing Kainate Receptor Inhibition to Treat Alcohol Addiction

Natalia A. Quijano-Cardé

Advisor: Mariella De Biasi, Ph.D.

Alcohol use disorder (AUD) is a serious neuropsychiatric condition affecting millions of people worldwide. The heterogeneity of the disease underscores the need to expand the number of pharmacotherapeutics to treat AUD patients. Topiramate (TPM) is an antiepileptic drug that has been shown to modulate ethanol drinking patterns in humans. TPM has many pharmacological targets and affects many cellular processes and, therefore the molecular target for its effects on AUD is not clear. Among several mechanisms, TPM acts as a non-selective antagonist of kainate receptors containing the GluK1 subunit (GluK1*KARs), which is encoded by GRIK1 in humans. Interestingly, pharmacogenetic studies have shown that a single nucleotide polymorphism (SNP, rs2832407) in GRIK1 exerts an influence on the predisposition to develop alcohol dependence and modulates the efficacy of topiramate treatment to reduce drinking. Thus, our study examined the ability of LY466195-mediated selective inhibition of GluK1*KAR to modulate responses to alcohol in a mouse model of alcohol dependence. Our results indicate that selective GluK1*KAR inhibition reduces ethanol intake and preference in mice undergoing short-term (24-h) and protracted (1 week) withdrawal in a dose-dependent manner. In mice undergoing short-term withdrawal, 20 mg/kg LY466195 treatment was sufficient to attenuate the manifestation of physical signs of withdrawal. Interestingly, we observed that chronic ethanol exposure in the intermittent two-bottle choice drinking paradigm affects the rewarding properties of ethanol as measured in the conditioned place preference (CPP) paradigm and with in vivo accumbal microdialysis. While mice chronically treated with ethanol in the I2BC failed to acquire/display ethanol CPP (1.5 g/kg ethanol), an acute administration of LY466195 (20 mg/kg) was sufficient to rescue the response observed in alcohol-naïve mice. We also found that LY466195 injection normalized dopamine responses to acute ethanol injection in mice undergoing short-term withdrawal from the I2BC. In summary, our data suggest that GluK1*KARs play an important role in modulating the reinforcing properties of ethanol that maintain addiction. Overall, our findings support the hypothesis that GluK1*KARs represent an attractive pharmacological target for the treatment of AUD.

Elucidating Epigenetic Mechanisms Involved in the Origins of Adult Metabolic Phenotypes Following *in utero* Di-(2-Ethylhexyl)-Phthalate Exposure

Nicole M. Robles-Matos

Advisor: Marisa S. Bartolomei, Ph.D.

Environmental exposure to Endocrine Disrupting Chemicals (EDCs) during fetal development may lead to molecular changes that increase susceptibility to adult diseases. For example, EDCs can alter fetal growth and metabolism *in utero* and disrupt critical set points that promote adult metabolic disorders. The EDC Di-(2-ethylhexyl)-phthalate (DEHP) is strongly associated with metabolic changes. DEHP is a ubiquitous plasticizer, present in food packaging, toys, medical devices, and personal care products. DEHP has anti-androgen functions in fetal/placental endocrine systems, interfering with hormonal action. As a result, DEHP exposure during pregnancy may result in adult metabolic defects. However, the mechanisms driving DEHP-induced changes in fetal metabolism and adult diseases are unknown. Recent evidence suggests that EDC-induced changes in metabolic gene profiles may stem from altered epigenetic landscapes. One epigenetic factor, DNA methylation, is particularly vulnerable to environmental exposures as it changes dynamically during fetal development. Thus, we hypothesize that DEHP exposure *in utero* disrupts DNA methylation in placenta, leading to abnormal cross-talk between the fetus and placenta, which in turn will predispose offspring to impaired metabolism in adulthood. To test this, dams were exposed to two DEHP doses (Lower: 50 $\mu\text{g}/\text{kg}\cdot\text{BW}/\text{day}$, Upper: 10 $\text{mg}/\text{kg}\cdot\text{BW}/\text{day}$) via their diet from pre-conception until embryonic day 10.5 (E10.5) or weaning. Post-weaning, offspring were placed on a control or Western Diet (WD) until postnatal day 182 (PND182). Global DNA methylation was assessed on E10.5 placentas using a Luminometric Methylation Assay. Maternal exposure to upper-DEHP was associated with significantly increased global DNA methylation of E10.5 male placentas. Our data suggest that DEHP alters E10.5 placental global DNA methylation in a dose- and sex-specific manner. Adult metabolic phenotyping included glucose tolerance tests, body weight and body fat. Phenotyping revealed that male offspring exposed to upper-DEHP and challenged with WD have impaired glucose tolerance at PND140 and increased body fat at PND182 while females were unaffected. These results suggest that *in utero* DEHP exposure at environmentally relevant doses disrupts glucose homeostasis in a sex-specific manner.

P30

Investigating the FUS-Rpt3 interaction and its role in protein homeostasis

Laura Romano

Advisor: Park-Cho Park, M.D., Ph.D.

Protein homeostasis (proteostasis) is a critical process for maintaining normal cellular function. It involves balance between two fundamental cellular processes: protein synthesis and protein degradation. These two processes must work together because an imbalance in one can create a toxic intracellular environment, such as formation of protein aggregates that sequester functional proteins. However, it is unknown whether protein synthesis and degradation work in a synchronous fashion. We have found that fused in sarcoma (FUS) and proteasome regulator Rpt3 are interacting partners. FUS is a DNA/RNA binding protein that regulates transcription, translation, splicing, and mRNA transport. Mutations in the FUS gene are implicated in neurodegenerative diseases such as frontotemporal dementia and amyotrophic lateral sclerosis. Rpt3 regulates proteasome activity and has been shown to activate 26S proteasome activity. The proteasome is a large complex that is responsible for degradation of intracellular proteins. With this interaction, we hypothesize that protein synthesis and degradation synchronize via the FUS-Rpt3 interaction. Uncovering the nature of this interaction may provide mechanistic insight towards neurodegenerative diseases and potential therapeutic targets.

Constitutive expression of $\Delta 133p53\alpha$ improves the cytotoxicity of CD19-directed chimeric antigen receptor T cells

Christopher Roselle

Advisor: Carl June, M.D.

Genetically engineered T cells expressing a chimeric antigen receptor (CAR) have generated unparalleled success in treatment of acute lymphoblastic leukemia (ALL) with durable response rates as high as 90%. However, the success of CAR T cell therapy in ALL has not been replicated for other tumors, particularly solid tumors, which account for ~90% of cancer deaths in the United States. A fundamental requirement for a successful antitumor response is that CAR T cells persist in a functional state long enough to complete and maintain tumor clearance. However, the enormous demands of tumor clearance, including prolonged antigen exposure, replication stress, and the suppressive tumor microenvironment (TME), can limit the functional persistence of CAR T cells by inducing dysfunctional states such as apoptosis, senescence and exhaustion. The molecular mechanisms driving T cell dysfunction during an antitumor response are unclear and likely multifactorial, however recent evidence suggests that the p53 signaling network may be an important component.

The p53 isoform $\Delta 133p53\alpha$ is an endogenous regulator of senescence in human T cells that declines with age and selectively inhibits transcriptional activity of full-length p53. Primary human T cells co-transduced with $\Delta 133p53\alpha$ and a CD19-directed CAR demonstrate unprecedented antitumor activity in vitro compared with CAR controls. Intriguingly, $\Delta 133p53\alpha$ -transduced CARs exhibit improved tumor clearance only after multiple days of co-culture with the highest tumor burdens, suggesting that $\Delta 133p53\alpha$ may improve tolerance to cellular stress. Our findings warrant further investigation of $\Delta 133p53\alpha$ as a target to improve the functional persistence of CAR T cells.

P32

Mechanisms of white matter loss due to HIV infection

Lindsay Roth

Advisor: Judith Grinspan, Ph.D. and Kelly Jordan-Sciutto, Ph.D

Despite combined antiretroviral therapy (cART), HIV-associated neurocognitive disorder (HAND) occurs in 30-50% of HIV+ patients. Furthermore, white matter pathologies persist in HIV and HAND patients regardless of effective viral control through cART. The thinning of the corpus callosum and disruption of white matter microstructures seen in HIV-positive patients suggest HIV infection may perturb oligodendrocyte (OL) differentiation and/or myelin production. Thus, we hypothesized that HIV infection alters OL differentiation, function, and/or survival, influencing the persistence of HAND in the post-cART era. To examine the effect of HIV infection in the CNS on OL differentiation, we stimulated primary rat oligodendrocyte precursor cells (OPCs) to differentiate into mature OLs, and treated them with HIV-infected monocyte derived macrophage supernatants (HIVMDMS). This model mimics the neuroinflammatory environment of an HIV-infected CNS. To generate HIVMDMS, primary monocytes were isolated and differentiated into macrophages, then infected with HIV. Using this model, HIVMDMS significantly inhibited the differentiation of OPCs, which may explain initial white matter loss in HIV-infected patients. We examined a pathway that might mediate the effect of HIVMDMS called the integrated stress response (ISR). The ISR is a stress response pathway that is initially cytoprotective, but with chronic stress can ultimately lead to cell death. Previously, we have shown that the ISR is activated in neurons and astrocytes of HAND patients via increased pEIF2 α staining in the mid-frontal cortex. Data show increased pEIF2 α in maturing OPCs after 2-hour treatment with HIVMDMS. Furthermore, pretreatment with ISR inhibitor, trans-ISRIB, prior to HIVMDMS treatment, rescued OL maturation. Finally, previous literature from our labs and others have shown excess glutamate in HIVMDMS mediates excitotoxicity in primary neuronal cultures. In order to examine the role of glutamate on OL maturation, we pretreated maturing OPCs with NMDA antagonist, MK801, prior to HIVMDMS treatment which did not rescue OL maturation; however, pretreatment with AMPA antagonist, CNQX, did rescue OL maturation. These data suggest HIVMDMS-driven inhibition of OL maturation is mediated through AMPA receptors and subsequent ISR activation. These studies demonstrate that further investigation into the effects of HIV are warranted to provide insights into the observed persistent white matter changes seen in HAND patients with implications for their contribution to cognitive impairment.

P33

TCRv β CAR T cell therapy for T cell malignant clones

Lauren Shaw

Advisor: Daniel J Powell Jr, Ph.D.

Peripheral T cell lymphomas (PTCLs) are a group of heterogeneous cancers associated with poor prognosis due to ineffective treatment options and high rates of relapse. Given the success of chimeric antigen receptor (CAR) T cell therapy with certain hematological malignancies, it is an attractive option for the treatment of PTCLs. However, developing a CAR T cell platform to treat T cell malignancies is challenging because there are no tumor-associated antigens (TAAs) to distinguish cancerous T cells from healthy T cells, which make up the immune repertoire of the patient as well as the CAR T cells themselves. A CAR T cell platform for PTCLs that avoids self-depletion, is effective, and avoids immunosuppression in the patient must therefore target a TAA with ubiquitous expression by malignant cells and limited expression by healthy T cells. PTCLs consist of mature, clonally expanded T cells so the malignant population will be derived from one of 24 T cell receptor beta chain variable region (TCRv β) families. We propose that CAR T cells specific for a TCRv β family mediates TCRv β family-specific lysis of malignant T cells while preserving the majority of the healthy T cell population. To demonstrate this, CAR constructs specific for individual TCRv β family members were designed and generated. The ability of T cells expressing these CARs to recognize and lyse target cells in vitro was assessed by (a) measuring self-depletion of the target TCRv β + cell subpopulation within the bulk CAR T cell population using flow cytometry, (b) measuring specific lysis of target cell lines with known TCRv β expression using functional killing assays, and (c) measuring lysis of the dominant malignant TCRv β clone in a patient sample. TCRv β -targeting CAR T cells were also shown to function against target malignant cells engrafted in immunodeficient mice. The development of TCRv β CAR T cell therapy has the potential to provide a high precision treatment option for patients with PTCL that limits healthy immune cell depletion.

P34

Elucidating the role of G Protein-Coupled Receptor Kinase-2 (GRK2) in mast cell mediated allergy and pseudo allergy

Monica Thapaliya

Advisor: Hydar Ali, Ph.D

It is well documented that aggregation of high-affinity IgE receptor (FcεRI) by allergen on mast cells (MC) plays a central role in the manifestation of allergic diseases, which is the 6th leading cause of chronic illness in the U.S. affecting over 50 million Americans. Recent evidence suggests that there is also an IgE-independent MC activation route mediated via a novel G Protein-Coupled Receptor (GPCR) known as MAS-related GPCR-X2 (MRGPRX2), which is predominantly expressed in human MC. This route of MC activation is commonly known as a pseudo allergic reaction, which accounts for 15% of all adverse drug reactions that often leads to life threatening anaphylaxis. Studies show that MRGPRX2 and its mouse orthologue Mrgprb2 is activated by many US Food and Drug Administration (FDA)-approved peptidergic drugs, neuropeptides, and antimicrobial host defense peptides (HDPs). GPCRs are extensively studied gene family and these receptors are regulated by a process of desensitization via phosphorylation by GPCR kinases (GRKs). A plethora of studies show that GRK2 plays an important role in the vascular function, immunity, and inflammation, but the role of GRK2 in the regulation of MC function was reported only recently that it acts as a positive regulator of IgE/FcεRI mediated MC degranulation. However, its role in MRGPRX2 signaling is largely unknown. This study is focused on identifying and elucidating the role of GRK2 in both IgE dependent (FcεRI) and independent (MRGPRX2) MC responses. Data shows that upon GRK2 overexpression in Rat Basophilic Leukemia (RBL-2H3) cells both IgE and MRGPRX2-ligands (48/80, Substance P) induced calcium mobilization is enhanced, whereas upon GRK2 knockdown in Human Mast Cell Line (HMC-1) the response is reduced. Similarly, in primary mast cells isolated from mast cell-specific GRK2 knockout mice, both IgE and MRGPRX2-ligand induced response is reduced. Taken together this data shows that GRK2 acts as a common positive regulator of both IgE/FcεRI and MRGPRX2/Mrgprb2 signaling. This is the first study that has introduced GRK2 in MRGPRX2/Mrgprb2 regulation. A comprehensive understanding of the mechanism of action of GRK2 will aid in the development of potential therapeutics in both allergic diseases and pseudo allergic drug reactions.

P35

Examining dendritic cell heterogeneity in the tumor microenvironment

Jerrick To

Advisor: Malay Haldar MD, Ph.D.

Dendritic cells (DCs) are a heterogeneous population of immune cells that survey local tissue environments and instruct T cell function during an immune response. DCs are present in the tumor microenvironment and are reported to have stimulatory properties that are critical for a successful T cell-mediated anti-tumor response but also tolerogenic properties that enable uncontrolled tumor growth. Thus, understanding the division of stimulatory and tolerogenic properties within tumor DCs is important to any considerations of targeting DCs for cancer immunotherapy. However, the study of bona fide DCs in the tumor is obstructed by shared surface markers with other related immune cells such as macrophages and monocytes. We analyzed the heterogeneity of DCs within murine tumors using genetically engineered DC-reporter mice and single cell RNA-sequencing. Consistent with existing literature, we identified CD103⁺ DCs and CD11b⁺ DCs in their resting, activated, and migratory states, which we further validated by FACS. Additionally, we uncovered a division within CD11b⁺ DCs into two subsets demarcated by the presence or absence of CD301b expression. CD11b⁺CD301b⁺ DCs have been described elsewhere to promote a Th2 profile, but their prevalence and role in solid tumors is poorly understood. Our preliminary data suggests that CD11b⁺CD301b⁺ tumor DCs may suppress anti-tumor immune responses. The proposed studies aim to characterize the function of CD11b⁺CD301⁺ DCs in tumor immunity.

P36

Premature induction of Lysyl Oxidase drives early arterial stiffening in Hutchinson-Gilford Progeria Syndrome

Ryan von Kleeck

Advisor: Richard Assoian, Ph.D.

Arterial stiffening is a hallmark of premature aging in Hutchinson-Gilford Progeria Syndrome (HGPS), but the key molecular regulators initiating arterial stiffening in HGPS remain unknown. To identify these early events, we compared arterial mechanics and ECM remodeling in very young HGPS (LMNAG609G/G609G) mice to those of age-matched and much older wild-type mice. Biaxial inflation-extension tests of carotid arteries of 2-month mice showed that circumferential stiffness of HGPS arteries was comparable to that of 24-month WT controls whereas axial arterial stiffening, an additional hallmark of normal aging, was mostly spared in HGPS. Transmission electron microscopy could identify increased amounts of collagen within the elastin folds of HGPS carotid arteries, but this change was barely detectable by immunostaining carotid cross sections or aortic qPCR. In contrast, immunostaining and RT-qPCR readily revealed an increased expression of Lysyl oxidase (LOX) and its family members in young HGPS arteries. Moreover, treatment of HGPS mice with the pan-Lox inhibitor beta-aminopropionitrile (BAPN) restored near-normal circumferential arterial mechanics to HGPS carotid arteries, causally linking LOX upregulation to premature arterial stiffening in HGPS. This premature increase in arterial LOX expression in HGPS foreshadowed the increased expression of LOX which accompanied circumferential arterial stiffening during normal aging.

P37

Investigating drug-induced neuroadaptations to the Medial Habenula circuitry

Kate Webb

Advisor: Mariella De Biasi, Ph.D.

Opioid dependence has emerged as one of the leading public health concerns of the 21st century. The opioid crisis been paralleled in time by a rise in the popularity of e-cigarettes and subsequent nicotine use, especially among adolescents . A specific

connection between nicotine and opioid use is clinically apparent, with a reported 73-94% of methadone-maintained patients smoking cigarettes. While a functional link between these drugs has been drawn via work in animal models, the circuits by which they exert their effects during states of co-dependence have yet to be fully described. One region of particular interest, but consistently understudied, is the medial habenula (MHb). The medial habenula is a bilateral epithalamic structure that has been shown to regulate aversive behavioral states associated with dependence on and withdrawal from various drugs, including nicotine and opioids. Utilizing a genetically encoded calcium indicator (GCaMP7b) and fiber photometry, I aim to identify nicotine and morphine-induced neuroadaptations to the medial habenula in live, freely behaving mice. First, pharmacologically and physiologically relevant methods of drug delivery were established with an electronic vapor delivery system (nicotine) and a two-bottle choice paradigm (morphine). Then, ability to specifically target the cholinergic neurons of the MHb was confirmed with stereotaxic injection of a Cre-dependent AAV virus encoding GCaMP7b in adolescent ChAT-Cre mice. Using these models and fiber photometry, I plan to study MHb cholinergic activity during states of initial exposure to, dependence on, and withdrawal from either nicotine or morphine. Following separate drug characterizations, I will study activity in the same circuit during a state of co-dependence to and withdrawal from both drugs. Elucidating the role of the medial habenula in nicotine-opioid co-dependence will provide valuable insight and aid in the identification of new targets to treat polysubstance use disorders and curb current drug epidemics.

P38

Understanding epigenome and proteome remodeling caused by novel germline histone H3.3 mutations during neurodevelopment

Khadija Wilson

Advisor: Benjamin A. Garcia, Ph.D.

Histone H3.3 (H3.3) is a histone variant that plays a role in cellular inheritance as ablation of H3.3 expression leads to loss of active gene states and dysfunction of heterochromatin telomeric structures. *H3F3A* and *H3F3B*, the two genes known to

encode H3.3, are ubiquitously expressed in all human cells with higher expression in the ovaries, testes, and brain. Somatic mutations in the *H3F3A* genes have been reported as oncogenic drivers of pediatric glioblastomas. More recently, here at the Center for Applied Genomics at the Children's Hospital of Philadelphia novel germline mutations in both *H3F3* genes have been discovered in a small cohort of patients who suffer from a common pattern of neurodevelopmental disorders, seizures and craniofacial abnormalities. Here we hypothesize that mutant H3.3 (mH3.3) change the regulatory capacity of mH3.3 containing chromatin and therefore modulate gene expression and ultimately the cellular proteome. To this end, we developed stable murine astrocyte cell lines expressing either wild type H3.3 or mH3.3 (G90R, T45I) to study by quantitative mass spectrometry the histone post translational modification changes to the mH3.3 containing nucleosomes and subsequent proteome alterations. Our preliminary data has identified downregulation of chromatin remodeler proteins, as well as upregulation of mitochondrial proteins following reprogramming of the mH3.3 encrusted epigenome. Ultimately, our studies aim to identify and validate potential epigenetic and proteome-wide factors involved in these novel neurodevelopmental disorders. Understanding the basic mechanisms of how these new histone mutations function in neurodevelopment may allow re-classification of epigenome reprogramming in neurological contexts.

P39

Analysis of how Structural Changes in Mutated ALK Kinase Domain Affect Drug Binding using Molecular Docking and Molecular Dynamics Simulations

Gabriela Witek

Advisor: Yaël Mossé, M.D.

Constitutive activation of receptor tyrosine kinases (RTKs) causes dysregulation of their signaling and can drive uncontrolled growth leading to cancer. Anaplastic Lymphoma

Kinase (*ALK*), an RTK in the insulin family, is the primary oncogenic driver in neuroblastoma (NB), most common cancer in infants. Mutations in the *ALK* kinase domain are responsible for the hereditary form of NB and are also somatically acquired in 14% of patients with the most aggressive form of the disease, positioning *ALK* as a promising target for NB therapy. The three most common *ALK* mutations at position R1275, F1245, and F1174, have transforming *in vitro* abilities and result in differential kinase activation. Crizotinib, a first-generation small molecule ATP-competitive inhibitor of the *ALK* tyrosine kinase, showed limited anti-tumor activity in patients with relapsed NB harboring *ALK F1174* and *F1245* mutations. It was recently demonstrated that lorlatinib, a novel ATP-competitive *ALK* inhibitor overcomes this *de novo* resistance. Moreover, studies suggest that these hot-spot mutations cause disruption of the auto-inhibitory interactions and result in *ALK* activation. Our combined computational work involving molecular docking and molecular dynamics simulations and experimental work involving biochemical assays on purified *ALK* kinase constructs aim to show how mutations within the *ALK* kinase domain cause structural changes and affect crizotinib and lorlatinib binding to the kinase.

P40

Synthetic DNA Delivery by Electroporation Promotes Robust in vivo Post-Translational Modification of Broadly Neutralizing anti-HIV Immunoadhesin

Ziyang Xu

Advisor: David Weiner, Ph.D.

Despite ongoing efforts, no vaccines have yet succeeded in inducing antibodies that are considered broadly neutralizing (bNabs) against HIV-1 in NHPs and humans. Passive transfer of bNabs is an important alternative preventive or therapeutic strategy for HIV-1. While exciting, this approach has only recently entered clinical evaluation and

warrants further investigation. For these mAbs to be efficacious in preventing HIV-1 infection, neutralization breadth remains a key issue. Accordingly, novel molecules possessing broader neutralization activity have been designed. Among these, the broadest and the most potent are immunoadhesins that contain extracellular domains of CD4 which impart these molecules neutralization breadths, and a peptide that mimics either the N-terminus of CCR5 or crucial binding site of CD4 inducible antibodies to enhance the neutralization potency. The biological production of these complex molecules can be challenging as these immunoahesins frequently require post-translational sulfation by enzymes to interact with the HIV envelope and achieve their full in vivo potency. Here, we report using synthetic DNA and electroporation (DNA/EP) to promote in vivo expression of an anti-HIV-1 immunoadhesin for at least 6 months. Additionally, we engineered a Tyrosylprotein Sulfotransferase 2 (TPST2) variant enzyme that efficiently trafficked to Trans-Golgi Network (TGN) to colocalize with the immunoadhesin. Binding ELISA assay was used to demonstrate that the engineered TPST2 variant delivered by synthetic DNA/EP optimally sulfated the target molecule in vivo at a low plasmid dose (1:1000 relative to plasmid immunoadhesin dose). Additionally, post-translational sulfation enhanced the potency of the immunoadhesin, decreasing its IC50 in neutralizing global panel HIV isolates (CE1176, 0.57 to 0.05 ug/mL; 25710, 1.09 to 0.16 ug/mL; X2278, 0.77 to 0.16 ug/mL; TRO, 0.38 to 0.18 ug/mL; BJOX, 0.56 to 0.19 ug/mL; X1632, 0.75 to 0.27 ug/mL; CH119, 1.66 to 0.52 ug/mL; CNE55 1.92 to 0.75 ug/mL; 246F3, 2.11 to 1.07 ug/mL) . This work provides a proof-of-concept for delivering anti-HIV immunoadhesins and other engineered complex molecules in vivo by advanced nucleic acid.

Recent Graduates



Cheyenne Allenby

School: Duke University
B.S. Neuroscience (2014)

Advisor: Caryn Lerman, Ph.D.
The Effects of Abstinence from Smoking on Stress Reactivity



Alejandro Arroyo

School: University of Puerto Rico, Río Piedras
B.S. Chemistry (2012)

Advisor: Jim Delikatny, Ph.D.
Development of bioactive probes for detection of tissue metabolic state using Cerenkov attenuation imaging



Grace Coggins

School: Vanderbilt University
B.A. Molecular and Cellular Biology, History of Art (2014)

Advisor: John Maris, Ph.D.
Exploiting resistance mechanisms to RAS-MAPK inhibition in relapsed neuroblastoma



Taylor Hughes

School: Franklin & Marshall College
B.S. Chemistry (2015)

Advisor: Vera Moiseenkova-Bell, Ph.D.
Insights into TRPV5 modulation and gating by cryo-EM



Isabelle Lee

School: Virginia Tech
B.S. Biochemistry (2012)

Advisor: Dr. Trevor Penning
Estrogenic activity of polycyclic aromatic hydrocarbon ortho-quinones in the human endometrium



Jessica Murray

School: College of William and Mary
B.S. Biology and Chemistry (2013)

Advisor: Trevor Penning, Ph.D.

The role of human aldo-keto reductases and Nrf2 signaling in the bioactivation of polycyclic aromatic hydrocarbons (PAHs) and their nitrated derivatives (nitro-PAHs).



Amber Wang

School: National Taiwan University
B.S. Pharmacy (2014)

Advisor: Klaus Kaestner, Ph.D.
Cell-type-specific expression profiling of repopulating hepatocytes



Madhumita Yennawar

School: Pennsylvania State University
B.S. Biochemistry and Molecular Biology (2013)

Advisor: Frances Jensen, M.D.

*AMPA receptor dysregulation and therapeutic interventions
in a mouse model of CDKL5 Deficiency Disorder*

First Year Students



Brandon Anderson

School: Brigham Young University



Kimberly Edwards

School: Mount Holyoke



Daniel Park

School: Rutgers University, Camden



Ryan Paulukinas

School: University of the Sciences



Elizabeth Pruzinsky

School: Drexel University



Alexander Starr

School: New York University



Alexandra Vazquez

School: University of Puerto Rico, Rio Piedras Campus



Eric Waite

School: University of Maryland, College Park



Alyssa Wiest

School: Muhlenberg College



Veronica Yakovishina

School: CUNY John Jay College of Criminal Justice

Current Students



Varun Bahl

School: University of California, Berkeley
B.A. Molecular and Cell Biology (2016)

Email: varunb@pennmedicine.upenn.edu

Laboratory Rotations

(1) Park Cho-Park, M.D., Ph.D.

Functional Characterization of PI31 in the Context of Protein Homeostasis.

(2) Klaus Kaestner, Ph.D.

Can Genomic Mosaicism Explain Regional Differences in Type I Diabetes?

(3) Doris Stoffers, M.D., Ph.D.

Elucidating the Role of Chac1, Slc7a1, and Gpt2 in stress-induced beta-cell survival.

Doctoral Thesis

Advisor: Dr. Klaus Kaestner

Regulation and Function of the MEG3 Locus in Human Beta-cells



Kayla Barekat

School: University of California, Irvine
B.S. Biological Sciences (2013)

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Laboratory Rotations

(1) Caryn Lerman, Ph.D.

Pilot Study for Transcranial Direct Current Stimulation as a Treatment for Adult ADHD

(2) Rebecca Simmons, M.D.

Transgenerational Bisphenol Exposure Alters Gene Expression in the Liver

(3) Tracy Bale, Ph.D.

Examining Signaling Between the Prefrontal Cortex and the Basolateral Amygdala in a Pubertal Stress Model

Doctoral Thesis

Advisor: Garret FitzGerald, MD, FRS

Exploring the role of the gut microbiome in NSAID-induced gastroenteropathy.

Presentations

SPATT Seminar, Philadelphia, PA, Jan 2018

- Title: "Exploring the role of the gut microbiome in NSAID-induced gastroenteropathy"

Annual PGG Student Symposium Poster, Philadelphia, PA, Nov 2017

- Title: "Exploring the role of the gut microbiome in NSAID-induced gastroenteropathy"

Candidacy Exam Presentation, Philadelphia, PA, Oct 2017

- Title: "Exploring the role of the gut microbiome in NSAID-induced gastroenteropathy"

Annual PGG Student Symposium Poster, Philadelphia, PA, Oct 2016

- Title: "Early prenatal stress predisposes individuals to stress-induced intestinal inflammation during puberty via dysregulation of bacterial signaling to the host immune system"

Fellowships

PGG T32 Training Grant, Jul 2017 - Jul 2018



Kryshawna Beard

School: University of Louisville

B.S. Chemistry, B.A. Biology (2017)

Email: krbeard@pennmedicine.upenn.edu

Laboratory Rotations

(1) Kelly Jordan-Sciutto, Ph.D.

Antioxidant effects of flaxseed lignin SDG in HIV associated neurocognitive disorder

(2) Jim Eberwine, Ph.D.

Single cell transcriptomics in neurons

(3) David Meaney, Ph.D.

Exosome-based biomarkers for traumatic brain injury

Doctoral Thesis

Advisor: David Meaney, Ph.D.

Exosomes as Biomarkers for Traumatic Brain Injury



Tatiana Blanchard

School: University of South Florida

B.S. Biomedical Science/Minor: Public Health
(2010)

University of Connecticut Health Center

Certificate in Clinical and Translational Research
(2011)

Email: btati@penmedicine.upenn.edu

Laboratory Rotations

(1) Carl June M.D.

CRISPR Genome Engineering of Primary Human T cells

(2) Daniel Powell Ph.D.

T cell target antigens for the treatment of Ovarian cancer and other gynecologic malignancies with chimeric antigen receptors (CARs)

(3) Beatriz Carreno Ph.D., and Gerald Linette M.D. Ph.D.

Identification of Novel Neoantigens for the treatment of Ovarian Cancer

Doctoral Thesis

Advisors: Carl June M.D., Beatriz Carreno Ph.D., Gerald Linette M.D. Ph.D.

Engineering Antigen-Specific T cells for Adoptive Cell Transfer - TET2

Abstracts/ Posters/Presentations

Genomics-Driven Immunomics Analysis reveal the vast landscape of tumor protective epitopes. 20th Annual CRI Cancer Immunotherapy Symposium, New York City, NY, October 2012. (Oral Presentation)

Duan F, Duitama Jorge, Al Seesi S, Blanchard T, McMahon D, Sidney J, Sette A, Mandoiu I, Srivastava P. A mutation in Transportin3 (Tnpo3) leads to generation of an individually distinct tumor-specific Kd-restricted epitope in the Meth A fibrosarcoma (TUM2P.899) Abstract. The Journal of Immunology May 1, 2014 vol.192 (1 Supplement) 71.23

Chislock E, Pletcher H, Yu L, Warner B, Blanchard T, Sterner C, Belka G, and Chodosh L. Molecular Analysis of Breast Cancer Disseminated Tumor Cells. Cancer Biology Retreat, Mohonk Mountain House, New Paltz, NY. June 15-17, 2015. (Poster)

Chislock E, Yu L, Ji X, Shih N, Smith M, Blanchard T, DeMuth W, Morschauser A, Blaesius R, Feldman M, Pletcher C, Moore J, Judge K, DeMichele, Chodosh L. Development of a Flow Cytometry-Based Assay for Clinical Detection and Molecular Characterization of Disseminated Tumor Cells in Bone Marrow. Cyto2017. (Poster)

Publications

-Blanchard T, Srivastava PK, Duan F. Vaccines against advanced melanoma. Clin Dermatol 31, 179-190 (2013).

-Duan F, Duitama J, Al Seesi S, Ayres CM, Corcelli SA, Pawashe AP, Blanchard T, McMahon D, Sidney J, Sette A, Baker BM, Mandoiu II, Srivastava PK. Genomic and bioinformatic profiling of mutational neoepitopes reveals new rules to predict anticancer immunogenicity. J Exp Med 211, 2231-2248 (2014).

-Yee S, Lieberman D, Blanchard T, Rader J, Zhao J, Troxel A, DeSloover D, Fox A, Daber R, Kakrecha B, Sukhadia S, Belka G, DeMichele A, Chodosh L, Morrissette J, Carpenter E. A novel approach for next-generation sequencing of rare circulating tumor cells. Hum Mutation (2015).

Awards

Florida Bright Futures: Florida Medallion Scholar Recipient August 2006-May 2010

National Society of Collegiate Scholars December 2006-present

University of South Florida Merit Scholarship August 2006-May 2010

Nominated as Conference Assistant at the Keystone Symposium - Emerging Cellular Therapies: T Cells and Beyond. Keystone Resort in Keystone, Colorado on Feb 11 - Feb 15, 2018 (Awarded a \$1200 scholarship)

Awarded a Predoctoral Training Grant in Pharmacology, T32GM008076. July 2018-July 2019



Dan Brown

School: University of Michigan, Ann Arbor
B.S. Cell and Molecular Biology (2014)

Email: dbrow@pennmedicine.upenn.edu

Laboratory Rotations

(1) Dan Powell, Ph.D.

(2) Saar Gill, M.D., Ph.D.

(3) Margaret Chou, Ph.D.

Doctoral Thesis

Advisor: Dr. Saar Gill



Keith Campagno

School: Rutgers University, New Brunswick, NJ
B.A. Cell Biology and Neuroscience (2015)

Email: campagno@penmedicine.upenn.edu

Laboratory Rotations

(1) R. Christopher Pierce, Ph.D.

Paternal Cocaine Exposure and Effects on Social Interaction in Progeny

(2) Benjamin Garcia, Ph.D.

Kinase Inhibitor Library and Phosphorylation-dependent Histone Posttranslational Modifications

(3) Doris Stoffers, M.D. Ph.D.

Neonatal Exendin-4 Administration Timing and the Effects on Adolescent Mice

Doctoral Thesis

Advisor: Claire Mitchell, Ph.D.

Lysosomal Dysregulation in Microglia and Neurodegeneration

Publications

Patel MV, Swiatkowski P, Kwon M, Rodriguez AR, Campagno K, Firestein BL. A Novel Short Isoform of Cytosolic PSD-95 Interactor (Cypin) Regulates Neuronal Development. *Mol Neurobiol.* 2018 Aug;55(8):6269-6281. doi: 10.1007/s12035-017-0849-z. Epub 2018 Jan 2.

Lu W, Gómez NM, Lim JC, Guha S, O'Brien-Jenkins A, Coffey EE, Campagno KE, McCaughey SA, Laties AM, Carlsson LG, Mitchell CH. The P2Y₁₂ Receptor Antagonist Ticagrelor Reduces Lysosomal pH and Autofluorescence in Retinal Pigmented Epithelial Cells From the ABCA4^{-/-} Mouse Model of Retinal Degeneration. *Front Pharmacol.* 2018 Apr 19;9:242. doi: 10.3389/fphar.2018.00242. eCollection 2018

Beckel JM, Gómez NM, Lu W, Campagno KE, Nabet B, Albalawi F, Lim JC, Boesze-Battaglia K, Mitchell CH. Stimulation of TLR3 triggers release of lysosomal ATP in astrocytes and epithelial cells that requires TRPML1 channels. *Sci Rep.* 2018 Apr 10;8(1):5726. doi: 10.1038/s41598-018-23877-3.

Gómez NM, Lu W, Lim JC, Kiselyov K, Campagno KE, Grishchuk Y, Slaugenhaupt SA, Pfeffer BA, Fliesler SJ, Mitchell CH. Robust lysosomal calcium signaling through channel TRPML1 is impaired



Marco Carpenter

School: Clark University, B.A. (2014)

Email: cmarco@pennmedicine.upenn.edu

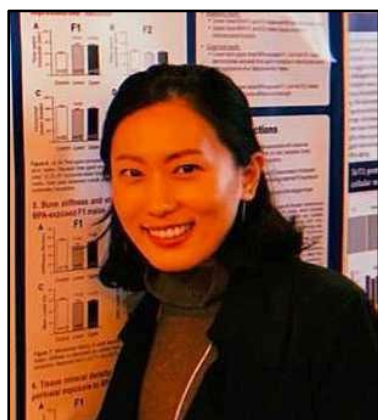
Doctoral Thesis

Advisor: Elizabeth Heller, Ph.D.

Isolation of Cocaine-Specific Molecular Targets Using A Mouse Self-Administration Paradigm

Publications

Sanchez, V., **Carpenter, M. D.**, Yohn, N. L., & Blendy, J. A. (2016). Long-lasting effects of adolescent oxycodone exposure on reward-related behavior and gene expression in mice. *Psychopharmacology*, 1-12.



Suhee Chang

School: Seoul National University, Seoul, Korea

B.S. Pharmacy (2012)

M.S. Pharmacy (2014)

Email: suheech@pennmedicine.upenn.edu

Laboratory Rotations

(1) Kelly Jordan-Sciutto, Ph.D.

ER stress-mediated Neurodegeneration in Antiretroviral Therapy for HIV Positive Patients

(2) Klaus Kaestner, Ph.D.

Foxl1⁺ cells are the essential source of Wnt signaling in the Intestinal stem cell niche

(3) Marisa Bartolomei, Ph.D.

Disrupted DNA methylation in human induced pluripotent cells

Doctoral Thesis

Advisor: Marisa Bartolomei, Ph.D.



Edward Chuang

School: Colby College

B.A. Biochemistry and Mathematics (2014)

Email: edchuang@penmedicine.upenn.edu

Laboratory Rotations

(1) Robert Siman, Ph.D.

Neuroinflammation and Innate Immunity in Mouse Model of Early Stage Alzheimer Tauopathy

(2) James Shorter, Ph.D.

Characterizing the mechanism of Hsp104(A503V) potentiation

(3) Kelly Jordan-Sciutto, Ph.D.

Effects of antiretroviral protease inhibitors in primary neurons

Doctoral Thesis

Advisor: James Shorter, Ph.D.

Studies the aggregation of RNA-binding proteins (RBPs) with prion-like domains such as FUS and TDP-43 that are hallmarks of many neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Recent literature suggests that human heat shock proteins Hsp40, Hsp70, and Hsp110 regulate RBP-rich stress granule dynamics and are capable of robust protein disaggregation. I aim to identify human chaperones that can disaggregate FUS and TDP-43 as therapeutic targets for the treatment of ALS and FTD, and to identify small-molecule enhancers of this disaggregase activity as potential drug candidates.

Publications

Torrente, M.P., E. Chuang, M.M. Noll, M.E. Jackrel, M.S. Go, and J. Shorter. (2016). Mechanistic insights into Hsp104 potentiation. *J. Biol. Chem.* DOI:10.1074/jbc.M115.707976.

Gates, S.N*, A.L. Yokom*, J. Lin, M.E. Jackrel, A.N. Rizo, N.M. Kendsersky, C.E. Buell, E.A. Sweeny, K.L. Mack, E. Chuang, M.P. Torrente, M. Su, J. Shorter, and D.R. Southworth. (2017). Ratchet-like polypeptide translocation mechanism of the AAA+ disaggregase Hsp104. *Science*. 357(6348):273-279. (*Co-first author).

Chuang, E.* , A.M. Hori*, C.D. Hesketh*, and J. Shorter[^]. (2018). Amyloid assembly and

disassembly. J. Cell. Sci. doi: 10.1242/jcs.189928. (*Co-first author. ^Corresponding author).

Pharmacology Predoctoral Training Grant - T32GM008076 (2015-2017)

Blavatnik Family Fellowship in Biomedical Research (2018-2019)



Ryan Cupo

School: Alvernia University

B.S. Chemistry and Mathematics (2015)

Email: ryancupo@pennmedicine.upenn.edu

Laboratory Rotations

(1) James Shorter, Ph.D.

Potential of mitochondrial chaperones Hsp78 and Skd3 to mediate toxic protein misfolding.

(2) Garret FitzGerald, M.D.

Differential effect of celecoxib and rofecoxib on mitochondrial quality control and OXPHOS gene expression in cardiac tissue.

(3) Michael Robinson, Ph.D.

Mitochondrial loss and astrocyte proliferation: Using an organotypic oxygen glucose deprivation model to probe the mechanisms of ischemic neuronal injury.

Doctoral Thesis

Advisor: James Shorter, Ph.D.

Our goal is to (1) understand the function of the mitochondrial ClpB chaperones Hsp78 and Skd3 and (2) engineer their activity against toxic disease proteins associated with neurodegenerative diseases.

Awards

2018-2021 NIH Ruth L. Kirschstein National Research Service Award (NRSA) Individual Fellowship (F31)

2017-2018 Structural Biology and Molecular Biophysics Training Grant

2017 NSF Graduate Research Fellowship, Honorable Mention

Publications

1. Cupo, Ryan; Augustine, Emily; Shorter, James, "Exploring and enhancing compartment-specific protein disaggregases to combat neurodegenerative diseases," Biophysical Society 62nd Annual Meeting. San Francisco, CA. February 17-21, 2018.

2. Cupo, Ryan; Augustine, Emily; Shorter, James, "Exploring compartment-specific protein disaggregases to combat neurodegenerative diseases," American Society for Cell Biology Annual Meeting, Philadelphia, PA, December 5, 2017.



Emily Fabyanic

School: West Virginia University
B.S. in Chemistry, Minor in Biology (2016)

Email: eblythe@penmedicine.upenn.edu

Laboratory Rotations

(1) Julie Blendy, Ph.D.

Transgenerational Inheritance of Adolescent Stress Exposure Alters Offspring Response to Cocaine

(2) Joe Zhou, Ph.D. / Hao Wu, Ph.D.

Adapting Drop-seq Technology for High-Throughput Transcriptome Analysis of Mature Neurons

(3) Klaus Kaestner, Ph.D.

Epigenetic Targeting: Inducing Proliferation Through CDKN1C Silencing

Doctoral Thesis

Adviser: Hao Wu, Ph.D.

Using single-cell techniques to study neural biology

Publications

Hu, P*, Fabyanic, E*, Kwon, D, Tang, S, Zhou, Z, Wu, H. Dissecting Cell-Type Composition and Activity-Dependent Transcriptional State in Mammalian Brains by Massively Parallel Single-Nucleus RNA-Seq. *Molecular Cell*. 2017; 68: 1005-1015.

Appointee of the Cell and Molecular Biology Training Grant (NIH T32 GM-07229) - July 2017

Awards

Supported under the Cell and Molecular Biology Training Grant



Mark Gerelus

School: Wake Forest University
B.A. Chemistry (2013); B.A. Economics (2013)

Wake Forest University School of Business
M.A. Management (2014)

Email: mgerelus@penmedicine.upenn.edu

Laboratory rotations

(1) Margaret Chou, Ph.D.

Mechanisms of Sarcomagenesis: Development of CRISPR-Cas9 screen to identify novel key regulators

(2) Yael Mosse, M.D.

The role of FAK in ALK-driven Neuroblastoma

(3) Donita Brady, Ph.D.

Combining copper chelation with pharmacological therapy to treat melanoma

Doctoral Thesis

Advisor: Yael Mosse, M.D.

Charactering the protein tyrosine phosphatase SHP2 as an oncoprotein and therapeutic target in neuroblastoma

The overall goal of my project is to determine if SHP2 is a molecular vulnerability in NB. I hypothesize that SHP2 is an integral factor in oncogenic signaling which contributes to the survival of NB cells. To test this hypothesis, I will characterize SHP2's role in a broad panel of NB cell lines. I will analyze phenotypic, transcriptional, and proteomic changes upon SHP2 depletion via CRISPR knockout and shRNA knockdown. Furthermore, I will characterize the effects of novel SHP2 inhibitors in vitro and in vivo in the context of extensively characterized NB cells and patient-derived xenografts (PDXs), as well as determine the anti-tumor activity of a novel SHP2 inhibitor in vivo. The significance of this project is that I will assess SHP2's potentially crucial role in NB, findings which will lead to the translation of pharmacological inhibition of SHP2 into the clinical setting as a novel targeted therapy.

Publications

Synergistic Modulation of Inflammatory but not Metabolic Effects of High-Fat Feeding by CCR2 and CX3CR1.

Zhang H, Hinkle CC, O'Neill SM, Shi J, Caughey J, Lynch E, Lynch G, Gerelus M, Tsai ASD, Shah R, Ferguson JF, Ahima RS, Reilly MP. Obesity (Silver Spring). 2017 Aug;25(8):1410-1420. doi: 10.1002/oby.21900.

PMID: 28650582

Lipid-Free Apolipoprotein A-I Reduces Progression of Atherosclerosis by Mobilizing Microdomain

Cholesterol and Attenuating the Number of CD131 Expressing Cells: Monitoring Cholesterol Homeostasis Using the Cellular Ester to Total Cholesterol Ratio.

Kaul S, Xu H, Zabalawi M, Maruko E, Fulp BE, Bluemn T, Brzoza-Lewis KL, Gerelus M, Weerasekera R, Kallinger R, James R, Zhang YS, Thomas MJ, Sorci-Thomas MG. J Am Heart Assoc. 2016 Nov 7;5(11). pii: e004401.
PMID: 27821400

Transcriptome-Wide Analysis Reveals Modulation of Human Macrophage Inflammatory Phenotype Through Alternative Splicing.

Lin J, Hu Y, Nunez S, Foulkes AS, Cieply B, Xue C, Gerelus M, Li W, Zhang H, Rader DJ, Musunuru K, Li M, Reilly MP.
Arterioscler Thromb Vasc Biol. 2016 Jul;36(7):1434-47. doi: 10.1161/ATVBAHA.116.307573.
PMID: 27230130

Procollagen C-endopeptidase Enhancer Protein 2 (PCPE2) Reduces Atherosclerosis in Mice by Enhancing Scavenger Receptor Class B1 (SR-BI)-mediated High-density Lipoprotein (HDL)-Cholesteryl Ester Uptake.

Pollard RD, Blesso CN, Zabalawi M, Fulp B, Gerelus M, Zhu X, Lyons EW, Nuradin N, Francone OL, Li XA, Sahoo D, Thomas MJ, Sorci-Thomas MG. J Biol Chem. 2015 Jun 19;290(25):15496-511. doi: 10.1074/jbc.M115.646240.
PMID: 25947382

Nascent high density lipoproteins formed by ABCA1 resemble lipid rafts and are structurally organized by three apoA-I monomers.

Sorci-Thomas MG, Owen JS, Fulp B, Bhat S, Zhu X, Parks JS, Shah D, Jerome WG, Gerelus M, Zabalawi M, Thomas MJ. J Lipid Res. 2012 Sep;53(9):1890-909. doi: 10.1194/jlr.M026674.



Shivesh Ghura

School: University of Illinois, Chicago
B.S. Bioengineering (2015)

Email: sghura@pennteam.upenn.edu

Laboratory Rotations

(1) Jordan-Sciutto, Ph.D.

Role of APP processing in HIV associated neurocognitive disorder.

(2) Dr. Lynch, M.D., Ph.D.

Stress induced alterations in MAM proteins IP3R and GRP75 in Friedrich Ataxia models.

(3) Benjamin Garcia, Ph.D.

Mass Spectrometry and Proteomics.

Doctoral Thesis

Advisor: Kelly Jordan-Sciutto, Ph.D.



Kevin Gillespie

School: Haverford College

B.A. Chemistry (2015)

American Chemical Society Certification

Email: kevingi@penmedicine.upenn.edu

Laboratory Rotations

(1) Ian Blair, Ph.D.

Impacts of Dimethyl Fumarate on Glutathione and Cellular Oxidation

(2) Aalim Weljie, Ph.D.

*HPLC-coupled NMR analysis of small polar metabolites in *Drosophila melanogaster**

(3) Marilyn Howarth, M.D.

Investigation into environmental health concerns with agricultural fertilizer applications

Doctoral Thesis

Advisor: Ian Blair, Ph.D.

Secreted HMGB1 Proteoforms as Biomarkers of DNA Damage

Publications

1. Xiao Zhao, Kristin Lorent, Benjamin J. Wilkins, Dylan M. Marchione, Kevin Gillespie, Orith Waisbourd-Zinman, Juhoon So, Kyung Ah Koo, Donghun Shin, John R. Porter, Rebecca G. Wells, Ian Blair, Michael Pack. Glutathione antioxidant pathway activity and reserve determine toxicity and specificity of the biliary toxin bilitresone in zebrafish. *Hepatology*, 2016. PubMed PMID: 27102575
2. Andrew J. Worth, Dylan M. Marchione, Robert C. Parry, Qingqing Wang, Kevin P. Gillespie, Noelle N. Saillant, Carrie Sims, Clementina Mesaros, Nathaniel W. Snyder, Ian A. Blair. LC-MS Analysis of Human Platelets as a Platform for Studying Mitochondrial Metabolism. *Journal of Visualized Experiments*, 2016. PubMed PMID: 27077278
3. Andrew J. Worth, Kevin P. Gillespie, Clementina Mesaros, Lili Guo, Sankha S. Basu, Nathaniel W. Snyder, and Ian A. Blair. Rotenone Stereospecifically Increases (S)-2-Hydroxyglutarate in SH-SY5Y Neuronal Cells. *Chemical Research in Toxicology* 2015. PubMed PMID: 25800467.
4. Nathaniel W. Snyder, Gregory Tomblin, Andrew J. Worth Robert C. Parry Jacob A. Silvers, Kevin P. Gillespie, Sankha S. Basu, Jonathan Millen, David S. Goldfarb, Ian A. Blair. Production of

stable isotope-labeled acyl-coenzyme A thioesters by yeast stable isotope labeling by essential nutrients in cell culture. *Analytical Biochemistry* 2015. PubMed PMID: 25572876; PubMed Central PMCID: PMC4413507.

Poster Presentations

Biliary toxin biliatresone depletes hepatic glutathione and forms glutathione adducts in larval zebrafish. **Kevin P. Gillespie** et al. Center for Excellence in Environmental Toxicology Symposium. Perelman School of Medicine, University of Pennsylvania. Philadelphia, PA. June 2016.

Asbestos Induced Oxidative Stress in Lung Cells. Liwei Weng, Clementina Mesaros, Nathaniel W. Snyder, **Kevin P. Gillespie**, Robert Parry, and Ian A. Blair. Society of Toxicology. New Orleans, LA. April 2016.

Effects of Asbestos Exposure on the Cellular Redox State Mitochondrial Metabolism. **Kevin P. Gillespie**, Robert Parry, Clementina Mesaros, Nathaniel W. Snyder, Andrew J. Worth, and Ian A. Blair. Superfund Research Program Annual Meeting. San Juan, PR. November 2015.

Monitoring the effects of asbestos on cellular redox state. **Kevin P. Gillespie** et al. Superfund Research Program Grant Update Site Visit. Perelman School of Medicine, University of Pennsylvania. Philadelphia, PA. August 2015.

Monitoring the effects of chemical insults on mitochondrial activity and acyl-CoA metabolism. **Kevin P. Gillespie** et al. Koshland Integrated Natural Science Center Undergraduate Science Research Symposium. Haverford College. Haverford, PA. October 2014.

Awards

CTSA Summer Undergraduate Summer Internship, University of Pennsylvania (2013)

Koshland Integrated Natural Science Center Summer Scholar, Haverford College (2014)

CEET T32 Training Grant (2016-2019)



Andrea Guzman

School: University of Puerto Rico, Rio Piedras Campus
B.S. in Chemistry (2016)

Email: guzma@penmedicine.upenn.edu

Laboratory Rotations

(1) Andrew Tsourkas, Ph.D.

Development of a Novel Targeted Photodynamic Therapy Against Prostate Cancer

(2) Donita Brady, Ph.D.

Elucidating the Role of Copper Chaperones in MAPK Signaling

(3) Jim Delikatny, Ph.D.

Synthesis and Characterization of a pH Sensitive Probe for Tumor Microenvironment Imaging

Doctoral Thesis

Advisor: Jim Delikatny, Ph.D.

Increased acidity in the tumor microenvironment has been shown to play a role in invasion and metastasis of cancer cells. This metabolic hallmark has sparked interest in the exploration of tumor pH measurement and imaging in vivo. The decrease in tumor microenvironment pH is due to a deregulated metabolism led by an increased glycolytic flux in cancer cells. Cerenkov radiation is a potential technique to image this type of metabolic trademark in vivo. The multispectral photon emission of Cerenkov-active radionuclides (such as ¹⁸F and ⁶⁸Ga) can be absorbed by pH-sensitive molecules and its attenuation at certain wavelengths can be quantified by Selective Bandwidth Quenching. Our lab has previously shown the potential of fluorinated naphthofluorescein for pH measurement using Cerenkov imaging. For this project, we will explore the conjugation of pH sensitive fluorophores with DOTA, with the purpose of chelating ⁶⁸Ga and Y90. This will allow the measurement of quantifiable Cerenkov radiation that will give differential signal due to Selective Bandwidth Quenching, dependent on tumor pH.

Memberships

UPenn Pharm 4 GOOD Co-Founder / Co-Chair

World Molecular Imaging Society Member

UPenn Biomedical Graduate Student Association- Social Chair

Presentations

November 2017 Pharmacology Graduate Group Symposium - Poster

Synthesis and Characterization of a pH-Sensitive Probe for Cerenkov Imaging of Tumor Microenvironment Guzmán-Ríos A.E., Arroyo A.D., Delikatny J.

September 2018 World Molecular Imaging Conference - Oral Presentation

Development of a Naphthofluorescein based pH-Sensitive Probe for in vivo Cerenkov Imaging Guzmán-Ríos A.E., Arroyo A.D., Delikatny J.

September 2018 World Molecular Imaging Conference - Poster

Development of a Naphthofluorescein based pH-Sensitive Probe for in vivo Cerenkov Imaging Guzmán-Ríos A.E., Arroyo A.D., Delikatny J.

Awards

Supported under T32 Training Grant



Michael Hart

Centre College

B.S. in Biochemistry and Molecular Biology (2017)

Email: mihart@pennmedicine.upenn.edu

Laboratory Rotations

(1) Kelly Jordan-Sciutto, Ph.D.

Determining the role of the copper transporter CTR1 in PERK activity in the activated unfolded protein response

(2) Yair Argon, Ph.D.

Examining the effects of glucolipotoxicity on the activation of the activity of IRE1, a key mediator of the unfolded protein response

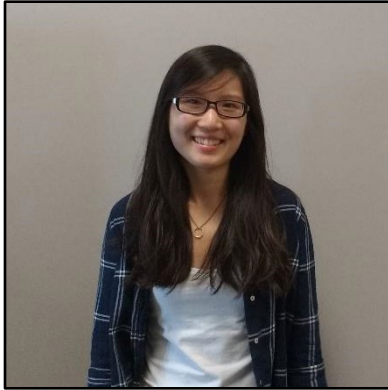
(3) Jim Delikatny, Ph.D.

Elucidating the pharmacology properties of JAS239, a novel near-infrared fluorescent probe in the imaging of tumors with increased choline kinase alpha activity

Doctoral Thesis

Advisor: Jim Delikatny, Ph.D.

Determining the mechanism of action of JAS239 in the cytotoxicity of cancer cells



Courtney Hong

School: University of Illinois, Urbana-Champaign
B.S. Molecular and Cellular Biology & Psychology (2014)

Email: cohong@pennmedicine.upenn.edu

Laboratory rotations

(1) Mark Kahn, M.D.

The role of endothelial MEKK3 signaling in embryonic hematopoiesis

(2) Margaret Chou, Ph.D.

Sinonasal sarcoma: pathogenic mechanisms of a novel gender dimorphic cancer

(3) Nancy Speck, Ph.D.

The role of endothelial MEKK3 signaling in embryonic hematopoiesis

Doctoral Thesis

Advisor: Mark Kahn, M.D.

Publications

Zhang, L., Trushin, S., Christensen, T.A., Tripathi, U., **Hong, C.**, Geroux, R.E., Howell, K.G., Poduslo, J.F., Trushina, E. (2018) Differential effect of amyloid beta peptides on mitochondrial axonal trafficking depends on their state of aggregation and binding to the plasma membrane. *Neurobiol Dis*, doi: 10.1016/j.nbd.2018.02.003.

Lu, Z., **Hong, C.C.**, Kong, G., Assumpção, A.L.F.V., Ong, I.M., Bresnick, E.H., Zhang, J., and Pan, X. (2018) Polycomb Group Protein YY1 Is an Essential Regulator of Hematopoietic Stem Cell Quiescence. *Cell Rep*, doi: 10.1016/j.celrep.2018.01.026.

Assumpção, A.L.F.V., Jark, P.C., **Hong, C.C.**, Lu, Z., Ruetten, H.M., Heaton, C.M., Pinkerton, M.E., Pan, X. (2018) STAT3 Expression and Activity are Up-Regulated in Diffuse Large B Cell Lymphoma of Dogs. *J Vet Intern Med*. doi:10.1111/jvim.14860.

Lu, Z., **Hong, C.C.**, Jark, P.C., Assumpção, A.L.F.V., Bollig, N., Kong, G. and Pan, X. (2017) JAK1/2 Inhibitors AZD1480 and CYT387 Inhibit Canine B-Cell Lymphoma Growth

Tang AT, Choi JP, Kotzin JJ, Yang Y, **Hong CC**, Hobson N, Girard R, Zeineddine HA, Lightle R, Moore T, Cao Y, Shenkar R, Chen M, Mericko P, Yang J, Li L, Tanes C, Kobuley D, Vösa U, Whitehead KJ, Li DY, Franke L, Hart B, Schwaninger M, Henao-Mejia J, Morrison L, Kim H, Awad IA, Zheng X, Kahn ML. *Nature*. 2017 May 10. doi: 10.1038/nature22075.

Awards

Supported under Pharmacology T32 Training Grant



Jack Jacobs

School: Chapman University
B.A. Biochemistry and Molecular Biology (2015)

Email: jacojack@penmedicine.upenn.edu

Laboratory Rotations

(1) Steve Thomas, M.D. Ph.D.

β_2 -adrenergic Signaling in Short-term Memory Formation

(2) Roderick Eckenhoff, M.D.

IV Administration of the Inhaled Anesthetic Sevoflurane and its Photoanalog Azisevoflurane

(3) Amita Sehgal, Ph.D.

Effects of Sleep and Circadian Rhythms on Glial Metabolism

Doctoral Thesis

Advisor: Amita Sehgal, Ph.D.

Identifying the molecular mechanisms responsible for endocannabinoid effects on sleep and seizures

Publications

Kellie A. Woll, Wesley Peng, Qiansheng Liang, Lianteng Zhi, Jack A. Jacobs, Lina Maciunas, Natarajan Bhanu, Benjamin A. Garcia, Manuel Covarrubias, Patrick J. Loll, William P. Dailey, and Roderic G. Eckenhoff. Photoaffinity Ligand for the Inhalational Anesthetic Sevoflurane Allows Mechanistic Insight into Potassium Channel Modulation. *ACS Chem. Biol.* 12, 1353–1362 (2017)



Daniel Jacome

School: Stevens Institute Tech
B.S. Chemical Biology (2017)

Email: jacome@penmedicine.upenn.edu

Laboratory Rotations

(1) Robert Mach, Ph.D.

Development of Dopamine D3R Selective Ligands

(2) Saar Gill, M.D., Ph.D.

Optimization of CAR-T 33

(3) Mark Sellmyer, M.D., Ph.D.

Small Molecule Sensing of Cell-Cell Interactions

Doctoral Thesis

Advisor: Sellmyer, M.D., Ph.D.

Small Molecule Sensing of Cell-Cell Interactions

Awards

NIH T32 Pharmacology Training Grant



Joseph Johnson

School: St. Joseph's University

B.S. (2016)

Email: joedward@penmedicine.upenn.edu

Laboratory Rotations

(1) Chang-Yu Hahn, Ph.D.

(2) Kelly Jordan Sciutto, Ph.D.

(3) Costas Koumenis, Ph.D.

(4) David Lynch, Ph.D.

Doctoral Thesis

Advisor: David Lynch, Ph.D.

The Functions and Role of Frataxin in Friedrich's Ataxia



Nathan Kendsersky

School: University of Pittsburgh
B.S. Molecular Biology, Minors in Chemistry and Music
(2016)

Email: namich@penmedicine.upenn.edu

Laboratory Rotations

(1) James Shorter, Ph.D.

Defining the structural and mechanistic basis for Hsp104 function

(2) Klaus Kaestner, Ph.D.

Stimulating β -cell proliferation through targeted epigenetic editing

(3) John Maris, M.D.

Characterizing the specificity of an antibody-drug conjugate in neuroblastoma cells

Doctoral Thesis

Advisor: John Maris, M.D.

Credentialing Delta-like ligand 3 as an oncoprotein and immunotherapeutic target in neuroblastoma.

Publications

Kristopher R Bosse, Pichai Raman, Zhongyu Zhu, Maria Lane, Daniel Martinez, Sabine Heitzeneder, Komal S Rathi, Nathan M Kendsersky, Michael Randall, Laura Donovan, Sorana Morrissy, Robyn T Sussman, Doncho V Zhelev, Yang Feng, Yanping Wang, Jennifer Hwang, Gonzalo Lopez, Jo L Harenza, Jun S Wei, Bruce Pawel, Tricia Bhatti, Mariarita Santi, Arupa Ganguly, Javed Khan, Marco A Marra, Michael D Taylor, Dimiter S Dimitrov, Crystal L Mackall, John M Maris. (2017) "Identification of GPC2 as an oncogene and candidate immunotherapeutic target in high-risk neuroblastoma." *Cancer Cell*. PMID: 28898695.

Stephanie N Gates, Adam L Yokom, JiaBei Lin, Meredith E Jackrel, Alexandra N Rizo, Nathan M Kendsersky, Courtney E Buell, Elizabeth A Sweeny, Korrie L Mack, Edward Chuang, Mariana P Torrente, Min Su, James Shorter, Daniel R Southworth. (2017) "Ratchet-like polypeptide translocation mechanism of the AAA+ disaggregase Hsp104." *Science*. PMID: 28619716



Jarrett Lindsay

School: University of Illinois, Springfield
B.S. Biochemistry (2017)

Email: jlinds@pennmedicine.upenn.edu

Laboratory Rotations

(1) Donita Brady, Ph.D.

Assessing the role of Copper Binding in PKM2 Function

(2) Margaret Chou, Ph.D.

Uncovering the role of USP6 in Ewing Sarcoma: turning “cold” tumors “hot”

(3) John Maris, M.D.

Investigating ALCAM as an antibody-drug conjugate target in neuroblastoma

Doctoral Thesis

Advisor: John Maris, M.D.

Investigating ALCAM as an antibody-drug conjugate target in neuroblastoma



Lumena Louis

School: CUNY, Brooklyn College

Email: lumenalo@pennmedicine.upenn.edu

Laboratory Rotations

(1) Margaret Chou, Ph.D.

Regulation of Ubiquitin-like Modification by Tre17/USP6

(2) Peter Klein, M.D. Ph.D.

Kinetics of Lithium Mediated Inhibition of GSK-3

(3) David Weiner, Ph.D.

Exploring IL-36 as a Potential Adjuvant in DNA Vaccines

Doctoral Thesis

Advisor: David Weiner, Ph.D.



Dania Malik

School: Stony Brook University
B.S. Biochemistry and Economics (2015)
MBA in Finance (2016)

Email: daniem@penmedicine.upenn.edu

Laboratory Rotations

(1) Margaret Chou, Ph.D.

Identification of Novel Drug Sensitivities to Target Liposarcoma

(2) David Lynch, M.D., Ph.D.

Frataxin and Its Link to Mitochondrial Function in a Friedreich's Ataxia Mouse Model

(3) Aalim Weljie, Ph.D.

Distinguishing Sleep Related Metabolic Rhythms in Drosophila

Doctoral Thesis

Advisor: Aalim Weljie, Ph.D.

Impact of Sleep Deprivation and Impaired Sleep on Metabolic Rhythms in Drosophila

Publications

Malik, D. M., Rhoades, S. & Weljie, A. Extraction and Analysis of Pan-metabolome Polar Metabolites by Ultra Performance Liquid Chromatography-Tandem Mass Spectrometry (UPLC-MS/MS). *Bio Protoc* **8**, doi:10.21769/BioProtoc.2715 (2018).

Awards

NIH Pharmacology T32 Training Grant (2017, 2018)



Dylan Marchione

School: University of Alabama
B.S. Biology
M.S. Molecular & Cellular Biology (2014)

Email: dyma@pennmedicine.upenn.edu

Laboratory Rotations

(1) Olivier Berton, Ph.D.

Investigating the role of histone deacetylase 6 in a mouse model of levodopa-induced dyskinesia

(2) Ian Blair, Ph.D.

Using LC-MS/MS to interrogate mitochondrial metabolism and the glutathione redox buffer system in cultured and primary human cells

(3) Benjamin Garcia, Ph.D.

Using a kinase inhibitor library to interrogate crosstalk between cytoplasmic signaling and histone post-translational modifications

Doctoral Thesis

Advisor: Benjamin Garcia, Ph.D.

The role of histone H3 lysine 36 dimethylation in diffuse intrinsic pontine glioma

Publications

Weinberg DN*, Papillon-Cavanagh S*, Chen H, Chen X, Rajagopalan K, Horth C, Yue Y, Nikbakht H, Marchione DM, et al. H3K36me2 recruits DNMT3A and shapes the intergenic DNA methylation landscape. *Nature*, In review (2018).

Krug B*, De Jay N*, Harutyunyan AS, Deshmukh S, Marchione DM, et al. Pervasive H3K27 acetylation leads to ERV expression and a therapeutic vulnerability in H3K27M gliomas. *Science*, In review (2018).

Harutyunyan AS*, Krug B*, Chen H, Papillon-Cavanagh S, Zeinieh M, Deshmukh S, Chen CC, Belle J, Mikael LG, Marchione DM, et al. H3K27M is essential for glioma tumorigenesis and affects H3K27me3 spread from PRC2 binding sites. *Science*, In review (2018).

Bhoj EJ, Li D, Marchione DM, et al. Germline mutations in Histone 3 Family 3A and 3B cause a novel pediatric neurologic disorder. *Nature Communications*, In review (2018).

Yuan ZF, Sidoli S, Marchione DM, Simithy J, Janssen KA, Szurgot MR, and Garcia BA. EpiProfile 2.0: A platform for processing epi-proteomics mass spectrometry data. *The Journal of Proteome Research*, doi: 10.1021/acs.jproteome.8b00133 (2018).

Simithy J, Sidoli S, Yuan ZF, Coradin M, Bhanu NV, Marchione DM, Klein BJ, Bazilevsky GA,

McCullough CE, Magin RS, Kutateladze TG, Snyder NW, Marmorstein R, and Garcia BA. Characterization of scarcely explored histone acylations links chromatin modifications with metabolism. *Nature Communications*, doi: 10.1038/s41467-017-01384-9 (2017).

Papillon-Cavanagh S*, Lu C*, Gayden T, Mikael LG, Bechet D, Karamboulas C, Ailles L, Karamchandani J, Marchione DM, Garcia BA, Weinreb I, Goldstein D, Lewis PW, Dancu OM, Dhaliwal S, Stecho W, Howlett CJ, Mymryk JS, Barrett JW, Nichols AC, Allis CD, Majewski J, and Jabado N. Impaired H3K36 methylation defines a subset of head and neck squamous cell carcinomas. *Nature Genetics*, doi:10.1038/ng.3757 (2017).

Lin S, Yuan ZF, Han Y, Marchione DM, and Garcia BA. Preferential phosphorylation on old histones during early mitosis in human cells. *Journal of Biological Chemistry*, doi: 10.1074/jbc.M116.726067 (2016).

Zhao X, Lorent K, Wilkins B, Marchione DM, Gillespie K, Waisbound-Zinman O, So J, Koo KA, Shin D, Porter J, Wells RG, Blair IA, and Pack M. Glutathione antioxidant pathway activity and reserve determine toxicity and cell-type specificity of the biliary toxin bilitresone. *Hepatology*, doi:10.1002/hep.28603 (2016).

Worth AJ*, Marchione DM*, Parry RC, Wang Q, Gillespie KP, Sallant N, Simms C, Mesaros CA, Snyder NW, and Blair IA. LC-MS analysis of human platelets as a platform for studying mitochondrial metabolism. *Journal of Visualized Experiments*, e53941, doi:10.3791/53941 (2016).

Awards

Clinical & Translational Science Award - NIH TL1TR001880 (Fall 2017)
US Human Proteome Organization Travel Stipend (Fall 2017)

Presentations

“Altered chromatin-reader interactions in histone-mutant pediatric gliomas.” The 65th Annual Conference of the American Society for Mass Spectrometry, Indianapolis IN. (06/07/2017) [Poster]

“Histone H3 mutations drive aberrant chromatin-reader interactions in diffuse intrinsic pontine glioma.” The 13th Annual Conference of the United States Human Proteome Organization, San Diego CA. (3/20/2017) [Oral]

“Epigenetic dysregulation in histone H3 K27M mutant pediatric glioblastoma.” Mahoney Institute for Neurosciences 33rd Annual Symposium, The University of Pennsylvania, Philadelphia PA. (1/10/2017) [Oral]

“The role of histone H3 lysine 36 dimethylation in diffuse intrinsic pontine glioma.” The 32nd Annual University of Pennsylvania Pharmacology Graduate Group Student Symposium, The College of Physicians of Philadelphia, Philadelphia PA. (10/13/2016) [Poster]

“LC-MS/MS of human platelets as a platform for studying mitochondrial metabolism.” Metabolism: Fueling Translational Research Symposium, Harvard Medical School, Boston MA. (10/10/2015) [Oral]

“LC/MS reveals distinct effects of menadione and 1,4-dimethoxy-2,3-naphthoquinone.” The 63rd



John Maurer

School: St. Louis University
B.S. Psychology (2014)

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Laboratory Rotations

(1) Mariella De Biasi, Ph.D.

Effects of e-cigarette flavorings on oral nicotine self-administration

(2) Elizabeth Heller, Ph.D.

Neuroepigenetic remodeling in cocaine addiction

(3) Shinjae Chung, Ph.D.

Activity of preoptic area GABAergic neurons during sleep

Doctoral Thesis

Advisor: Dr. Shinjae Chung

Neuronal and homeostatic regulation of sleep by the preoptic area and tuberomammillary nucleus

Publications

J. J. Maurer and H.D. Schmidt (2019). "Nicotine addiction and alpha4beta2* nicotinic acetylcholine receptors". Book chapter in "The Neuroscience Of Nicotine: Mechanisms and Treatment". Elsevier.



Claire Meurice

School: University of Michigan
B.S. Neuroscience Honors (2013)

Email: meclaire@pennmedicine.upenn.edu

Laboratory Rotations

(1) Steven Thomas, M.D. Ph.D.

Investigating the role of norepinephrine and histamine in aversive memory retrieval

(2) Kelly Jordan-Sciutto, Ph.D.

Contributions of HIV Antiretroviral Therapy to the Neurotoxicity in HAND and Identifying Potential Targets for Adjunct Therapies

(3) Paul Axelsen, M.D.

Thioflavin T: Does it bind to fibrils or defects in fibrils?

Doctoral Thesis

Advisor: Kelly Jordan Sciutto, Ph.D.

Mechanisms of E2F1-mediated synaptic damage and maintenance in HIV-associated neurocognitive disorders

We are interested in the role that the transcription factor E2F1 plays in the development of HIV-associated neurocognitive disorders (HAND). In a variety of neurodegenerative diseases, E2F1 levels are increased, and in an in vitro model of HIV-induced neurotoxicity, calpain-mediated truncation of E2F1 precedes neuronal death. Therefore we aim to identify the protein domain and/or necessary binding partners behind E2F1-mediated maintenance of synaptodendritic health using primary neuronal/neuroglial cultures and a variety of molecular biology techniques.

Publications

Kumar, V., Ridzwan, I. E., Grivas, K., Lewis, J. W., Clark, M. J., Meurice, C., Jimenez-Gomez, C., Pogozheva, I., Mosberg, H., Traynor, J.R., & Husbands, S. M. (2014). Selectively promiscuous opioid ligands: discovery of high affinity/low efficacy opioid ligands with substantial nociceptin opioid peptide receptor affinity. *Journal of medicinal chemistry*, 57(10), 4049-4057.

Jackson D.P., Ting J.H., Pozniak P.D., Meurice C, Schleidt S.S., Dao A., Lee A.H., Klinman E., & Jordan-Sciutto K.L. (2018). Identification and characterization of two novel alternatively spliced E2F1 transcripts in the rat CNS. *Molecular and Cellular Neuroscience*, [Epub ahead of print].

McPherson, K., Leff, E., Li M., Meurice C., Tai S., Traynor J., and Ingram S. (2018). Regulators of G protein Signaling (RGS) proteins promote receptor coupling to G protein-coupled inwardly-rectifying potassium (GIRK) channels. *Journal of Neuroscience*, [Epub ahead of print].

Awards

Pharmacology T32 Training Grant



Nick Minutolo

School: University of Connecticut
B.S. Molecular and Cell Biology (2012)
M.S. Molecular and Cell Biology (2012)

Email: minutolo@penmedicine.upenn.edu

Laboratory Rotations

(1) Andrew Tsourkas, Ph.D.

Site specific attachment of a chemical cross-linkers to the antibody Fc region

(2) Robert Levy, M.D.

Determining the Optimal Coating Method for Gene Eluting Stents

(3) Daniel Powell, Jr., Ph.D.

Redirecting gene-engineered T cells through covalent attachment of targeting ligands to a universal immune receptor

Doctoral Thesis

Advisor: Daniel Powell, Jr., Ph.D.

Redirecting gene-engineered T cells through covalent attachment of targeting ligands to a universal immune receptor

Presentations

Poster and Oral Presentation, Translational Research Cancer Centers Consortium 2016

Awards

2016 Society for Immunotherapy of Cancer Young Investigators Travel Award



Jessica Murray

School: College of William and Mary
B.S. Biology and Chemistry (2013)

Email: murrayj@penmedicine.upenn.edu

Laboratory Rotations

(1) Trevor Penning, Ph.D.

Metabolic Activation of Nitroarenes Catalyzed by Aldo-keto Reductases

(2) Rebecca Simmons, M.D.

Epigenetic Regulation of BDNF following Prenatal Lead Exposure

(3) Marilyn Howarth, M.D.

Carcinogenic Risk Assessment for Eastwick, PA: Analysis of Air Toxics and the Clearview Landfill

Doctoral Thesis

Advisor: Trevor Penning, Ph.D.

The role of human aldo-keto reductases and Nrf2 signaling in the bioactivation of polycyclic aromatic hydrocarbons (PAHs) and their nitrated derivatives (nitro-PAHs).

Awards/Honors

Solomon Erulkar Traveling Fellowship

Celebrating Women in Toxicology, Society of Toxicology

Graduate Student Travel Award, Society of Toxicology

ACS TOXI Graduate Student Poster Award, 1st Place

PhRMA Pre-Doctoral Fellowship in Pharmacology/Toxicology

NIEHS T32 Training Grant in Environmental Health Sciences

ACS TOXI Travel Award

Publications

Murray JR, Penning TM. "Carcinogenic polycyclic aromatic hydrocarbons." *Comprehensive Toxicology*, 3e. Charlene McQueen (Ed.). Elsevier, 2017, 3e. DOI: 10.1016/b978-0-12-801238-3.95691-5.

Murray JR, Mesaros C, Arlt VM, Seidel A, Blair IA, Penning TM. "Role of Human Aldo-Keto Reductases in the Metabolic Activation of the Carcinogenic Air Pollutant 3-Nitrobenzanthrone." Submitted to *Chemical Research in Toxicology*., Aug 2018.

Selected Abstracts

Murray JR, Huang M, Mesaros C, Blair IA, and Penning TM. Competing Roles of Human Aldo-keto Reductases and NADPH:Quinone Oxidoreductase in the Bioactivation of 3-Nitrobenzanthrone – Kinetic and Expression Analyses. Society of Toxicology Annual Meeting, San Antonio, TX; March 2018. (Poster Presentation)

Murray JR, Huang M, Mesaros C, Arlt VM, El-Bayoumy K, Blair IA, and Penning TM. Nrf2-Keap1 Signaling and Implications for the Metabolic Activation of Nitroarenes. American Chemical Society, Washington, DC; August 2017. (Poster Presentation)

- Also presented at Cellular and Molecular Mechanisms of Toxicity: Gordon Research Conference, Andover, NH; August 2017.

Murray JR, Huang M, Mesaros C, Arlt VM, El-Bayoumy K, Seidel A, Blair IA, and Penning TM. Nrf2-Keap1 Signaling and Implications for the Metabolic Activation of Nitroarenes. Society of Toxicology Annual Meeting, Baltimore, MD; March 2017. (Poster Presentation)

Murray JR, Howarth MV. Evaluating Cancer Risks for Eastwick, PA: Analysis of Air Toxics and the Clearview Landfill. Community Outreach and Engagement Core (COEC) Stakeholder Advisory Board Meeting. Philadelphia, PA; January, 2016. (Oral Presentation)

Murray JR, Huang M, Mesaros C, Arlt VM, El-Bayoumy K, Blair IA, and Penning TM. Metabolic Activation of Nitroarenes by Human Aldo-Keto Reductases (AKR1C1-AKR1C3). 11th Annual Symposium for the Center of Excellence in Environmental Toxicology. Philadelphia, PA; June, 2016. (Poster Presentation)

Murray JR, Zang T, Arlt VM, Schmeiser HH, Mesaros C, Blair IA, and Penning TM. Metabolic activation of 3-nitrobenzanthrone by aldo-keto reductases (AKR1C1—AKR1C4): evidence for 6-electron reduction. 250th American Chemical Society National Meeting. Boston, MA; August, 2015. (Oral Presentation)

Murray JR, Huang M, Zang T, Arlt VM, Schmeiser HH, and Penning TM. Metabolic activation of 3-nitrobenzanthrone by human aldo-keto reductases (AKR1C1-AKR1C4). American Association for Cancer Research Annual Meeting. Philadelphia, PA; April, 2015. (Poster Presentation)



Rebecca Myers

School: Rutgers University
B.S. Biological Sciences, Minor in Psychology (2014)

Email: rmy@penmedicine.upenn.edu

Laboratory Rotations

(1) Patrick Viatour, Pharm.D. Ph.D.

The cell of origin for hepatocellular carcinoma

(2) Peter Klein, M.D. Ph.D.

APC regulation of GSK-3 in colon cancer and FAP

(3) XianXin Hua, M.D. Ph.D.

Possible interactions between menin and the AMPK pathway

Doctoral Thesis

Advisor: Peter Klein, M.D. Ph.D.

APC Regulation of GSK-3: A Novel Role for APC

Publications

Jensen HA, Bunaciu RP, Ibabao CN, **Myers R**, Varner JD, Yen A. Retinoic Acid Therapy Resistance Progresses from Unilineage to Bilineage in HL-60 Leukemia Blasts. *PloS One*. 9(6):e98929.doi:10.1371/journal.pone.0098929. 2014 June 12.

Presentations

Presented a poster "APC Regulation of GSK-3" at the 17th Annual Center for Digestive, Liver & Pancreatic Medicine Retreat- September 2016



Sofya Osharovich

School: West Chester University of Pennsylvania
B.S. Biology (2013)

Email: sofyaosh@penmedicine.upenn.edu

Laboratory Rotations

(1) James Shorter, Ph.D.

Buffering aberrant oncogene activity with potentiated Hsp104 variants

(2) Ian Blair, Ph.D.

Dimethyl fumarate forms adducts with GSH, depleting intracellular GSH stores in SH-SY5Y cells

(3) Edward J. Delikatny, Ph.D.

Near-Infrared Fluorescent Choline Kinase α Inhibitors for Lung Cancer Imaging and Therapy

Doctoral Thesis

Advisor: Edward J. Delikatny, Ph.D.

Publications

Liebov B, Arroyo A, Rubtsova N, Osharovich S, Delikatny J, Popov A. "Non-Protecting Group Synthesis of a Phospholipase C Activatable Probe with an Azo-Free Quencher." ACS Omega. 3:6 (2018): 6867–6873.

Awards

Magna Cum Laude Scientific Abstract Award, Pendergrass Symposium, University of Pennsylvania Student Travel Stipend, World Molecular Imaging Congress



Theresa Patten

School: Wake Forest University
B.S. Chemistry (2014)

Email: tpatten@penmedicine.upenn.edu

Laboratory Rotations

(1) Julie Blendy, Ph.D.

OPRM1 A118G SNP: Effects on the rewarding value of food and weight gain during nicotine withdrawal

(2) Mariella De Biasi, Ph.D.

Role of $\alpha 5$ -containing nicotinic receptors in nicotine/cocaine co-dependence

(3) Tracy Bale, Ph.D.

Effects of early prenatal stress on placental permeability and programming of offspring exosomes

Doctoral Thesis

Advisor: Mariella De Biasi, Ph.D.

The short and long-term effects of e-cigarette flavorants on nicotine reward

Publications

Blume, L. C., Patten, T., Eldeeb, K., Leone-Kabler, S., Ilyasov, A. A., Keegan, B. M., ... Howlett, A. C. (2016). Cannabinoid Receptor Interacting Protein (CRIP) 1a competition with β -arrestin for CB1 receptor binding sites. *Mol Pharmacol.* 2017 Feb;91(2):75-86. PMID: 27895162

Poster Presentations

De Biasi, M., Patten T., Perez, E. Influence of flavor additives on e-cigarette consumption during adolescence: development and validation of a mouse model. Society for Research on Nicotine and Tobacco Annual Meeting (2016).

Patten, T.; Perez, E.; Fleites, V.; Johnston S.H.; McLaughlin, I.; De Biasi, M. Sweet flavorants enhance adolescent nicotine reward: a mouse model to study e-cigarettes. Psychiatry Research Day. Philadelphia, PA (2016)

Patten, T.; Perez, E.; Fleites, V.; Johnston S.H.; McLaughlin, I.; De Biasi, M. Sweet flavorants enhance adolescent nicotine reward: a mouse model to study e-cigarettes. Annual PGG Student Symposium. Philadelphia, PA (2016)

Patten T.; Perez, E.; De Biasi, M. Influence of flavor additives on adolescent nicotine reward: development of a mouse model using commercial e-cigarettes. Annual PGG Student Symposium. Philadelphia, PA (2017)

Patten T.; Perez, E.; De Biasi, M. Influence of flavor additives on adolescent nicotine reward: development of a mouse model using commercial e-cigarettes. American College of Neuropsychopharmacology Annual Meeting (2017)

Awards

2017 - Chapter Recognition Award for Student Travel - Association for Women in Science Philadelphia

Oral Presentations/Lectures

April 2017 - Guest Lecturer; Rutgers University-Camden; "A History and Review of Tobacco, E-cigarettes, and Flavored Products"

June 2018 - Guest Lecturer; Bryn Mawr College – STEM Posse Mini Symposium; "My journey through science and the study of flavored e-cigarettes using a mouse model"



Ross Pirnie

School: Bucknell University
B.S. Biochemistry/Cell Biology (2017)

Email: rpirnie@penmedicine.upenn.edu

Laboratory Rotations

(1) Aalim Weljie, Ph.D.

Detecting the Metabolic Effects of Sleep Restriction

(2) Ian Blair, Ph.D.

Proteomics Investigation of HSA Cysteine-Drug Adduct Formation

(3) Robert Levy, M.D.

Optimization of Gene Therapy Vector Delivery from Metal Stents

Doctoral Thesis

Advisor: Dr. Ian Blair

Understanding the Mechanisms of Drug Induce Liver Injury



Izmarie Poventud-Fuentes

School: University of Puerto Rico, Mayagüez
B.S. Industrial Biotechnology (2013)

Email: ipov@penmedicine.upenn.edu

Laboratory Rotations

(1) Richard Assoian, Ph.D

Role of extracellular matrix stiffness on the regulation of NF- κ B

(2) Lawrence Brass, M.D. Ph.D.

Characterization of Tissue Factor localization in blood vessels

(3) Paul Janmey, Ph.D.

Platelet adhesion and spreading in response to different ligands and stiffness

Doctoral Thesis

Advisor: Lawrence Brass, M.D. Ph.D.

Project description:

Development of a microfluidic system to model and study hemostasis using human blood. Studies in our laboratory and others have shown that upon vessel injury in mice, a gradient of the agonists is generated within the vessel wall that result in a heterogeneous architecture of the hemostatic plug. Although the studies in mice give us valuable information, the platelet biology of mice and humans is similar but not the same. There is a need to understand how much of the observations in in vivo systems apply to human blood.

The goal of my project is to develop a microfluidic system with the essential components to recapitulate key features of hemostasis using human blood to investigate clot consolidation, and the distribution of mechanical forces during hemostatic response.

Awards

T32 Predoctoral Training Grant in Pharmacology (2015-2017)

T32 Hematology Clinical Research Training Grant (2017-present)

Publications

Welsh JD, Poventud-Fuentes I, Sampietro S, Diamond SL, Stalker TJ, and Brass LF. (2017), Hierarchical organization of the hemostatic response to penetrating injuries in the mouse microvasculature. *J Thromb Haemost*, doi: 10.1111/jth.13600

Matsuyama S, Palmer J, Bates A, **Poventud-Fuentes I**, Wong K, Ngo J, and Matsuyama M. (2016) Bax-induced apoptosis shortens the life span of DNA repair defect Ku70-knockout mice by inducing

emphysema. *Exp Biol Med*, 241(12): 1265-71.

Ngo J, Matsuyama M, Kim C, **Poventud-Fuentes I**, Bates A, Siedlak SL, Lee H-g, Doughman YQ, Watanabe M, Liner A, Hoit B, Voelkel N, Gerson S, Hasty P, and Matsuyama S. (2015) Bax deficiency extends the survival of Ku70 knockout mice that develop lung and heart diseases. *Cell Death and Disease*, 6: e1706.

Rao W, Zhang W, **Poventud-Fuentes I**, Wang Y, Lei Y, Weekes B, Li C, Lu X, Yu J, and He X. (2014) Thermally responsive nanocapsule-encapsulated curcumin and its combination with mild hyperthermia for enhanced cancer cell destruction. *Acta Biomater*, 10 (2): 831-842.

Cui M, Naczynski DJ, Zevon M, Griffith CK, Sheihet L, **Poventud-Fuentes I**, Chen S, Roth CM, and Moghe PV. (2013) Multifunctional albumin nanoparticles as combination drug carriers for intratumoral chemotherapy. *Adv Healthc Mater*, 2: 1236–1245.

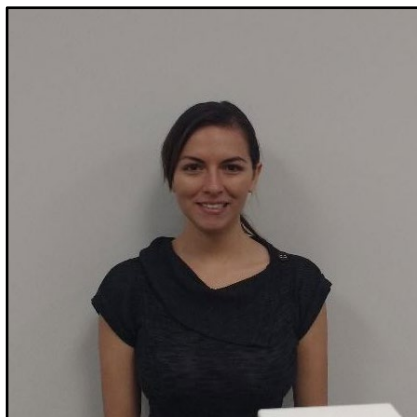
Recent Presentations

Poster: “Development of a microfluidic platform to assess thrombin generation in FVIII deficient whole blood under flow conditions”. Hemostasis Gordon Research Seminar and Conference, Waterville Valley, NH. July 2018.

Talk: “Development of a microfluidic system to understand the interplay of platelets and coagulation factors in the process of hemostasis”. Platelet Club, University of Pennsylvania, Philadelphia, PA. March 2018.

Talk: “Development of an in vitro system to model human hemostatic response”. Systems of Pharmacology and Translational Therapeutics (SPATT) Seminar, University of Pennsylvania, Philadelphia, PA. January 2018.

Poster: “Synthetic blood vessels as tools to understand hemostasis in humans”. 33rd Annual Student Symposium, Pharmacology Graduate Group, College of Physicians of Philadelphia, Philadelphia, PA. November 2017



Laura Puentes

School: University of Central Florida
B.Sc Biotechnology

School: University of Oxford
M.Sc Pharmacology

Email: lpuentes@penmedicine.upenn.edu

Laboratory rotations

(1) Robert H. Mach, Ph.D.

Targeting PARP-1 to deliver Alpha-Particles to Cancer Chromatin

(2) Vladimir Muzykantov, M.D. Ph.D.

Red Blood Cell Hitchhiking with Affinity Ligands

(3) Eric Brown, Ph.D.

Identifying ATRi Dependence on PARP-1 Expression

Doctoral Thesis

Advisor: Robert H. Mach, Ph.D.

The goal of my project is to evaluate PARP-1-specific PET tracers to image and quantify PARP-1 expression levels in glioblastoma and measure target engagement of small molecule PARP inhibitors in real time.

Publications

Reilly, S., Puentes, L., Hsieh, C., Makvandi, M. and Mach, R. (2018). Altering Nitrogen Heterocycles of AZD2461 Affords High Affinity PARP Inhibitors with Improved P-glycoprotein Properties. *ACS Omega*, 3(8), pp.9997-10001.

Reilly, S., Puentes, L., Wilson, K., Hsieh, C., Weng, C., Makvandi, M. and Mach, R. (2018). Examination of Diazaspiro Cores as Piperazine Bioisosteres in the Olaparib Framework Shows Reduced DNA Damage and Cytotoxicity. *Journal of Medicinal Chemistry*, 61(12), pp.5367-5379.

Goldblatt, Greg et al. (2015). Site-Specific Structural Changes in Unmodified and Pyroglutamylated Amyloid Beta Peptide by Isotope-Edited FTIR. *Biophysical Journal*, 108 (2), pp. 524a.

Presentations (Poster):

Puentes L. Evidence of PARP-1 dependent cytotoxic agents with low target affinity. Poster presented at American Association for Cancer Research Annual Meeting; 2018; Chicago, IL.

Puentes L. Targeting PARP-1 to deliver alpha-particles to cancer chromatin.. Poster presented at American Association for Cancer Research Annual Meeting; 2017; Washington D.C.

Awards



Natalia Quijano Cardé

School: University of Puerto Rico, Mayagüez
B.S. Industrial Biotechnology (2015)

Email: qnatalia@pennmedicine.upenn.edu

Laboratory Rotations

(1) Mariella De Biasi, Ph.D

Role of kainate receptor antagonism in the treatment of alcohol dependence

(2) R. Christopher Pierce, Ph.D.

Validation of a mouse model to study cocaine-related epigenetic marks in the nucleus accumbens

(3) Elizabeth Heller, Ph.D.

Cocaine self-administration paradigm to study neuroepigenetics of cocaine addiction in mice

Doctoral Thesis

Advisor: Mariella De Biasi, Ph.D.

Effect of CHRNA5 Genetic Variation on Responses to Ethanol and Nicotine

Publications

Perez E, **Quijano Cardé N**, De Biasi M (2015). Nicotinic mechanisms modulate ethanol withdrawal and modify time course and symptoms severity of simultaneous withdrawal from alcohol and nicotine. *Neuropsychopharmacology* **40**: 2327-2336.



Nicole Robles-Matos

School: University of Puerto Rico, Rio Piedras
B.S. Chemistry (2017)

Email: nroble@penmedicine.upenn.edu

Laboratory Rotations

(1) Trevor Penning, Ph.D.

Expression of Estrogen Receptors and the Effect of Estradiol in Mesothelioma Cell Growth

(2) Rebecca Simmons, M.D.

Effects of Maternal Bisphenol A Exposure on Mouse Pancreatic Immune System

(3) Marisa Bartolomei, Ph.D.

Investigating the Mechanisms Involved in Adverse Health Effects Following In Utero EDC Exposure

Doctoral Thesis

Advisor: Marisa Bartolomei

Our lab wants to explore in more depth gene-environment interactions in the development of diseases. Specifically, our aim is to investigate how an adverse early life event, like environmental exposure to Endocrine Disrupting Chemicals (EDCs), can lead to an increase risk to develop diseases later in life. Since the exact molecular mechanisms linking an adverse early life event to adult diseases remain unclear, we are considering epigenetic mechanisms as potential mechanisms driving the adult phenotypes since epigenetics can be altered by the exposure to EDCs like BPA and DEHP. Currently, project focuses on the effects of maternal exposure to BPA and DEHP in metabolic, reproductive, neurological and skeletal outcomes in the offspring during adulthood. The ultimate goal of this project is to better understand the effects of prenatal EDCs exposure and the mechanisms through which they work to improve our knowledge of the risks to human health.

Awards

CEET T32 Training Grant in Environmental Health Sciences



Laura Romano

School: Rutgers University
B.S. Biochemistry (2015)

Email: lromano@penmedicine.upenn.edu

Laboratory Rotations

(1) Jeffrey Field, Ph.D.

Potential Role Of The Pak Inhibitor, IPA-3, To Induce Oxidative Stress

(2) Benjamin Garcia, Ph.D.

Potential Epigenetic Role Of Oral Contraceptive-Mediated Protection Against High Grade Serous Ovarian Carcinoma

(3) Park Cho-Park, M.D., Ph.D.

Mapping the Binding Interaction Between PI31 and TDP-43

Doctoral Thesis

Dr. Park Cho-Park



Chris Roselle

School: Ithaca College
BS Biochemistry (2008)

School: Lehigh University
MS Chemistry (2015)

E-mail: crosele@penmedicine.upenn.edu

Laboratory Rotations

(1) Mitchell Lazar, M.D. Ph.D.

Effects of a non-circadian light schedule on hepatic lipid metabolism

(2) Carl June, M.D. Ph.D.

Effect of $\Delta 133p53$ on CAR T cell proliferation and senescence

(3) Roger Greenberg, M.D. Ph.D.

Identifying New Genetic Vulnerabilities in BRCA-mutant Cancers

Doctoral Thesis

Advisor: Carl June, M.D. Ph.D

"Investigating the role of $\Delta 133p53\alpha$ in improving the cytotoxicity and functional persistence of chimeric antigen receptor T cells"

Publications

Roselle C, Verch T, Shank-Retzlaff M. "Mitigation of Microtiter Plate Positioning Effects Using a Block Randomization Scheme." *Analytical and Bioanalytical Chemistry* (2016)

Verch T, Roselle C, Shank-Retzlaff M. "Reduction of Dilution Error in ELISAs Using an Internal Standard." *Bioanalysis* (2016)

Roselle, C., et al., "Evaluation of a digital dispenser for direct curve dilutions in a vaccine potency assay." *J. Immunol. Methods* (2017)



Lindsay Roth

School: Smith College
B.A. Biochemistry (2015)

E-mail: rothlind@penmedicine.upenn.edu

Laboratory Rotations

(1) Julie Blendy, Ph.D.

Multigenerational Effects of Parental Morphine Exposure

(2) Kelly Jordan-Sciutto, Ph.D. and Judith Grinspan, Ph.D.

The Effect of Antiretroviral Therapies on Oligodendrocyte Growth and Maturation

(3) Roderich Eckenhoff, M.D.

Structure-Activity Relationship of Dexmedetomidine and Characterization of Photoaffinity Ligands

Doctoral Thesis

Kelly Jordan-Sciutto & Judith Grinspan. Multiple projects examining the effects of HIV and ART drugs on Oligodendrocyte Maturation. Projects focus on the role of the integrated stress response, stress granule formation and dynamics and the role of RNA-binding protein, TDP-43, in these processes.



Lauren Shaw

School: University of Pennsylvania
B.S. Biochemistry (2017)

Email: lashaw@penmedicine.upenn.edu

Laboratory Rotations

(1) Julie Blendy, Ph.D.

Neurobiological mechanisms of early opioid exposure

(2) Karin Eisinger, Ph.D.

Mechanistic studies of soft tissue sarcoma metastasis

(3) Daniel Powell, Ph.D. R

Redirecting gene-engineered T-cells through attachment of targeting ligands to universal immune receptors

Doctoral Thesis

Dr. Daniel Powell, Development of universal immune receptors



Monica Thapaliya

School: Claflin University
B.S. Biochemistry/Mathematics (2016)

Email: thmonica@penmedicine.upenn.edu

Laboratory Rotations

(1) Margaret Chou, Ph.D.

(2) Park Cho-Park, M.D., Ph.D.

(3) Hydar Ali, Ph.D. and Rebecca Simmons, M.D.

Doctoral Thesis

Advisor: Dr. Hydar Ali, Ph.D.



Jerrick To

College of Wooster

B.A. Biochemistry and Molecular Biology (2017)

Email: totsun@penmedicine.upenn.edu

Laboratory Rotations

(1) Saar Gill, M.D., Ph.D.

Development of anti-IL1RAP CAR T Cells

(2) Dmitry Gabilovich, M.D., Ph.D.

Lipid Regulation of Suppressive Function in PMN-MDSCs

(3) Malay Haldar, M.D., Ph.D.

Effect of Retinoic Acid on Antigen-Presenting Cells in Solid Tumors

Doctoral Thesis

Advisor: Malay Haldar, M.D., Ph.D.



Ryan von Kleeck

School: Franklin and Marshall College
B.S. Biochemistry and Molecular Biology (2015)

Email: ryanvon@penmedicine.upenn.edu

Laboratory Rotations

(1) Richard Assoian, Ph.D.

NFKB's role in the stiffness dependent expression of COX2

(2) Costas Koumenis, Ph.D.

MTHFD2 and SHMT2: proteins critical for survival in Myc driven tumors

(3) Patrick Seale, Ph.D.

Regulation of UCP1 by Early B-Cell Factor 2

Doctoral Thesis

Advisor: Richard Assoian, Ph.D.

Arterial mechanics in Hutchinson-Gilford Progeria Syndrome

Publications

The two SAMP repeats and their phosphorylation state in Drosophila Adenomatous polyposis coli-2 play mechanistically distinct roles in negatively regulating Wnt signaling. *Mol Biol Cell* (2015). Kunttas-Tatli E, **Von Kleeck RA**, Greaves BD, Vinson D, Roberts DM, McCartney BM.

The Poly(ADP-ribose) Polymerase Enzyme Tankyrase Antagonizes Activity of the β -Catenin Destruction Complex through ADP-ribosylation of Axin and APC2. *J. Biol Chem* (2016). Croy HE, Fuller CN, Giannotti J, Robinson P, Foley AV, Yamulla RJ, Cosgriff S, Greaves BD, **von Kleeck RA**, An HH, Powers CM, Tran JK, Tocker AM, Jacob KD, Davis BK, Roberts DM.

Awards

Pharmacology T32 Training Grant



Amber Wang

School: National Taiwan University
B.S. Pharmacy (2014)

Email: wamber@penncmedicine.upenn.edu

Laboratory Rotations

(1) Kelly Jordan-Sciutto, Ph.D.

Assessing potential neurotoxicity of antiretroviral therapy

(2) Klaus Kaestner, Ph.D.

Identifying key regulators of liver regeneration

(3) Mitchell Lazar, M.D. Ph.D.

Developing assay of transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) in the liver

Doctoral Thesis

Advisor: Klaus Kaestner, Ph.D.

Cell-type-specific expression profiling of repopulating hepatocytes

Publications

1. Postnatal DNA demethylation and its role in tissue maturation. Reizel Y, Sabag O, Skversky Y, Spiro A, Steinberg B, Bernstein D, Wang A, Kieckhaefer J, Li C, Pikarsky E, Levin-Klein R, Goren A, Rajewsky K, Kaestner KH, Cedar H. *Nat Commun.* 2018 May 23;9(1):2040.
2. TRAP-seq identifies cystine/glutamate antiporter as a driver of recovery from liver injury. Wang AW, Wangenstein KJ, Wang YJ, Zahm AM, Moss NG, Erez N, Kaestner KH. *J Clin Invest.* 2018 Jun 1;128(6):2297-2309.
3. Combinatorial genetics in liver repopulation and carcinogenesis with a novel in vivo CRISPR activation platform. Wangenstein KJ, Wang YJ, Dou Z, Wang AW, Mosleh-Shirazi E, Horlbeck MA, Gilbert LA, Weissman JS, Berger SL, Kaestner KH. *Hepatology.* 2017 Nov 1. doi: 10.1002/hep.29626. [Epub ahead of print]

Awards

1. Travel Award. FASEB Science Research Conference on Fundamental Biology and Pathophysiology of the Liver. 2018
2. Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (F31DK113666), National Institute of Diabetes and Digestive and Kidney Diseases. 2017-present
3. Biomedical Graduate Studies Travel Grant, University of Pennsylvania. 2015, 2016, 2017
4. Presidential Poster of Distinction Award, AASLD The Liver Meeting. 2016

5. Predoctoral Training Grant in Pharmacology (T32GM008076), University of Pennsylvania. 2016-2017

Oral Presentations

TRAP-seq identifies cystine/glutamate antiporter as a driver of recovery from liver injury. Wang AW, Wangensteen KJ, Wang YJ, Zahm AM, Moss NG, Erez N, Kaestner KH. FASEB Science Research Conference on Fundamental Biology and Pathophysiology of the Liver. 2018



Katherine Webb

School: University of Pittsburgh
B.S. Neuroscience (2017)

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Laboratory Rotations

(1) Wade Berrentini, M.D., Ph.D.

L1 Retrotransposition and Cocaine Addiction

(2) Mariella De Biasi, Ph.D.

Inflammation in the Medial habenula- Interpeduncular Nucleus Axis and Alcohol Use Disorder

(3) Elizabeth Heller, Ph.D.

The Epigenetics of Cocaine Addiction - Elucidating a Role for Splice Factors

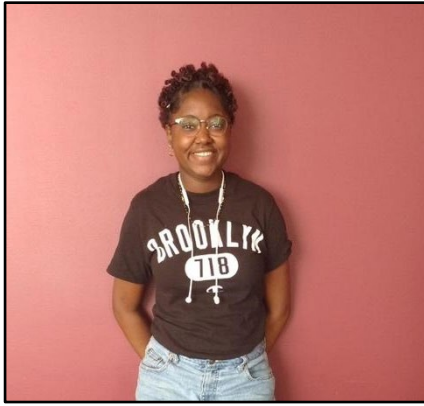
Doctoral Thesis

Advisor: Mariella De Biasi, Ph.D.

Using a novel micro drive system for in-vivo tetrode recording to characterize neuronal activity in the Medial Habenula and use this tool to understand the neuroadaptations induced in this circuitry owing to nicotine exposure and nicotine withdrawal.

Awards

T32 Pharmacology Training Grant



Khadija Wilson

School: Brooklyn College
B.S. Biology (2017)

Email: wilsonkh@pennmedicine.upenn.edu

Laboratory Rotations

(1) Benjamin Garcia, Ph.D.

Characterization of A549 multicellular tumor spheroid's proteome and histone post translational modifications using MS

(2) Robert Mach, Ph.D.

In silico docking analysis of non-selective and selective dopamine D2/D3 receptor radioligands

(3) Frances E. Jensen, M.D., FACP

Characterization of mouse hippocampal proteome post-seizure using MS

Doctoral Thesis

Advisory: Benjamin A. Garcia, Ph.D.

My project aims to determine how mutations of the histone variant, H3.3, affects neurodevelopment.



Gabriela Witek

School: Stony Brook University
B.S. Pharmacology (2016)

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Laboratory Rotations

(1) Yaël Mossé, M.D.

Optimization of Organoid Primary Cultures from Neuroblastoma Patient-derived Xenografts

(2) Jeffrey Michael Field, Ph.D.

Role of Polo-like Kinase 1 inhibitors effect on NF1 and NF2 Malignant Peripheral Nerve Sheath Tumor Cell Lines

(3) Ravi Radhakrishnan, Ph.D.

Understanding Drug Resistance through Docking and Molecular Dynamics Simulations

Doctoral Thesis

Advisor: Yaël Mossé, M.D.

Elucidating the role of Anaplastic Lymphoma Kinase signaling in Neuroblastoma

Publications

Guo, J., Grovola, M. R., Xie, H., Coggins, G. E., Duggan, P., Hasan, R., Juang, J., Lin, D. W., Song, C., **Witek, G. M.**, Berritt, S., Schultz, D. C., Field, J. (2017). Comprehensive pharmacological profiling of neurofibromatosis cell lines. *American Journal of Cancer Research*, 7(4), 923–934.



Ziyang Xu

School: Northwestern University
B.A. (2015)

Email: zxu@wistar.org

Doctoral Thesis

Advisor: David Weiner, Ph.D.

DNA encoded HIV vaccine

Presentations

Oral presentation at 2018 ISV (pending, Atlanta Georgia)

Publications

"Synthetic DNA Delivery by Electroporation Promotes Robust in vivo Sulfation of Broadly Neutralizing anti-HIV Immunoadhesin eCD4-Ig"; EBioMedicine, 2018 (in revision)

The Pharmacology Graduate Group's
35th Annual Student Symposium



Faculty Biographies



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Research Overview

Mast cells are granulated cells of hematopoietic lineage that reside close to blood vessels primarily at sites exposed to the external environment, such as the skin, oral/gastrointestinal mucosa and respiratory tract. They contribute to vascular homeostasis, innate/adaptive immunity and wound healing. Mast cells are, however, best known for their roles in allergic and inflammatory diseases such as anaphylaxis, food allergy, rhinitis, itch, urticaria, periodontitis, atopic dermatitis and asthma. Mast cells express a newly discovered G protein coupled receptor (GPCR) known as Mas-related G protein coupled receptor X2 (MRGPRX2) and the high affinity IgE receptor (FceRI). As the only mast cell lab at Penn, we are interested in delineating how MRGPRX2 and FceRI contribute to host defense and allergic/inflammatory diseases.

MRGPRX2: Activation of surface epithelial cells by pathogen-associated molecular patterns (PAMPs) results in the generation of host defense antimicrobial peptides (HDPs). These HDPs display potent antimicrobial activity and modulate immune responses via the activation of mast cells through MRGPRX2. In addition to its immunomodulatory function, MRGPRX2 likely participates in pseudo-allergic drug reactions and chronic inflammatory diseases such as urticaria, periodontitis and asthma exacerbation. A unique feature of MRGPRX2 that distinguishes it from other GPCRs is that it is activated by multiple cationic ligands including HDPs, neuropeptides (substance P and hemokinin-1), eosinophil major basic protein (MBP), eosinophil peroxidase (EPO), the neutrophil-derived cathelicidin LL-37 and many FDA approved peptidergic drugs. We are currently using cellular, molecular and imaging approaches to delineate the mechanisms involved in the regulation of MRGPRX2 in vitro and humanized mice to study its function in vivo.

FceRI: Aggregation of FceRI on mast cells by antigen and the release of proinflammatory mediators contribute to the pathogenesis of anaphylaxis and allergic asthma. It is well documented that GPCR kinases (GRKs) and the adapter protein β -arrestin contribute to the desensitization of most GPCRs. We recently made the unexpected observation that GRK2 and β -arrestin2 regulate FceRI-mediated mast cell chemotaxis, degranulation and cytokine gene expression. We are currently utilizing both in vitro and in vivo approaches to delineate how GRK2 and β -arrestin2 regulate FceRI signaling in mast cells to modulate anaphylaxis and allergic asthma.

Selected Publication

Wichayapha Manorak, Chizobam Idahosa, Kshitij Gupta, Saptarshi Roy, Reynold Panettieri Jr and Hydar Ali: *Upregulation of Mas-related G Protein coupled receptor X2 in asthmatic lung mast cells and its activation by the novel neuropeptide hemokinin-1* Respiratory Research 19(1): doi: 10.1186/s12931-017-0698-3. January 2018.

Ali, H: *Emerging Roles for MAS-Related G Protein-Coupled Receptor-X2 in Host Defense Peptide, Opioid, and Neuropeptide-Mediated Inflammatory Reactions*. Advances in Immunology. Arun Shukla (eds.). Elsevier, 136: 123-162, September 2017.

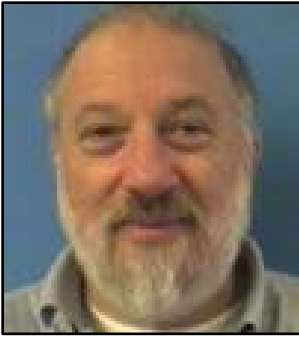
Gupta, K, Idahosa, C., Roy, S, Lee, D., Subramanian, H., Dhingra, A., Boesze-Battaglia, K, Korostoff, J., Ali, H.: *Differential Regulation of Mas-Related G Protein-Coupled Receptor X2-Mediated Mast Cell Degranulation by Antimicrobial Host Defense Peptides and Porphyromonas gingivalis Lipopolysaccharide*. Infection and

Immunity 85(10): 10 e00246-17 September 2017.

Subramanian, H., Gupta, K., Ali, H.: *Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases.* J Allergy Clin Immunol 2016.

Gupta, K., Kotian, A., Subramanian, H., Daniell, H., Ali, H.: *Activation of human mast cells by retrocyclin and protegrin highlight their immunomodulatory and antimicrobial properties.* Oncotarget 2015.

Subramanian, H., Gupta, K., Parameswaran, N., Ali, H.: *Regulation of FcRI Signaling in Mast Cells by G Protein-coupled Receptor Kinase 2 and Its RH Domain.* J Biol Chem 289(30): 20917-20927, 2014. _



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Description of Research

Communication among cells through secreted ligands and their receptors underlies the organization of tissues. The proper expression of receptors and secretion of protein ligands are dependent on accessory proteins, molecular chaperones, which regulate their biosynthesis and minimize their misfolding. Our work focuses on the molecular chaperones in the endoplasmic reticulum, where membrane and secreted proteins are synthesized.

BiP is a peptide binding protein that controls folding of antigen receptors by binding selectively to some peptides in the newly synthesized proteins. Because of this ability, BiP provides an important quality control function in screening somatically mutated molecules. One project in the lab concerns how BiP recognizes normal Ig sequences and distinguishes them from aggregation-prone somatic mutants. A second project examines the use of BiP as an inhibitor of the pathologic polymerization of antibodies into amyloid fibers.

GRP94 has a different mode of action and therefore biological activity. Although it binds peptides, its specificity is different from BiP. We use combinatorial genetic and biochemical techniques to characterize its preferred binder peptides and identify the features that it recognizes in client proteins. We developed the first cell-based assay for the chaperone function of GRP94, relying on the discovery that GRP94 is needed for production of Insulin-like growth factors, which are needed for cultured cells to cope with stress. We assay variants of GRP94 by expressing them in stressed chaperone-deficient cells. The more functional the variant chaperone, the higher the level of growth factor that is produced and the higher the survival of the cells under stress. This assay enables us to dissect the biochemical mode of action of GRP94.

Another project explores the GRP94-IGF axis in muscle physiology, using mice with targeted deletion of GRP94 in skeletal muscle. We use this model to understand what are the major client proteins of the chaperone in myocytes and to ask how modulation of GRP94 expression affect the recovery of muscle from injury.

A third project utilizes proteomic approaches to identify the interactions among ER chaperones as well as their co-factors, to understand the dynamic nature of the chaperone network and the changes in it during physiological ER stress.

Selected Publications

Ostrovsky O, Makarewich CA, Snapp EL, Argon Y.: An essential role for ATP binding and hydrolysis in the chaperone activity of GRP94 in cells. *Proc. Nat. Acad. Sci* 106(28): 11600-5, 2009 PMID: PMC2710619.

Ostrovsky O, Ahmed NT, Argon Y: The chaperone activity of GRP94 toward insulin-like growth factor II is necessary for the stress response to serum deprivation. *Mol. Biol. Cell* 20(6): 1855-64, 2009 PMID: PMC2655248.

Biswas C, Ostrovsky O, Makarewich CA, Wanderling S, Gidalevitz T, Argon Y.: The peptide binding activity of GRP94 is regulated by calcium *Biochem. J* 405(2): 233-41, 2007.

Wanderling S, Simen BB, Ostrovsky O, Ahmed NT, Vogen SM, Gidalevitz T, Argon Y.: GRP94 is essential for mesoderm induction and muscle development because it regulates IGF-II. *Mol. Biol. Cell* 18(10): 3764-75, 2007.

Elkabetz Y, Argon Y, Bar-Nun S.: Cysteines in the CH1 domain underlie retention of unassembled Ig heavy

chains. *J. Biol. Chem* 280(15): 14402-12, 2005.

Davis PD, Raffin R, Dul LJ, Vogen MS, Williamson KE, Stevens JF, Argon Y.: Inhibition of amyloid fiber assembly by both BiP and its target peptide. *Immunity* 13(4): 433-442, 2000.

Dul JL1, Davis DP, Williamson EK, Stevens FJ, Argon Y.: Hsp70 and antifibrillogenic peptides promote degradation and inhibit intracellular aggregation of amyloidogenic light chains. *J. Cell. Biol* 152(4): 705-16, 2001.

Davis DP1, Gallo G, Vogen SM, Dul JL, Sciarretta KL, Kumar A, Raffin R, Stevens FJ, Argon Y.: Both the environment and somatic mutations govern the aggregation pathway of pathogenic immunoglobulin light chain. *J. Mol. Biol* 313(5): 1023-1036, 2001.

Vogen S, Gidalevitz T, Biswas C, Simen BB, Stein E, Gulmen F, Argon Y.: Radicicol-sensitive peptide binding to the N-terminal portion of GRP94. *J. Biol. Chem* 277(43): 40742-50, 2002.

Gidalevitz T, Biswas C, Ding H, Schneidman-Duhovny D, Wolfson HJ, Stevens F, Radford S, Argon Y.: Identification of the N-terminal peptide binding site of glucose-regulated protein 94. *J. Biol. Chem.* 279(16): 16543-52, 2004.



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Research Professor, Department of Anesthesia and Critical Care

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Research Interests

Control of cerebral hemodynamics during physiologic and pathologic conditions such as traumatic brain injury, stroke, and cerebral ischemia/reperfusion.

Research Techniques

Closed cranial window for measurement of pial artery diameter and collection of cortical periarachnoid CSF for vasoactive metabolite concentration determination by RIA, fluid percussion brain injury, global cerebral ischemia, photothrombotic cerebral injury, radiolabelled microsphere regional cerebral blood flow determination.

Research Summary

Dr. Armstead's research focuses on characterizing mechanisms important in the control of cerebral hemodynamics under physiologic and pathologic conditions such as traumatic brain injury (TBI), stroke, and cerebral hypoxia/ischemia, particularly in the newborn. Current projects focus on interactions between the NMDA receptor and plasminogen activators after TBI, optimizing the efficacy/toxicity ratio of tPA, the only FDA approved treatment for stroke and translational research concerning the roles of sex and age in outcome after pediatric TBI.

Selected Publications

Armstead WM, Hekierski H, Pastor, Yarovoi S, Higazai AAR, Cines DB.: *Release of IL-6 after stroke contributes to impaired cerebral autoregulation and hippocampal neuronal necrosis through NMDA receptor activation and upregulation of ET-1 and JNK. Transl Stroke Research, in press.* Translational Stroke Research 2018 Notes: In press.

Curvello V, Hekierski H, Pastor P, Vavilala M, Armstead WM. : *Dopamine protects cerebral autoregulation and prevents hippocampal necrosis after traumatic brain injury via block of ERK MAPK in juvenile pigs.* Brain Research 1670: 118-124, 2017.

Curvello V, Hekierski H, Riley J, Vavilala M, Armstead WM.: *Sex and age differences in phenylephrine mechanisms and outcomes after piglet brain injury.* Ped Res 82: 108-113, 2017.

Armstead WM, Riley J, Vavilala MS.: *K channel impairment determines sex and age differences in epinephrine-mediated outcomes after brain injury.* J of Neuroscience Research 95: 1917-1926, 2017.

Armstead WM, Riley J, Vavilala M: *Sex and age differences in epinephrine mechanisms and outcomes after brain injury.* J Neurotrauma 34: 1666-1675, 2017.

Armstead WM, Hekierski H, Yarovoi S, Higazi AAR, Cines DB. : *tPA-A296-299 prevents impairment of cerebral autoregulation and necrosis of hippocampal neurons after stroke by inhibiting upregulation of ET-1.* J of Neuroscience Research 96: 128-137, 2017.

Armstead WM, Riley J, Vavilala MS. : *Preferential protection of cerebral auto regulation and reduction of hippocampal necrosis with norepinephrine after traumatic brain injury in female piglets.* *Pediatr Crit Care Med* 17: e130-e137, 2016.

Bohman LE, Riley J, Milovanova TN, Sanborn MR, Thom SR, Armstead, WM: *Microparticles Impair Hypotensive Cerebrovasodilation and Cause Hippocampal Neuronal Cell Injury after Traumatic Brain Injury.* *J Neurotrauma* 33: 168-174, 2016.

Armstead WM, Riley J, Vavilala MS: *Norepinephrine protects autoregulation and reduces hippocampal necrosis after traumatic brain injury via block of ERK MAPK and IL-6 in juvenile pigs.* *J Neurotrauma* 33: 1761-1767, 2016.

Armstead WM, Riley J, Yarovoi S, Higazi AAR, Cines DB: *A296-299 prevents impairment of cerebral autoregulation after Stroke through LRP dependent increase in cAMP and p38.* *Stroke* 47: 2096-2102, 2016.



Rebecca L. Ashare, Ph.D.

Assistant Professor of Psychology in Psychiatry at the Hospital of the University of Pennsylvania

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Description of Research Expertise

I am a clinical psychologist and conduct research in translational science, medication development, and neurocognition applied to nicotine dependence. My primary area of research has focused on identifying risk factors for smoking relapse, with a focus on cognitive control, decision-making, and stress, and evaluating novel treatments to improve abstinence rates. My work leverages tools from the fields of psychology, neuropharmacology, and cognitive neuroscience to understand the mechanisms that underlie smoking relapse and mechanisms of efficacy of novel interventions.

Research Projects

Several of my current research projects are focused on the intersection of smoking, HIV, and cognitive function:

One project is investigating whether HIV-infected smokers experience greater withdrawal-related cognitive deficits and whether these deficits explain the high smoking rate in this population.

In collaboration with Center for AIDS Research, we are also evaluating whether targeting the cholinergic pathway among HIV-infected individuals suppresses inflammation and reverses neurocognitive deficits and whether this effect is stronger in chronic tobacco users.

Selected Publications

Hawk, L.W., Jr., Ashare, R.L., Lohnes, S.F., Schlienz, N.J., Rhodes, J.D., Tiffany, S.T., Gass, J.C., Cummings, K.M. & Mahoney, M.C.: The effects of extended pre-quit varenicline on smoking behavior and short-term abstinence. *Clinical Pharmacology & Therapeutics*, 91(2):172-180, 2012.

Ashare, R.L., Kimmey, B. A., Rupprecht, L. E., Bowers, M.E., Hayes, M. R. & Schmidt, H. D. Repeated administration of an acetylcholinesterase inhibitor attenuates nicotine taking in rats and smoking behavior in human smokers *Translational Psychiatry*, Jan 19;6: e713, 2016.

Ashare R.L., Lerman C., Tyndale R.F., Hawk L.W., Jr., George T.P., Cinciripini P. & Schnoll, R.A. Sleep disturbance during smoking cessation: Nicotine withdrawal or side effect of treatment? *Journal of Smoking Cessation*, Epub 2016/4/12.

Harrison J, Dochney J, Blazekovic S, Leone F, Metzger D, Frank I, Gross R, Hole A, Mounzer K, Siegel S, Schnoll RA, Ashare RL. The Nature and Consequences of Cognitive Deficits among Tobacco Smokers with HIV: A Comparison to Tobacco Smokers without HIV. *J Neurovirol*, in press.



Richard K. Assoian, Ph.D.

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Overview of laboratory research:

We are an interactive group of cell/molecular biologists and bioengineers interested in understanding how cells sense changes in the physical properties of their microenvironment and how they convert this information into chemical signals, behavior and function. Within this broad area, we try to understand how physiological and pathological changes in the stiffness of the extracellular matrix (ECM) affects adhesion receptor signaling, the actin cytoskeleton, and fate decisions such as proliferation, migration and differentiation. We perform mechanistic analyses in cell culture, use genome- and proteome-wide approaches, assess mechanical properties of tissues and cells, and ultimately test physiological and pathological relevance in mouse models of vascular aging, injury, and atherosclerosis.

We are currently working in the following areas.

i) Cell Mechanobiology.

The ECM is a dynamic structure that provides both chemical and mechanical cues to cells. Remodeling of the ECM occurs in several diseases and generally tends to increase the stiffness of a cell's microenvironment. The effects of extracellular stiffness on cellular function are difficult to study when cells are cultured on traditional rigid plastic or glass substrata that are irrelevant to in vivo microenvironments. We therefore use deformable substrata (ECM-coated hydrogels) to model the stiffness of tissues that cells inhabit in vivo. With this approach, we can determine how changes in ECM stiffness affect adhesion receptor (integrin and cadherin) expression and signaling as well as downstream gene expression, proliferation, motility and differentiation. High throughput approaches are used to identify transcriptional and post-transcriptional responses to ECM stiffening. We have also used micropatterned substrata to examine the effect of cell-cell adhesion on the spreading and shape requirements for cell proliferation. Recent work with these approaches has led to the identification of stiffness-dependent signaling pathways, specific focal adhesion components controlling cyclin D1 expression, and novel mechanisms of crosstalk between cell-ECM and N-cadherin mediated cell-cell adhesion.

ii) Tissue Mechanobiology.

We are using atomic force microscopy (AFM) and pressure myography ex vivo to interrogate how changes in ECM composition and mechanosensory proteins--often through genetic manipulation of mice--affects vessel mechanics. AFM allows us to detect microheterogeneity in the stiffness of isolated arteries. Pressure myography allows us to probe stress-strain relationships in the pressurized artery and can help to distinguish effects mediated by elastin vs. collagens. Much of our current interest in this area is related to the effects of age on vessel mechanics and mechanosensing.

iii) In vivo Mechanobiology

We place significant effort on in vivo mouse models to document the relevance of adhesion receptor signaling and stiffness-sensing to mammalian biology. For example, we use mice to study adhesion receptor signaling and vascular smooth muscle cell (SMC) proliferation during the in vivo response to vascular injury, a model of acute arterial stiffening. By comparing the degree of SMC proliferation in wild-type mice and mice with knock-outs/knock-ins of integrin-regulated, mechanosensing, and cell cycle genes, we can test the importance of the

adhesion- and stiffness-regulated events we detect in primary SMCs cultured on hydrogels as described above. Similar studies are exploring the proliferative effects of N-cadherin and the role of arterial stiffening in SMC de-differentiation/re-differentiation.

We are also identifying regulators of mechanosensitive signaling, ECM remodeling, and arterial stiffening in vascular disease. One set of studies has focused on apolipoprotein E (apoE). Although best known for its role in reverse cholesterol transport, we found that apoE suppresses the expression of several ECM genes including those for collagen-I, collagen-VIII, fibronectin and lysyl oxidase. These effects protect against arterial stiffening, reduce monocyte adhesion to subendothelial ECM, and provide cholesterol-independent protection against atherosclerosis in mice. Ongoing work focuses on MMP12 as a global inducer of arterial stiffening with age, vascular injury and atherosclerosis. Finally, our newest interest is in mechano-signaling and ECM remodeling in Hutchinson-Guilford Progeria Syndrome, a genetic disease of premature aging and death that is associated with arterial stiffening, atherosclerosis and stroke.

Selected Publications

Cosgrove BD, Mui KL, Driscoll TP, Caliari SR, Mehta KD, Assoian RK, Burdick JA, Mauck RL. : N-cadherin adhesive interactions modulate matrix mechanosensing and fate commitment of mesenchymal stem cells. *Nature Materials* 15: 1297-1306, 2016.

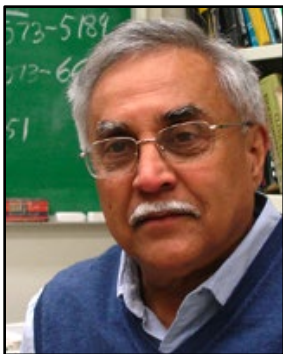
Liu SL, Bae YH, Yu C, Monslow J, Hawthorne EA, Castagnino P, Branchetti E, Ferrari G, Damrauer SM, Puré E, Assoian RK: Matrix metalloproteinase-12 is an essential mediator of acute and chronic arterial stiffening. *Scientific Reports* 5: 17189, 2015.

Mui, KM., Bae, YH, Gao, L., Liu, S-L. Xu, T., Radice, GL., Chen, CS, and Assoian, RK: N-cadherin induction by ECM stiffness and FAK overrides the spreading requirement for proliferation of vascular smooth muscle cells. *Cell Reports* 10: 1477-1486, 2015.

Bae YH, Mui KL, Hsu BY, Liu SL, Cretu A, Razinia Z, Xu T, Puré E, Assoian RK. : A FAK-Cas-Rac-Lamellipodin Signaling Module Transduces Extracellular Matrix Stiffness into Mechanosensitive Cell Cycling. *Science Signaling* 7: ra57, 2014.

Kothapalli, D.* , Liu, S.L.* , Bae, Y.H., Monslow, J., Xu, T., Hawthorne, E.A., Castagnino, P., Byfield, F.J., Rao, S., Rader, D.J., Pure, E., Phillips, M.C., Lund-Katz, S., Janmey, P.A., Assoian, R.K.: Cardiovascular protection by apoE and apoE-HDL linked to suppression of ECM gene expression and arterial stiffening. *Cell Reports* 2: 1259-1271, 2012.

Klein, E.A., Yin, L., Kothapalli, D., Castagnino, P., Byfield, F.J., Xu, T., Levantal, I., Hawthorne, E., Janmey, P.A., and Assoian, R.K.: Cell cycle control by physiological matrix elasticity and in vivo tissue stiffening. *Current Biology* 19: 1511-8, 2009.



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Research Overview

The research in Dr. Avadhani's laboratory is focused on the following aspects of mitochondrial genetics and regulation of mitochondrial membrane biogenesis in mammalian cells:

1. Mechanisms of dual targeting of cytochrome P450 and related proteins to ER and mitochondria and mechanisms of activation of the chimeric N-terminal signal by cAMP and other physiological factors.
2. Characterization of a novel mitochondria-to-nucleus stress signaling in cells subjected to mitochondrial specific genetic, and or, metabolic stress, which operates through altered $[Ca^{2+}]_c$, and the role of mitochondrial stress signaling in tumor progression and metastasis.
3. Regulation of cytochrome oxidase gene expression, and modulation of enzyme assembly/activity under chemical and oxidative stress conditions.
4. Role of mitochondrial stress signaling in Embryonic Stem Cell function/differentiation, and mammalian mitochondrial transcription under chemical and oxidative stress in ES cells.

Selected Publications

Iqbal Jameel, Sun Li, Cao Jay, Yuen Tony, Lu Ping, Bab Itai, Leu N Adrian, Srinivasan Satish, Wagage Sagie, Hunter Christopher A, Nebert Daniel W, Zaidi Mone, Avadhani Narayan G: Smoke carcinogens cause bone loss through the aryl hydrocarbon receptor and induction of Cyp1 enzymes. *Proceedings of the National Academy of Sciences of the United States of America* 110(27): 11115-20, Jul 2013.

Bajpai Prachi, Sangar Michelle C, Singh Shilpee, Tang Weigang, Bansal Seema, Chowdhury Goutam, Cheng Qian, Fang Ji-Kang, Martin Martha V, Guengerich F Peter, Avadhani Narayan G: Metabolism of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by mitochondrion-targeted cytochrome P450 2D6: implications in Parkinson disease. *The Journal of biological chemistry* 288(6): 4436-51, Feb 2013.

Bansal Seema, Anandatheerthavarada Hindupur K, Prabu Govindaswamy K, Milne Ginger L, Martin Martha V, Guengerich F Peter, Avadhani Narayan G: Human cytochrome P450 2E1 mutations that alter mitochondrial targeting efficiency and susceptibility to ethanol-induced toxicity in cellular models. *The Journal of biological chemistry* 288(18): 12627-44, May 2013.

Sleeper Meg M, Rosato Bradley P, Bansal Seema, Avadhani Narayan G: Mitochondrial dysfunction in myocardium obtained from clinically normal dogs, clinically normal anesthetized dogs, and dogs with dilated cardiomyopathy. *American journal of veterinary research* 73(11): 1759-64, Nov 2012.

Ren Ling, Hong Sung-Hyeok, Chen Qing-Rong, Briggs Joseph, Cassavaugh Jessica, Srinivasan Satish, Lizardo Michael M, Mendoza Arnulfo, Xia Ashley Y, Avadhani Narayan, Khan Javed, Khanna Chand: Dysregulation of ezrin phosphorylation prevents metastasis and alters cellular metabolism in osteosarcoma. *Cancer research* 72(4): 1001-12, Feb 2012.

Bansal Seema, Srinivasan Satish, Anandasadagopan Sureshkumar, Chowdhury Anindya Roy, Selvaraj Venkatesh, Kalyanaraman Balaraman, Joseph Joy, Avadhani Narayan G: Additive effects of mitochondrion-targeted cytochrome CYP2E1 and alcohol toxicity on cytochrome c oxidase function and stability of respirosome complexes. *The Journal of biological chemistry* 287(19): 15284-97, May 2012.



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Description of Research Expertise

The Axelsen laboratory is focused on the pathogenesis of Alzheimer's disease, particularly in the roles of oxidative stress and protein lipid interactions. A variety of whole-animal models and in vitro systems are used, as well as a large repository of human brain samples. The laboratory has developed novel isotope-based techniques for characterizing oxidative stress in brain using mass spectrometry and various forms of optical spectroscopy, including infrared, fluorescence, and internal reflection spectroscopy.

Selected Publications

Furman, R, Lee, JV, Axelsen, PH: Analysis of eicosanoid oxidation products in Alzheimer brain by LC-MS with uniformly ¹³C-labeled internal standards. *free radical biology and medicine* 118: 108-118, APR 2018.

Eskici, G, Axelsen, PH: Mass Exchange and Equilibration Processes in AOT Reverse Micelles. *langmuir* 34(7): 2522-2530, FEB 20 2018.

Grasso, G, Axelsen, PH: Effects of covalent modification by 4-hydroxy-2-nonenal on the noncovalent oligomerization of ubiquitin. *journal of mass spectrometry* 52(1): 36-42, JAN 2017.

Grasso, G, Komatsu, H, Axelsen, PH: Covalent modifications of the amyloid beta peptide by hydroxynonenal: Effects on metal ion binding by monomers and insights into the fibril topology. *journal of inorganic biochemistry* 174: 130-136, SEP 2017.

Eskici, G, Axelsen, PH: Amyloid Beta Peptide Folding in Reverse Micelles. *journal of the american chemical society* 139(28): 9566-9575, JUL 19 2017.

Eskici, G, Axelsen, PH: The Size of AOT Reverse Micelles. *journal of physical chemistry b* 120(44): 11337-11347, NOV 10 2016.

Axelsen, PH, Murphy, RC, Igarashi, M, Rapoport, SI: Increased omega 6-Containing Phospholipids and Primary omega 6 Oxidation Products in the Brain Tissue of Rats on an omega 3-Deficient Diet. *plos one* 11(10), OCT 27 2016.

Furman, R, Murray, IVJ, Schall, HE, Liu, QW, Ghiwot, Y, Axelsen, PH: Amyloid Plaque-Associated Oxidative Degradation of Uniformly Radiolabeled Arachidonic Acid. *acs chemical neuroscience* 7(3): 367-377, MAR 2016.

Klinger, AL, Kiselar, J, Ilchenko, S, Komatsu, H, Chance, MR, Axelsen, PH: A Synchrotron-Based Hydroxyl Radical Footprinting Analysis of Amyloid Fibrils and Prefibrillar Intermediates with Residue-Specific Resolution. *biochemistry* 53(49): 7724-7734, DEC 16 2014.

Murphy, RC, Axelsen, PH: MASS SPECTROMETRIC ANALYSIS OF LONG-CHAIN LIPIDS. *mass spectrometry reviews* 30(4): 579-599, JUL-AUG 2011.

Axelsen, PH, Komatsu, H, Murray, IVJ: Oxidative Stress and Cell Membranes in the Pathogenesis of Alzheimer's Disease. *physiology* 26(1): 54-69, FEB 2011.

Komatsu, H, Feingold-Link, E, Sharp, KA, Rastogi, T, Axelsen, PH: Intrinsic Linear Heterogeneity of Amyloid beta Protein Fibrils Revealed by Higher Resolution Mass-per-length Determinations. *journal of biological chemistry* 285(53): 41843-41851, DEC 31 2010.



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Description of Research Expertise

I study transitions during early development. Transitions are important developmental epochs during which time there are substantial changes in how infants/children/adolescents process information. I am particularly interested in mechanisms of stress, pain and recovery from damage to the nervous system from that developmental perspective. I study models of acute and chronic pain, infant-mother attachment, the therapeutic and adverse effects of analgesics, especially opiates, and spinal cord injury and recovery from injury. Our lab develops and uses sophisticated behavioral assays in young animals in conjunction with a number of anatomical and neurochemical assays to understand mechanisms by which these transitions occur.

Selected Publications

Sperry, M.M, Benjamin M Kandel, B.M., Wehrl, S.L., S Das, S.R.; Bass, K.N., Dhillon, P.S., Gee, J.C. and Barr, G.A.: Mapping of pain circuitry in early post-natal development using manganese-enhanced MRI in rats. *Neuroscience* 352: 180-189, March 2017.

Butkevich, I.P. , Mikhailenko, V.A. , Vershinina, E.A., Aloisi, A.M. , Barr, G.A. : Long-Term Effects of Chronic Bupropion During Adolescence Reduce The Adverse Influences of Neonatal Inflammatory Pain and Stress on Adaptive Behavior in Adult Male Rats *Frontiers in Behavioral Neuroscience*. *Frontiers in*, 11: 1-11, January 2017 Notes: DOI: 10.3389/fnbeh.2017.00011

Barr, G.A., Wang, S., Weisshaar, C.L., and Winkelstein, B.A. : Developmental changes in pain and spinal immune gene expression after radicular trauma in the rat *Frontiers in Neurology* 7(223): 1-12, December 2016 Notes: doi: 10.3389/fneur.2016.00223.

Oliver, C.R., Kabitzke, P., Serrano, P., Egan, L.J., Barr, G.A., Shair, H.N., Wiedenmayer, C.P.: Repeated recall and PKM ζ maintain fear memories in juvenile rats. *Learning and Memory* 23: 710-713, November 2016.

Rincón-Cortés, M., Barr, G.A., Mouly, A-M., Shionoyag, K., Nuñez, B.S., Sullivan, R.M. : Enduring good memories of infant trauma: Rescue of adult neurobehavioral deficits via an amygdala 5-HT/CORT interaction. *Proceedings of the National Academy of Sciences* 112(3): 881-886, January 2015.

Barr, G.A. and Hunter, D.A.: Interactions between immune and pain processes during early development. *Developmental Psychobiology* 56(8): 1698-1710, 2014.

Sarro, E.C., Sullivan, R.M. and Barr, G.A.: Unpredictable neonatal stress enhances adult anxiety and alters amygdala gene expression related to serotonin and GABA. *Neuroscience* 258: 147-161, 2014..



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Description of Research Expertise

One aspect of the research in my laboratory focuses on the study of genomic imprinting in mice. While affecting only a subset of genes in mammals, genomic imprinting results in the unequal expression of the maternal and paternal alleles of a gene. As a consequence, the maternal and paternal genomes are functionally non-equivalent and both are required for normal mammalian development. One imprinted gene, H19, is exclusively expressed from the maternally-derived allele in mice and humans. There are a number of important questions concerning the control of imprinting that are being addressed using the mouse H19 gene. These questions include how and when the inactive and active alleles are differentiated, what sequences designate that a gene is to be imprinted, and what factors function to imprint the gene. Moreover, we are also determining how the environment, including procedures used in Assisted Reproductive Technologies (ART) and endocrine disruptors, affect imprinting and epigenetic gene regulation.

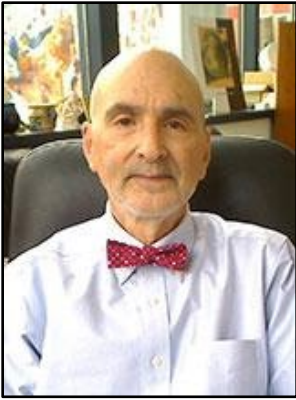
My laboratory also studies the process of X inactivation in mice. X inactivation is the dosage compensation mechanism that female mammals use to silence one X chromosome and to achieve equivalent X-linked expression to males. Certain aspects of this complex multi-step process have been well established, but the molecular and genetic mechanisms controlling this process remain poorly characterized. To isolate factors involved in X inactivation we have employed the following strategies: we have collaborated with Huntington Willard (Duke University) in conducting ENU mutagenesis in the mouse to select for mutations that affect X inactivation; we have participated in studies that assay reactivation of X-linked genes; and we have examined the effects of various mutations and environmental perturbations on X inactivation.

Selected Publications

SanMiguel Jennifer M, Abramowitz Lara K, Bartolomei Marisa S: *Imprinted gene dysregulation in a null mouse model is stochastic and variable in the germline and offspring*. *Development* (Cambridge, England) 145(7), Mar 2018.

Wang Ting, Pehrsson Erica C, Purushotham Deepak, Li Daofeng, Zhuo Xiaoyu, Zhang Bo, Lawson Heather A, Province Michael A, Krapp Christopher, Lan Yemin, Coarfa Cristian, Katz Tiffany A, Tang Wan Yee, Wang Zhibin, Biswal Shyam, Rajagopalan Sanjay, Colacino Justin A, Tsai Zing Tsung-Yeh, Sartor Maureen A, Neier Kari, Dolinoy Dana C, Pinto Jayant, Hamanaka Robert B, Mutlu Gokhan M, Patisaul Heather B, Aylor David L, Crawford Gregory E, Wiltshire Tim, Chadwick Lisa H, Duncan Christopher G, Garton Amanda E, McAllister Kimberly A, Bartolomei Marisa S, Walker Cheryl L, Tyson Frederick L: *The NIEHS TaRGET II Consortium and environmental epigenomics*. *Nature biotechnology* 36(3): 225-227, Mar 2018.

- Hur Stella K, Freschi Andrea, Ideraabdullah Folami, Thorvaldsen Joanne L, Luense Lacey J, Weller Angela H, Berger Shelley L, Cerrato Flavia, Riccio Andrea, Bartolomei Marisa S: *Humanized H19/Igf2 locus reveals diverged imprinting mechanism between mouse and human and reflects Silver-Russell syndrome phenotypes*. Proceedings of the National Academy of Sciences of the United States of America 113(39): 10938-43, Sep 2016.
- Ginart Paul, Kalish Jennifer M, Jiang Connie L, Yu Alice C, Bartolomei Marisa S, Raj Arjun: *Visualizing allele-specific expression in single cells reveals epigenetic mosaicism in an H19 loss-of-imprinting mutant*. Genes & development 30(5): 567-78, Mar 2016.
- Plasschaert Robert N, Bartolomei Marisa S: *Tissue-specific regulation and function of Grb10 during growth and neuronal commitment*. Proceedings of the National Academy of Sciences of the United States of America 112(22): 6841-7, Jun 2015.
- de Waal Eric, Vrooman Lisa A, Fischer Erin, Ord Teri, Mainigi Monica A, Coutifaris Christos, Schultz Richard M, Bartolomei Marisa S: *The cumulative effect of assisted reproduction procedures on placental development and epigenetic perturbations in a mouse model*. Human molecular genetics 24(24): 6975-85, Dec 2015.
- Susiarjo Martha, Xin Frances, Bansal Amita, Stefaniak Martha, Li Changhong, Simmons Rebecca A, Bartolomei Marisa S: *Bisphenol a exposure disrupts metabolic health across multiple generations in the mouse*. Endocrinology 156(6): 2049-58, Jun 2015.
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Research Overview

An area of interest is the function of a delta opioid receptor SNP, rs678849, in cocaine addiction and in therapeutic response of opioid addicted persons to buprenorphine and methadone.

Another area of interest is somatic DNA variation in CNS disorders, as a source of risk for those illnesses. We have projects in temporal lobe epilepsy, schizophrenia and cocaine addiction, using DNA from human brains of persons with these illnesses to map one type of somatic variation, long interspersed elements (LINE-1s).

A third area of interest is a double-blind, placebo-controlled phase II randomized clinical trial of a novel triple monoamine reuptake inhibitor in cocaine addiction.

Selected Publications

Crist RC, Clarke TK, Ang A, Ambrose-Lanci LM, Lohoff FW, Saxon AJ, Ling W², Hillhouse MP, Bruce RD, Woody G, Berrettini WH: An intronic variant in OPRD1 predicts treatment outcome for opioid dependence in African-Americans. *Neuropsychopharmacology* 38:2003-10, 2013.

Crist RC, Ambrose-Lanci LM, Vaswani M, Clarke TK, Zeng A, Yuan C, Ferraro TN, Hakonarson H, Kampman KM, Dackis CA, Pettinati HM, O'Brien CP, Oslin DW, Doyle GA, Lohoff FW, Berrettini WH: Case-control association analysis of polymorphisms in the delta-opioid receptor, OPRD1, with cocaine and opioid addicted populations. *Drug Alcohol Depend.* 127:122-8. 2013.

Doyle GA, Berrettini WH. Somatic DNA Variation in Brain as a Source of Risk for CNS Diseases. *Neuropsychopharmacology* 41:386-7, 2016.



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Description of Research Expertise

Our long term goal is to understand why some individuals are vulnerable or resilient to the potentially adverse effects of chronic stress. Chronic stress is a critical factor contributing to the development of affective and anxiety disorders and can precipitate relapse of depression and post-traumatic stress disorder. This intimate association between repeated/chronic stress and affective and anxiety disorders underscores the need to understand fully the neural circuitry that regulates the physiological and behavioral consequences of repeated stress.

We approach this need in two ways, using rat models. First, we are examining the neural circuits that are impacted by stress exposure and how these circuits, in turn, produce dysfunction in physiology and behavior. In these studies, we use state-of-the-art neuroscience techniques, including multiplex PCR and protein arrays, optogenetic stimulation of peptide release, in situ hybridization, tract tracing, immunocytochemistry and western blots, as well as behavioral and pharmacological approaches that allow us to pinpoint the brain regions of interest and to identify specific neural mechanisms. We have used these technical approaches to examine specific cortico-limbic circuits important for regulating stress reactivity. We have found that neural adaptations to chronic stress develop over time and, once developed, are stable.

Second, we examine individual differences in reactivity to stress to understand how some are vulnerable and others resistant to the effects of stress. We have observed that individual differences in how adult animals cope with defeat by a dominant animal have neural and behavioral repercussions. In addition, we have observed that prenatal and early postnatal environmental factors produce enduring effects on neural circuitry regulating stress reactivity. Recently, we have observed the stress of isolation during adolescence produces enduring effects on behavioral, neuroendocrine and neural reactivity to stress and these effects are more pronounced in females. In these developmental studies, we are collaborating to use emerging neuroimaging techniques to examine development of fiber tracts and gray matter in addition to the techniques mentioned above.

Selected Publications

- Grafe, L.A., Eacret, D., Luz, S., Gotter, A.L., Winrow, C.J., Bhatnagar S. Orexin 2 receptor regulation of the hypothalamic-pituitary-adrenal (HPA) response to acute and repeated stress. *Neuroscience*. 2017 Apr 21;348:313-323. doi: 10.1016/j.neuroscience.2017.02.038. PMID: 28257896
- Grafe, L., Eacret, D., Luz, S., Bhatnagar, S. Orexins modulate sex differences in habituation to stress and cognitive flexibility. *Biol Psychiatry*. 2017 Apr 15;81(8):683-692. doi: 10.1016/j.biopsych.2016.10.013. Epub 2016 Oct 18. PMID: 27955897
- Holmes, A. Sex and Orexins: Uncovering a mechanism underlying sex differences in stress susceptibility. *Biological Psychiatry*, Volume 81, Issue 8, 15 April 2017, pages 642-644.
- Chen, R.J., Kelly, G., Sengupta, A., Heydendael, W., Nicholas, B., Beltrami, S., Luz, S., Peixoto, L., Abel, T. Bhatnagar, S. (2015) Circulating microRNAs as biomarkers for stress resilience or vulnerability. *Neuroscience* Oct 1; 305:36-48 PMID: 26208845



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Description of Research Expertise

Establish the use of high-resolution mass spectrometry and molecular biology as tools for conducting sophisticated proteomics, DNA-adductomics, metabolomics, and lipidomics research with a particular emphasis on discovering biomarkers for the early detection of cancer and biomarkers of response in rare diseases

1. Early detection biomarkers of asbestos exposure, mesothelioma, and non-small lung cancer,

Amyloid β -peptides and high-mobility group box 1 (HMGB1) a non-histone chromosomal protein are the two most intensively studied endogenous cellular danger signals known as danger-associated molecular pattern (DAMP) molecules. DAMPs together with pathogen-associated molecular patterns alert the innate immune system by activating signal transduction pathways through binding to pattern recognition receptors (PRRs). PRRs include the receptor for advanced glycation end products (RAGE), toll-like receptors (TLRs), chemokine (C-X-C motif) receptor (CXCR), and T cell immunoglobulin mucin (TIM). Binding to PRRs induces pro-inflammatory cascades, which trigger the release of cytokines. PRRs are expressed by cells of the innate immune system such as macrophages, leukocytes and dendritic cells. They are also expressed on the surface of vascular cells, fibroblasts and epithelial cells. We have recently demonstrated that HMGB1 is secreted when blood is allowed to clot. Numerous studies have reported that HMGB1 is secreted in the circulation by cancer patients. However, many of these studies are flawed because they used serum instead of plasma. Furthermore there are 29 reported sites of acetylation on HMGB1 so it is essential that the methodology is available to quantify each of the individual proteoforms. We are currently developing an approach for the analysis of HMGB1 proteoforms in plasma samples from patients with mesothelioma and non-small cell lung cancer as well as subjects who had a heavy exposure to asbestos. We are also quantifying lipid hydroperoxide-mediated DNA damage in lymphocytes from the same population in order to further understand the etiology of the disease. Finally, metabolomics and lipidomics studies are being conducted in order to discover additional biomarkers.

2. Biomarkers of therapeutic response in rare diseases.

There are > 40 rare genetic diseases that result from aberrant protein expression including, Duchene's muscular dystrophy (DMD), spinocerebellar ataxia 1 (SCA-1), and Friedreich's ataxia (FA). Current approaches to developing therapies for these rare diseases primarily involve increasing expression of the normal protein. The necessity for monitoring protein levels was highlighted recently during the US Food and

Drug Administration (FDA) fast-track approval process for the drug eteplirsen (Exondys 51) to treat DMD. The lack of a rigorously validated method to assess up-regulation of dystrophin levels in DMD patients made it difficult to show a therapeutic response. FA is characterized by slowly progressive ataxia and hypertrophic cardiomyopathy. Lifespan is significantly reduced in FA with an average of death of 37-years, most commonly from cardiac-related pathologies. There are no approved treatments for FA, although numerous experimental approaches are being tested, which primarily involve up-regulation of frataxin protein. We have developed a strategy to monitor improvements in mitochondrial metabolism using FA platelets. We are now developing more direct measure of frataxin expression. This will also provide an approach to monitor new therapies that are being developed for rare genetic diseases of aberrant protein expression such as DMD24 and SCA-1.

Selected Publications

- Weng L, Guo L, Vachani A, Mesaros CA, Blair IA: *Quantification of Serum High Mobility Group Box-1 by Liquid Chromatography High Resolution Mass Spectrometry: Implications for its role in Immunity, Inflammation, and Cancer*. Anal Chem May 2018.
- O'Connor RS, Guo L, Ghassemi S, Snyder NW, Worth AJ, Weng L, Kam Y, Philipson B, Trefely S, Nunez-Cruz S, Blair IA, June CH, Milone MC: *The CPT1a inhibitor, etomoxir induces severe oxidative stress at commonly used concentrations*. Sci Rep 8(1): 6289, Apr 2018.
- Friedman ES, Bittinger K, Esipova TV, Hou L, Chau L, Jiang J, Mesaros C, Lund PJ, Liang X, FitzGerald GA, Goulian M, Lee D, Garcia BA, Blair IA, Vinogradov SA, Wu GD: *Microbes vs. chemistry in the origin of the anaerobic gut lumen*. Proc Natl Acad Sci USA 115(16): 4170-4175, Apr 2018.
- Ecker C, Guo L, Voicu S, Gil-de-Gómez L, Medvec A, Cortina L, Pajda J, Andolina M, Torres-Castillo M, Donato JL, Mansour S, Zynda ER, Lin PY, Varela-Rohena A, Blair IA, Riley JL: *Differential Reliance on Lipid Metabolism as a Salvage Pathway Underlies Functional Differences of T Cell Subsets in Poor Nutrient Environments*. Cell Rep 23(3): 741-755, APR 2018.
- Yue W, Wang J, Atkins KA, Bottalico L, Mesaros C, Blair IA, Santen RJ: *Effect of a tissue selective estrogen complex (TSEC) on breast cancer: Role of unique properties of conjugated equine estrogen*. Int J Cancer Mar 2018 Notes: doi: 10.1002/ijc.31401. [Epub ahead of print]
- Mazaleuskaya LL, Salamatipour A, Sarantopoulou D, Weng L, FitzGerald GA, Blair IA, Mesaros C. : *Analysis of hydroxyeicosatetraenoic acids (HETEs) in human whole blood by chiral ultrahigh performance liquid chromatography (UHPLC)-electron capture atmospheric pressure chemical ionization/high resolution mass spectrometry (ECAPCI/HRMS)*. J Lipid Res. 59(3): 564-575, Mar 2018.
- Shrimp JH, Garlick JM, Tezil T, Sorum AW, Worth AJ, Blair IA, Verdin E, Snyder NW, Meier JL.: *Defining Metabolic and Nonmetabolic Regulation of Histone Acetylation by NSAID Chemotypes*. Mol Pharm. 15(3): 729-736, Mar 2018.
- Wang Q, Guo L, Strawser CJ, Hauser LA, Hwang WT, Snyder NW, Lynch DR, Mesaros C, Blair IA : *Low apolipoprotein A-I levels in Friedreich's ataxia and in frataxin-deficient cells: Implications for therapy*. PLoS One 13(2): e0192779, Feb 2018.
- Guo L, Wang Q, Weng L, Hauser LA, Strawser CJ, Rocha AG, Dancis A, Mesaros C, Lynch DR, Blair IA. : *Liquid Chromatography-High Resolution Mass Spectrometry Analysis of Platelet Frataxin as a Protein Biomarker for the Rare Disease Friedreich's Ataxia*. Anal Chem. 90(3): 2216-2223, Feb 2018.
- Huang M, Mesaros C, Hackfeld LC, Hodge RP, Blair IA, Penning TM.: *Potential Metabolic Activation of Representative Alkylated Polycyclic Aromatic Hydrocarbons 1-Methylphenanthrene and 9-Ethylphenanthrene Associated with the Deepwater Horizon Oil Spill in Human Hepatoma (HepG2) Cells*. Chem Res Toxicol. 30(12): 2140-2150, Dec 2017.
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Research Overview

My research is aimed at understanding the molecular basis for the biochemical and behavioral changes associated with chronic drug use. How drugs exert effects that lead to long-term adaptations within the central nervous system is not well understood. However, alterations in gene expression are a likely mechanism. A group of transcription factors, CREB (cAMP response element binding protein) and CREM (cAMP response element modulatory protein), have been identified as key proteins mediating a transcriptional response to elevated levels of cAMP and/or Ca⁺⁺. We have shown that mice deficient in CREB show paradoxical responses in behavioral conditioning paradigms to morphine and cocaine. Current projects are aimed at investigating the molecular basis for this differential response with techniques ranging from EMSA's (electromobility shift assays), Western analyses, real time PCR, RNase protection assays and immunohistochemistry. In addition, recent studies in our lab have identified alterations in depression-like phenotypes in CREB deficient mice, The clinical co-morbidity between addiction and depression is striking. While little is known regarding the cause-effect relationship between these disease states, there are striking similarities at a molecular level, and, as in the case of drugs of abuse, cAMP mediated gene transcription has been implicated in the mechanism(s) of action of antidepressant drugs. Future studies involve the development and use of tissue specific gene-targeting (Cre/loxP system) to inactivate known and/or novel CREB targets to further characterize the molecules and neural circuitry involved in the mechanism of action of drugs of abuse as well as antidepressant drugs. The combined use of pharmacological, behavioral and molecular studies should lead to a better understanding of the biological basis of addiction and depression.

Selected Publications

Yohn NL, Blendy JA.: *Adolescent Chronic Unpredictable Stress Exposure Is a Sensitive Window for Long-Term Changes in Adult Behavior in Mice*. *Neuropsychopharmacology* doi: 10.1038/npp.2017.11, 2017.

Sanchez V, Carpenter MD, Yohn NL, Blendy JA.: *Long-lasting effects of adolescent oxycodone exposure on reward-related behavior and gene expression in mice*. *Psychopharmacology (Berl)*. 23-24(233): 3991-4002, Dec 2016.

Wood KH, Johnson BS, Welsh SA, Lee JY, Cui Y, Krizman E, Brodtkin ES, Blendy JA, Robinson MB, Bartolomei MS, Zhou Z.: *Tagging methyl-CpG-binding domain proteins reveals different spatiotemporal expression and supports distinct functions*. *Epigenomics* 8(4): 455-73, Apr 2016.

Forcelli Patrick A, Turner Jill R, Lee Bridgin G, Olson Thao T, Xie Teresa, Xiao Yingxian, Blendy Julie A, Kellar Kenneth J: *Anxiolytic- and antidepressant-like effects of the methadone metabolite 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline (EMDP)*. *Neuropharmacology* 101: 46-56, Feb 2016.

Falcone Mary, Lee Bridgin, Lerman Caryn, Blendy Julie A: *Translational Research on Nicotine Dependence*. *Current topics in behavioral neurosciences* Feb 2016.

Lee Bridgin G, Anastasia Agustin, Hempstead Barbara L, Lee Francis S, Blendy Julie A: *Effects of the BDNF Val66Met Polymorphism on Anxiety-Like Behavior Following Nicotine Withdrawal in Mice*. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 17(12): 1428-35, Dec 2015.

- Yohn Nicole L, Bartolomei Marisa S, Blendy Julie A: *Multigenerational and transgenerational inheritance of drug exposure: The effects of alcohol, opiates, cocaine, marijuana, and nicotine*. Progress in biophysics and molecular biology 118(1-2): 21-33, Jul 2015.
- Zhang Yong, Picetti Roberto, Butelman Eduardo R, Ho Ann, Blendy Julie A, Kreek Mary Jeanne: *Mouse model of the OPRM1 (A118G) polymorphism: differential heroin self-administration behavior compared with wild-type mice*. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 40(5): 1091-100, Apr 2015.
- Briand Lisa A, Lee Bridgin G, Lelay John, Kaestner Klaus H, Blendy Julie A: *Serine 133 phosphorylation is not required for hippocampal CREB-mediated transcription and behavior*. Learning & memory (Cold Spring Harbor, N.Y.) 22(2): 109-15, Feb 2015.
- Briand Lisa A, Hilario Monica, Dow Holly C, Brodtkin Edward S, Blendy Julie A, Berton Olivier: *Mouse model of OPRM1 (A118G) polymorphism increases sociability and dominance and confers resilience to social defeat*. The Journal of neuroscience : the official journal of the Society for Neuroscience 35(8): 3582-90, Feb 2015.
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Description of Research

Our lab focuses on the genetic and epigenetic control of hematopoiesis and its disorders. Specifically, we study how tissue-specific transcription factors govern the specification and maintenance of hematopoietic cell lineages. We examine how transcription programs are epigenetically transmitted through mitosis to maintain lineage identity. Our work is leading us deeply into the analysis of chromatin structure, its modifications and organization. For example, we investigate how regulatory elements are spatially organized in the nucleus. We are developing approaches to manipulate higher order chromatin organization as a therapeutic tool for the treatment of diseases affecting the globin genes. For our studies we combine molecular, genomic, biochemical, and imaging approaches with studies in normal and gene targeted mice.

Selected Publications

Grevet JD, Lan X, Hamagami N, Edwards CR, Sankaranarayanan L, Ji X, Bhardwaj SK, Face CJ, Posocco DF, Abdulmalik O, Keller CA, Giardine B, Sidoli S, Garcia BA, Chou ST, Liebhaber SA, Hardison RC, Shi J, and Blobel GA: *Domain-focused CRISPR-screen identifies HRI as a fetal hemoglobin regulator in human erythroid cells*. Science 2018.

Behera V, Evans P, Face CJ, Hamagami N, Sankaranarayanan L, Keller CA, Giardine B, Tan K, Hardison RC, Shi J, Blobel GA: *Exploiting genetic variation to uncover rules of transcription factor binding and chromatin accessibility*. Nature Communications 2018.

Huang P, Keller CA, Giardine B, Grevet JD, Davies JOJ, Hughes JR, Kurita R, Nakamura Y, Hardison RC, Blobel GA.: *Comparative analysis of three-dimensional chromosomal architecture identifies a novel fetal hemoglobin regulatory element*. Genes and Development 2017.

Hsu SC, Gilgenast TG, Bartman CR, Edwards CR, Stonestrom AJ, Huang P, Emerson DJ, Evans P, Werner MT, Keller CA, Giardine B, Hardison RC, Raj A, Phillips-Cremins JE, Blobel GA: *The BET Protein BRD2 Cooperates with CTCF to Enforce Transcriptional and Architectural Boundaries*. Molecular Cell 2017.

Hsiung CC, Bartman CR, Huang P, Ginart P, Stonestrom AJ, Keller CA, Face C, Jahn KS, Evans P, Sankaranarayanan L, Giardine B, Hardison RC, Raj A, Blobel GA.: *A hyperactive transcriptional state marks genome reactivation at the mitosis-G1 transition*. Genes and Development 2016.

Bartman CR, Hsu SC, Hsiung CC, Raj A, Blobel GA: *Enhancer Regulation of Transcriptional Bursting Parameters Revealed by Forced Chromatin Looping*. Molecular Cell 2016.

Lee K, Hsiung CC, Huang P, Raj A, Blobel GA: *Dynamic enhancer-gene body contacts during transcription elongation*. Genes and Development 2015.

Deng W, Rupon JW, Krivega I, Breda L, Motta I, Jahn KS, Reik A, Gregory PD, Rivella S, Dean A, Blobel GA: *Reactivation of developmentally silenced globin genes by forced chromatin looping*. Cell 2014.

Kadauke S, Udugama MI, Pawlicki JM, Achtman JC, Jain DP, Cheng Y, Hardison RC, and Blobel GA: *Tissue-specific Mitotic Bookmarking by Hematopoietic Transcription Factor GATA1*. Cell 2012.

Deng W, Lee J, Wang H, Miller J, Reik A, Gregory PD, Dean A, Blobel GA: *Controlling long-range genomic interactions at a native locus by targeted tethering of a looping factor*. Cell 2012.



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Research Details:

Transition metals are tightly regulated metabolites that function as structural or catalytic cofactors for specific proteins critical to normal physiology and development. Copper (Cu) is an essential transition metal for a diverse array of biological processes. Aberrant Cu excretion and absorption are manifested in the extremely rare genetic diseases Menkes and Wilson, respectively. The study of these diseases helped elucidate the cellular machinery responsible for the proper acquisition, distribution, and utilization of Cu. Recently Cu has been found to modulate signaling cascades and gene expression signatures in the context of normal physiology as well as the pathophysiology of diseases such as cancer.

For example, while investigating pharmacologically accessible signaling pathways downstream of oncogenic RAS, we recently demonstrated that genetic ablation of the high affinity Cu transporter CTR1 responsible for Cu uptake resulted in decreased RAF-MEK-ERK signaling through loss of the interaction between Cu and the kinases MEK1/2. This is the first example demonstrating Cu directly regulates the activity of a mammalian kinase, and hence has opened up a new way to explore how metals interact with signaling pathways. Capitalizing on the dependence of oncogenic mutations in the RAS effector protein BRAF for MEK1/2 activity, a multifaceted approach was used to examine this new signaling mechanism in the context of BRAF mutation-positive cancer. Specifically, we reported that decreasing the levels of CTR1, or introducing mutations in MEK1 that disrupt Cu binding, decreased BRAFV600E-driven signaling and tumorigenesis. Furthermore, Cu chelators used in the treatment of Wilson disease decreased the tumor growth of cells either transformed by BRAFV600E or engineered to be resistant to BRAF inhibition. This novel signaling paradigm provides a concrete intersection between Cu availability and MAPK signaling and led to the initiation of a phase I clinical trial (NCT02068079) to combine a Cu chelator with a BRAF inhibitor for the treatment of BRAF mutation-positive melanoma.

However, the molecular mechanisms by which Cu directly cooperates with specific signaling molecules to govern diverse cellular functions remain largely undefined. As such, there is a great need for a better understanding of precisely how Cu and other metals are integrated into kinase signaling networks during normal homeostasis and cancer. Moreover, these findings highlight the prospect of manipulating Cu regulation as a novel means to target essential kinase signal transduction pathways in cancer via a novel mechanism of regulation. As such, our laboratory will pioneer this new area of research by utilizing a multidisciplinary approach, from in vivo mouse models of cancer, biochemistry, molecular biology, and pharmacologic interventions.

In this regard, we are focusing on three interconnected research areas. Specifically, i) elucidating the molecular mechanisms and cellular contexts that underlie Cu integration into the MAPK pathway, ii) systematically mapping the landscape of sensitivity and resistance to perturbations in Cu availability as a new strategy to target kinase signal transduction in cancer, and iii) applying these findings to other transition metals and signaling networks in cancer.

Selected Publications

- Sadeghi R.S., Kulej, K., Kathayat, R.S., Garcia, B.A., Dickinson, B.C., Brady, D.C.#, & Witze, E.S.# : Wnt5a Signaling Induced Phosphorylation Increases Acyl Protein Thioesterase 1 Activity and Promotes Melanoma Metastatic Behavior. *Elife In Press*, 2018 Notes: (* shared first authorship or # shared corresponding author).
- Rebecca, V.W.*, Nicastrì, M.C.*, McLaughlin, N., Fennelly, C., McAfee, Q.W., Ronghe, A., Nofal, M., Lim, C.Y., Witze, E.S., Chude, C.I., Zhang, G., Alicea, G.M., Piao, S., Murugan, S., Ojha, R., Levi, S., Wei, Z., Barber-Rotenberg, J., Murphy, M.E., Dr. Mills, G.B., Lu, Y., Rabinowitz, J.D., Marmorstein, R., Liu, Q., Liu, S., Xu, X., Herlyn, M., Zoncu, R., Brady, D.C., Speicher, D.W., Winkler, J.D.#, & Amaravadi, R.K.# : A unified approach to targeting the lysosome's degradative and growth signaling roles. *Cancer Discov* 7(11): 1266-1283 Nov 2017 Notes: (* shared first authorship or # shared corresponding author).
- Brady, D.C.*#, Crowe, M.S.*, Greenberg, D.N., & Counter, C.M.#: Copper chelation inhibits BRAFV600E driven melanomagenesis and counters resistance to BRAFV600E and MEK1/2 inhibitors. *Cancer Res* 77(22): 6240-6252, Nov 2017 Notes: (* shared first authorship or # shared corresponding author).
- Brady DC, Crowe MS, Turski ML, Hobbs GA, Yao X, Chaikuad A, Knapp S, Xiao K, Campbell SL, Thiele DJ, Counter CM: Copper is required for oncogenic BRAF signalling and tumorigenesis. *Nature* 509(7501): 492-496, May 2014.
- Turski, M. L.*, Brady, D. C.*, Kim, H. J., Kim, B. E., Nose, Y., Counter, C. M., Winge, D. R. & Thiele, D. J. : A novel role for copper in Ras/mitogen-activated protein kinase signaling. *Mol Cell Biol* 32(7): 1284-1295, April 2012 Notes: (* shared first authorship or # shared corresponding author).
- Kashatus, D. F., Lim, K. H., Brady, D. C., Pershing, N. L., Cox, A. D. & Counter, C. M. : RALA and RALBP1 regulate mitochondrial fission at mitosis. *Nat Cell Biol* 13(9): 1108-1115, Sept 2011.
- Zipfel, P. A., Brady, D. C., Kashatus, D. F., Ancrile, B. D., Tyler, D. S.# & Counter, C. M.# : Ral activation promotes melanomagenesis. *Oncogene* 29(34): 4859-4864, Aug 2010 Notes: (* shared first authorship or # shared corresponding author).
- Lim, K. H.*, Brady, D. C.*, Kashatus, D. F., Ancrile, B. B., Der, C. J., Cox, A. D.# & Counter, C. M.# : Aurora-A phosphorylates, activates, and relocalizes the small GTPase RalA. *Mol Cell Biol* 30(2): 508-523, Jan 2010 Notes: (* shared first authorship or # shared corresponding author).
- O'Hayer, K. M., Brady, D. C. & Counter, C. M.: ELR+ CXC chemokines and oncogenic Ras-mediated tumorigenesis. *Carcinogenesis* 30(11): 1841-1847, Nov 2009.
- Madigan J.P., Bodemann B.O., Brady D.C., Dewar B.J., Keller P.J., Leitges M., Philips M.R., Ridley A.J., Der C.J., & Cox A.D.: Regulation of Rnd3 localization and function by protein kinase C alpha-mediated phosphorylation. *Biochem J* 424(1): 153-161, Nov 2009.
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Research Overview

My longstanding research and clinical interest is in platelet biology and the mechanisms of platelet activation in response to vascular injury and disease. Platelets are blood cells best known for their role in halting bleeding after vascular injury, but they do many other things as well, not all of which are healthy for humans. People that lack platelets are at risk for life-threatening bleeding. People that have platelets are at risk for the kinds of acute arterial thrombosis that leads to heart attacks and strokes, especially in the setting of atherosclerotic cardiovascular disease. Our goal is to understand the former and prevent the latter. The work we are doing focuses on human biology and pathology, but makes extensive use of genetically engineered mouse models and systems biology approaches as well. Studies currently funded by the NIH Heart, Lung and Blood Institute (NHLBI) and the American Heart Association include efforts to understand how platelet activation is initiated and regulated, how contacts between activated platelets foster thrombus growth and stability, in part by establishing a protected local environment, and how differences among platelets affect responses to injury. Methods that we employ range from the manipulation of gene expression in megakaryocytes to intravital high resolution confocal microscopy and computerized modeling. Campus collaborations include strong links to the School of Engineering and to investigators in the Departments of Medicine, Pediatrics and Pharmacology. Potential rotation and thesis projects can be identified in any of these areas.

Recent publications

Welsh John D, Stalker Timothy J, Voronov Roman, Muthard Ryan W, Tomaiuolo Maurizio, Diamond Scott L, Brass Lawrence F: A systems approach to hemostasis: 1. The interdependence of thrombus architecture and agonist movements in the gaps between platelets. *Blood* 124(11): 1808-15, Sep 2014 Notes: Epub 2014 June 20.

Tomaiuolo Maurizio, Stalker Timothy J, Welsh John D, Diamond Scott L, Sinno Talid, Brass Lawrence F: A systems approach to hemostasis: 2. Computational analysis of molecular transport in the thrombus microenvironment. *Blood* 124(11): 1816-23, Sep 2014 Notes: Epub 2014 June 20.

Stalker Timothy J, Welsh John D, Tomaiuolo Maurizio, Wu Jie, Colace Thomas V, Diamond Scott L, Brass Lawrence F: A systems approach to hemostasis: 3. Thrombus consolidation regulates intrathrombus solute transport and local thrombin activity. *Blood* 124(11): 1824-31, Sep 2014 Notes: Epub 2014 June 20.

Wannemacher K M, Jiang H, Hess P R, Shin Y, Suzuki-Inoue K, Brass L F: An expanded role for semaphorin 4D in platelets includes contact-dependent amplification of Clec-2 signaling. *Journal of thrombosis and haemostasis* : *JTH* 11(12): 2190-3, Dec 2013.

Brass Lawrence F, Tomaiuolo Maurizio, Stalker Timothy J: Harnessing the platelet signaling network to produce an optimal hemostatic response. *Hematology/oncology clinics of North America* 27(3): 381-409, Jun 2013.

- Voronov Roman S, Stalker Timothy J, Brass Lawrence F, Diamond Scott L: Simulation of intrathrombus fluid and solute transport using in vivo clot structures with single platelet resolution. *Annals of biomedical engineering* 41(6): 1297-307, Jun 2013.
- Mou Peipei, Zeng Zhao, Li Qiang, Liu Xiaohui, Xin Xiaoran, Wannemacher Kenneth M, Ruan Changgeng, Li Renhao, Brass Lawrence F, Zhu Li: Identification of a calmodulin-binding domain in Sema4D that regulates its exodomain shedding in platelets. *Blood* 121(20): 4221-30, May 2013.
- Stalker Timothy J, Traxler Elizabeth A, Wu Jie, Wannemacher Kenneth M, Cermignano Samantha L, Voronov Roman, Diamond Scott L, Brass Lawrence F: Hierarchical organization in the hemostatic response and its relationship to the platelet-signaling network. *Blood* 121(10): 1875-85, Mar 2013.
- Welsh J D, Colace T V, Muthard R W, Stalker T J, Brass L F, Diamond S L: Platelet-targeting sensor reveals thrombin gradients within blood clots forming in microfluidic assays and in mouse. *Journal of thrombosis and haemostasis* : JTH 10(11): 2344-53, Nov 2012.
- Flamm Matthew H, Colace Thomas V, Chatterjee Manash S, Jing Huiyan, Zhou Songtao, Jaeger Daniel, Brass Lawrence F, Sinno Talid, Diamond Scott L: Multiscale prediction of patient-specific platelet function under flow. *Blood* 120(1): 190-8, Jul 2012.
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Research Overview

My laboratory is interested in understanding the components of the blood coagulation system, how they interface with activated cells, and how disturbances in their function lead to bleeding and thrombosis. We are also interested in developing therapeutic approaches (protein and gene-based) to mitigate these events which are major causes of morbidity and mortality worldwide. We are interested in questions related to the enzymology, biochemistry, and molecular genetics of enzyme complexes involved in blood coagulation. Numerous systems are employed to answer these questions including kinetic, biophysical, and structural approaches in addition to using in vivo models to make meaningful contributions to the field. The current areas of investigation in the laboratory include:

1. Molecular basis of procofactor activation: We are interested in understanding how FV and FVIII are preserved as inactive procofactors and defining their mechanism of activation. Our work has uncovered surprising and unexpected observations that have fundamentally shifted current thinking about FV activation and its regulation by TFPI.
2. Structural correlates of protease function-basic and translational research: We seek to better understand how processing of inactive serine protease zymogens such as FX and FIX, to their active forms contributes to the expression of binding sites critical to their function. Knowledge from these biochemical studies has been applied to translational studies, some in collaboration with companies, to develop novel protein therapeutics to treat bleeding in hemophilia, trauma, or other conditions.
3. Imaging coagulation reactions in vivo. We have taken advantage of fluorescence approaches developed for physical studies of coagulation enzyme function to develop enabling technologies that permit quantitative measurements of enzyme complex assembly and function in vivo.
4. Employ gene therapy strategies for hemophilia A/B by employing novel modifications to the protein cofactor, factor VIII or zymogen FIX. Using different bioengineering strategies we are interested in modifying FVIII or FIX with unique properties that could be useful in a gene-based approach.

Selected Publications

- Jarocho, D., Vo, K.K., Lyde, R.B., Hayes, V., Camire, R.M., and Poncz, M: Enhancing functional platelet release in vivo from in vitro-grown megakaryocytic using small molecule inhibitors. *Blood Advances* 2(6): 597-606, 2018.
- Gunaratne, R., Kumar, S., Frederiksen, J.W., Stayrook, S., Lohrmann, J.L., Perry, K., Bompiani, K.M., Chabada, C.V., Thalji, N.K., Ho, M.D., Arepally, G., Camire, R.M., Krishnaswamy, K., and Sullenger, B.A: Combination of aptamer and drug for reversible anticoagulation in cardiopulmonary bypass. *Nat. Biotechnol.* In Press, 2018.
- Sim, X., Jarocho, D., Hayes, V., Haney, H.A., Marks, M.S., Camire, R.M., French, D.L., Poncz, M., and Gadue, P: Identifying and enriching the platelet-producing human stem cell-derived megakaryocytic using factor V uptake. *Blood* 130: 192-204, 2017 Notes: Commentary on paper/Cover page of journal.

- Lee, E. J., Dykas, D. J., Leavitt, A. D., Camire, R. M., Ebberink, E., de Frutos, P. G., Gnanasambandan, K., Gu, S.X., Huntington, J.A., Lentz, S.R., Mertens, K., Parish, C.R., Rezaie, A.R., Sayeski, P.P., Cromwell, C., Bar, N., Halene, S., Neparidze, N., Parker, T.L., Burns, A.J., Dumont, A., Yao, X., Lyad Ochoa Chaar, C., Connors, J.M., Bale, A.E., and Lee, A.I: Whole-exome sequencing in evaluation of patients with venous thromboembolism. *Blood Advances* 1(16): 1224-1237, 2017.
- Polderdijk, S.G.I., Adams, T.E., Ivanciu, L., Camire, R.M., Baglin, T.P., and Huntington, J.A: Design and characterization of an APC-specific serpin for the treatment of hemophilia. *Blood* 129(1): 105-113, 2017.
- Nguyen, G.N., George, L.A., Siner, J.I., Davidson, R.J., Zander, C.B., Zheng, X.L., Arruda, V.R., Camire, R.M., and Sabatino, S.E: Novel factor VIII variants with a modified furin cleavage site improve the efficacy of gene therapy for hemophilia A. *J. Thromb. Haemost.* 15(1): 110-121, 2017.
- Vadivel, K., Kumar, Y., Bunce, M.W., Camire, R.M., Bajaj, M.S., and Bajaj, S.P: Interaction of factor V B-domain acidic region with its basic region and TFPI/TFPI2: Structural insights from molecular modeling studies. *International Biology Review* 1(1): 1-12, 2017.
- Santamaria, S., Reglinska-Matveyev, N., Gierula, M., Camire, R.M., Crawley, J.T.B., Lane, D.A., and Ahnstrom, J: Factor V anticoagulant cofactor activity that targets the early phase of coagulation. *J. Biol. Chem.* 292: 9335-9344, 2017.
- Thalji, N.K., Ivanciu, L., Davidson, R., Gimotty, P.A., Krishnaswamy, S., and Camire, R.M: A rapid pro-hemostatic approach to overcome direct oral anticoagulants. *Nat. Med.* 22(8): 924-932, 2016.
- Siner, J.I., Samelson-Jones, B.J., Crudele, J.M., French, R.A., Lee, B.J., Zhou, S., Merricks, E., Raymer, R., Nichols, T.C., Camire, R.M., and Arruda, V.R: Circumventing burin enhances factor VIII biological activity and ameliorates bleeding phenotypes in hemophilia models. *JCI Insight* 1(16): e89371, 2016.
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Selected Publications

Carreno, B.M., Mardis, E.R. : A Shot against Cancer. Scientific American April 2016.

Hundal, J., Carreno, B. M., Petti, A. A., Linette, G. P., Griffith, O. L., Mardis, E. R., Griffith, M.: pVAC-Seq: A genome-guided in silico approach to identifying tumor neoantigens. Genome Med 8(1): 11, Jan 2016.

Carreno, B. M., Magrini, V., Becker-Hapak, M., Kaabinejadian, S., Hundal, J., Petti, A. A., Ly, A., Lie, W. R., Hildebrand, W. H., Mardis, E. R., Linette, G. P.: Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 348(6236): 803-8, May 2015.

Carreno, B. M., Magrini, V., Becker-Hapak, M., Kaabinejadian, S., Hundal, J., Petti, A. A., Ly, A., Lie, W. R., Hildebrand, W. H., Mardis, E. R., Linette, G. P : Vaccination Increases the Breadth and Diversity of Melanoma Neoantigen-specific T cell Immunity. 106th AACR Annual Meeting , Philadelphia, PA Apr 2015 Notes: Poster presentation.

Carreno, B.M.: Building Cancer Vaccines From Tumor Mutations. NPR, Science Friday April 2015 Notes: <http://www.sciencefriday.com/segments/building-cancer-vaccines-from-tumor-mutations>.

Linette, G.P. and B.M. Carreno: Cancer Immunotherapy. The Washington Manual of Oncology, 3rd edition. Govindan, R. and Morgensztern, D. (eds.). Wolters Kluwer, Netherlands, Page: 79, 2015 Notes: Chapter.

Carreno, B.M., Becker-Hapak, M, Cornelius, L., Linette, G.P. : High level IL-12p70 producing DC vaccine elicits Tc1-polarized immunity in patients with metastatic melanom. 13th International Symposium on Dendritic Cells, Tours, France Sep 2014 Notes: Poster presentation.

Linette, G. P., Carreno, B. M.: Dendritic cell-based vaccines: Shining the spotlight on signal 3. Oncoimmunology 2(11): e26512, Nov 2013 Notes: Review. Epub 2013 Oct 10.

Carreno, B.M.: Multiplexed Protein Detection Assay. EMD Millipore Webinar Oct 2013.

Carreno, B. M., Becker-Hapak, M., Huang, A., Chan, M., Alyasiry, A., Lie, W. R., Aft, R. L., Cornelius, L. A., Trinkaus, K. M., Linette, G. P.: IL-12p70-producing patient DC vaccine elicits Tc1-polarized immunity. J Clin Invest 123(8): 3383-94, Aug 2013 Notes: doi: 10.1172/JCI68395. Epub 2013 Jul 11.



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Description of Research

Breast cancer is the most common cancer as well as the leading cause of death from cancer among women worldwide. The Chodosh laboratory uses genetically engineered mouse models, patient samples and computational biology to study the mechanisms by which breast cancers develop, become resistant to therapy, and ultimately contribute to cancer mortality. A broad array of basic and translational research approaches are used to address problems of fundamental clinical importance to cancer patients by elucidating pathways and principles common to human cancers. Particular areas of interest include: pathways regulating cancer development, metastasis, tumor dormancy and recurrence; the use of genomics and computational approaches to understand genetic programs in cancer; the impact of obesity on cancer recurrence; the mechanisms by which pregnancy protects against breast cancer; and the use of non-invasive imaging approaches to study tumor biology. These approaches employ molecular, cellular, animal, human, and in silico model systems to study the function of key regulatory molecules in tumor biology using genetics, genomics, molecular biology, biochemistry, cell biology, computational biology, functional imaging, animal studies, preclinical trials and clinical investigation.

Recent Publications

- Maxwell KN, Soucier-Ernst D, Tahirovic E, Troxel AB, Clark C, Feldman M, Colameco C, Kakrecha B, Langer M, Lieberman D, Morrissette JJD, Paul MR, Pan TC, Yee S, Shih N, Carpenter E, Chodosh LA and DeMichele A: Comparative clinical utility of tumor genomic testing and cell-free DNA in metastatic breast cancer. *Breast Cancer Research and Treatment* 164: 627-638, 2017.
- Winkels RM, Sturgeon KM, Kallan MJ, Dean LT, Zhang Z, Evangelisti M, Brown JC, Sarwer DB, Troxel AB, Denlinger C, Laudermilk M, Fornash A, DeMichele A, Chodosh LA and Schmitz KH: The women in steady exercise research (WISER) survivor trial: The innovative transdisciplinary design of a randomized controlled trial of exercise and weight-loss interventions among breast cancer survivors with lymphedema. *Contemporary Clinical Trials* 61: 63-72, 2017.
- Abravanel DL, Belka GK, Pan TC, Pant DK, Collins MA, Sterner CJ and Chodosh LA: Notch promotes recurrence of dormant tumor cells following HER2/neu-targeted therapy. *Journal of Clinical Investigation* 125: 2484-96, 2015.
- Alvarez JV, Belka GK, Pan TC, Chen CC, Blankemeyer E, Alavi A, Karp JS and Chodosh LA: Oncogene pathway activation in mammary tumors dictates FDG-PET uptake. *Cancer Research* 74: 7583-7598, 2014.
- Feng Y, Pan TC, Pant DK, Chakrabarti KR, Alvarez JV, Ruth JR and Chodosh LA: SPSB1 promotes breast cancer recurrence by potentiating c-MET signaling. *Cancer Discovery* 4: 790-803, 2014.
- Alvarez JV, Pan TC, Ruth J, Feng Y, Zhou AY, Pant D, Grimley JS, Wandless TJ, DeMichele A, I-SPY 1 Trial Investigators and Chodosh LA: Par-4 down-regulation promotes breast cancer recurrence by preventing multinucleation following targeted therapy. *Cancer Cell* 24: 30-44, 2013.

- Chen CC, Stairs DB, Boxer RB, Belka GK, Horseman ND, Alvarez JV and Chodosh LA: Autocrine prolactin induced by the Pten-Akt pathway is required for lactation initiation and provides a direct link between the Akt and Stat5 pathways. *Genes & Development* 26: 2154-2168, 2012.
- Sarkisian CJ, Keister BA, Stairs DB, Boxer RB, Moody SE, and Chodosh LA: Dose-dependent oncogene-induced senescence in vivo and its evasion during mammary tumorigenesis. *Nature Cell Biology* 9: 493-505, 2007.
- Boxer RB, Stairs DB, Dugan KD, Notarfrancesco KL, Portocarrero CP, Keister BA, Belka GK, Cho H, Rathmell J, Thompson CB, Birnbaum MJ, and Chodosh LA: Isoform-specific requirement for Akt1 in the developmental regulation of cellular metabolism during lactation *Cell Metabolism* 4: 475-490, 2006.
- Moody SE, Perez D, Pan TC, Sarkisian CJ, Portocarrero C, Sterner CJ, Notarfrancesco K, Cardiff RD and Chodosh LA: The transcriptional repressor, Snail, promotes mammary tumor recurrence. *Cancer Cell* 8: 197-209, 2005.
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Description of Research

My career interest is to understand the mechanisms underlying malignant transformation. The progression of a normal cell into a cancerous one entails profound changes in numerous cellular functions, including its proliferation, survival, and motility/invasiveness, all of which contribute to metastatic behavior. These cell autonomous changes are coupled with alterations in the tumor cells' microenvironment, which exhibits a mutual regulation with the tumor cells and impacts upon the above properties. My work has been aimed at identifying the signaling pathways that play pivotal roles in these processes.

Most recently, we have focused our efforts on elucidating critical pathogenic factors in the development of bone and soft tissue tumors (BSTTs). In comparison to carcinomas and hematological malignancies, much less is known about the etiology of BSTTs, some of which preferentially affect children. A subset of pediatric BSTTs are driven by pathognomonic chromosomal translocations, including Ewing sarcoma, alveolar rhabdomyosarcoma, and aneurysmal bone cyst. Studies in my laboratory are aimed at identifying the mechanisms by which they contribute in disease pathogenesis. We have recently determined that the TRE17/USP6 oncogene acts as a critical pathogenic agent across a number of BSTTs. TRE17 affects multiple aspects of tumor cell biology and simultaneously modulates the tumor microenvironment. The goals of my laboratory are to determine the molecular mechanisms by which TRE17 functions, to identify additional cellular pathways critical for BSTT pathogenesis, and to develop murine models of BSTTs to ultimately allow development of novel therapeutic strategies.

My laboratory also focuses on pathogenic mechanisms of Ewing sarcoma, alveolar rhabdomyosarcoma, and a newly described cancer, sinonasal sarcoma. Efforts are underway to identify the mechanism by which their respective pathognomonic translocations function in these cancers, and identifying novel sensitivities to cytotoxic agents.

Selected Publications

Pringle L M, Young R, Quick L, Riquelme D N, Oliveira A M, May M J, Chou M M: Atypical mechanism of NF- κ B activation by TRE17/ubiquitin-specific protease 6 (USP6) oncogene and its requirement in tumorigenesis. *Oncogene* 31(30): 3525-35, Jul 2012.

Oliveira Andre M, Chou Margaret M: The TRE17/USP6 oncogene: a riddle wrapped in a mystery inside an enigma. *Frontiers in bioscience (Scholar edition)* 4: 321-34, Jan 1 2012.

Erickson-Johnson Michele R, Chou Margaret M, Evers Barbara R, Roth Christopher W, Seys Amber R, Jin Long, Ye Ying, Lau Alan W, Wang Xiaoke, Oliveira Andre M: Nodular fasciitis: a novel model of transient neoplasia induced by MYH9-USP6 gene fusion. *Laboratory investigation; a journal of technical methods and pathology* 91(10): 1427-33, Oct 2011.

Pietschmann Matthias F, Oliveira Andre M, Chou Margaret M, Ihrler Stefan, Niederhagen Manuel, Baur-Melnyk Andrea, Dürr Hans Roland: Aneurysmal bone cysts of soft tissue represent true neoplasms: a report of two cases. *The Journal of bone and joint surgery. American volume* 93(9): e45, May 2011.

Lau Alan W, Pringle Lashon M, Quick Laura, Riquelme Daisy N, Ye Ying, Oliveira Andre M, Chou Margaret M: TRE17/ubiquitin-specific protease 6 (USP6) oncogene translocated in aneurysmal bone cyst blocks osteoblastic maturation via an autocrine mechanism involving bone morphogenetic protein dysregulation.

The Journal of biological chemistry 285(47): 37111-20, Nov 2010.

Ye Y, Pringle LM, Lau AW, Riquelme DN, Wang H, Jiang T, Lev D, Welman A, Blobel GA, Oliveira AM, Chou MM.: TRE17/USP6 oncogene translocated in aneurysmal bone cyst induces matrix metalloproteinase production via activation of NF-kappaB. *Oncogene* In press, April 2010.

Blobel, G.A., Kadauke, S., Wang, E., Lau, A.W., Zuber, J., Chou, M.M., and Vakoc, C.R.: A reconfigured pattern of MLL occupancy within mitotic chromatin promotes rapid transcriptional reactivation following mitotic exit. *Molecular Cell* 36(6): 970-983, December 2009.

Fellig, Y., Oliveira, A.M., Margolin, E., Gomori, J.M., Erickson-Johnson, M.R., Chou, M.M., Umansky, F., and Soffer, D.: Extrasosseous aneurysmal bone cyst of cerebello-pontine angle with USP6 rearrangement. *Acta Neuropathology* 118: 579-581, Sept 2009.

Lau, AW and Chou, MM.: The adaptor complex AP-2 regulates post-endocytic trafficking through the non-clathrin Arf6-dependent endocytic pathway. *Journal of Cell Science* 121(24): 4008-4017, Nov 2008.



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Research summary

The goal of our lab is to identify the molecular and neural mechanisms controlling sleep, and to understand how these are interconnected with the neural circuits regulating emotional states in health and disease. To accomplish this, we employ a multi-disciplinary approach including optogenetics, in vivo electrophysiology, imaging, virus-mediated circuit mapping and gene profiling.

Selected Publications

- Chung S, Weber F, Zhong P, Tan CL, Nguyen TN, Beier KT, Hörmann N, Chang WC, Zhang Z, Do JP, Yao S, Krashes MJ, Tasic B, Cetin A, Zeng H, Knight ZA, Luo L, Dan Y: : Identification of preoptic sleep neurons using retrograde labelling and gene profiling. *Nature* 545: 477–481, May 2017.
- Xu M, Chung S, Zhang S, Zhong P, Ma C, Chang WC, Weissbourd B, Sakai N, Luo L, Nishino S, Dan Y: Basal forebrain circuit for sleep-wake control. *Nature Neuroscience* 18(11): 1641-7, Nov 2015 Notes: Xu and Chung are co-first author.
- Weber F, Chung S, Beier KT, Xu M, Luo L, Dan Y: Control of REM sleep by ventral medulla GABAergic neurons. *Nature* 526(7573): 435-8, Oct 2015.
- Chung S, Liao XH, Di Cosmo C, Van Sande J, Wang Z, Refetoff S, Civelli O: Disruption of the melanin-concentrating hormone receptor 1 (MCH1R) affects thyroid function. *Endocrinology* 153(12): 6145-54, Dec 2012.
- Chung S, Verheij MM, Hesseling P, van Vugt RW, Buell M, Belluzzi JD, Geyer MA, Martens GJ, Civelli O: The melanin-concentrating hormone (MCH) system modulates behaviors associated with psychiatric disorders. *PloS One* 6(7): e19286, Jul 2011.
- Chung S, Wong T, Nagasaki H, Civelli O: Acute homeostatic responses to increased fat consumption in MCH1R knockout mice. *Journal of Molecular Neuroscience* 42(3): 459-63, Nov 2010.
- Miyamoto-Matsubara M, Chung S, Saito Y: Functional interaction of regulator of G protein signaling-2 with melanin-concentrating hormone receptor 1. *Annals of the New York Academy of Sciences* 1200: 112-9, Jul 2010.
- Chung S, Hopf FW, Nagasaki H, Li CY, Belluzzi JD, Bonci A, Civelli O: The melanin-concentrating hormone system modulates cocaine reward. *Proceedings of the National Academy of Sciences, USA* 106(16): 6772-7, Apr 2009.
- Chung S, Pohl S, Zeng J, Civelli O, Reinscheid RK: Endogenous orphanin FQ/nociceptin is involved in the development of morphine tolerance. *The Journal of Pharmacology and Experimental Therapeutics* 318(1): 262-7, Jul 2006.
- Nagasaki H, Chung S, Dooley CT, Wang Z, Li C, Saito Y, Clark SD, Houghten RA, Civelli O: The pharmacological properties of a novel MCH1 receptor antagonist isolated from combinatorial libraries. *European Journal of*



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Research Summary

Our principal research interest is focused on the fundamental cellular and molecular mechanisms that underlie cognitive impairments associated with traumatic brain injury. We are primarily concerned with alterations in neuronal excitability in the limbic system of the brain. This system has been shown to play a primary role in higher cognitive function e.g. learning and memory and is damaged in traumatic brain injury. We incorporate a variety of techniques to understand the nature and functional consequences of injury-induced alterations.

Our studies begin with conditioned fear response behavior to assess cognitive impairments and extracellular recording to evaluate injured hippocampal function. Unbiased stereology is then used to quantify the degree of cell death. Excitatory and inhibitory synaptic recording is utilized to further determine the function of surviving neurons. Immunocytochemical and biochemical techniques are used to examine specific proteins that have been altered by injury and may be underlying synaptic and/or circuit dysfunction. The combination of these methodologies should help elucidate putative mechanisms causing injury-induced cognitive deficits. A better understanding of these injury-induced alterations will provide insight for directing the development of potential therapies that would ameliorate cognitive dysfunction in traumatic brain injured patients.

Selected Publications

Paterno Rosalia, Metheny Hannah, Cohen Akiva S: Memory deficit in an object location task after mild TBI is associated with impaired early object exploration and both are restored by branched chain amino acid dietary therapy. *Journal of neurotrauma* May 2018.

Elliott Jonathan E, De Luche Samuel E, Churchill Madeline J, Moore Cindy, Cohen Akiva S, Meshul Charles K, Lim Miranda M: Dietary therapy restores glutamatergic input to orexin/hypocretin neurons after traumatic brain injury in mice. *Sleep* 41(3), Mar 2018.

Folweiler Kaitlin, Samuel Sandy, Metheny Hannah, Cohen Akiva S: Diminished dentate gyrus filtering of cortical input leads to enhanced area CA3 excitability after mild traumatic brain injury. *Journal of neurotrauma* Jan 2018.

Xiong Guoxiang, Metheny Hannah, Johnson Brian N, Cohen Akiva S: A Comparison of Different Slicing Planes in Preservation of Major Hippocampal Pathway Fibers in the Mouse. *Frontiers in neuroanatomy* 11: 107, Nov 2017.

Wolf John A, Johnson Brian N, Johnson Victoria E, Putt Mary E, Browne Kevin D, Mietus Constance J, Brown Daniel P, Wofford Kathryn L, Smith Douglas H, Grady M Sean, Cohen Akiva S, Cullen D Kacy: Concussion Induces Hippocampal Circuitry Disruption in Swine. *Journal of neurotrauma* 34(14): 2303-2314, Jul 2017.

Yuan Feng, Xiong Guoxiang, Cohen Noam A, Cohen Akiva S: Optimized Protocol of Methanol Treatment for Immunofluorescent Staining in Fixed Brain Slices. *Applied immunohistochemistry & molecular morphology* : AIMM 25(3): 221-224, Mar 2017.

Paterno Rosalia, Metheny Hannah, Xiong Guoxiang, Elkind Jaclynn, Cohen Akiva S: Mild Traumatic Brain Injury Decreases Broadband Power in Area CA1. *Journal of neurotrauma* 33(17): 1645-9, Sep 2016.

Beamer Matthew, Tummala Shanti R, Gullotti David, Kopil Kathryn, Gorka Samuel, Ted Abel , Bass Cameron R Dale, Morrison Barclay, Cohen Akiva S, Meaney David F: Primary blast injury causes cognitive impairments and hippocampal circuit alterations. *Experimental neurology* 283(Pt A): 16-28, May 2016.

Palmer Christopher P, Metheny Hannah E, Elkind Jaclynn A, Cohen Akiva S: Diminished amygdala activation and behavioral threat response following traumatic brain injury. *Experimental neurology* 277: 215-226, Jan 2016.

Kimball Bruce A, Cohen Akiva S, Gordon Amy R, Opiekun Maryanne, Martin Talia, Elkind Jaclynn, Lundström Johan N, Beauchamp Gary K: Brain Injury Alters Volatile Metabolome. *Chemical senses* 41(5): 407-14, 06 2016.



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Description Of Research Expertise

The focus of the Cullen Lab's research in Neurotrauma is the application of engineering principles to better understand the causative mechanisms and pathophysiological responses following traumatic injury to the nervous system. Specific attention is given to neural injury biomechanics and mechanisms of acute biophysical cellular/tissue damage. In the arena of Neural Engineering, the objective is to develop neurotechnology to mitigate trauma-induced deficits or augment the body's capacity for regeneration. Here, focus is given to neural tissue engineering strategies and the development of biohybridized technologies for long-term neurobiological-electrical interfaces.

Selected Publications

Winter, C. C., Katiyar, K. S. (co-first author), Hernandez, N. S., Song, Y. J., Struzyna, L. A., Harris, J. P., Cullen, D. K.: Transplantable living scaffolds comprised of micro-tissue engineered aligned astrocyte networks to facilitate central nervous system regeneration. *Acta Biomaterialia* 38: 44-58, 2016.

Harris, J. P., Struzyna, L. A., Murphy, P. L., Adewole, O. I., Kuo, E., Cullen, D. K.: Advanced biomaterial strategies to transplant preformed micro-tissue engineered neural networks into the brain. *J Neural Engineering* 13(1): 016019, 2016.

Katiyar, K. S., Winter, C. C., Struzyna, L. A., Harris, J. P., Cullen, D. K. : Mechanical elongation of astrocyte processes to create living scaffolds for nervous system regeneration. *Tissue Engin & Regen Med* June 7, 2016 Notes: [Epub Ahead of Print] Doi.10.1002/term.2168.

Struzyna, L. A., Wolf, J. A., Mietus, C. J., Chen, H. I., Smith, D. H., Cullen, D. K.: Rebuilding brain circuitry with living micro-tissue engineered neural networks. *Tissue Engineering (Part A)* 21(21-22): 2744-56, 2015.

- Struzyna, L. A., Harris, J. P., Katiyar, K. S., Chen, H. I., Cullen, D. K.: Restoring nervous system structure and function using tissue engineered living scaffolds *Neural Regeneration Research* 10(5): 679-85, 2015.
- Struzyna, L. A., Katiyar, K. S., Cullen, D. K.: Living scaffolds for neuroregeneration. *Current Opinion in Solid State & Material Science* 18(6): 308-18, 2014 Notes: cover article.
- Cullen, D. K., Smith D. H.: Bionic connections: living bridges to connect bionic limbs to the nervous system. *Scientific American* 308(1): 52-7, 2013.
- Cullen, D. K., Tang-Schomer, M. D., Struzyna, L. A., Patel, A. R., Johnson, V. E., Wolf, J. A., Smith, D. H.: Micro-tissue engineered constructs with living axons for targeted tract reconstruction. *Tissue Engineering (Part A)* 18(21-22): 2280-89, 2012.
- Cullen, D. K., Wolf, J. A., Vernekar, V. N., Vukasinovic, J., LaPlaca, M. C.: Neural tissue engineering and biohybridized microsystems for neurobiological investigation in vitro (part 1). *Critical Reviews in Biomedical Engineering* 39(3): 201-240, 2011.
- Cullen, D. K., Wolf, J. A., Smith, D. H., Pfister, B. J.: Neural tissue engineering for neuroregeneration and biohybridized interface microsystems in vivo (part 2). *Critical Reviews in Biomedical Engineering* 39(3): 241-259, 2011.
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Description of Research Expertise

Mariella De Biasi has made significant contributions to the nicotinic field by characterizing a number of nicotinic receptor mutant mice. Her laboratory unveiled the role of various nicotinic acetylcholine receptor (nAChR) subtypes in autonomic function, the mechanisms of anxiety, and the brain circuits underlying nicotine withdrawal. The main focus has been the analysis of mice null for the $\alpha 3$, $\alpha 5$, and $\beta 4$ nAChR subunits. Studies have indicated a prominent role for those subunits in the behavioral effects of both low and high nicotine doses as well as their specific influence on the physical manifestations of nicotine withdrawal. Dr. De Biasi's lab has either generated or acquired a number of viral vectors that we are using to change nAChR expression levels in the whole brain as well as in specific neuronal subtypes.

Selected Publications

- Teng Y, Rezvani K, De Biasi M. UBXN2A regulates nicotinic receptor degradation by modulating the E3 ligase activity of CHIP. *Biochemical Pharmacology*. 97: 518-30. PMID 26265139 DOI: 10.1016/j.bcp.2015.08.084.
- Perez EE, De Biasi M. Assessment of affective and somatic signs of ethanol withdrawal in C57BL/6J mice using a short-term ethanol treatment. *Alcohol (Fayetteville, N.Y.)*. 49: 237-43. PMID 25817777 DOI: 10.1016/j.alcohol.2015.02.003
- Perez E, Quijano-Cardé N, De Biasi M. Nicotinic Mechanisms Modulate Ethanol Withdrawal and Modify Time Course and Symptoms Severity of Simultaneous Withdrawal from Alcohol and Nicotine. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*.

PMID 25790020 DOI: 10.1038/npp.2015.80

McLaughlin I, Dani JA, De Biasi M. Nicotine withdrawal. *Current Topics in Behavioral Neurosciences*. 24: 99-123. PMID 25638335 DOI: 10.1007/978-3-319-13482-6_4

Jackson KJ, Muldoon PP, De Biasi M, Damaj MI. New mechanisms and perspectives in nicotine withdrawal. *Neuropharmacology*. 96: 223-34. PMID 25433149 DOI: 10.1016/j.neuropharm.2014.11.009.

Teng Y, Rezvani K, De Biasi M. UBXN2A regulates nicotinic receptor degradation by modulating the E3 ligase activity of CHIP *Biochemical Pharmacology*. DOI: 10.1016/j.bcp.2015.08.084

Acevedo-Rodriguez A, Zhang L, Zhou F, Gong S, Gu H, De Biasi M, Zhou FM, Dani JA. Cocaine inhibition of nicotinic acetylcholine receptors influences dopamine release. *Frontiers in Synaptic Neuroscience*. 6: 19. PMID 25237305 DOI: 10.3389/fnsyn.2014.00019



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Research Overview

The main interest of this group is the non-invasive detection of metabolic changes that occur during tumor development and in response to anticancer drugs in models of human breast cancer. We employ a number of imaging modalities that include near infrared fluorescence optical imaging, MRI and MRS, PET and Cerenkov imaging. We have an active program in the design, synthesis and characterization of NIR optical contrast agents for the detection of phospholipase and choline kinase expression and activity in tumors and for the detection of pH and redox changes in the tumor microenvironment. Changes in lipid metabolite levels are monitored using MRS to determine potential biochemical markers for the detection of tumors and their early response to therapy and correlated with near-infrared optical imaging using enzyme-activated fluorescent contrast agents to detect enzyme activity in situ. We are pioneering the development of Cerenkov imaging by creating novel radiolabeled probes suitable for determining both location and function using dual PET and optical imaging.

Selected Publications

Liebov, B.K., Arroyo, A.D., Rubtsova, N.I., Osharovich, S.A., Delikatny, E.J. and Popov, A.V.: Nonprotecting group synthesis of a phospholipase C activatable probe with an azo-free quencher. *ACS Omega* 30(3): 6867-6873, Jun 2018.

Buljan, V.A., Graeber, M.B., Holsinger, R.M.D., Brown, D., Hambly, B.D., Delikatny, E.J., Vuletic, V.R., Krebs, X.N., Tomas, I.B., Bohorquez-Florez, J.J., Liu, G.J. and Banati, R.B.: Calcium-axonemal microtubuli interactions underlie mechanism(s) of primary cilia morphological changes. *J. Biol. Phys.* 44(1): 53-80, Mar 2018.

Kall, S.L., Delikatny, E.J. and Lavie, A.: Identification of a unique inhibitor-binding Site on Choline Kinase α . *Biochemistry* 57(8): 1316-1325, Feb 2018.

Predina, J.D., Newton, A.D., Keating, J., Barbosa, E.M. Jr, Okusanya, O., Xia, L., Dunbar, A., Connolly, C., Baldassari, M.P., Mizelle, J., Delikatny, E.J., Kucharczuk, J.C., Deshpande, C., Kularatne, S.A., Low, P., Drebin, J. and Singhal S.: Intraoperative molecular imaging combined with Positron Emission Tomography improves surgical management of peripheral malignant pulmonary nodules. *Annals of Surgery* 266(3): 479-488, Sep 2017.

Kachur, A.V., Arroyo, A.D., Bryan, N.W., Saylor, S.J., Popov, A.V. and Delikatny, E.J.: Synthesis of pH indicators for Cerenkov imaging by electrophilic substitution of bromine by fluorine in an aromatic system. *Journal of Fluorine Chemistry* 200: 146-152, Aug 2017.

Arlaukas, S.P., Kumar, M., Popov, A.V., Poptani, H. and Delikatny, E.J.: Near infrared fluorescent imaging of choline kinase alpha expression and inhibition in breast tumors. *Oncotarget* 8(10): 16518-30, Feb 2017.

Keating, J., Newton, A., Venegas, O., Nims, S., Zeh, R., Predina, J., Deshpande, C., Kucharczuk, J., Nie, S., Delikatny, E.J. and Singhal, S.: Near-infrared intraoperative molecular imaging can locate metastases to the lung. *Ann. Thorac. Surg.* 103(2): 390-398, Feb 2017.

- Karunamuni, R., Naha, P.C., Lau, K.C., Al-Zaki, A., Popov, A.V., Delikatny, E.J., Tsourkas, A.T., Cormode, D.A., and Maidment, A.D.A.: Development of silica-encapsulated silver nanoparticles as contrast agents intended for dual-energy mammography. *European Radiology* 26(9): 3301-9, Sep 2016.
- Kalogiannis, M., Delikatny, E.J. and Jeitner, T.M.: Serotonin as a putative scavenger of hypohalous acid in the brain. *Biochimica Biophysica Acta - Molecular Basis of Disease* 1862(4): 651-661, Apr 2016.
- Chiorazzo, M.G., Bloch, N.B., Popov, A.V. and Delikatny, E.J.: Synthesis and evaluation of cytosolic phospholipase A2 activatable fluorophores for cancer imaging. *Bioconjugate Chemistry* 26(12): 2360-2370, Dec 2015.
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Research Interests

- Drug delivery via polymer engineering.
- Cell eng'g and therapy
- Macrophages & phagocytosis: Foreign vs Self
- Molecular & cell biophysics: from extracellular matrix and stem cells to nucleus.
- Diseases ranging from cancer to muscular dystrophy and anemias.

Research Description

Dr. Discher's research focuses on novel drug delivery systems and cell therapy fundamentals. His lab develops polymer matrices that are optimized for cell growth and differentiation. Among their latest studies are macrophages recognition and phagocytosis, controlling stem cell differentiation with materials, shrinking tumors, developing new polymer forms.

Selected Publications

- D.E. Discher, D.M. Mooney, P. Zandstra. Growth factors, matrices, and forces combine and control stem cells. *Science* 324: 1673-1677 (2009).
- J-W. Shin, J. Swift, K.R. Spinler, and D.E. Discher. Myosin-II inhibition and soft 2D matrix maximize multi-nucleation and cellular projections typical of platelet-producing megakaryocytes. *Proceedings of the National Academy of Sciences – USA* 108: 11458-11463 (2011).
- J. Swift, I.L. Ivanovska, A. Buxboim, T. Harada, P.C. D.P. Dingal, J. Pinter, J.D. Pajerowski, K. Spinler, J-W. Shin, M. Tewari, F. Rehfeldt, D.W. Speicher, and D.E. Discher. Nuclear Lamin-A Scales with Tissue Stiffness and Enhances Matrix-directed Differentiation. *Science* 341: 1240104-1 to 15 (2013).
- P.L. Rodriguez, T. Harada, D.A. Christian, D.A. Pantano, R.K. Tsai, and D.E. Discher. Minimal 'Self' peptides that inhibit phagocytic clearance and enhance delivery of nanoparticles. *Science* 339: 971-975 (2013).
- J-W. Shin, A. Buxboim, K.R. Spinler, J. Swift, D.A. Christian, C.A. Hunter, C. Léon, C. Gachet, P.C. Dave P. Dingal, I.L. Ivanovska, F. Rehfeldt, J.A. Chasis, and D.E. Discher. Contractile forces sustain and polarize hematopoiesis from stem and progenitor cells. *Cell Stem Cell* 14: 81-93 (2014).
- T. Harada, J. Swift, J. Irianto, J-W. Shin, K.R. Spinler, A. Athirasala, R. Diegmiller, P.C. D.P. Dingal, I.L. Ivanovska, and D.E. Discher. Nuclear lamin stiffness is a barrier to 3D-migration, but softness can limit survival. *Journal of Cell Biology* 204:669-682 (2014).
- N.G. Sosale, T. Rouhiparkouhi, A.M. Bradshaw, R. Dimova, R. Lipowsky, and D.E. Discher. Cell Rigidity and Shape override CD47's 'Self' signaling in Phagocytosis by Hyperactivating Myosin-II. *Blood* 125:542-52 (2015).
- N.G. Sosale, K.R. Spinler, C. Alvey, and D.E. Discher. Macrophage engulfment of a cell or nanoparticle is regulated by unavoidable opsonization, a species-specific 'Marker of Self' CD47, and target physical properties. *Current Opinion in Immunology* 35:107-12 (2015).



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Description of Research

Age related macular degeneration (AMD) is the most common cause of irreversible blindness, yet its pathogenesis is poorly understood. Evidence suggests that cumulative oxidative damage contributes to AMD and aging in general. The Dunaief lab has found that AMD retinas have iron overload, which can cause oxidative stress. Increased understanding of retinal iron homeostasis may lead to treatments for AMD. To investigate the mechanisms of retinal iron regulation, the lab uses conditional knockout mouse models, human retinal tissue, and retinal cell tissue culture. A mouse line deficient in the iron transporting ferroxidases ceruloplasmin and hephaestin develops age-dependent retinal iron overload and retinal degeneration with features of AMD (Hahn et al., PNAS, 2004). Recent research in the lab indicates that inflammation promotes cellular iron overload in a vicious cycle leading to cell death. Our current focus is on the mechanisms of retinal iron homeostasis and development of therapeutics to protect the retina.

Selected Publications

- Theurl M, Song D, Clark E, Sterling J, Grieco S, Altamura S, Galy B, Hentze M, Muckenthaler MU, Dunaief JL: Mice with hepcidin-resistant ferroportin accumulate iron in the retina. *FASEB J* 30(2): 813-23, Feb 2016.
- Song D, Song J, Wang C, Li Y, Dunaief JL : Berberine protects against light-induced photoreceptor degeneration in the mouse retina. *Exp Eye Res* 145: 1-9, Apr 2016.
- Bhoiwala DL, Dunaief JL : Retinal abnormalities in β -thalassemia major. *Surv Ophthalmol* 61(1): 33-50, Jan 2016.
- Zhao L, Hadziahmetovic M, Wang C, Xu X, Song Y, Jinnah HA, Wodzinska J, Iacovelli J, Wolkow N, Krajacic P, Weissberger AC, Connelly J, Spino M, Lee MK, Connor J, Giasson B, Harris ZL, Dunaief JL: Cp/Heph mutant mice have iron-induced neurodegeneration diminished by deferiprone. *J Neurochem* 135(5): 958-74, Dec 2015.
- Bhoiwala Devang L, Song Ying, Cwanger Alyssa, Clark Esther, Zhao Liang-liang, Wang Chenguang, Li Yafeng, Song Delu, Dunaief Joshua L: CD1 Mouse Retina Is Shielded From Iron Overload Caused by a High Iron Diet. *Investigative ophthalmology & visual science* 56(9): 5344-52, Aug 2015.
- Gelfand Bradley D, Wright Charles B, Kim Younghee, Yasuma Tetsuhiro, Yasuma Reo, Li Shengjian, Fowler Benjamin J, Bastos-Carvalho Ana, Kerur Nagaraj, Uittenbogaard Annette, Han Youn Seon, Lou Dingyuan, Kleinman Mark E, McDonald W Hayes, Núñez Gabriel, Georgel Philippe, Dunaief Joshua L, Ambati Jayakrishna: Iron Toxicity in the Retina Requires Alu RNA and the NLRP3 Inflammasome. *Cell reports* 11(11): 1686-93, Jun 2015.

Li Y, Song D, Song Y, Zhao L, Wolkow N, Tobias JW, Song W, Dunaief JL: Iron-induced Local Complement Component 3 (C3) Up-regulation via Non-Canonical TGF- β Signaling in the Retinal Pigment Epithelium. *Journal Biol Chem* 290(19): 11918-34, May 2015.

Guo LY, Alekseev O, Li Y, Song Y, Dunaief JL: Iron Increases APP Translation and Amyloid-Beta Production in the Retina. *Exp Eye Res* 129: 31-7, Dec 2014.

Hahn, Paul. Qian, Ying. Dentchev, Tzvete. Chen, Lin. Beard, John. Harris, Zena Leah. Dunaief, Joshua L.: Disruption of ceruloplasmin and hephaestin in mice causes retinal iron overload and retinal degeneration with features of age-related macular degeneration. *Proceedings of the National Academy of Sciences of the United States of America* 101(38): 13850-5, Sep 2004.

Dunaief, J L. Strober, B E. Guha, S. Khavari, P A. Alin, K. Luban, J. Begemann, M. Crabtree, G R. Goff, S P.: The retinoblastoma protein and BRG1 form a complex and cooperate to induce cell cycle arrest. *Cell* 79(1): 119-30, Oct 7 1994.



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Research summary

The research efforts of my laboratory are directed towards understanding the molecular basis of neuronal functioning. Our experimental approach is reductionist in nature and involves analysis of gene expression in individual cells dispersed in culture, in the live slice preparation or from fixed pathological tissue specimens. We have developed various procedures that have enabled the analysis of cellular functioning using single cells as the experimental model. These procedures include those that permit an analysis of the mRNA complement, the protein complement and an assessment of mRNA movement and translation within single cells. This level of analysis is important since an individual cells biochemical composition may be diluted by that of surrounding cells. We are currently generating molecular and bioprocess fingerprints of various cell types and disease states. When this is complete, we hope that it will be possible to alter the cellular response to various challenges by altering the levels of these biological processes in a predictable manner. As part of these studies, we are examining the role of subcellular localization of mRNAs in regulating cellular function. We have shown that multiple mRNAs are localized in neuronal dendrites and have provided a formal proof of local mRNA translation in dendrites. Further, we have recently shown that the intracellular sites of localization and translation of these mRNAs can be altered by synaptic stimulation highlighting for the first time that in vivo translation of a mRNA can occur at different rates in distinct regions of a single cell (translation is primarily exponential in dendrites and linear in the cell soma). These insights into the cell biology of neuronal function highlight the complexities that remain to be understood.

Selected Publications

Bell TJ, Miyashiro KY, Sul, J-Y, McCullough R, Buckley PT, Jochems J, Meaney DF, Haydon P, Cantor C, Parsons TD, Eberwine, J: *Cytoplasmic BK(Ca) channel intron-containing mRNAs contribute to the intrinsic excitability of hippocampal neurons*. *Proc Natl Acad Sci USA* 105: 1901-1906, 2008.

Wu C-K, Zeng, F, Eberwine, J: *mRNA transport to and translation in neuronal dendrites [Review]* *Anal Bioanal Chem* 387: 59-62, 2007.

- Barrett LE, Sul JY, Takano H, Van Bockstaele EJ, Haydon PG, Eberwine JH: *Region-directed phototransfection reveals the functional significance of a dendritically synthesized transcription factor*. Nature Methods 3: 455-460, 2006.
- Zielinski J, Kilk K, Peritz T, Kannanayakal T, Miyashiro KY, Eiriksdottir E, Jochems J, Langel U, Eberwine J: *In vivo identification of ribonucleoprotein-RNA interactions*. Proc National Acad Sci USA 103: 1557-1562, 2006.
- Zeng F, Peritz T, Kannanayakal TJ, Kilk K, Eiriksdottir E, Langel U, Eberwine J: *A protocol for PAIR: PNA-assisted identification of RNA binding proteins in living cells*. Nature Protocols 1: 920-7, 2006.
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Research Overview

MOLECULAR PHARMACOLOGY OF INHALED ANESTHETICS

The inhaled anesthetics are considered one of the most important medical advances of all time, are used in over 100 million patients every year, and yet remain the most toxic and poorly understood of all drugs. The goal of my laboratory is a translational understanding of inhaled anesthetic pharmacology. Most of the current work uses biophysical and chemical biological characterization of anesthetic/macromolecular interactions because of the importance of establishing a foundation of knowledge at this most basic level, on which the subsequent superstructure of molecular, cellular and organism understanding will be built. We have developed a wide variety of experimental approaches to study inhaled anesthetics binding to proteins, and the structural and dynamic consequences. Thus, photoaffinity labeling, fluorescence spectroscopy, amide hydrogen exchange, low-affinity elution chromatography and differential/isothermal calorimetry have all been introduced and validated for this purpose. Many protein and peptide models are used, including serum albumin and its domains, odorant binding protein, rhodopsin and other G-protein-coupled receptors, ferritin, and de novo designed helical bundles. Our group also uses NMR spectroscopy, x-ray crystallography and molecular dynamic simulations via close collaborations to gain a detailed atomic-level appreciation for the interactions and consequences in both time and space. In collaboration with Pat Loll of Drexel University, we have characterized halothane, isoflurane and propofol complexes with various proteins. In collaboration with the Dailey and Dmochowski labs (Chemistry), we synthesize novel reagents to allow photolabeling, click chemistry and fluorescence imaging to further identify cellular and molecular substrates of anesthetic action. Proteomic and genomic approaches have permitted initial forays into cell and organism implications of our binding results. Wide collaborations with many other departments and institutions have facilitated a rapid, multidisciplinary attack on some of the most fundamental questions in anesthetic pharmacology.

NEURODEGENERATIVE DISORDERS

Our studies of inhaled anesthetics led to the observation that they can potently promote aggregation of selected peptides and proteins. Since a common feature of most neurodegenerative disorders is aggregation of endogenous peptide, inhaled anesthetics may enhance this process, and accelerate the onset of the disorder. Examination of this possibility in a fully translational manner is a growing focus of my laboratory. Current efforts include cell culture, transgenic animals, clinical biomarker studies and associative database studies.

Selected Publications

Woll Kellie A, Murlidaran Sruthi, Pinch Benika J, Hénin Jérôme, Wang Xiaoshi, Salari Reza, Covarrubias Manuel, Dailey William P, Brannigan Grace, Garcia Benjamin A, Eckenhoff Roderic G: A Novel Bifunctional Alkylphenol Anesthetic Allows Characterization of γ -Aminobutyric Acid, Type A (GABAA), Receptor Subunit Binding Selectivity in Synaptosomes. *The Journal of biological chemistry* 291(39): 20473-86, Sep 2016.

Ho J, Perez-Aguilar JM, Gao L, Saven JG, Matsunami H, Eckenhoff RG: Molecular recognition of ketamine by a subset of olfactory G protein-coupled receptors. *Sci. Signal.* 8(370), April 2015.

Weiser Brian P, Eckenhoff Roderic G: Propofol Inhibits SIRT2 Deacetylase through a Conformation-specific, Allosteric Site. *The Journal of biological chemistry* 290(13): 8559-68, Mar 2015.

McKinstry-Wu Andrew R, Bu Weiming, Rai Ganesha, Lea Wendy A, Weiser Brian P, Liang David F, Simeonov

- Anton, Jadhav Ajit, Maloney David J, Eckenhoff Roderic G: Discovery of a novel general anesthetic chemotype using high-throughput screening. *Anesthesiology* 122(2): 325-33, Feb 2015.
- Tang Junxia X, Mardini Feras, Janik Luke S, Garrity Sean T, Li Rosie Q, Bachlani Gulnaz, Eckenhoff Roderic G, Eckenhoff Maryellen F: Modulation of murine Alzheimer pathogenesis and behavior by surgery. *Annals of surgery* 257(3): 439-48, Mar 2013.
- Emerson DJ, Weiser BP, Psonis J, Liao Z, Taratula O, Fiamengo A, Wang X, Sugasawa K, Smith A, Eckenhoff RG, Dmochowski IJ. : Direct modulation of microtubule stability contributes to anthracene general anesthesia. *J. Am. Chem. Soc.* 2013.
- Hall Michael A, Xi Jin, Lor Chong, Dai Shuiping, Pearce Robert, Dailey William P, Eckenhoff Roderic G: m-Azipropofol (AziPm) a photoactive analogue of the intravenous general anesthetic propofol. *Journal of medicinal chemistry* 53(15): 5667-75, Aug 2010.
- Liu R, Loll PJ, Eckenhoff RG: Structural basis for high-affinity volatile anesthetic binding in a natural 4-helix bundle protein. *FASEB J.* 19(6): 567-76, Apr 2005.
- Eckenhoff RG, Johansson JS, Wei H, Carnini A, Kang B, Wei W, Pidikiti R, Keller JM, Eckenhoff MF: Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology* 101(3): 703-9, Sep 2004.
- Eckenhoff RG: Promiscuous ligands and attractive cavities; How do the inhaled anesthetics work? *Mol. Interventions* 1: 258-268, 2001.
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Description of Research Expertise

I am a neuroscientist with a broad interest in how molecular and cellular changes – such as the changes in the number of neurons generated in the hippocampus, a brain region important for learning/memory and regulation of anxiety and the stress response – influence both normal behavior and cognitive functioning. I am interested in how developmental and adult neurogenesis in particular and dentate gyrus plasticity in general contribute to abnormal functioning with relevance to developmental, psychiatric, and neurological disorders. Current Eisch Lab projects span genetic, molecular, cellular, circuit, and functional/behavioral levels, and are funded by NASA and NIH (both the National Institute on Drug Abuse and National Institute on Mental Health).

Selected Publications

- Yun S, Reynolds RP, Petrof I, White A, Rivera PD, Segev A, Gibson AD, Suarez M, Desalle MJ, Ito N, Mukherjee S, Richardson DR, Kang CE, Ahrens-Nicklas RC, Soler I, Chetkovich DM, Kourrich S, Coulter DA, Eisch AJ. : *Stimulation of entorhinal cortex-dentate gyrus circuitry is antidepressive*. *Nature Medicine* 24(5): 658-666 April 2018.
- Ochoa Escamilla C*, Filonova I*, Walker AK, Xuan Z, Holehonnur R, Espinosa F, Liu S, Thyme SB, Lopez-Garcia IA, Mendoza DB, Usui N, Ellegood J, Eisch AJ, Konopka G, Lerch JP, Schier AF, Speed HE, Powell CM. : *Kctd13 deletion reduces synaptic transmission via increased RhoA*. *Nature* 9(551): 227-231, November 2017.
- Whoolery CW, Walker AK, Lucero MJ, Richardson DR, Reynolds RP, Beddow DH, Clark KL, Shih H-Y, LeBlanc JA, Cole MG, Amaral WZ, Mukherjee S, Zhang S, Ahn F, Bulin SE, DeCarolis NA, Rivera PD, Chen BPC, Yun S, Eisch AJ. : *Whole Body Exposure to 28Si Radiation Dose-Dependently Disrupts Dentate Gyrus Neurogenesis and Proliferation in the Short-Term and New Neuron Survival and Contextual Fear Conditioning in the Long-Term*. *Radiation Research* 2017.
- Celen C, Chuang J-C, Luo X, Walker AK, Nijem N, Chung A, Nguyen LH, Nassour I, Budhipramono A, Sun X, Zhang S, Bok LA, McEntagart M, Gevers E, Birnbaum SG, Eisch AJ, Santen G.W.E., Chahrour M, Zhu H: *Arid1b haploinsufficient mice reveal neuropsychiatric phenotypes and reversible causes of growth impairment*. *eLife* 2017.
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Research Expertise

The role of the Hippo pathway in soft tissue sarcomas

Nearly 15,000 Americans are diagnosed with a form of soft-tissue sarcoma every year and roughly 30% of these tumors will result in potentially lethal lung metastases. The roughly 65 sarcoma subtypes, derived from a variety of mesenchymal tissues including, bone, muscle, cartilage, and fat, present a complex research problem. This complexity has resulted in a distressing lack of funding and no targeted therapies. In fact, sarcoma treatment has not changed significantly in 25 years. Patients are limited to radiation, toxic chemotherapy, and surgery. The discovery of novel targets and mechanisms is therefore critical. Several studies, including my own, have shown that deregulation of the Hippo pathway, and its main downstream effector YAP1, is required for proliferation in several common sarcoma subtypes, including fibrosarcoma, liposarcoma and undifferentiated pleomorphic sarcoma (UPS).

The Hippo pathway is required for proliferation control in sarcoma cells. This signaling hub consists of a kinase cascade whose purpose is to phosphorylate YAP1 leading to its proteasomal degradation. Inactivation of the pathway in response to upstream growth signals leaves YAP1 unphosphorylated allowing its nuclear localization. Nuclear YAP1 co-activates transcription of pro-survival and proliferation targets (i.e. BIRC5, FOXM1), though it can also repress transcription of certain genes. Though it is implicated in sarcomagenesis, regulation of YAP1 and its critical downstream transcriptional targets are virtually unknown in this context. Investigation of these mechanisms will reveal novel therapeutic opportunities for sarcoma patients and potentially in epithelial tumors as well. The “epithelial-to-mesenchymal transition” (EMT) is critical for metastasis of epithelial cancers (i.e. breast, pancreas). Characterization of YAP1 and its targets in mesenchymal cells may help elucidate the role of YAP1 during EMT and metastasis. Interestingly, no common mutations in Hippo pathway components have been reported in sarcomas and copy number loss of the key proteins occurs in only 25% of reported cases. Our recent work highlighted the role of epigenetic silencing in sarcoma; therefore we are investigating the possibility that YAP1 modulators are epigenetically regulated.

Mechanisms of sarcoma metastasis

Metastasis is the most lethal aspect of cancer. 30%-50% of all malignancies will metastasize resulting in more than 90% of cancer-related fatalities. There is a critical need for a thorough understanding of metastatic processes and the development of new approaches targeting metastatic cells. For many types of cancer including breast, prostate, kidney and soft tissue tumors the lung is the most common site of metastasis. In fact, soft tissue sarcomas disseminate almost exclusively to the lungs in both humans and preclinical mouse models, highlighting the usefulness of sarcoma models in the study of pulmonary metastasis. The lack of novel therapies against pulmonary metastases can be attributed in part to the technical difficulties associated with studying metastatic cells. Vascular adherence and extravasation have been particularly challenging to investigate due to the difficulty in modeling these processes. One recent hypothesis is that platelets promote metastasis by enhancing extravasation. The role of collagen in activating platelets, through the surface receptor GPVI, during wound healing is well understood; however the contribution of collagen-activated platelets to tumor cell

extravasation and metastasis is unknown. Upon activation, platelets secrete the contents of their alpha and dense granules, which contain signaling molecules that open the endothelial wall of blood vessels during wound healing in order to recruit additional platelets and other cells necessary for repair. During metastasis, this process could be repurposed to allow tumor cells to exit the vasculature and enter the lung.

The tools to evaluate this question mechanistically have not been widely available. However, we have now identified the technology, assays, and models to evaluate tumor cell adherence and platelet-mediated extravasation in the physiologically relevant setting of spontaneous in vivo undifferentiated pleomorphic sarcoma (UPS) metastasis to the lung. These tumors are highly metastatic and we can model pulmonary metastasis using multiple tools already available in my lab including human UPS cells for xenograft, as well as two independent autochthonous genetic models (*KrasG12D/+; Ink4a/Arffl/fl* and *KrasG12D/+; Trp53fl/fl* (5)), and allografts of murine tumor cells derived from these genetic models. Our published work using these systems has reported that lung metastases in sarcoma are associated with increased primary tumor expression of the intracellular collagen-modifying enzyme PLOD2/lysyl hydroxylase 2. Excessive lysyl hydroxylation, due to PLOD2, results in secretion of immature collagen molecule aggregates able to physically associate with tumor cells. Other groups have reproduced this observation in breast and liver cancers, suggesting broad implications for our work. We have also shown that PLOD2 is required for the vascular adhesion and extravasation stages of metastasis. However, we do not yet understand how PLOD2 regulates this process. We have found metastatic sarcoma cells residing in pulmonary vessels where they deposit significant amounts of collagen but the importance of this ECM deposition and modification in sarcoma cell extravasation and lung colonization is essentially unknown. These questions are critical as the answers may explain why lung metastases can be successfully ablated only to reappear within several months. Intravascular tumor cells may be protected from exposure to chemo and radiotherapy due to their vascular adherence and surrounding collagen. Thus, when lung resident tumor cells are killed by chemo/radiation therapy, they can be replaced by surviving cells from the “source blood vessel”. The role of deposited collagen in the vessel may be two-fold: 1) to physically allow tumor cell adherence to vascular endothelial cells and 2) GPVI receptor-mediated platelet activation. Our work will evaluate these hypotheses and determine the role of collagen in vascular adherence and extravasation for the purpose of identifying novel therapeutics that could target the molecular processes underlying pulmonary metastases in sarcoma and other cancers..

Selected Publications

Ye S, Lawlor MA, Rivera-Reyes A, Egolf S, Chor S, Pak K, Ciotti GE, Lee AC, Marino G, Shah J, Niedzwicki D1, Weber K, Park PMC, Alam MZ, Grazioli A, Haldar M, Xu M, Perry JA, Qi J, Eisinger-Mathason TSK: YAP1-mediated suppression of USP31 enhances NF- κ B activity to promote sarcomagenesis. *Cancer Research* Epub, Feb 2018.

Sesen, J., Casaos, J., Scotland, S.J., Seva, C., Eisinger-Mathason, T.S.K., Skuli, N: INT6/eIF3e: the good and the bad *Frontiers in Bioscience* 1(22): 1-20, Jan 2017.

Volpin, F., Casaos, J., Sesen, J., Mangraviti, A., Frickeche, J., Lott, T., Felder, R., Scotland S.J., Eisinger-Mathason, T.S.K., Brem, H., Tyler, B., Skuli, N: Use of an anti-viral drug, Ribavirin, as an anti-glioblastoma therapeutic. *Oncogene* 36(21): 3037-3047, Dec 2016 Notes: Epub 2016 Dec 12. doi: 10.1038/onc.2016.457.

Lewis, D., Park, K.Y., Tang, V., Xu, Y., Pak, K., Eisinger-Mathason, T.S.K., Simon, M.C., Gerecht, S. : Intratumoral oxygen gradients mediate sarcoma cell invasion. *Proc Natl Acad Sci U S A* 113(33): 9292-7, Aug 2016 Notes: Epub 2016 Aug 2. doi: 10.1073/pnas.1605317113.

Michael S. Nakazawa, T.S.K Eisinger-Mathason, Navid Sadri, Joshua Ochocki, Terrence Gade, M. Celeste simon: Epigenetic re-expression of HIF-2 α suppresses soft tissue sarcoma growth. *Nature Communications* 3(7): 10539, Feb 2016.

Ye S., Eisinger-Mathason TS: Targeting the Hippo Pathway: Clinical Implications and Therapeutics. *Pharmacology Research* 103: 270-8, Jan 2016.

Eisinger-Mathason, T.S.K., Mucaj, V., Biju, K.M., Nakazawa, M.S., Gohil, Cash, T.P., M. Yoon, S.S., Park, K.M., Skuli, N., Gerecht, S., Simon, M.C.: Deregulation of the Hippo pathway in soft tissue sarcoma promotes FOXM1 expression and tumorigenesis. PNAS 112(26): E3402-11, Jun 2015 Notes: Epub 2015 Jun 15. doi: 10.1073/pnas.1420005112.

Yoon, C., Lee, H.J., Park, D.J., Lee, Y.Y., Tap, W.D., Eisinger-Mathason, T.S.K, Hart, C.P., Choy, E., Simon, M.C., Yoon, S.S. : Hypoxia-activated chemotherapeutic TH-302 enhances the effects of VEGF-A inhibition and radiation on sarcomas. British Journal of Cancer 113(1): 46-56, Jun 2015 Notes: Epub 2015 May 26. doi: 10.1038/bjc.2015.186.

Mathew, L.K., Huang, Y., Mucaj, V., Lee, S.S, Skuli, N., Eisinger-Mathason, T.S.K., Biju, K.M., Li, B., Veneti, S., Lal, P., Lathia, J.D., Rich, J.N., Keith, B., Simon, M.C.: Feedback circuitry between mir-218 repression and RTK activation in glioblastoma. Science Signaling 8(375): ra42, May 2015.



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Selected Publications

Chen X, Yang Y, Berger I, Khalid U, Patel A, Cai J, Farwell MD, Langer C, Aggarwal C, Albelda SM, Katz SI: Early detection of pemetrexed-induced inhibition of thymidylate synthase in non-small cell lung cancer with FLT-PET imaging. Oncotarget 8(15): 24213-24223, 2017.

Lameka K, Farwell MD, Ichise M: Positron Emission Tomography. Handb Clin Neurol. 135: 209-227, 2016.

Mankoff DA, Edmonds CE, Farwell MD, Pryma DA: Development of Companion Diagnostics. Semin Nucl Med. 46(1): 47-56, 2016.

Shah NN, Torigian DA, Farwell MD, Hwang WT, Frey NV, Nasta S, Landsburg DJ, Mato AR, June CH, Schuster SJ, Porter DL, Svoboda J: Utility of FDG-PET/CT in lymphoma patients undergoing immunotherapy with autologous CTL019 T-cells. J Clin Oncol. ASCO annual meeting, 2015.

Mankoff DA, Farwell MD, Clark AS, Pryma DA: How imaging can impact clinical trial design: molecular imaging as a biomarker for targeted cancer therapy. Cancer J. 21(3): 218-224, 2015.

Farwell MD, Clark AS, Mankoff DA: How imaging biomarkers can inform clinical trials and clinical practice in the era of targeted cancer therapy. JAMA Oncology 1(4): 421-422, 2015.

Farwell MD, Pryma DA, Mankoff DA: PET/CT imaging in cancer: Current applications and future directions. Cancer 120(22): 3433-3445, 2014.

Harris PE, Farwell MD, Ichise M: PET quantification of pancreatic VMAT 2 binding using (+) and (-) enantiomers of [18F]FP-DTBZ in baboons. Nucl Med Biol. 40(1): 60-64, 2013.

Farwell MD, Chong DJ, Iida Y, Bae SA, Easwaramoorthy B, Ichise M: Imaging P-glycoprotein function in rats using [(11)C]-N-desmethyl-loperamide. Ann Nucl Med. 27(7): 618-624, 2013.



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Research Overview

Systems Pharmacology of Ras signaling in cancer:

Mutations in genes called oncogenes lead to the uncontrolled growth that is the hallmark of cancer. Oncogenes express proteins that regulate signaling pathways essential to the tumor cell. We study the Ras oncogene, one of the most commonly mutated oncogenes. Mutational activation of Ras causes changes in three basic properties of cells. These are: (1) increases in cell proliferation to stimulate growth, (2) reorganization of the actin cytoskeleton to promote invasion and metastases and (3) inhibition of apoptosis to prevent tumor cells from undergoing programmed cell death. Previously, we studied Ras signaling in tumors focusing on the role of Pak kinases, providing the first proof-of-principle that Pak kinases are targets for new targeted therapies. Indeed, numerous companies and academic groups are developing small molecule inhibitors of Pak. More recently we developed a systems approach to study Ras tumors using genomics, high throughput screening and siRNA screening. Ongoing studies are validating lead compounds and genes identified in screens as well as developing new screening platforms. Despite some successes in targeting other oncogenes, Ras presently un-druggable and our screens promise to identify targets and validate drugs against Ras in several cancer models.

Cytoskeletal signaling pathways:

We discovered a family of proteins in yeast known as cyclase associated proteins (CAP). In yeast, they are required for Ras signaling, but in mammalian cells, they participate in cytoskeletal signaling. Current studies with CAP use in vivo models to study CAP2 function in cardiac physiology and signaling.

Mechanisms of environmental toxicology:

We also use a systems approach to study environmental toxicology. Past work linked one of the most potent carcinogens in tobacco with the most widely reported stress in smokers—oxidative stress.

I direct two graduate courses (Pharm 623 and Pharm 495). Pharm 495 teaches high throughput screening using a hands-on approach to systems cancer biology. I also direct the TREES summer program for High School students and the STEER summer program for college students, two community outreach programs that provide mentoring opportunities for graduate students.

Selected Publications

Guo Jianman, Grovola Michael R, Xie Hong, Coggins Grace E, Duggan Patrick, Hasan Rukhsana, Huang Jiale, Lin Danny W, Song Claire, Witek Gabriela M, Berritt Simon, Schultz David C, Field Jeffrey: Comprehensive pharmacological profiling of neurofibromatosis cell lines. American journal of cancer research 7(4): 923-934, 2017.

- Lu Hezhe, Liu Shujing, Zhang Gao, Bin Wu , Zhu Yueyao, Frederick Dennie T, Hu Yi, Zhong Wenqun, Randell Sergio, Sadek Norah, Zhang Wei, Chen Gang, Cheng Chaoran, Zeng Jingwen, Wu Lawrence W, Zhang Jie, Liu Xiaoming, Xu Wei, Krepler Clemens, Sproesser Katrin, Xiao Min, Miao Benchun, Liu Jianglan, Song Claire D, Liu Jephrey Y, Karakousis Giorgos C, Schuchter Lynn M, Lu Yiling, Mills Gordon, Cong Yusheng, Chernoff Jonathan, Guo Jun, Boland Genevieve M, Sullivan Ryan J, Wei Zhi, Field Jeffrey, Amaravadi Ravi K, Flaherty Keith T, Herlyn Meenhard, Xu Xiaowei, Guo Wei: PAK signalling drives acquired drug resistance to MAPK inhibitors in BRAF-mutant melanomas. *Nature* 550(7674): 133-136, Oct 2017.
- Field J, Ye DZ, Shinde M, Liu F, Schillinger KJ, Lu M, Wang T, Skettini M, Xiong Y, Brice AK, Chung DC, Patel VV: CAP2 in cardiac conduction, sudden cardiac death and eye development. *Sci Rep* 5: 17256, Nov 2015.
- Zhou, G. L., Zhang, H., Wu, H., Ghai, P., Field, J.: Phosphorylation of the cytoskeletal protein CAP1 controls its association with cofilin and actin. *J Cell Sci* 127: 5052-5065, 2014.
- Licciulli, S., Maksimoska, J., Zhou, C., Troutman, S., Kota, S., Liu, Q., Duron, S., Campbell, D., Chernoff, J., Field, J., Marmorstein, R., Kissil, J. L.: FRAX597, a small molecule inhibitor of the p21-activated kinases, inhibits tumorigenesis of NF2-associated schwannomas. *J Biol Chem* 288: 29105-29114, 2013.
- Ye, Diana Zi, Field, Jeffrey: PAK signaling in cancer. *Cellular Logistics*. Landes Bioscience Inc. 2(2): 105-116, 2012.
- Sen, Sushmita, Bhojnagarwala, Pratik, Francey, Lauren, Lu, Ding, Penning, Trevor M., Field, Jeffrey: p53 Mutagenesis by Benzo[a]pyrene Derived Radical Cations. *Chemical Research in Toxicology*. American Chemical Society, 25(10): 2117-2126, 2012.
- Park J-H, Gelhaus S, Vedantam S, Oliva AL, Batra A, Blair IA, Troxel AB, Field J, Penning TM: The pattern of p53 mutations caused by PAH o-quinones is driven by 8-oxo-dGuo formation while the spectrum of mutations is determined by biological selection for dominance. *Chem Res Toxicol* 21: 1039-1049, 2008.
- Williams J, Su HS, Bernards A, Field J, Sehgal A: A circadian output in Drosophila mediated by neurofibromatosis-1 and Ras/MAPK. *Science* 293: 2251-2256, 2001.
- Tang Y, Marwaha S, Rutkowski JL, Tennekoon GI, Phillips PC, Field J: A role for Pak protein kinases in Schwann cell transformation. *Proc Natl Acad Sci USA* 95: 5139-5144, 1998.
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Research Overview

Our laboratory has two areas of interest – prostanoid biology and the role of peripheral molecular clocks in cardiovascular biology, metabolism and aging. Perhaps the distinguishing feature of our groups is that we pursue interdisciplinary translational science with a focus on therapeutics. Thus, we work in different model systems – mammalian cells, worms, fish and mice – but also in humans. Ideally we develop quantitative approaches that can be projected from our experiments in the model systems to guide elucidation of drug action in humans. To this end, we have long utilized mass spectrometry, initially to target the arachidonate derived lipidome, but also the proteome.

Currently, we are interested in several aspects of prostanoid research. We utilize a remarkably broad array of mutant mice to elucidate the biology of the two COX enzymes and the prostanoid receptors. We are particularly interested in the genomic and environmental factors that contribute to variability in response to nonsteroidal anti-inflammatory drugs and integrate data from model systems and humans to predict analgesic efficacy and cardiovascular risk.

We are interested in the comparative efficacy and safety of pharmacological inhibition of COXs versus the microsomal PGE synthase-1 and have interest in targeting the macrophage mPGES-1 and the F prostanoid receptor.

In the area of clock biology, we are using cell specific deletions of core clock components to look at how between discrete peripheral clocks influence cardiovascular biology and metabolism. We have a major initiative integrating remote sensing and multi-omics approaches to characterize the human physiological chronobiome as a prelude to seeking discordance in diseases with time dependent phenotypes, such as myocardial infarction, stroke, asthma and depression.

Recent Publications:

Liang X., Bushman R and FitzGerald G.A. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. *PNAS* 112(33):10479-84, 2015.

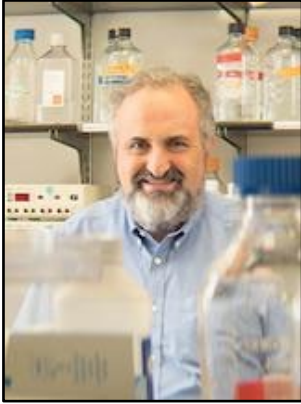
Skarke C., Almuddin N., Lawson J.A., Ferguson J., Reilly M. and FitzGerald G.A. Bioactive Products formed in Humans from Marine Lipids. *J. Lipid Res.* 56: 1808-20 2015.

Liang X., Bettinger K., Abernathy D., Bushman R., and FitzGerald G.A. Bidirectional interactions between indomethacin and the murine intestinal microbiota. *Elife* 2015; 10.7554/eLife.08973.

Tang S.Y., Pawelzik S.-C., Chen, L., Lawson, J., and FitzGerald, G.A. Cardiovascular Consequences of Prostanoid I Receptor Deletion in Microsomal Prostaglandin E Synthase-1 -Deficient Hyperlipidemic Mice . *Circulation* 134(4):328-38, 2016

Mazaleuskaya, L.L., Lawson, J.A., Li, X., Grant G., Ricciotti E. and FitzGerald G.A. A broad-spectrum lipidomics screen of anti-inflammatory drug combinations in human blood. JCI Insight 1(12):e87031, 2016.

Yang G., Chen L, Grant G.R., Paschos G., Musiek E.S., Song W-L., Lee V., McLoughlin S.C., Grosser T., Cotsarelis G., and FitzGerald G.A. Timed expression of Bmal1 influences postnatal aging and survival. Sci. Trans. Med. 8(324):324ra16 2016.



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Research Interests

The laboratory of Dmitry Gabrilovich focuses on understanding of the role of tumor microenvironment in regulation of immune responses in cancer and tumor progression with specific emphasis on myeloid cells. Based on advances in basic research in the lab they develop new methods of cancer therapy.

Myeloid cells play a major role in regulation of immune responses. They include professional antigen-presenting cells, dendritic cells (DC), macrophages and myeloid-derived suppressor cells. Data generated in his laboratory have demonstrated that differentiation and function of various myeloid cells in cancer is severely affected. Gabrilovich and his team was one of the first who identified the phenomenon of abnormal regulation of DC differentiation and cancer and described the mechanisms regulating this phenomenon. They proposed several therapeutic strategies to overcome those defects. Some of them are currently being tested in clinical trials.

Gabrilovich and his group have found that defects in differentiation of DC are associated with accumulation of immature myeloid cells in tumor-bearing animals and patients with cancer. Under normal conditions, these cells represent an intermediate stage of myeloid cell differentiation. In cancer, however, they lose the ability to differentiate into mature myeloid cells, including granulocytes, DC, and macrophages. They become functionally defective and acquire the ability to suppress immune responses. Gabrilovich together with investigators from other institutions coined the term “myeloid-derived suppressor cells (MDSC)” which is now widely used to characterize these cells. Since 2007, when the term was introduced by Gabrilovich and colleagues, more than 2200 papers studying these cells were published.

His lab looks at different aspects of immature myeloid cell biology in cancer. First, they are trying to understand the signaling pathways that are responsible for accumulation and functional defects of immature myeloid cells in cancer. These pathways include NF- κ B, Jak-STAT, Notch, Wnt, Rb, and others. Second, they are investigating cellular and molecular mechanisms of T-cell suppression and tolerance induced as a result of abnormal differentiation of myeloid cells and abnormal DC function. The main focus of this group is on the role of reactive oxygen species and peroxynitrite in regulation of T-cell function. His work demonstrates that reactive oxygen species produced by immature myeloid cells in vitro and in tumor-bearing animals in the presence of tumor-derived soluble factors are substantial contributors to the immunosuppression mediated by these cells in cancer. In recent years Dr. Gabrilovich is focused on the role of lipid accumulation in the defective function of DCs and MDSC in cancer as well as on the mechanisms regulating MDSC migration to form pre-metastatic niche and activate dormant tumor cells.

Gabrilovich and his groups also investigate new immune therapy strategies in cancer. They are exploring several different approaches, including genetically modified DCs, T-cell transfers, checkpoint blockade, and others. In recent years the focus of the lab on the emerging new paradigm of combining conventional chemotherapy, radiation therapy, and immunotherapy.

Recent Publications

Cheng P, Kumar V, Liu H, Youn JI, Fishman M, Sherman S, Gabrilovich D. Effects of Notch signaling on regulation of myeloid cell differentiation in cancer. *Cancer Res.* 2014 74(1):141-152.

Ramakrishnan R, Tuyrin VA, Veglia F, Condamine T, Amoscato A, Mohammadyani D, Johnson JJ, Min Zhang L, Klein-Seetharaman J, Celis E, Kagan VE, Gabrilovich DI. Oxidized Lipids Block Antigen Cross-Presentation by Dendritic Cells in Cancer. *J Immunol.* 2014, 192: 2920-2931.

Condamine T, Kumar V, Ramachandran IR, Youn JI, Celis E, Finnberg N, El-Deiry WS, Winograd R, Vonderheide RH, English NR, Knight SC, Yagita H, McCaffrey JC, Antonia S, Hockstein N, Witt R, Masters G, Bauer T, Gabrilovich DI. ER stress regulates myeloid-derived suppressor cell fate through TRAIL-R-mediated apoptosis. *J Clin Invest.* 2014, 124, 2626-2639.

Condamine T, Gabrilovich DI. Can the Suppressive Activity of Myeloid-Derived Suppressor Cells Be "Chop"ped? *Immunity* 2014; 41(3):341-2.

Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. *Annu Rev Med.* 2015;66:97-110.

Ortiz M, Kumar V, Martner A, Mony S, Donthireddy L, Condamine T, Seykora J, Knight S, Malietzis G, Lee G, Moorghen M, Lenox B, Luetke N, Celis E, Gabrilovich D. Immature myeloid cells directly contribute to skin tumor development by recruiting IL-17 producing CD4+ T cells. *J Exp Med.* 2015, 212, 351-367.

Marvel D, Gabrilovich DI. Myeloid -derived suppressor cells in the tumor microenvironment: expect the unexpected. *J Clin Invest.* 2015 Jul 13:1-9.



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Research Interests

Quantitative Mass Spectrometry Based Proteomics for Characterizing Modified Proteins and Proteomes

The sequences of the human genome and genomes of many other organisms are now readily available and have revolutionized modern biological research. Nevertheless, the next challenge presently on the horizon (after the post-genome era) is the comprehensive characterization of cellular proteins (i.e. the “proteome”), the ‘active/expressed’ part of the genome. DNA sequence or mRNA levels alone cannot predict the dynamic aspects of cellular function. Proteins, their post-translational modifications (PTMs) and the multi-protein complexes they form are the driving forces of cellular machinery that control a diverse number of physiological events. These observations have led to the emergence of a new sub-field of contemporary biology called Proteomics: the characterization of the protein complement expressed by a genome of a particular organism, tissue or cell. At the heart of proteomic experiments is the use of nanoflow liquid chromatography-tandem mass spectrometry for the analysis of complex protein mixtures, which is arguably the most rapid, sensitive and accurate technique available for sequence characterization of proteins.

The Garcia laboratory is focused on developing novel mass spectrometry based proteomic methodologies for quantitatively characterizing changes in protein and proteome expression and post-translational modification state during significant biological events, or in response to external perturbation. Our goal is to utilize large-scale proteomic data to improve our understanding of biological processes at the molecular level. Application of our proteomic technology spans several areas of cellular biology, but a couple of main interests are described below.

Towards deciphering the epigenetic Histone Code

Epigenetics refers to stable heritable changes in gene expression that are not due to changes in DNA sequence, such as DNA methylation, RNA interference and histone PTMs. These epigenetic changes are responsible for generating different cell types originating from the exact same genome. Emerging as one key regulator of cellular memory are histones. Histones are small basic proteins that function to package genomic DNA into repeating nucleosomal units (containing ~146 bp of DNA wrapped around two copies each of histones H3, H4, H2A and H2B) forming the chromatin fiber and hence our chromosomes. In general, the packaging of DNA into chromatin is recognized to be a major mechanism by which the access of genomic DNA is restricted. This physical barrier to the underlying DNA is precisely regulated, at least in part, by the PTMs on histones. A wide number of studies show that several single covalent histone modifications such as methylation, acetylation, phosphorylation and ubiquitination located in the N-terminal tails correlate with both the regulation of chromatin structure during active gene expression, or heterochromatin formation during gene silencing (i.e. the “Histone Code”). Nevertheless, it is currently unknown what effects, if any, multiple combinations of histone modifications might exert, and translating the combinatorial modification patterns of histones into biological significance remains a significant challenge. Additionally, these histone PTMs occur on multiple but specific sites, suggesting that histones can act as signaling platforms for proteins that bind or “read” these marks. In support, several proteins that contain special domains that bind various PTM sites on histones have been discovered. The Garcia lab has developed proteomics techniques that are considered state of the art for histone PTM analyses and are used world-wide by many research groups. Therefore, we feel that the utilization of advanced proteomic technology in the chromatin biology field will enhance investigations of histone modifications to a much higher scale. In combination with cell and biochemical experimentation, bioinformatics analysis and other “omics” technologies;

we feel that our large-scale proteomic data will help provide a systems biology outlook on epigenetic processes that will lay the foundation for development of drug treatments for human diseases that are believed to involve epigenetic mechanisms.

Dynamics of proteome-wide PTM mediated signaling pathways

Another goal of the Garcia lab is to develop and apply novel proteomics based methodology to understand how signaling pathways affect cellular functions and ultimately cell phenotypes. We use quantitative mass spectrometry to measure dynamic changes in protein abundances, protein PTM states, and to characterize protein:protein interactions. For example, we are specifically developing large-scale approaches to isolate and characterize a variety of different types of PTM modified proteomes (e.g. protein phosphorylation, methylation, acetylation, glycosylation, ADP-ribosylation, etc.). These types of approaches allow for example, the detection of thousands of modified proteins from cells or tissues. When combined with quantitative proteomics techniques such as stable isotope labeling of amino acids in cell culture (SILAC), these cutting-edge tools allow us to examine with unprecedented detail, the molecular level events involved in various biological processes such as during stem cell differentiation, viral infection, metabolic disorder or cancer progression. We are also very interested in the dynamics of protein modification, and have developed in vivo cellular metabolic labeling strategies to specifically label newly modified proteins. This methodology allows us to determine protein modification turnover rates or kinetics in response to external stimuli. These experiments have allowed us to define for the first time the dynamics of particular classes of modified proteins on a proteome scale. Lastly, we are extremely interested in how these different protein PTM signaling pathways crosstalk with one another, and we are developing the platforms to determine which modifications are found simultaneously on the same proteins, and how this biological code is then transformed to direct a myriad of cellular functions.

Recent Publications

Distinct Roles of Two Histone Methyltransferases in Transmitting H3K36me3-Based Epigenetic Memory Across Generations in *Caenorhabditis elegans*. Kreher J, Takasaki T, Cockrum C, Sidoli S, Garcia BA, Jensen ON, Strome S. *Genetics*. 2018 Sep 14. pii: genetics.301353.2018. doi: 10.1534/genetics.118.301353. [Epub ahead of print]

Extensive Characterization of Heavily Modified Histone Tails by 193 nm Ultraviolet Photodissociation Mass Spectrometry via a Middle-Down Strategy. Greer SM, Sidoli S, Coradin M, Schack Jespersen M, Schwämmle V, Jensen ON, Garcia BA, Brodbelt JS. *Anal Chem*. 2018 Jul 31. doi: 10.1021/acs.analchem.8b02320. [Epub ahead of print]

Domain-focused CRISPR screen identifies HRI as a fetal hemoglobin regulator in human erythroid cells. Grevet JD, Lan X, Hamagami N, Edwards CR, Sankaranarayanan L, Ji X, Bhardwaj SK, Face CJ, Posocco DF, Abdulmalik O, Keller CA, Giardine B, Sidoli S, Garcia BA, Chou ST, Liebhaber SA, Hardison RC, Shi J, Blobel GA. *Science*. 2018 Jul 20;361(6399):285-290

Capturing the Onset of PRC2-Mediated Repressive Domain Formation. Oksuz O, Narendra V, Lee CH, Descostes N, LeRoy G, Raviram R, Blumenberg L, Karch K, Rocha PP, Garcia BA, Skok JA, Reinberg D. *Mol Cell*. 2018 Jun 21;70(6):1149-1162.

Interrogation of nonconserved human adipose lincRNAs identifies a regulatory role of linc-ADAL in adipocyte metabolism. Zhang X, Xue C, Lin J, Ferguson JF, Weiner A, Liu W, Han Y, Hinkle C, Li W, Jiang H, Gosai S, Hachet M, Garcia BA, Gregory BD, Soccio RE, Hogenesch JB, Seale P, Li M, Reilly MP. *Sci Transl Med*. 2018 Jun 20;10(446).

Rpp29 regulates histone H3.3 chromatin assembly through transcriptional mechanisms. Shastrula PK, Lund PJ, Garcia BA, Janicki SM. *J Biol Chem*. 2018 Jun 19. pii: jbc.RA118.001845. doi: 10.1074/jbc.RA118.001845. [Epub ahead of print]

High-Quality Genome Assemblies Reveal Long Non-coding RNAs Expressed in Ant Brains. Shields EJ, Sheng L, Weiner AK, Garcia BA, Bonasio R. *Cell Rep*. 2018 Jun 5;23(10):3078-3090.

An allosteric propofol-binding site in kinesin disrupts kinesin-mediated processive movement on microtubules. Woll KA, Guzik-Lendrum S, Bensel BM, Bhanu NV, Dailey WP, Garcia BA, Gilbert SP, Eckenhoff RG. J Biol Chem. 2018 Jul 20;293(29):11283-11295.

EpiProfile 2.0: A Computational Platform for Processing Epi-Proteomics Mass Spectrometry Data. Yuan ZF, Sidoli S, Marchione DM, Simithy J, Janssen KA, Szurgot MR, Garcia BA. J Proteome Res. 2018 Jul 6;17(7):2533-2541.

Allosteric Activation Dictates PRC2 Activity Independent of Its Recruitment to Chromatin. Lee CH, Yu JR, Kumar S, Jin Y, LeRoy G, Bhanu N, Kaneko S, Garcia BA, Hamilton AD, Reinberg D. Mol Cell. 2018 May 3;70(3):422-434.



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Description of Research Expertise

Tumor Immunology
Chimeric Antigen Receptor T cells
Mouse Models of Human Leukemia
Murine Xenografts
Adoptive Cellular Therapy
Genetic Engineering of T cells
Flow Cytometry

Investigators in the Gill laboratory work on aspects of cellular immunotherapy for hematologic malignancies, in particular leukemia and lymphoma. We follow an iterative process of target discovery, production of novel chimeric antigen receptors, and their validation in both in vitro and in vivo models. Our goal is to translate new, potent and safe antigen-specific immunotherapy from brainchild to therapeutic agent as quickly as possible.

Selected Publications

Ganetsky Alex, Frey Noelle V, Hexner Elizabeth O, Loren Alison W, Gill Saar I, Luger Selina M, Mangan James K, Martin Mary Ellen, Babushok Daria V, Drobyski William R, Smith Jacqueline, Timlin Colleen, Freyer Craig W, Stadtmauer Edward A, Porter David L: Tocilizumab for the treatment of severe steroid-refractory acute graft-versus-host disease of the lower gastrointestinal tract. Bone marrow transplantation May 2018.

Kim Miriam Y, Yu Kyung-Rok, Kenderian Saad S, Ruella Marco, Chen Shirley, Shin Tae-Hoon, Aljanahi Aisha A, Schreeder Daniel, Klichinsky Michael, Shestova Olga, Kozlowski Miroslaw S, Cummins Katherine D, Shan Xinhe, Shestov Maksim, Bagg Adam, Morrisette Jennifer J D, Sekhri Palak, Lazzarotto Cicera R, Calvo

Katherine R, Kuhns Douglas B, Donahue Robert E, Behbehani Gregory K, Tsai Shengdar Q, Dunbar Cynthia E, Gill Saar: Genetic Inactivation of CD33 in Hematopoietic Stem Cells to Enable CAR T Cell Immunotherapy for Acute Myeloid Leukemia. *Cell* 173(6): 1439-1453.e19, May 2018.

Hosoya Hitomi, Levine Jeffrey, Abt Peter, Henry David, Porter David L, Gill Saar: Toward dual hematopoietic stem-cell transplantation and solid-organ transplantation for sickle-cell disease. *Blood advances* 2(5): 575-585, Mar 2018.

Uribe-Herranz Mireia, Bittinger Kyle, Rafail Stavros, Guedan Sonia, Pierini Stefano, Tanes Ceylan, Ganetsky Alex, Morgan Mark A, Gill Saar, Tanyi Janos L, Bushman Frederic D, June Carl H, Facciabene Andrea: Gut microbiota modulates adoptive cell therapy via CD8 α dendritic cells and IL-12. *JCI insight* 3(4), Feb 2018.

Cummins KD*, Frey N*, Nelson AM*, Schmidt A*, Luger S, Isaacs RE*, Lacey SF, Hexner E, Melenhorst JJ, June CH, Porter DL, Gill SI. : Treating Relapsed / Refractory (RR) AML with Biodegradable AntiCD123 CAR Modified T Cells American Society for Hematology Annual Meeting, Atlanta, GA Dec 2017 Notes: "Poster Presentation"

Ruella M*, Maude SL*, Engels B*, Barrett DM*, Frey N*, Marcucci K, Shestova O, Singh N, Perazzelli J, Christian DA, Hunter CA, Haagen D, Lacey S, Melenhorst J, Brogdon J, Young R, Porter DL, June CH, Grupp S, Gill S.: Clinical efficacy of anti-CD22 chimeric antigen receptor T cells for B-cell acute lymphoblastic leukemia is correlated with the length of the scFv linker and can be predicted using xenograft models. American Society for Hematology Annual Meeting, Atlanta, GA Dec 2017 Notes: "Oral Presentation"

Ruella M, Xu J, Barrett DM*, Kulikovskaya I*, Ambrose DE*, Patel PR*, Reich T*, Scholler J*, Nazimuddin F*, Fraietta JA*, Maude SL, Gill SI, Levine BL, Nobles CL*, Bushman FD*, Orlando E*, Grupp SA, June CH, Melenhorst JJ, Lacey SF.: Iatrogenic Induction of Chimeric Antigen Receptor Therapy Resistance American Society of Hematology Annual Meeting, Atlanta, GA Dec 2017 Notes: "Poster Presentation"

Ruella M, Klichinsky M, Kenderian SS, Shestova O, Ziober A, Kraft DO, Feldman M, Wasik MA, June CH, Gill S: Overcoming the Immunosuppressive Tumor Microenvironment of Hodgkin Lymphoma Using Chimeric Antigen Receptor T Cells. *Cancer Discovery* 7(10): 1154-67, Oct 2017 Notes: doi: 10.1158/2159-8290.

Cummins Katherine D, Gill Saar: Anti-CD123 chimeric antigen receptor T-cells (CART): an evolving treatment strategy for hematological malignancies, and a potential ace-in-the-hole against antigen-negative relapse. *Leukemia & Lymphoma* Page: 1-15, Sep 2017



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Research Interests

Prediction and Early Detection of Response of non-Hodgkin's Lymphoma

My laboratory initiated the field of NMR spectroscopy of tumors in mice in about 1980 by demonstrating that tumors exhibited detectable changes in bioenergetics, pH and phospholipid metabolism that could be utilized for detection and prediction of therapeutic response. In 2011 I shared the Gold Medal of the International Society of Magnetic Resonance in Medicine with John Griffiths of Cambridge University for our pioneer work on MRS of cancer. My laboratory has been developing ³¹P, ¹H and ¹³C MRS methods as well as physiologically sensitive MRI techniques for monitoring metabolic changes in tumors that predict or detect therapeutic response; we generally develop these methods in perfused cells and mice and then translate them to human patients. Our focus is largely on non-Hodgkin's lymphoma (NHL) since this malignancy exhibits roughly a 50% response rate. We have recently discovered that NHL tumors in mice are quite unique in that they exhibit extremely well resolved ¹³C MR spectra. By monitoring the kinetics of ¹³C-isotope exchange and fitting these data to a metabolic network model, we can quantitate flux through specific pathways of tumor energy and phospholipid metabolism and translate this into the amount of ATP that is produced from various substrates in tumors. We are also exploring the use of hyperpolarized ¹³C-labeled substrates to the study of tumors. Detecting tumor response to inhibitors of signal transduction pathways is a major challenge in the clinic. We have recently demonstrated that administration of specific inhibitors of mTOR produces a marked reduction in glycolytic metabolism as a consequence of decreased expression of hexokinase-2 and other glycolytic enzymes. We can readily detect this effect by monitoring lactic acid in the tumor (in both mice and men). We are extending this approach to other signaling pathways such as ALK and PI3K/AKT inhibitors.

Selective Acidification of Melanoma by inhibition of monocarboxylic acid transporters

Melanoma is the deadliest skin cancer and the most rapidly increasing malignancy among Caucasian populations throughout the world. It can only be cured by surgical excision, but the tumor recurs in about 20% of the cases. There is currently no effective way to treat the disseminated disease. Targeted therapies are under development and show promising activity but are generally not curative since tumors exhibit a remarkable facility for circumventing these agents. We have been developing a method that does not target a specific gene or antigen but instead targets a key metabolic property of tumors – their preference for glycolytic metabolism (the Warburg effect). The end product of glycolysis is pyruvate, the majority of which is converted to lactate and transported out of the cell via monocarboxylic acid transporters (MCT). We have been using lonidamine, which is believed to inhibit MCT1, the key pathway for lactate export, thereby trapping lactic acid in the tumor cell. This decreases the intracellular pH of melanomas in mice (pHi) from about 7 to 6.4. It also dramatically decreases the ATP level in the tumor, probably by inhibiting a putative pyruvate transporter in the mitochondrial membrane (thus blocking oxidative metabolism in the tumor). These effects are remarkably specific for the tumor and produce minimal effects on normal tissues in the body. We are exploiting this selective acidification of the tumor and de-energization of tumor cells by lonidamine to dramatically increase melanoma response to two drugs, melphalan and doxorubicin, that normally are not effective against this disease but whose activity is markedly

increased under acidic conditions in tumor cells. We believe that by combining this metabolic strategy with the targeted therapies under development by pharmaceutical companies, we may be able to approach a cure of this deadly disease.

Imaging the Metastatic Potential of Tumors

We have also been studying the mechanism underlying tumor metastasis. We use a panel of human melanoma xenografts that vary in metastatic potential from highly indolent to highly aggressive (invasive). Using an MRI method that employs a paramagnetic contrast agent, GdDTPA, we can demonstrate that contrary to general belief, the indolent tumor is actually much better perfused (i.e., has a better blood supply) than the aggressive tumors. The aggressive tumors have a well-perfused rim but a poorly perfused central core. Using a low temperature fluorescence technique that Britton Chance developed at Penn in the 1980s, we found that the indolent tumors exhibited much higher levels of NADH that was relatively uniformly distributed throughout the tumor. Since NADH and FADH₂ are the key substrates for oxidative phosphorylation, the indolent tumors were well supplied with energy. However, the aggressive melanomas showed a high level of NADH in their outer rim but a low level in their central core, which instead contained high levels of oxidized flavoproteins. In short, the aggressive tumors had a poorly perfused core in which the tumor cells were starved for substrates. We hypothesize that this highly inhospitable microenvironment in the core of the tumor provides an evolutionary pressure favoring the survival of tumor cells with the ability to move to more hospitable environments, i.e. to metastasize. It also induces these tumors to become cannibalistic and break down their own tissues to generate substrates for generating energy and to support proliferation. This phenomenon is called autophagy, and there are ways to inhibit this process and kill the tumor cells that depend on it. This theory still needs to be validated, but its implications for controlling tumor metastatic potential, the key cause of death in cancer, is considerable.

Carbon-13 NMR Studies of Tumor Intermediary Metabolism

We have been using ¹³C MRS to study the bioenergetics of melanoma tumor cells. We have been able to demonstrate that the DB1 melanoma tumor line obtains about 46% of its ATP from glycolysis and 54% from oxidative phosphorylation. The method for measuring flux through these metabolic pathways is called bonded cumomer analysis and involves the solution of ~150 differential equations. It was developed by our collaborator, Alex Shestov, at the University of Minnesota. We are extending this method to all the pathways of tumor intermediary metabolism. A key objective will be to apply this method to human cancer patients. Melanoma may not prove to be the ideal tumor for this purpose, but NHL appears to be a much better target because for reasons that are poorly understood, this tumor yields much more well resolved ¹³C NMR spectra. In addition, we could apply this method to any hematological cancer like leukemia since leukemic cells are routinely removed from the body and can be grown in a bioreactor. We have constructed various bioreactors for studying various types of perfused cells. Another potential application of this technology is to targeted lymphocytes that Carl June and coworkers are developing for treatment of various malignancies.

Lipoproteins as Marker Genes and Theranostic Agents

Since lipoproteins are naturally occurring nanoparticles, they are generally acceptable to humans and other immunocompetent animals. We have been developing lipoproteins as carriers of near infrared and NMR indicators for in vivo tracking and for delivery of drugs and photodynamic therapy agents for cancer therapy. Because lipoprotein receptors are not unique to cancer, we have been developing novel strategies for retargeting these agents to more cancer-specific receptors such as folate receptors. Much of this research has been directed against ovarian cancer, a malignancy that overexpresses folic acid receptors.

Recent Publications

He N. Xu, Min Feng, Kavindra Nath, David Nelson, Jeff Roman, Huaqing Zhao, Zhenwu Lin, Jerry Glickson, Lin Z. Li: Optical Redox Imaging of Lonidamine Treatment Response of Melanoma Cells and Xenografts Molecular Imaging and Biology. Springer, in press, 2018 Notes: DOI: 10.1007/s11307-018-1258-z.

Nath K, Nelson DS, Roman J, Putt ME, Lee SC, Leeper DB, Glickson JD: Effect of Lonidamine on Systemic Therapy of DB-1 Human Melanoma Xenografts with Temozolomide. Anticancer Res. 37(7): 3413-3421, JULY 2017.

- Nath K, Guo L, Nancolas B, Nelson DS, Shestov AA, Lee SC, Roman J, Zhou R, Leeper DB, Halestrap AP, Blair IA, Glickson JD.: Mechanism of antineoplastic activity of lonidamine. *Biochim Biophys Acta* 2016 Dec. Page: 151-162, Dec 2016 Notes: 1866(2):151-162. doi: 10.1016/j.bbcan.2016.08.001. [Epub ahead of print] Review.
- Guo L, Worth AJ, Mesaros C, Snyder NW, Glickson JD, Blair IA.: 1. Diisopropylethylamine/hexafluoroisopropanol-mediated ion-pairing ultra-high-performance liquid chromatography/mass spectrometry for phosphate and carboxylate metabolite analysis: utility for studying cellular metabolism. *Rapid Commun Mass Spectrom*. 2016 Aug 30;30(16):1835-45. doi: 10.1002/rcm.7667. Page: 1835-45, Aug 2016 Notes: [PubMed - in process]
- Nath K, Nelson DS, Putt ME, Leeper DB, Garman B, Nathanson KL, Glickson JD: Comparison of the Lonidamine Potentiated Effect of Nitrogen mustard Alkylating Agents on the Systemic Treatment of DB-1 Human Melanoma Xenografts in Mice. *PLoS One* June 2016.
- Shestov AA, Lee SC, Nath K, Guo L, Nelson DS, Roman JC, Leeper DB, Wasik MA, Blair IA, Glickson JD.: (13)C MRS and LC-MS Flux Analysis of Tumor Intermediary Metabolism. *Front Oncol*. 2016 Jun 15;6:135. doi: 10.3389/fonc.2016.00135. eCollection 2016. June 2016 Notes: [PubMed] Free PMC Article
- Nancolas B, Guo L, Zhou R, Nath K, Nelson DS, Leeper DB, Blair IA, Glickson JD, Halestrap AP.: The anti-tumour agent lonidamine is a potent inhibitor of the mitochondrial pyruvate carrier and plasma membrane monocarboxylate transporters. *Biochem J* Page: 929-936, April 1 2016 Notes: 473(7):929-36. doi: 10.1042/BJ20151120. Epub 2016 Feb 1.
- Shestov AA, Mancuso A, Lee SC, Guo L, Nelson DS, Roman JC, Henry PG, Leeper DB, Blair IA, Glickson JD.: Bonded Cumomer Analysis of Human Melanoma Metabolism Monitored by 13C NMR Spectroscopy of Perfused Tumor Cells. *J Biol Chem* Page: 5157-5171, March 4 2016 Notes: 291(10):5157-71. doi: 10.1074/jbc.M115.701862. Epub 2015 Dec 24.
- Guo L, Shestov AA, Worth AJ, Nath K, Nelson DS, Leeper DB, Glickson JD, Blair IA: Inhibition of Mitochondrial Complex II by the Anticancer Agent Lonidamine. *J BIOL CHEM* Jan 2016.
- Nath K, Nelson D, Heijan D, Leeper DB, Zhou R, Glickson JD: Lonidamine induces intracellular tumor acidification and ATP depletion in breast, prostate and ovarian cancer xenografts and potentiates response to doxorubicin. *NMR in BIOMED* 28(3): 281-290, March 2015.
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Description of Research Expertise

Our overarching goal is to transform how we understand complex biological systems by developing and applying computational algorithms that effectively model processes by integrating multiple types of big data from diverse experiments. This allows us to infer the key contextual information required to interpret such data, and facilitates both the computationally driven asking and answering of basic science and translational research questions.

Selected Publications

Weissman Gary E, Hubbard Rebecca A, Ungar Lyle H, Harhay Michael O, Greene Casey S, Himes Blanca E, Halpern Scott D: Inclusion of Unstructured Clinical Text Improves Early Prediction of Death or Prolonged ICU Stay. *Critical Care Medicine* 46(7): 1125-1132, Apr 2018.

Sanchez-Vega Francisco, Mina Marco, Armenia Joshua, Chatila Walid K, Luna Augustin, La Konnor C, Dimitriadou Sofia, Liu David L, Kantheti Havish S, Saghafinia Sadegh, Chakravarty Debyani, Daian Foysal, Gao Qingsong, Bailey Matthew H, Liang Wen-Wei, Foltz Steven M, Shmulevich Ilya, Ding Li, Heins Zachary, Ochoa Angelica, Gross Benjamin, Gao Jianjiong, Zhang Hongxin, Kundra Ritika, Kandoth Cyriac, Bahceci Istemi, Dervishi Leonard, Dogrusoz Ugur, Zhou Wanding, Shen Hui, Laird Peter W, Way Gregory P, Greene Casey S, Liang Han, Xiao Yonghong, Wang Chen, Iavarone Antonio, Berger Alice H, Bivona Trevor G, Lazar Alexander J, Hammer Gary D, Giordano Thomas, Kwong Lawrence N, McArthur Grant, Huang Chenfei, Tward Aaron D, Frederick Mitchell J, McCormick Frank, Meyerson Matthew, Van Allen Eliezer M, Cherniack Andrew D, Ciriello Giovanni, Sander Chris, Schultz Nikolaus: Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell* 173(2): 321-337.e10, Apr 2018.

Knijnenburg Theo A, Wang Linghua, Zimmermann Michael T, Chambwe Nyasha, Gao Galen F, Cherniack Andrew D, Fan Huihui, Shen Hui, Way Gregory P, Greene Casey S, Liu Yuexin, Akbani Rehan, Feng Bin, Donehower Lawrence A, Miller Chase, Shen Yang, Karimi Mostafa, Chen Haoran, Kim Pora, Jia Peilin, Shinbrot Eve, Zhang Shaojun, Liu Jianfang, Hu Hai, Bailey Matthew H, Yau Christina, Wolf Denise, Zhao Zhongming, Weinstein John N, Li Lei, Ding Li, Mills Gordon B, Laird Peter W, Wheeler David A, Shmulevich Ilya, Monnat Raymond J, Xiao Yonghong, Wang Chen: Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas. *Cell reports* 23(1): 239-254.e6, Apr 2018.

Way Gregory P, Sanchez-Vega Francisco, La Konnor, Armenia Joshua, Chatila Walid K, Luna Augustin, Sander Chris, Cherniack Andrew D, Mina Marco, Ciriello Giovanni, Schultz Nikolaus, Sanchez Yolanda, Greene Casey S: Machine Learning Detects Pan-cancer Ras Pathway Activation in The Cancer Genome Atlas. *Cell reports* 23(1): 172-180.e3, Apr 2018.

Himmelstein Daniel S, Romero Ariel Rodriguez, Levernier Jacob G, Munro Thomas Anthony, McLaughlin Stephen Reid, Greshake Tzovaras Bastian, Greene Casey S: Sci-Hub provides access to nearly all scholarly literature. *eLife* 7, Mar 2018.

Dahlstrom Kurt M, Collins Alan J, Doing Georgia, Taroni Jaclyn N, Gauvin Timothy J, Greene Casey S, Hogan Deborah A, O'Toole George A: A Multimodal Strategy Used By A Large c-di-GMP Network. *Journal of bacteriology* 200(8), Jan 2018.

- Way Gregory P, Greene Casey S: Extracting a biologically relevant latent space from cancer transcriptomes with variational autoencoders. *Pac Symp Biocomput* 23: 80-91, Jan 2018.
- Harrington Lia X, Way Gregory P, Doherty Jennifer A, Greene Casey S: Functional network community detection can disaggregate and filter multiple underlying pathways in enrichment analyses. *Pac Symp Biocomput* 23: 157-167, Jan 2018.
- Skarke Carsten, Lahens Nicholas F, Rhoades Seth D, Campbell Amy, Bittinger Kyle, Bailey Aubrey, Hoffmann Christian, Olson Randal S, Chen Lihong, Yang Guangrui, Price Thomas S, Moore Jason H, Bushman Frederic D, Greene Casey S, Grant Gregory R, Weljie Aalim M, FitzGerald Garret A: A Pilot Characterization of the Human Chronobiome. *Scientific reports* 7(1): 17141, Dec 2017.
- Tan Jie, Huyck Matthew, Hu Dongbo, Zelaya René A, Hogan Deborah A, Greene Casey S: ADAGE signature analysis: differential expression analysis with data-defined gene sets. *BMC bioinformatics* 18(1): 512, Nov 2017.
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Research Interests

In the central nervous system, oligodendrocytes synthesize myelin as an extension of their plasma membranes. This myelin wraps axons and facilitates rapid and efficient conduction of nervous impulses as well as axonal nourishment and protection. Destruction of myelin through injury, such as birth injury leading to cerebral palsy, or disease, such as multiple sclerosis or HIV, causes loss of motor and cognitive function. Oligodendrocyte precursors and stem cells remain in the CNS following the pathology and are potentially capable of forming mature oligodendrocytes and then myelin. However, their maturation is severely limited. Reasons for this include processes such as oxidative stress and inflammation which signal to inhibitors present in the area that impede maturation. Our goal is to identify factors in the CNS that inhibit the development of mature oligodendrocytes both during development and disease. We have identified several key signaling factors that regulate developmental myelination and are increased during demyelinating disease. On-going areas of investigation in the lab include: 1) The role of white matter loss and demyelination in HIV-associated neurocognitive deficits. 2) Factors which limit myelination in perinatal white matter injury. 3) The role of lipid signaling in developmental myelination and remyelination following demyelinating disease.

Selected Publications

- Monnerie, H., Romer, M., Jensen, B., Millar, J., Jordan-Sciutto, K., Kim, S.F., Grinspan, J.B.: Reduced Sterol Regulatory Element-Binding Protein (SREBP) Processing through Site-1 Protease (S1P) Inhibition Alters Oligodendrocyte differentiation In Vitro. *J. Neurochem.* 140: 53-67, 2017.
- Jensen, B.K., Monnerie, H., Mannell, M.V., Gannon, P.J., Espinoza-Akay, C., Erickson, M.A., Bruce-Keller, A.J., Gelman, B.B., Briand, L.A., R. Pierce, R.C., Jordan-Sciutto, K.L., Grinspan, J.B. : Altered Oligodendrocyte Maturation and Myelin Maintenance: The Role of Anti-Retrovirals in HIV-Associated Neurocognitive Disorders. *Journal of Neuropathology Experimental Neurology* 74(11): 1093-1118, November 2015.
- Veasey, S.C., Lear, J., Zhu, Y., Grinspan, J. B., Hare, D.J., Wang, S., Bunch, D., Lim, D.C., Doble, P.A., Robinson, S.R.: Long-term Intermittent Hypoxia Elevates Cobalt Levels in the Brain and Injures White Matter in Adult Mice. *Sleep* 36: 1471-1481, 2013.
- Reid, M.V., Murray, K. A., Marsh, E.D., Golden, J. A., Simmons, R.A., Grinspan, J. B.: Delayed myelination in an intrauterine growth retardation model is mediated by oxidative stress upregulating BMP4. *Journal of Neuropathology Experimental Neurology* 71(7): 640-653, 2012.
- Feigenson, K., Reid, M., See, J., Crenshaw, E.B. III, Grinspan, J. B. : Canonical Wnt signaling requires the BMP pathway to inhibit oligodendrocyte maturation. *ASN NEURO* 3: 147-158, 2011.
- French, H. M., Reid, M., Mamontov, P., Simmons, R. A., Grinspan, J. B.: Oxidative stress disrupts oligodendrocyte maturation. *Journal of Neuroscience Research* 87: 3076-3087, 2009.
- Feigenson, K., Reid, M., See, J., Crenshaw E.B. III, Grinspan, J. B.: Wnt signaling is sufficient to perturb oligodendrocyte maturation. *Molecular and Cellular Neuroscience* 42: 255-265, 2009.
- Ara, J., See, J., Mamontov, P., Hahn, A., Bannerman, P. Pleasure, D., Grinspan, J.B.: Bone morphogenetic proteins 4, 6, and 7 are upregulated in mouse spinal cord during experimental autoimmune encephalomyelitis. *Journal of Neuroscience Research* 86: 125-135, 2008.
- See, J., Mamontov, P., Ahn K., Wine-Lee, L., Crenshaw III, E.B., Grinspan, J. B.: BMP mutant mice exhibit glial cell maturation defects. *Molecular and Cellular Neuroscience* 35: 171-182, 2007.
- See, J., Zhang, X., Eraydin, N. Mun, S.B., Mamontov, P., Golden, J. Grinspan, J.B.: Oligodendrocyte maturation is inhibited by bone morphogenetic protein. *Molecular and Cellular Neuroscience* 26: 481-492, 2004.



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Research Interests

Non-steroidal anti-inflammatory drugs (NSAIDs), which include both traditional NSAIDs (e.g. naproxen, ibuprofen) and NSAIDs selective for cyclooxygenase (COX)-2 (rofecoxib, valdecoxib, etoricoxib, lumiracoxib, celecoxib) relieve pain, inflammation and fever by inhibiting the formation of bioactive prostanoids. Despite their efficacy in the relief of pain and inflammation, NSAIDs may be associated with gastrointestinal complications, including serious bleeds. Selectivity for COX-2 has been shown to reduce the incidence of these serious events, but is more likely to cause serious cardiovascular events than non-selective COX inhibition.

Dr. Grosser is studying the mechanisms of these complications using genomics, proteomics, lipidomics approaches in model organisms and in proof-of-concept studies in healthy volunteers. One aim of this research is to identify approaches to the personalization of NSAID therapy.

Recent Publications

Grosser T, Woolf CJ, FitzGerald GA: Time for nonaddictive relief of pain. *Science* 355(6329): 1026-1027, 2017.

Bhatt DL, Grosser T, Dong JF, Logan D, Jeske W, Angiolillo DJ, Frelinger AL 3rd, Lei L, Liang J, Moore JE, Cryer B, Marathi U.: Enteric Coating and Aspirin Nonresponsiveness in Patients With Type 2 Diabetes Mellitus. *J Am Coll Cardiol* 69(6): 603-612, 2017.

Yang G, Chen L, Grant GR, Paschos G, Song WL, Musiek ES, Lee V, McLoughlin SC, Grosser T, Cotsarelis G, FitzGerald GA: Timing of expression of the core clock gene *Bmal1* influences its effects on aging and survival. *Sci Transl Med* 8: 324, 2016.

Greene CS, Krishnan A, Wong AK, Ricciotti E, Zelaya RA, Himmelstein DS, Zhang R, Hartmann BM, Zaslavsky E, Sealfon SC, Chasman DI, FitzGerald GA, Dolinski K, Grosser T, Troyanskaya OG.: Understanding multicellular function and disease with human tissue-specific networks. *Nat Genet* 47(6): 569-76, 2015.

Li X, Fries S, Li R, Lawson JA, Probert KJ, Diamond SL, Blair IA, FitzGerald GA, Grosser T: Differential impairment of aspirin-dependent platelet cyclooxygenase acetylation by nonsteroidal antiinflammatory drugs. *Proc Natl Acad Sci U S A*. 111(47): 16830-5, 2014 Notes: [Open Access: <http://www.pnas.org/content/111/47/16830.long>]

Grosser T, Fries S, Lawson JA, Kapoor SC, Grant GR, FitzGerald GA: Drug Resistance and Pseudoresistance: An Unintended Consequence of Enteric Coating Aspirin. *Circulation* 127(3): 377-85, 2013 Notes: [Open Access: <http://circ.ahajournals.org/content/127/3/377.full>]

Grosser T, Yu Y, FitzGerald GA: Emotion recollected in tranquility: Lessons learned from the COX-2 saga. *Annu Rev Med* 61: 17-33, 2010.

Lucitt MB, Price TS, Pizarro A, Wu W, Yocum AK, Seiler C, Pack MA, Blair IA, FitzGerald GA, Grosser T: Analysis of the zebrafish proteome during embryonic development. *Mol Cell Proteomics* 7(5): 981-94, 2008 Notes: [Cover image]

Price TS, Lucitt MB, Wu W, Austin DJ, Pizarro A, Yocum AK, Blair IA, Fitzgerald GA, Grosser T: EBP: Protein identification using multiple tandem mass spectrometry datasets. *Mol Cell Proteomics* 6: 527-536, 2007.

Fries S*, Grosser T* [* Co-First Authors], Price TS, Lawson JA, Kapoor S, DeMarco S, Pletcher MT, Wiltshire T, Fitzgerald GA: Marked interindividual variability in the response to selective inhibitors of cyclooxygenase-2. *Gastroenterology* 130: 55-64, 2006.



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Research Overview

The primary interest of my laboratory program lies with the molecular and cellular pathophysiology of psychotic and mood disorders. Directing the Neuropsychiatric Signaling Program in the department of psychiatry, my research has a special focus on identifying intracellular and molecular alterations in neural tissues derived from patients and investigating their underlying mechanisms in animal and in vitro models. Examining molecular and cellular processes occurring in patients has been one of fundamental challenges in the field. In response, my laboratory has taken a path of developing new research paradigms to address questions that could not have been otherwise.

There are two lines of research paradigms that we have developed: analyses of subcellular proteome and intracellular signaling in postmortem brains and of olfactory neuroepithelial biopsy tissues derived from patients. Postmortem brain tissues may harbor biological characteristics linked to the subjects' clinical profiles, but study of intracellular signaling in those tissues has been hampered. To that end, we have established a series of research paradigms to monitor receptor-mediated activation of intracellular signaling to isolate subcellular fractions enriched for post-synaptic density and synaptic membranes, to assess kinase activity in synaptic membranes and to capture protein complexes followed by mass spectrometer based quantitative proteomics. The olfactory neuroepithelial (OE) biopsy approach offers unique opportunities to obtain neural tissues of living patients that can be studied using ex vivo and in vitro paradigms. This paradigm permits us to address clinically relevant molecular and cellular mechanisms of neuropsychiatric illnesses, specifically pertinent to certain phase or state of illnesses. We have established olfactory neuroepithelial cell lines derived from more than 400 subjects with various psychiatric illnesses. Presently we examine these cells for various molecular pathways implicated for schizophrenia, bipolar disorder and depression using an induced neuronal cell paradigm.

Recent Publications

Turetsky Bruce I, Hahn Chang-Gyu, Arnold Steven E, Moberg Paul J: Olfactory receptor neuron dysfunction in schizophrenia. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology* 34(3): 767-74, Feb 2009.

Borgmann-Winter K E, Rawson N E, Wang H-Y, Wang H, Macdonald M L, Ozdener M H, Yee K K, Gomez G, Xu J, Bryant B, Adamek G, Mirza N, Pribitkin E, Hahn C-G: Human olfactory epithelial cells generated in vitro express diverse neuronal characteristics. *Neuroscience* 158(2): 642-53, Jan 2009.

- McNamara Robert K, Hahn Chang-Gyu, Jandacek Ronald, Rider Therese, Tso Patrick, Stanford Kevin E, Richtand Neil M: Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biological psychiatry* 62(1): 17-24, Jul 2007.
- Hahn Chang-Gyu, Wang Hoau-Yan, Cho Dan-Sung, Talbot Konrad, Gur Raquel E, Berrettini Wade H, Bakshi Kalindi, Kamins Joshua, Borgmann-Winter Karin E, Siegel Steven J, Gallop Robert J, Arnold Steven E: Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. *Nature medicine* 12(7): 824-8, Jul 2006.
- Hahn Chang-Gyu, Umapathy , Wang Hoau-Yan, Koneru Ramesh, Levinson Douglas F, Friedman Eitan: Lithium and valproic acid treatments reduce PKC activation and receptor-G protein coupling in platelets of bipolar manic patients. *Journal of psychiatric research* 39(4): 355-63, Jul 2005.
- Hahn Chang-Gyu, Gomez George, Restrepo Diego, Friedman Eitan, Josiassen Richard, Pribitkin Edmund A, Lowry Louis D, Gallop Robert J, Rawson Nancy E: Aberrant intracellular calcium signaling in olfactory neurons from patients with bipolar disorder. *The American journal of psychiatry* 162(3): 616-8, Mar 2005.
- Hahn Chang-Gyu, Han Li-Ying, Rawson Nancy E, Mirza Natasha, Borgmann-Winter Karin, Lenox Robert H, Arnold Steven E: In vivo and in vitro neurogenesis in human olfactory epithelium. *The Journal of comparative neurology* 483(2): 154-63, Mar 2005.
- Talbot Konrad, Eidem Wess L, Tinsley Caroline L, Benson Matthew A, Thompson Edward W, Smith Rachel J, Hahn Chang-Gyu, Siegel Steven J, Trojanowski John Q, Gur Raquel E, Blake Derek J, Arnold Steven E: Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. *The Journal of clinical investigation* 113(9): 1353-63, May 2004.
- Arnold S E, Han L Y, Moberg P J, Turetsky B I, Gur R E, Trojanowski J Q, Hahn C G: Dysregulation of olfactory receptor neuron lineage in schizophrenia. *Archives of general psychiatry* 58(9): 829-35, Sep 2001.
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Description of Research Expertise

Research in our laboratory is at the intersection of innate immune system and solid tumor biology. Specifically, we study the mononuclear phagocyte system (MPS) with an emphasis on their role in the tumor microenvironment. MPS is part of the innate immune system and comprises of monocytes, macrophages, and dendritic cells (DC). These cells are functionally, phenotypically, and developmentally heterogeneous with many distinct subsets. We are interested in understanding the molecular basis of this developmental and functional heterogeneity within the MPS. A major focus in our laboratory is to understand the role of MPS within the microenvironment of a group of solid tumors known as sarcomas. DCs and macrophages are thought to play important role in cancer by modulating host-immune responses against the tumor cells, promoting metastasis, angiogenesis, etc. Additionally, the ability of these cells to regulate lymphocyte function makes them an important determinant in the success of cancer immunotherapy. Using a combination of advanced genetically engineered mouse models in conjunction with patient-derived samples, we aim to uncover the molecular pathways underlying tumor-MPS interaction with the overarching goal of targeting them for therapeutic purposes.

Selected Publications

Briseño CG*, Haldar M*, Kretzer NM, Wu X, Theisen DJ, Kc W, Durai V, Grajales-Reyes GE, Iwata A, Bagadia P, Murphy TL, Murphy KM.: *Distinct Transcriptional Programs Control Cross-Priming in Classical and Monocyte-Derived Dendritic Cells*. Cell Reports June 2016.

Jones KB, Barrott JJ, Xie M, Haldar M, Jin H, Zhu JF, Monument MJ, Mosbrugger TL, Langer EM, Randall RL, Wilson RK, Cairns BR, Ding L, Capecchi MR.: *The impact of chromosomal translocation locus and fusion oncogene coding sequence in synovial sarcomagenesis*. Oncogene March 2016.

Jeffrey J. Bednarski, Ruchi Pandey, Emily Schulte, Lynn S. White, Bo-Ruei Chen, Gabriel J. Sandoval, Masako Kohyama, Malay Haldar, Andrew Nickless, Amanda Trott, Genhong Cheng, Kenneth M. Murphy, Craig H. Bassing, Jacqueline E. Payton and Barry P. Sleckman: *RAG-mediated DNA double strand breaks activate a cell-type-specific checkpoint to inhibit pre-B cell receptor signals*. The Journal of Experimental Medicine In press, 2016.

Grajales-Reyes GE, Iwata A, Albring J, Wu X, Tussiwand R, Kc W, Kretzer NM, Briseño CG, Durai V, Bagadia P, Haldar M, Schönheit J, Rosenbauer F, Murphy TL, Murphy KM.: *Batf3 maintains autoactivation of Irf8 for commitment of a CD8 α (+) conventional DC clonogenic progenitor*. Nature Immunology July 2015.

Haldar Malay, Murphy Kenneth M: *Origin, development, and homeostasis of tissue-resident macrophages*. Immunological reviews 262(1): 25-35, Nov 2014.



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Description of Research Expertise

The Heller Lab studies the mechanisms by which epigenome remodeling regulates neuronal gene function and behavior. To approach this problem, we directly manipulate histone and DNA modifications at specific genes in vivo, using viral delivery of novel epigenetic editing tools, such as zinc-finger transcription factors and CRISPR/dCas9-fusion proteins. We use high-throughput sequencing to identify genes at which drug- or stress-regulation of a known epigenomic signature correlates with changes in expression. We can then target individual modifications and examine their causal relevance to transcriptional regulation and subsequent behavioral adaptations. This 'bottom-up' approach allows direct elucidation of the causal relevance of epigenetic remodeling in the brain. Because addiction and depression persist long after cessation of the harmful experience, epigenetic remodeling is an attractive underlying mechanism and presents an intriguing target for therapeutic intervention.

Selected Publications

Cates HM, Heller EA, Lardner CK, Purushothaman I, Peña CJ, Walker DM, Cahill ME, Neve RL, Shen L, Bagot RC, Nestler EJ.: Transcription Factor E2F3a in Nucleus Accumbens Affects Cocaine Action via Transcription and Alternative Splicing. *Biol Psychiatry* 84(3): 167-179, Aug 2018.

Xu SJ, Heller EA: Single sample sequencing (S3EQ) of epigenome and transcriptome in nucleus accumbens. *J Neurosci Methods* 308: 62-73, Jul 2018.

Pierce R, Fant B, Swinford-Jackson S, Heller E, Berrettini W, Wimmer M. : Environmental, genetic and epigenetic contributions to cocaine addiction. *Neuropsychopharmacology* 43(7): 1471-1480, June 2018 Notes: doi: 10.1038/s41386-018-0008-x.

Aleyasin H, Flanigan ME, Golden SA, Takahashi A, Menard C, Pfau ML, Multer J, Pina J, McCabe KA, Bhatti N, Hodes GE, Heshmati M, Neve RL, Nestler EJ, Heller EA, Russo SJ. : Cell-Type-Specific Role of Δ FosB in Nucleus Accumbens In Modulating Intermale Aggression. *J Neuroscience* 38(26): 5913-5924, Jun 2018.

Hamilton PJ, Burek DJ, Lombroso SI, Neve RL, Robison AJ, Nestler EJ, Heller EA: Cell-Type-Specific Epigenetic Editing at the Fosb Gene Controls Susceptibility to Social Defeat Stress. *Neuropsychopharmacology* 43(2): 272-284, Jan 2018.

Hamilton PJ, Lim CJ, Nestler EJ, Heller EA.: Viral Expression of Epigenome Editing Tools in Rodent Brain Using Stereotaxic Surgery Techniques. *Methods Mol Biol. Rots MG & Jeltsch A (eds.). 1767: 205-214, 2018.*

Sase AN, Lombroso SI, Santhumayor BS, Heller EA: Sex-specific regulation of fear memory by targeted epigenetic editing of Cdk5. Under Revision, *Biol Psychiatry*. 2018.

Hu Q, Greene CS, Heller EA: Specific histone modifications associate with alternative exon selection during mammalian development. Under Review, *Nucleic Acids Research* 2018.

Hamilton PJ, Lim CJ, Nestler EJ, Heller EA.: Neuroepigenetic editing. *Methods Mol Biol. Rots MG & Jeltsch A (eds.). 1767: 205-214, 2018.*



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Clinical Expertise

Occupational and Environmental Exposure Assessment

Community Exposure Assessment

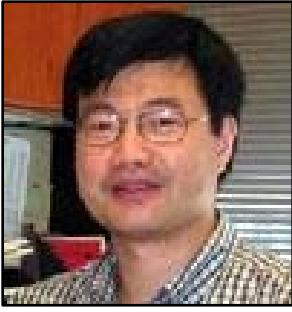
Selected Publications

Howarth MV: *Chemical Exposure in the Healthcare Setting and Managing Latex Allergy*. Medical Center Occupational Health and Safety. American College of Occupational and Environmental Medicine, taped CME presentation in Chicago, II April 2002.

Marilyn V. Howarth: *The Latex Sensitive Healthcare Worker*. Occupational health in the Healthcare Industry, Clinics in Occupational and Environmental Medicine. Philadelphia, PA: Saunders, Page: 395-408, May 2001.

Amy Behrman and Marilyn V. Howarth: *Latex Allergy*. eMedicine: Emergency Medicine. Adler J et al (eds.). Boston: eMedicine Corporation, 2001.

Howarth MV: *The Management of Latex Allergy and Chemical Exposure in the Healthcare Setting*. Medical Center Occupational Health and Safety. American College of Occupational and Environmental Medicine, taped CME presentation in San Francisco, CA April 2001.



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Description of Research

Our research focuses on elucidating the molecular mechanisms whereby menin, a scaffold protein interacting with multiple epigenetic regulators, regulates endocrine cells, including pancreatic beta cells, endocrine tumors, and MLL fusion protein-induced leukemia. In particular, we are interested in dissecting the function of menin, which is mutated in hereditary human tumor syndrome, Multiple Endocrine Neoplasia Type 1 (MEN1), in repressing beta cells and endocrine tumors and in promoting leukemogenesis.

1. We seek to elucidate how menin suppresses endocrine cells, such as pancreatic beta cells, via regulating histone methylations and expression of pro-proliferative genes. We are also interested in identifying menin-regulated key pathways that can be suppressed to inhibit neuroendocrine tumors.
2. Determining how menin, which acts as a tumor promoter in MLL fusion protein-induced leukemia, cooperates with wild-type MLL protein to promote leukemia and how the menin and wt MLL axis can be suppressed to improve therapy for this aggressive leukemia.
3. Understanding how inhibition of menin leads to reversal of established diabetes in mouse models and determining whether the menin pathway could be explored to ameliorate diabetes.
4. Investigating the interplay between menin, post-transcriptional modifications of menin, and TGF- β signaling in repressing pancreatic beta cells. As both menin and TGF- β inhibit cell proliferation, we will test whether menin and TGF- β cooperate to suppress beta cell proliferation and the underlying mechanisms, using biochemical studies and mouse models.

These comprehensive approaches will provide novel insights into the molecular mechanisms for MEN1 tumorigenesis, regulation of beta cells, and leukemogenesis, shedding light on improving therapy against neuroendocrine tumors, leukemia, and diabetes.

Selected Publications

Matkar S, Sharma P, Gao S, Gurung B, Katona BW, Liao J, Muhammad AB, Kong XC, Wang L, Jin G, Dang CV, Hua X: *An Epigenetic Pathway Regulates Sensitivity of Breast Cancer Cells to HER2 Inhibition via FOXO/c-Myc Axis*. *Cancer Cell* 28(4): 472-85, Oct 2015.

Zhu J, Sammons MA, Donahue G, Dou Z, Vedadi M, Getlik M, Barsyte-Lovejoy D, Al-awar R, Katona BW, Shilatifard A, Huang J, Hua X, Arrowsmith CH, Berger SL: *Gain-of-function p53 mutants co-opt chromatin pathways to drive cancer growth*. *Nature* 525(7568): 206-11, Sep 2015.

Matkar S, Katona BW, Hua X: *Harnessing the Hidden Antitumor Power of the MLL-AF4 Oncogene to Fight Leukemia*. *Cancer Cell* 25(4): 411-3, Apr 2014.

Matkar, S, Thiel, A, and Hua, X: *Menin: a scaffold protein that controls gene transcription and cell signaling*. *Trends in Biochemical Sciences (TIBS)* 38(8): 394-402, Aug 2013.

Austin T. Thiel, Zijie Feng, Dhruv K. Pant, Lewis A. Chodosh and Hua X: *The Trithorax Protein Partner Menin*

Acts in Tandem with EZH2 to Suppress C/EBPa and Differentiation in MLL-AF9 Leukemia. Haematologica 98(6): 918, Jun 2013.

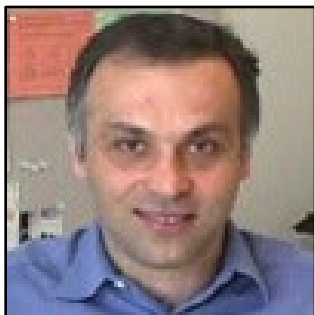
Gurung B, Feng Z, Iwamoto DV, Thiel A, Jin G, Fan C-M, Ng JM, Curran T, Hua X: *Menin Epigenetically Represses Hedgehog signaling in MEN1 Tumor Syndrome.* Cancer Research 73(8): 2650-8, Apr 2013.

Jing Huang, Buddha Gurung, Bingbing Wan, Smita Matkar, Natalia A. Veniaminova, Ke Wan, Juanita L. Merchant, Xianxin Hua*, and Ming Lei* (*co-corresponding author): *The same pocket in menin binds both MLL and JunD, but oppositely regulates transcription.* Nature 432(7386): 542-6, 2012.

Yang, Y., Gurung, B., Wu, T., Wang, H., Stoffers, D. A. and Hua, X: *Reversal of pre-existing hyperglycemia in diabetic mice by acute deletion of Men1.* Proc Natl Acad Sci USA 107(47): 20358-63, Nov 2010.

Thiel, A.T., Blessington, P., Zou, T., Feather, D, Wu, X., Zhang, H., Liu, L., Koretzky, G., Ernst, P., and Hua, X: *MLL-AF9-induced leukemic transformation requires co-expression of wild type MLL allele.* Cancer Cell 17: 148-159, 2010 Notes: The work was featured on the cover of this issue of Cancer Cell.

Yuqing Yang, Haoren Wang, and Xianxin Hua: *Deletion of the Men1 gene prevents streptozotocin-induced hyperglycemia in mice.* Exp Diabetes Res. 2010 2010.



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Research Interests

Biological chemistry of nitric oxide in cardiovascular and neuronal systems. Oxidative processes in protein aggregation and neurodegeneration. Non-invasive, mass spectrometry-based discovery and validation of disease biomarkers.

Research Summary

We investigate the biological chemistry and molecular mechanisms of nitric oxide signaling. Nitric oxide is a free radical that mediates blood flow and many other physiological responses within every major organ system.

Currently mass spectrometry-based proteomic data in conjunction with structure-function analysis explore the biochemical and biophysical specificity of two nitric oxide-mediated post-translational modifications cysteine S-nitrosation and tyrosine nitration. Studies explore the consequences of these modifications on protein function in metabolic processes and mitochondrial bioenergetics.

We are also generating inventories of mouse brain proteomes, phosphoproteomes, S-nitrosoproteomes and secretomes. These inventories are used to create 3D-functional landscapes of the mouse brain extracellular space and to identify signaling pathways that influence neuron physiology and neurodegeneration.

Research Techniques

Biochemical analysis of post-translational modifications; liquid chromatography-mass spectrometry; proteomics; nitric oxide detection; cell model systems of neuronal injury.

Recent Publications

Doulias P-T, Tenopoulou M, Greene, JL, Raju, K and Ischiropoulos H. Nitric oxide regulates mitochondrial fatty acid metabolism through reversible protein S-nitrosylation. *Sci. Signal.* 6: rs1-7, 2013, PMID: 23281369, PMCID: PMC4010156

Gould NS, Evans P, Martínez-Acedo P, Marino SM, Gladyshev VN, Carroll KS, Ischiropoulos H. Site-specific proteomic mapping identifies selectively modified regulatory cysteine residues in functionally distinct protein networks. *Chem Biol.* 22:965-75, 2015, PMID: 26165157 PMCID:PMC4515171.

Raju K, Doulias PT, Evans P, Krizman EN, Jackson JG, Horyn O, Daikhin Y, Nissim I, Yudkoff M, Nissim I, Sharp KA, Robinson MB, Ischiropoulos H. Regulation of brain glutamate metabolism by nitric oxide and S-nitrosylation. *Sci Signal.* 2015 8:ra68. PMID: 26152695; PMCID:PMC4746709.



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Research Overview

The primary focus of my research is to investigate pathophysiological mechanisms of epilepsy and stroke, and secondary effects on synaptic plasticity. A secondary goal is to elucidate age-dependent differences in such mechanisms, and to examine the interactions between brain development, excitotoxic brain injury, epilepsy and cognition. Neurotransmitter receptors are developmentally regulated, and we have specifically demonstrated critical roles of these receptors, as well as their upstream modulators and downstream effectors, in neuronal and glial cells that are unique to the immature, implying age-specific disease mechanisms. The overall aim is to develop new targets based on novel mechanisms for the treatment of epilepsy, stroke, and autism.

Summary of major research findings:

1. Establishment of in vivo and in vitro rodent models of neonatal seizures and perinatal hypoxic/ischemic cerebral injury for examination of cellular and molecular factors influencing age-specific susceptibility, epileptogenicity, and cellular injury.
2. Demonstration that calcium-permeable AMPA receptors are constitutively expressed on neurons and glia in developing rodent and human hippocampus and neocortex, and that these are critical to the mechanisms of seizures and ischemic injury in the developing brain.
3. First demonstration that AMPA receptor antagonists selectively block seizures in the immature brain, but not in the adult. Additional demonstration that the clinically available drugs topiramate and lamotrigine attenuate AMPA receptor currents and suppress neonatal seizures and stroke, including periventricular leukomalacia, in rat models.
4. Elucidation of novel calcium-mediated signaling pathways downstream from the AMPA receptor that play critical roles in the pathogenesis of epilepsy in the immature brain, and preclinical efficacy of preventative or rescue treatment in rodent models. Specific pathways include those mediated by early post-translational changes to glutamate and GABA receptors that increase synaptic excitability. First demonstration that AMPA receptor antagonists including NBQX, topiramate and lamotrigine can reverse these changes when administered as post-seizure treatment, and prevent long term changes.
5. Identification of novel phosphorylation sites Ser 831 and Ser 845 on the GluR1 subunit of the AMPA receptor that are required for the epileptogenic effect of early life seizures, suggesting a novel mechanism for epileptogenesis.
6. Development of novel antiepileptic and neuroprotective strategies that are permissive of neuronal plasticity and long term potentiation. These include the NMDA receptor redox site modulator pyrroloquinoline quinone, and the use-dependent, uncompetitive NMDA blocker memantine as highly protective in vivo and in vitro stroke models, without significant neurocognitive effects.
7. Identified parallel patterns of relative underexpression of the KCC2 chloride transporter versus NKCC1 transporter in human and rodent perinatal cortex during developmental period when GABA receptor agonists are ineffective as antiepileptic agents. This result is the first to strongly implicate the presence of depolarizing GABA receptors in human neonates. This data provided the preclinical target validation that was critical for translation of the use of the NKCC1 inhibitor bumetanide in an FDA approved NIH-funded ongoing clinical trial

at CHB and Partners – Phase I/II safety PK trial in neonatal seizures.

8. Elucidation of abnormal patterns of glutamate and GABA receptors, in human tissue from malformations of cortical development, such as Tuberous Sclerosis, and that these changes are associated with epileptic foci. These results are presently under evaluation with respect to the generation of new clinical treatment trials.

9. Demonstration of convergence of signaling deficits in early life seizures and autism. Alterations in canonical autism-related pathways, including mTOR, FMRP and MeCP2, occur secondary to seizures in the developing brain.

In summary, the emphasis of this translational research program is to identify age-specific mechanisms of brain injury at the cellular level using a variety of in vivo and in vitro techniques, and to use this information to explore and devise experimental therapeutic strategies with clinical potential. Several therapeutic strategies developed in the laboratory are being considered for clinical development. We have established IRBs that have created a repository of human tissue from surgical specimens and autopsy material, and routinely obtain brain tissue directly from surgery for electrophysiological investigation.

Selected Publications:

Jantzie Lauren L, Talos Delia M, Jackson Michele C, Park Hyun-Kyung, Graham Dionne A, Lechpammer Mirna, Folkerth Rebecca D, Volpe Joseph J, Jensen Frances E: *Developmental Expression of N-Methyl-D-Aspartate (NMDA) Receptor Subunits in Human White and Gray Matter: Potential Mechanism of Increased Vulnerability in the Immature Brain*. Cerebral cortex (New York, N.Y. : 1991) : 2013.

Engel J Jr, Pitkänen A, Loeb JA, Edward Dudek F, Bertram EH 3rd, Cole AJ, Moshé SL, Wiebe S, Jensen FE, Mody I, Nehlig A, Vezzani A.: *Epilepsy Biomarkers* Epilepsia : 2013.

Pitkänen Asla, Nehlig Astrid, Brooks-Kayal Amy R, Dudek F Edward, Friedman Daniel, Galanopoulou Aristeia S, Jensen Frances E, Kaminski Rafal M, Kapur Jaideep, Klitgaard Henrik, Löscher Wolfgang, Mody Istvan, Schmidt Dieter: *Issues related to development of antiepileptogenic therapies*. Epilepsia 54 Suppl 4 : 35-43,2013.

Brooks-Kayal Amy R, Bath Kevin G, Berg Anne T, Galanopoulou Aristeia S, Holmes Gregory L, Jensen Frances E, Kanner Andres M, O'Brien Terence J, Whittemore Vicky H, Winawer Melodie R, Patel Manisha, Scharfman Helen E: *Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy*. Epilepsia 54 Suppl 4 : 44-60,2013.

Wintermark Pia, Lechpammer Mirna, Warfield Simon K, Kosaras Bela, Takeoka Masanori, Poduri Annapurna, Madsen Joseph R, Bergin Ann M, Whalen Stephen, Jensen Frances E: *Perfusion Imaging of Focal Cortical Dysplasia Using Arterial Spin Labeling: Correlation With Histopathological Vascular Density*. Journal of child neurology : 2013.



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Research Overview

Our laboratory investigates molecular mechanisms underlying neurodegenerative processes in the hopes of identifying common and unique players in determining neuronal dysfunction and survival among several neurodegenerative diseases driven by neuroinflammation. Currently we are focusing our research efforts on the role of cell cycle proteins, the endogenous antioxidant response and unfolded protein response in three neurodegenerative disorders: HIV encephalitis (HIVE), Alzheimer's disease (AD), and Parkinson's disease (PD).

While HIVE, AD, and PD exhibit different pathologic features, theories as to their etiology share common molecular mechanisms including changes in the trophic factor environment, oxidative stress, and activation of CNS inflammatory components. We hypothesize that neuronal response to these neurodegenerative stimuli includes alterations in expression and/or activity of cell cycle proteins. To this end, we and others have shown that key regulators of cell cycle progression, Retinoblastoma susceptibility gene (pRb), E2F1, and/or p53, exhibit altered levels and patterns of expression in HIVE, PD, and AD. These changes are associated with areas of pathology suggesting a role in degenerative processes. In vitro models of neurodegeneration in each of these diseases also exhibit alterations in cell cycle protein subcellular localization. We are using both human tissue and in vitro models to uncover the role of cell cycle proteins, E2F1, MDMx (a p53 and E2F1 regulatory protein), and pRb in interpreting neuroprotective vs neurotoxic stimuli in primary human, rat, and mouse neuroglial cultures stimulated with trophic factors, chemokines, dopamine, free radicals, beta-amyloid, and HIV-infected macrophage supernatant. These studies are aimed at determining how cell cycle proteins regulate neuronal survival in response to varied and conflicting stimuli. In vitro findings are then used to assess potential roles for these proteins in animal models as well as autopsy tissue relevant to each neurodegenerative condition. Our investigation of E2F1 has resulted in the discovery of a role for this protein in activation of a calpain-dependent death pathway which has not been previously described. Interestingly, neurons responding to HIV-infected macrophage supernatants (our in vitro model of neuronal response to inflammatory infiltrate which mediates HIV encephalitis) activate calpain and increase E2F1 protein levels. One of our immediate lines of investigation is testing the hypothesis that E2F1 induces neuronal death in HIV encephalitis via calpain activation, a novel pathway.

A second area of research in our laboratory is the study of the endogenous anti-oxidant response and its failure to prevent accumulation of oxidative damage and neuronal loss in neurodegenerative disorders. The two proteins of direct interest to the laboratory are Keap1 and Nrf2. Nrf2 is a transcription factor that regulates the expression of the enzymes responsible for the antioxidant response. Normally, Nrf2 is bound in the cytoplasm by the Kelch ECH associated protein 1 (Keap1). However, in response to oxidative stress, sulfhydryl groups on Keap1 become oxidized releasing Nrf2 for translocation into the nucleus. We have recently shown that Nrf2 is aberrantly expressed in AD indicating it is not responding to oxidative stress in neurons of affected brain regions. Interestingly, Nrf2 does appear to be responding appropriately in neurons affected in PD. This has led us to hypothesize that the endogenous antioxidant response is aberrant in AD, but insufficient in PD. Our current studies focus on identifying differences in regulation of the endogenous antioxidant response in AD and PD. The

goal of these studies is to explore this pathway as a therapeutic target for neurodegenerative conditions. By enhancing the endogenous anti-oxidant response, neuronal toxicity may decrease leading to increased neuronal function in these patients.

A final area of interest on which our other two lines of investigation has converged is the role of the unfolded protein response (UPR). Induction of the unfolded protein response results in activation of Nrf2 and calpain, proteins activated in response to the endogenous antioxidant response and the E2F1 cell cycle protein respectively. This has led to our investigation of the UPR in neurodegenerative conditions. We are currently looking at pathways activated by the UPR in our various models of HIV, AD, and PD. The key regulators of this response include pancreatic endoplasmic reticulum kinase (PERK), IRE1, and ATF6. We have already identified increased PERK and phosphorylation of PERK substrate eukaryotic initiation factor 2[?] in AD tissue and an in vitro model of HIV. This is consistent with findings by Ryu, E. J., et al. (2002, *J. Neuroscience* 22:10690) indicating a role for UPR in an in vitro PD model. However, our results indicate that Nrf2 a PERK substrate is not activated in AD suggesting the pathway is compromised in AD. Our future investigations are to determine what parts of the pathway are aberrant in disease progression and identify small molecule inhibitors to block chronic UPR pathway activation which is contributing to neuronal dysfunction and loss.

By assessing the interaction of these three convergent pathways in neurons responding to neurodegenerative stimuli such as oxidative damage, misfolded proteins, and inflammation, we hope to gain a greater understanding of the basic mechanisms underlying neuronal damage, dysfunction and loss in neurodegenerative diseases and identify drugable targets for treatment of AD, PD, and HIV.

Selected Publications

Gannon, P. J. Akay-Espinoza, C. Yee, A. C. Briand, L. A. Erickson, M. A. Gelman, B. B. Gao, Y. Haughey, N. J. Zink, M. C. Clements, J. E. Kim, N. S. Van De Walle, G. Jensen, B. K. Vassar, R. Pierce, R. C. Gill, A. J. Kolson, D. L. Diehl, J. A. Mankowski, J. L. Jordan-Sciutto, K. L.: HIV Protease Inhibitors Alter Amyloid Precursor Protein Processing via beta-Site Amyloid Precursor Protein Cleaving Enzyme-1 Translational Up-Regulation. *Am J Pathol* 187(1): 91-109, JAN 2017.

Monnerie, H. Romer, M. Jensen, B. K. Millar, J. S. Jordan-Sciutto, K. L. Kim, S. F. Grinspan, J. B.: Reduced sterol regulatory element-binding protein (SREBP) processing through site-1 protease (S1P) inhibition alters oligodendrocyte differentiation in vitro. *J Neurochem* 140(1): 53-67, 2017.

Erickson, M. A. Jude, J. Zhao, H. Rhea, E. M. Salameh, T. S. Jester, W. Pu, S. Harrowitz, J. Nguyen, N. Banks, W. A. Panettieri, R. A., Jr. Jordan-Sciutto, K. L.: Serum amyloid A: an ozone-induced circulating factor with potentially important functions in the lung-brain axis. *FASEB J* 31(9): 3950-3965, 2017.

Stern, A. L. Lee, R. N. Panvelker, N. Li, J. Harowitz, J. Jordan-Sciutto, K. L. Akay-Espinoza, C.: Differential Effects of Antiretroviral Drugs on Neurons In Vitro: Roles for Oxidative Stress and Integrated Stress Response. *J Neuroimmune Pharmacol* 2017.

Colacurcio, D. J. Zyskind, J. W. Jordan-Sciutto, K. L. Espinoza, C. A.: Caspase-dependent degradation of MDMx/MDM4 cell cycle regulatory protein in amyloid beta-induced neuronal damage. *Neurosci Lett* 609: 182-8, 2015.

Jensen, B. K. Monnerie, H. Mannell, M. V. Gannon, P. J. Espinoza, C. A. Erickson, M. A. Bruce-Keller, A. J. Gelman, B. B. Briand, L. A. Pierce, R. C. Jordan-Sciutto, K. L. Grinspan, J. B.: Altered Oligodendrocyte Maturation and Myelin Maintenance: The Role of Antiretrovirals in HIV-Associated Neurocognitive Disorders. *J Neuropathol Exp Neurol* 74(11): 1093-118, 2015.

Zyskind, J. W. Wang, Y. Cho, G. Ting, J. H. Kolson, D. L. Lynch, D. R. Jordan-Sciutto, K. L.: E2F1 in neurons is cleaved by calpain in an NMDA receptor-dependent manner in a model of HIV-induced neurotoxicity. *J Neurochem* 132(6): 742-55, 2015.

Ting, J. H., Marks, D. R., Schleidt, S. S., Wu, J. N., Zyskind, J. W., Lindl, K. A., Blendy, J. A., Pierce, R. C., Jordan-Sciutto, K. L.: Targeted gene mutation of E2F1 evokes age-dependent synaptic disruption and behavioral deficits. *J Neurochem* 129(5): 850-63, 2014.

Al-Harhi, L., Buch, S., Geiger, J. D., Gendelman, H. E., He, J. J., Jordan-Sciutto, K. L., Kolson, D. L., Rappaport, J., Roy, S., Zheng, J., Fox, H. S.: Cellular Interactions and Signaling in neuroAIDS: Emerging Issues Colloquium. *J Neuroimmune Pharmacol* 9(3): 269-76, 2014.

Akay, C., Cooper, M., Odeleye, A., Jensen, B. K., White, M. G., Vassoler, F., Gannon, P. J., Mankowski, J., Dorsey, J. L., Buch, A. M., Cross, S. A., Cook, D. R., Pena, M. M., Andersen, E. S., Christofidou-Solomidou, M., Lindl, K. A., Zink, M. C., Clements, J., Pierce, R. C., Kolson, D. L., Jordan-Sciutto, K. L.: Antiretroviral drugs induce oxidative stress and neuronal damage in the central nervous system. *J Neurovirol* 20(1): 39-53, 2014.



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Research Interests

The June Lab is primarily responsible for developing new CARs and new vectors for current and proposed indications. This lab also fosters the development of Penn students both in doctoral and post-doctoral programs. The June Laboratory provides researchers with the tools they need to translate laboratory insights into safe and effective cancer therapies. The June Laboratory works with University of Pennsylvania faculty members interested in moving biologically-focused research ideas into clinical trials. In addition, the June Laboratory has a cadre of faculty researchers focused on developing ways to enhance the ability of the natural immune system to recognize and eliminate tumor cells. Translational research is a core unit of the The Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center at the University of Pennsylvania. Created in December 1997 with a \$100 million pledge from the Abramson Family Foundation, the Cancer Research Institute integrates research, education, and comprehensive patient care at the Abramson Cancer Center at the University of Pennsylvania. For more information, see the Translational Research Mission Statement.

Selected Publications

Porter David L, Levine Bruce L, Kalos Michael, Bagg Adam, June Carl H: *Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia*. The New England journal of medicine 365(8): 725-33, Aug 2011.

Kalos Michael, Levine Bruce L, Porter David L, Katz Sharyn, Grupp Stephan A, Bagg Adam, June Carl H: *T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced Leukemia*. Science translational medicine 3(95): 95ra73, Aug 2011.

Rapoport Aaron P, Aqui Nicole A, Stadtmauer Edward A, Vogl Dan T, Fang Hong-Bin, Cai Ling, Janofsky Stephen, Chew Anne, Storek Jan, Akpek Gorgun, Badros Ashraf, Yanovich Saul, Tan Ming

T, Veloso Elizabeth, Pasetti Marcela F, Cross Alan, Philip Sunita, Murphy Heather, Bhagat Rita, Zheng Zhaohui, Milliron Todd, Cotte Julio, Cannon Andrea, Levine Bruce L, Vonderheide Robert H, June Carl H: *Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma*. Blood 117(3): 788-97, Jan 2011.

Perez EE, Wang J, Miller JC, Jouvenot Y, Kim KA, Liu O, Wang N, Lee G, Bartsevich VV, Lee YL, Guschin DY, Rupniewski I, Waite AJ, Carpenito C, Carroll RG, Orange JS, Urnov FD, Rebar EJ, Ando D, Gregory PD, Riley JL, Holmes MC, June CH.: *Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases*. Nat Biotechnol. 7: 808-16, Jul. 26 2008.



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Research Interests

Epigenomic rejuvenation of human pancreatic beta-cells.

The prevalence of Diabetes Mellitus has reached epidemic proportions world-wide, and is predicted to increase rapidly in the years to come, putting a tremendous strain on health care budgets in both developed and developing countries. There are two major forms of diabetes and both are associated with decreased beta-cell mass. No treatments have been devised that increase beta-cell mass in vivo in humans, and transplantation of beta-cells is extremely limited due to lack of appropriate donors. For these reasons, increasing functional beta-cell mass in vitro, or in vivo prior to or after transplantation, has become a “Holy Grail” of diabetes research. Our previous studies clearly show that adult human beta-cells can be induced to replicate, and – importantly - that cells can maintain normal glucose responsiveness after cell division. However, the replication rate achieved was still low, likely due in part to the known age-related decline in the ability of the beta-cell to replicate. We propose to build on our previous findings and to develop more efficacious methods to increase functional beta-cell mass by inducing replication of adult beta-cells, and by restoring juvenile functional properties to aged beta-cells. We will focus on mechanisms derived from studies of non-neoplastic human disease as well as age-related phenotypic changes in human beta-cells. In Aim 1, we will target the genes altered in patients with marked beta-cell hyperplasia, such as those suffering from Beckwith-Wiedemann Syndrome or Multiple Endocrine Neoplasia. Expression of these genes will be altered in human beta-cells via shRNA-mediated gene suppression and locus-specific epigenetic targeting. Success will be assessed in transplanted human islets by determination of beta-cell replication rate and retention of function. In Aim 2, we will determine the mechanisms of age-related decline in beta-cell function and replicative capacity, by mapping the changes in the beta-cell epigenome that occur with age. Selected genes will then be targeted as in Aim 1 to improve human beta-cell function, as assessed by glucose responsiveness. To accomplish these aims, we will use cutting-edge and emerging technologies that are already established or are being developed in our laboratories. The research team combines clinical experience with expertise in molecular biology and extensive experience in genomic modification aimed at enhancing beta-cell replication. By basing interventions on changes found in human disease and normal aging, this approach will increase the chances that discoveries made can be translated more rapidly into clinically relevant protocols.

Regulatory cascades in differentiation and proliferation of the gastrointestinal epithelium.

The mammalian gut epithelium is a highly organized and dynamic system which requires continuous controlled proliferation and differentiation throughout life. Proliferation, cell migration and cell adhesion all must be tightly controlled in order to prevent either inflammatory diseases or epithelial cancers. As with many other vertebrate organs, the digestive tract develops from heterogeneous embryonic origins. While the musculature and the connective tissue are derived from lateral plate mesoderm, the epithelium is derived from the endoderm. We have identified a novel member of the winged helix gene family termed Foxl1 which is expressed in the gut mesoderm and have begun its functional analysis in vivo through targeted mutagenesis in mice. Null mutations in the mesodermal transcription factor Foxl1 result in dramatic alterations in endoderm development, including epithelial hyperproliferation. We have now identified APC/Min and GSK3 as downstream targets of Foxl1 and

have begun the analysis of these genes in gastrointestinal differentiation by tissue-specific gene ablation.

Innovative Genetic Approaches for Hepatic Repopulation

A better understanding of the liver's response to toxic injury, which includes hepatocyte proliferation, activation and differentiation of facultative hepatic stem cells ("oval cells"), and – unfortunately – an increased risk for hepatocellular carcinoma, is a prerequisite for the development of novel clinical treatments for chronic liver disease and improved cancer prevention. Likewise, cell replacement therapy, either through direct hepatocyte transplantation or in bio-artificial liver devices, needs to be improved in order to become a reliable alternative to liver transplantation. To date, investigations of hepatocyte proliferation have frequently focused on the partial hepatectomy paradigm, a "non-injury" model that is not reflective of liver injury in humans and which has therefore failed to identify specific targets for either improved regeneration following toxic injury or for limiting proliferation in HCC in humans. In Specific Aim 1, we will determine which genes and gene combinations promote or repress hepatocyte repopulation following toxic liver injury using an innovative genetic approach. In Specific Aim 2, we will employ expression of key hepatic transcription factors to improve the differentiation of hepatic progenitor cells to functional hepatocytes. Together, these approaches will provide an improved understanding of the liver's response to toxic injury, and facilitate the discovery of new cell replacement therapies to treat chronic liver disease and liver failure.

Selected Publications

Michal Shoshkes-Carmel, Yue J. Wang, Kirk J. Wangenstein, Beáta Tóth, Ayano Kondo, Efi E. Massasa, Shalev Itzkovitz, and Klaus H. Kaestner: Subepithelial telocytes are an important source of Wnts that supports intestinal crypts. *Nature* doi: 10.1038/s41586-018-0084-4, May 2018.

Wang AW, Wangenstein KJ, Wang YJ, Zahm AM, Moss NG, Erez N, Kaestner KH: TRAP-seq identifies cystine/glutamate antiporters as a driver of recovery from liver injury. *J Clin Invest* Page: DOI: 10.1172/JCI95120, April 2018.

Wangenstein Kirk J, Wang Yue J, Dou Zhixun, Wang Amber W, Mosleh-Shirazi Elham, Horlbeck Max A, Gilbert Luke A, Weissman Jonathan S, Berger Shelley L, Kaestner Klaus H: Combinatorial genetics in liver repopulation and carcinogenesis with a novel in vivo CRISPR activation platform. *Hepatology* (Baltimore, Md.) Nov 2017.

Kim, R., Sheaffer, K.L., Choi, I., Won, K.-J., and Kaestner, K.H.: Epigenetic regulation of intestinal stem cells by Tet1-mediated DNA hydroxymethylation. *Genes Dev* in press, December 2016.

Bernstein, D.A., Le Lay, J.E., Ruano, E.G. and Kaestner, K.H.: TALE-mediated epigenetic suppression of CDKN2A increases replication in human fibroblasts. *J. Clin. Invest.* 125(5): 1998-2006, May 2015.

Wang YJ, Schug J, Won KJ, Liu C, Naji A, Avrahami D, Golson ML, Kaestner KH: Single cell transcriptomics of the human endocrine pancreas. *Diabetes* 65(10): 3028-38, October 2016.

Wangenstein KJ, Zhang S, Greenbaum LE, Kaestner KH.: A genetic screen reveals Foxa3 and TNFR1 as key regulators of liver repopulation. *Genes Dev* 29(9): 904-9, May 2015.

Avrahami D, Li C, Zhang J, Schug J, Avrahami R, Rao S, Stadler MB, Burger L, Schübeler D, Glaser B, Kaestner KH.: Aging-Dependent Demethylation of Regulatory Elements Correlates with Chromatin State and Improved β Cell Function. *Cell Metabolism* 22(4): 619-32, October 2015.

Sheaffer, K.L., Kim, R., Aoki, R., Elliott, E.N., Schug, J., Burger, L., Schubeler, D., and Kaestner, K.H.: DNA methylation is required for the control of stem cell differentiation in the small intestine. *Genes Dev* 28(6): 652-664 March 2014.

Bramswig, N., Evertt, L., Schug, J., Dorrell, C., Liu, C., Luo, Y., Streeter, P., Naji, A., Grompe, M., And Kaestner, K.H.: Epigenomic plasticity enables human pancreatic α to β cell reprogramming. *J. Clin. Invest.* 123(3): 1275-84, March 2013.

Li, Z, Gadue, P, Chen, K, Jiao, Y, Tuteja, G, Schug, J, Li, W, and Kaestner, KH: Foxa2 and H2A.Z Mediate Nucleosome Depletion during Embryonic Stem Cell Differentiation. *Cell* 151(7): 1608-16, December 2012.

Li, Z., Tuteja, G., Schug, J. and Kaestner, K.H.: Foxa1 and Foxa2 are Essential for Sexual Dimorphism in Liver
Cancer Cell 148: 72-83, January 2012.



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Research Interests

Our lab investigates signaling pathways that regulate cardiovascular biology and diseases. We are interested in both lymphatic and blood vessel regulatory pathways, and in the interactions between blood cells and vascular endothelium. Most of the pathways we investigate are known to cause human vascular diseases. We apply vertebrate genetic approaches as well as biochemical and state of the art molecular approaches to understand the function of these pathways during normal development and in disease models.

Selected Publications

Goddard LM, Duchemin A-L, Ramalingan H, Wu B, Chen M, Bamezai S, Yang J, Li L, Morely M, Wang T, Scherrer-Crosbie M, Frank DB, Engleka KA, Jameson SC, Morrissey EE, Carroll TJ, Zhou B, Vermot J, Kahn ML: Hemodynamic forces sculpt developing heart valves through a KLF2-Wnt9b paracrine signaling axis. *Developmental Cell* 43(3): 274-289, Nov 2017.

Goddard LM, Kahn ML.: A BMPy Road for Venous Development *Developmental Cell* 42(5): 435-36, Sep 2017.

Tang Alan T, Choi Jaesung P, Kotzin Jonathan J, Yang Yiqing, Hong Courtney C, Hobson Nicholas, Girard Romuald, Zeineddine Hussein A, Lightle Rhonda, Moore Thomas, Cao Ying, Shenkar Robert, Chen Mei, Mericko Patricia, Yang Jisheng, Li Li, Tanes Ceylan, Kobuley Dmytro, Vösa Urmo, Whitehead Kevin J, Li Dean Y, Franke Lude, Hart Blaine, Schwaninger Markus, Henao-Mejia Jorge, Morrison Leslie, Kim Helen, Awad Issam A, Zheng Xiangjian, Kahn Mark L: Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. *Nature* 545(7654): 305-310, May 2017 Notes: Covered in the NYT: <https://www.nytimes.com/2017/05/10/health/brain-defect-gut-bacteria-microbiome.html>.

Welsh John D, Kahn Mark L, Sweet Daniel T: Lymphovenous hemostasis and the role of platelets in regulating lymphatic flow and lymphatic vessel maturation. *Blood* 128(9): 1169-73, Sep 2016.

Girard Romuald, Zeineddine Hussein A, Orsbon Courtney, Tan Huan, Moore Thomas, Hobson Nick, Shenkar Robert, Lightle Rhonda, Shi Changbin, Fam Maged D, Cao Ying, Shen Le, Neander April I, Rorrer Autumn, Gallione Carol, Tang Alan T, Kahn Mark L, Marchuk Douglas A, Luo Zhe-Xi, Awad Issam A: Micro-computed tomography in murine models of cerebral cavernous malformations as a paradigm for brain disease. *Journal of Neuroscience Methods* 271: 14-24, Sep 2016.

Cha Boksik, Geng Xin, Mahamud Md Riaj, Fu Jianxin, Mukherjee Anish, Kim Yeunhee, Jho Eek-Hoon, Kim Tae Hoon, Kahn Mark L, Xia Lijun, Dixon J Brandon, Chen Hong, Srinivasan R Sathish: Mechanotransduction activates canonical Wnt/ β -catenin signaling to promote lymphatic vascular patterning and the development of lymphatic and lymphovenous valves. *Genes & Development* 30(12): 1454-69, Jun 2016.

Bui Hung M, Enis David, Robciuc Marius R, Nurmi Harri J, Cohen Jennifer, Chen Mei, Yang Yiqing, Dhillon Veerpal, Johnson Kathy, Zhang Hong, Kirkpatrick Robert, Traxler Elizabeth, Anisimov Andrey, Alitalo Kari, Kahn Mark L: Proteolytic activation defines distinct lymphangiogenic mechanisms for VEGFC and VEGFD. *The Journal of Clinical Investigation* 126(6): 2167-80, May 2016.

Zhou Z, Tang AT, Wong WY, Bamezai S, Goddard LM, Shenkar R, Zhou S, Yang J, Wright AC, Foley M, Arthur JS, Whitehead KJ, Awad IA, Li DY, Zheng X, Kahn ML: Cerebral cavernous malformations arise from endothelial gain of MEKK3-KLF2/4 signaling. *Nature* 532(7597): 122-6, April 2016.

Maltzman Jonathan S, Reed Hasina Outtz, Kahn Mark L: HA-ving lymphatics improves lung transplantation. *The Journal of clinical investigation* 125(11): 3999-4001, Nov 2015.

Sweet DT, Jiménez JM, Chang J, Hess PR, Mericko-Ishizuka P, Fu J, Xia L, Davies PF, Kahn ML: Lymph flow regulates collecting lymphatic vessel maturation in vivo. *Journal of Clinical Investigation* 125(8): 2995-3007, Aug 2015.



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Research Overview

The Kazanietz laboratory studies signaling mechanisms implicated in tumorigenesis and metastasis. A major area of research is the involvement of serine-threonine kinases of the PKC family in the control of proliferation, transformation, invasion and survival of cancer cells. PKC isozymes are the receptors for the phorbol ester tumor promoters and diacylglycerol (DAG), an important intracellular second messenger generated upon activation of tyrosine-kinase receptors and GPCRs. Our laboratory established key roles for PKCdelta and PKCepsilon in prostate and lung tumorigenesis, characterized their interactions with oncogenes and tumor suppressors, and identified kinase effectors responsible for their effects. A second area of research involves the study of small GTPases of the Rac/Rho family in cancer progression. We have recently identified the Rac-GEF P-Rex1 as a key mediator of breast cancer metastasis. Our studies found that P-Rex1 is a downstream effector of ErbB/HER receptors that is required for luminal breast cancer cell motility. A major goal is to dissect the networks, genes and effectors controlled by these cancer signaling molecules, and established their relevance as therapeutic targets for cancer and other diseases.

Selected Publications

- Griner, E., and Kazanietz, M.G. Protein kinase C and other diacylglycerol effectors in cancer. *Nature Reviews Cancer* 7: 281-294 (2007).
- Sosa, M.S., Lopez-Haber, C., Yang, C., Lemmon, M.A., Busillo, J.M., Luo, J., Benovic, J.L., Klein-Szanto, A., Yagi, H., Gutkind, J.S., Parsons, R.E, and Kazanietz, M.G. Identification of the Rac-GEF P-Rex1 as an essential mediator of ErbB signaling in breast cancer. *Mol. Cell* 40: 877-892 (2010).
- Barrio-Real, L., and Kazanietz, M.G. Rho GEFs and cancer: linking gene expression and metastatic dissemination. *Science Signal*. 5:pe43 (2012).
- Caino, M.C., Lopez-Haber, C., Kim, J., and Kazanietz, M.G. Protein kinase C epsilon is required for non-small cell lung carcinoma tumor growth and regulates the expression of apoptotic genes. *Oncogene* 31:2593-2600 (2012).
- Gutierrez-Uzquiza, A., Colon-Gonzalez, F., Leonard, T.A., Canagarajah, B.J., Wang, H., Mayer, B.J., Hurley, J.H., and Kazanietz, M.G. An atypical proline-rich domain in the diacylglycerol-regulated Rac- -chimaerin mediates its interaction with Nck1 and activation. *Nature Communications* 4:1849 (2013).
- Garg, R., Benedetti, L.G., Abera, M.B., Wang, H., Abba, M., and Kazanietz, M.G. Protein kinase C isozymes and cancer: what we know and what we do not. *Oncogene* 33:5225-5237 (2014).
- Wang, H., Gutierrez-Uzquiza, A., Garg, R. Barrio-Real, L., Abera, M.B., Rosemlit, C., Lu, H., and Kazanietz, M.G. Transcriptional regulation of oncogenic protein kinase C δ (PKC δ) by STAT1 and Sp1 proteins. *J. Biol. Chem.* 289:19823-19838 (2014).
- Gutierrez-Uzquiza, A., Lopez-Haber, C., Jernigan, D.L., Fatatis, A., and Kazanietz, M.G. PKC δ is a mediator of prostate cancer bone metastasis. *Mol. Cancer Res.* 13:1336-1346 (2015).

- Lopez-Haber, C., Barrio-Real, L., Casado-Medrano, V., and Kazanietz M.G. Heregulin/ErbB3 signaling enhances CXCR4-driven Rac1 activation and breast cancer cell motility via hypoxia-inducible factor 1 α . *Mol. Cell. Biol.* 36:2011-2016 (2016).
- Baker, M.J., Cooke, M., and Kazanietz, M.G. Nuclear PKC α -ECT2-Rac1 and ribosome biogenesis: A novel axis in lung tumorigenesis. *Cancer Cell* 31:167-169 (2017).
- Garg, R., Blando, J.M., Perez, C.J., Abba, M.C., Benavides, F., and Kazanietz, M.G. Protein Kinase C epsilon cooperates with PTEN loss for prostate tumorigenesis through the CXCL13-CXCR5 pathway. *Cell Rep.* 19:375-388 (2017).
- Kazanietz, M.G and Caloca, M.J. The Rac GTPase in cancer: From old concepts to new paradigms. *Cancer Res.* doi: 10.1158/0008-5472 [Epub ahead of print] (2017)
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Research Interests

Convergence of Sleep and Anesthesia: Insights from Narcolepsy

The wet blanket theory postulates that anesthetic drugs work non-specifically, binding promiscuously at the molecular level and globally at the neuronal (and glial) level to envelope the entire brain and comprehensively perturb brain function to enhance inhibitory signaling and inhibit excitatory signaling and consequently yield states of unconsciousness. However, alternative theories highlighting shared traits among the hypnotic states common to both NREM sleep and sub-surgical levels of many anesthetic drugs suggest that a component of the hypnotic state may arise through specific targeted actions of anesthetics upon the endogenous neural circuits that generate natural sleep.

Some of the most important clues for site-specific actions of anesthetic drugs have been provided by the clinical observation that a subset of patients suffering from narcolepsy (a primary neurological disorder in the organization of sleep and wakefulness) have problems exiting states of anesthesia. As narcolepsy is a disease that arises from a loss of orexin/hypocretin neurons confined to the hypothalamus, this finding which the Kelz lab replicated in mice, suggests that general anesthetics can and do have specific interactions with discrete populations of neurons in the CNS. Work in the Kelz lab uses combinations of molecular genetics, histochemistry, circuit mapping, electrophysiology, and behavioral assessments to phenotype the anesthetic state in multiple ways.

Anesthetics Enhance Firing in Endogenous Sleep-Promoting Neurons

As drugs that classically enhance inhibitory signaling and inhibit excitatory signaling, general anesthetics are not predicted to directly depolarize neurons in the CNS. However, work in the Kelz lab has found that of all the neurons that could be depolarized and increase their firing in response to anesthetics exposure, discrete populations of putative-sleep promoting neurons are indeed activated by general anesthetic drugs.

OptoAnesthesia

In order to localize and characterize the important features of inhaled anesthetic protein targets, we, in collaboration with the Eckenhoff lab, have found anesthetic-like activity of recently developed novel anesthetic photolabels in a variety of in vitro systems and the tadpole. Our lab is translating these findings to rodents to better understand anesthetic binding and actions in the brain and anesthetic sensitivity in mammals. This project will provide the foundation for a novel mechanism of drug action, which will ultimately lead to better anesthetic management in patients and new and better anesthetic drugs for patients.

Translational Studies in Humans

Together with our collaborators and other investigators in the Neurobiology of Unconsciousness group, the Kelz lab conducts volunteer studies in humans designed to reveal insights into the ways in which the human brain

enters and exits states of general anesthesia, to determine how the CNS “reboots” after leaving the abyss of general anesthesia, and how signatures of the anesthetic state as measured both through high density EEG and ECoG may help to reveal whether patients are adequately anesthetized to block conscious perception and new memory formation.

Selected Publications

Mashour GA, Kelz MB: Systems Neuroscience: The Exciting Journey to Oblivion. *Current Biology* 28(5): R223-4, Mar 2018.

Shortal Brenna P, Reitz Sarah L, Aggarwal Adeeti, Meng Qing C, McKinstry-Wu Andrew R, Kelz Max B, Proekt Alex: Development and validation of brain target controlled infusion of propofol in mice. *PLoS one* 13(4): e0194949, 2018.

Wasilczuk AZ, Maier KL, Kelz MB: The Mouse as a Model Organism for Assessing Anesthetic Sensitivity. *Methods in enzymology* 602: 211-228, 2018.

McKinstry-Wu A, Carspecken CW, Proekt A, Kelz MB: Xenon Anesthesia and CT: Noninvasive Measures of Brain Anesthetic Concentration. *Methods in enzymology* 602: 289-98, 2018.

McKinstry-Wu Andrew R, Kelz Max B: Optoanesthesia: Use of Anesthetic Photolabels In Vivo. *Methods in enzymology* 603: 171-180, 2018.

Richardson Andrew G, Liu Xilin, Weigand Pauline K, Hudgins Eric D, Stein Joel M, Das Sandhitsu R, Proekt Alexander, Kelz Max B, Zhang Milin, Van der Spiegel Jan, Lucas Timothy H: Hippocampal gamma-slow oscillation coupling in macaques during sedation and sleep. *Hippocampus* Jul 2017.

Blain-Moraes Stefanie, Tarnal Vijay, Vanini Giancarlo, Bel-Behar Tarik, Janke Ellen, Picton Paul, Golmirzaie Goodarz, Palanca Ben J A, Avidan Michael S, Kelz Max B, Mashour George A: Network Efficiency and Posterior Alpha Patterns Are Markers of Recovery from General Anesthesia: A High-Density Electroencephalography Study in Healthy Volunteers. *Frontiers in human neuroscience* 11: 328, 2017.

Maier Kaitlyn L, McKinstry-Wu Andrew R, Palanca Ben Julian A, Tarnal Vijay, Blain-Moraes Stefanie, Basner Mathias, Avidan Michael S, Mashour George A, Kelz Max B: Protocol for the Reconstructing Consciousness and Cognition (ReCCognition) Study. *Frontiers in human neuroscience* 11: 284, 2017.

Wasilczuk AZ, Proekt A, Kelz MB, McKinstry-Wu AR.: High-density Electroencephalographic Acquisition in a Rodent Model Using Low-cost and Open-source Resources. *J Vis Exp.* 117: e54908, Nov 2016.

Erickson RL, Terzi MC, Jaber SM, Hankenson FC, McKinstry-Wu A, Kelz MB, Marx JO.: Intraperitoneal Continuous-Rate Infusion for the Maintenance of Anesthesia in Laboratory Mice (*Mus musculus*). *J Am Assoc Lab Anim Sci.* 55(5): 548-57, September 2016..



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Description of Research

This lab studies patterning in early vertebrate development, the regulation of stem cell self-renewal in the hematopoietic system, adult neurogenesis, Wnt signaling, and the molecular mechanisms in the pathogenesis and treatment of neuropsychiatric disorders. Areas of current research include:

1) Wnt signaling modifies chromatin architecture to control early development: We have found that Wnt signaling through β -catenin establishes poised chromatin architecture at Wnt target promoters in the early embryo. We have identified Prmt2 as a histone H3 arginine-8 methyltransferase and shown that it is recruited by β -catenin to Wnt target gene promoters and is required for dorsal-ventral patterning. We are currently examining the requirement for Prmt2 in other Wnt-regulated contexts in development and in somatic stem cell populations. We are also exploring the regulation of zygotic gene expression before the midblastula transition, focusing on the role of preMBT transcription in germ layer specification. These experiments are being carried out in *Xenopus laevis* embryos and in mouse hematopoietic stem cells, and involve microinjection, microsurgical procedures, molecular analysis of chromatin structure and gene expression, and biochemical analysis of the Wnt signaling pathway.

2) Wnt and GSK-3 regulation of hematopoietic stem cell (HSC) self-renewal: We are studying the roles of GSK-3 and Wnt signaling in HSC homeostasis *in vivo* and in primary HSC culture. We are exploring novel *ex vivo* culture techniques to define the signaling pathways required for and the gene expression profile associated with HSC self-renewal. In collaboration with Wei Tong at CHOP, we are also studying how JAK/STAT signaling interacts with GSK-3 and Wnts to regulate HSC renewal. These experiments are being carried out with mouse and human hematopoietic stem cells, using novel *ex vivo* culture techniques and stem cell transplantation assays in mice. These experiments also involve flow cytometry and cell sorting, RNA interference, and biochemical analysis of transmembrane signaling pathways. Our long-term interest is to adapt these findings to clinical applications including hematopoietic stem cell transplantation in humans and treatment of bone marrow failure disorders.

3) Neural signaling pathways that mediate the response to mood stabilizing drugs, with a focus on lithium, GSK-3, and Wnt signaling in the adult central nervous system, in order to understand the molecular pathogenesis and pharmacotherapy of bipolar disorder. This laboratory identified GSK-3 as a direct target of lithium, the most widely used and effective treatment for bipolar disorder. We are currently investigating the downstream molecular targets and the neuronal cell populations within the brain that mediate the response to mood stabilizing drugs. For these experiments, we use neural specific gene knockout and transgenic mice, multiple behavioral assays in adult mice, and *in vivo* analysis of neural stem cell proliferation and differentiation. In collaboration with Celeste Simon, we are examining interaction between hypoxia inducible factors, GSK-3, and the Wnt pathway in regulating neuronal stem/progenitor cells and the potential role of this cell population in mood disorders.

4) Molecular mechanisms of Wnt signaling: We are also investigating the molecular mechanisms of Wnt signaling, with a focus on how GSK-3 activity is regulated by Wnts. We have found that GSK-3 is positively regulated by the tumor suppressor APC. We are exploring the hypothesis that APC regulates multiple targets

through the regulation of GSK-3 activity.

Selected Publications

- Valvezan AJ, Huang J, Lengner CJ, Pack M, and PS Klein: Oncogenic mutations in Adenomatous Polyposis Coli (Apc) activate mechanistic Target of Rapamycin Complex 1 (mTORC1). *Disease Models and Mechanisms* 7(1): 63-71, Jan 2014.
- Huang J, Nguyen-McCarty M, Hexner EO, Danet-Desnoyers G, and PS Klein, : Maintenance of Hematopoietic Stem Cells through regulation of Wnt and mTOR Pathways. *Nature Medicine* 18: 1778-1785, Nov 11 2012
Notes: doi: 10.1038/nm.2984.
- Valvezan AJ, Zhang FS, Diehl JA, and PS Klein: Adenomatous Polyposis Coli (APC) regulates multiple signaling pathways by enhancing glycogen synthase kinase-3 (GSK-3) activity. *Journal of Biological Chemistry* 287: 3823-3832, 2012.
- Skirkanich J, Luxardi G, Yang J, Kodjabachian L, and PS Klein: An essential role for transcription before the MBT in *Xenopus laevis*. *Developmental Biology* 357: 478-491, 2011.
- O'Brien WT, Huang J, Buccafusca R, Garskof J, Valvezan AJ, Berry GT, and PS Klein: Glycogen synthase kinase-3 is essential for β -arrestin-2 complex formation and lithium-sensitive behaviors in mice. *Journal of Clinical Investigation* 121: 3756-3762, 2011.
- Blythe SA and Klein PS: Prepatterning embryonic development: tabula scripta? *Developmental Cell* 21: 977-978, 2011.
- Blythe SA, Cha SW, Tadjuidje E, Heasman J, Klein PS,: beta-Catenin primes organizer gene expression by recruiting a histone H3 arginine 8 methyltransferase, Prmt2. *Developmental Cell* 19(2): 220-231, Aug 2010.
- Mazumdar J, O'Brien WT, Johnson RS, LaManna JC, Chavez JC, Klein PS, Simon MC: O2 regulates stem cells through Wnt/ β -catenin signalling. *Nature Cell Biology* 12(10): 1007-13, Oct 2010.
- Huang J, Zhang Y, Bersenev A, O'Brien WT, Tong W, Emerson SG, Klein PS: Pivotal role for glycogen synthase kinase-3 in hematopoietic stem cell homeostasis in mice. *Journal of Clinical Investigation* 119(12): 3519-29, Dec 2009.
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Research Overview

Our laboratory broadly focuses on DNA modifying enzymes and pathways, particularly those that contribute to genomic plasticity. We utilize a broad array of approaches, including biochemical characterization of enzyme mechanisms, chemical synthesis of enzyme probes, and biological assays spanning immunology and virology to study the fundamental question of how a genomic diversity arises in nature.

Mutation and modification of the genome play an important role in several physiologically relevant areas and our areas of interest include:

1. Decipher the molecular basis for deamination by AID/APOBEC enzymes and perturb deaminase immunological functions

From the host immune perspective, the generation of genomic diversity is used as both a defensive and an offensive weapon. Host mutator enzymes such as Activation-Induced Cytidine Deaminase (AID) seed diversity in the adaptive immune system by introducing targeted mutations into the immunoglobulin locus that result in antibody maturation. Related deaminases of the innate immune system can directly attack retroviral threats by garbling the pathogen genome through mutation, as accomplished by the deaminase APOBEC3G, which restricts infection with HIV. Immune mutator enzymes, however, also pose a risk to the host, as overexpression or dysregulation have been associated with oncogenesis.

2. Explore the interplay of cytosine modifying enzymes on DNA demethylation

The singular genome is responsible for a wealth of different cell types, each of which can respond and adapt to environmental cues. In part, these epigenetic differences are linked to DNA modification. These modifications center around cytosine, where DNA deamination (AID/APOBEC enzymes), oxidation (TET family enzymes) and methylation (DNMTs) can all interplay and tune the genome's potential. We are interested in the enzymatic activities of these cytosine modifying enzymes, particularly in the process of DNA demethylation which plays a role in embryogenesis, gene regulation and a potential pathological role in cancer.

3. Target pathogen pathways that promote evolution and resistance.

From the pathogen perspective, alteration in key antigenic determinants at a rate that outpaces immune responses is a potent means for evasion. Further, rapid mutation may allow for the development of resistance to antimicrobials. In bacteria, adaptation and evolution are closely linked to the stress response of SOS pathway. The SOS pathway can be triggered by numerous stressors, including antibiotics, and the net result

is accelerated acquisition of drug resistance. We aim to characterize the key regulatory and effector enzymes from the SOS pathway and to target the pathway as a means to combat antibiotic resistance.

Our research program aims to understand these pathways of purposeful DNA modification and mutation. Additionally, we apply chemical biology to decipher and target these pathways, to impede the development of multidrug-resistance in pathogens or prevent the neoplastic transformations that can result from genomic mutation.

Selected Publications

Culyba MJ, Mo CY, Kohli RM: Targets for Combating the Evolution of Acquired Antibiotic Resistance. *Biochemistry* 54(23): 3573-82, Jun 2015.

Mo CY, Birdwell LD, Kohli RM: Specificity Determinants for Autoproteolysis of LexA, a Key Regulator of Bacterial SOS Mutagenesis. *Biochemistry* 53(19): 3158-68, May 2014.

Kohli RM, Zhang Y: TET enzymes, TDG and the Dynamics of DNA Demethylation. *Nature* 502: 472-9, Oct 2013.

Nabel CS, Lee JW, Wang LC, Kohli RM: Nucleic acid determinants for selective deamination of DNA over RNA by activation-induced deaminase. *Proc Natl Acad Sci USA* 110(35): 14225-30, Aug 2013.

Nabel CS, Manning SA, Kohli RM: The Curious Chemical Biology of Cytosine: Deamination, Methylation and Oxidation as Modulators of Genomic Potential. *ACS Chemical Biology* 7(1): 20-30, Jan 2012.

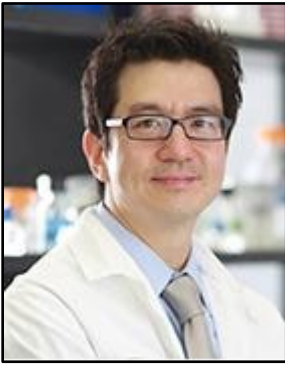
Nabel CS, Jia H, Ye Y, Shen L, Goldschmidt HL, Stivers JT, Zhang Y, Kohli RM: AID/APOBEC deaminases disfavor modified cytosines implicated in DNA demethylation. *Nature Chem Biol* 8(9): 751-758, Sep 2012.

Nabel CS, Kohli RM: Molecular biology. Demystifying DNA Demethylation. *Science* 333(6047): 1229-1230, Sep 2011.

Kohli RM: Grand Challenge Commentary: The Chemistry of a Dynamic Genome. *Nature Chem Biol* 6(12): 866-868, Dec 2010.

Kohli RM, Burke MD, Tao J, Walsh CT: Chemoenzymatic route to macrocyclic hybrid peptide/polyketide-like molecules. *J Am Chem Soc* 125(24): 7160-7161, Jun 2003.

Kohli RM, Walsh CT, Burkart MD: Biomimetic synthesis and optimization of cyclic peptide antibiotics. *Nature* 418(6898): 658-661, Aug 2002.



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Research Overview

The laboratory of Dr. Koo focuses on understanding the relationship between biofilms and oral infectious diseases and seeking novel therapeutic strategies to control pathogenic biofilms, including those associated with dental caries.

Biofilms are structured communities of microbial cells that are attached to a surface and enmeshed in a self-produced three-dimensional (3D) matrix of extracellular polymeric substances (EPS). The matrix provides an essential scaffold for the initial assembly and further development of biofilms. It promotes microbial adhesion, cohesion and protection as well as hindering diffusion. Importantly, the matrix also creates spatial and microenvironmental heterogeneities in biofilms, modulating the growth and survival of pathogens locally. The matrix is considered a key factor for the existence of the biofilm lifestyle and full expression of virulence by several bacterial pathogens.

Dr. Koo's research is particularly interested in elucidating three major questions:

1. How the extracellular matrix assembles dynamically in 3D. In particular, we are interested in understanding the structural organization of EPS, and how they modulate cell adhesion-cohesion, the 3D matrix-scaffold and mechanical stability of biofilms over time.
2. How the matrix modulates the microenvironmental heterogeneity within biofilms. Here, we focus on spatio-temporal characterization of local pH and oxygen levels, microbial organization/positioning and gene expression in situ, and how these properties influence the virulence of biofilms as a whole.
3. How to disrupt the EPS production and target the pathogens embedded in the matrix. We are interested in finding new strategies to prevent biofilm initiation or disrupt existing biofilms using naturally occurring molecules, as well as using in silico methods. We are also employing novel (nano/bio)technologies to create anti-biofilm materials and target the biofilm microenvironments.

To accomplish these goals, our lab uses a combination of molecular, biochemical, imaging and biophysical techniques, which include enzymatic, confocal fluorescence microscopy, AFM/rheometry, transcriptomic-proteomic and bioengineering approaches. Several in vitro and in vivo models to study the assembly of mixed-species biofilms are available in our laboratory. We also use these biofilm models to evaluate the effectiveness of novel anti-biofilm approaches.

Selected Publications

- Liu Y, Naha PC, Hwang G, Kim D, Huang Y, Simon-Soro A, Jung HI, Ren Z, Li Y, Gubara S, Alawi F, Zero D, Hara AT, Cormode DP, Koo H. Topical ferumoxytol nanoparticles disrupt biofilms and prevent tooth decay in vivo via intrinsic catalytic activity. *Nat Commun*, 9(1):2920, Jul 2018.
- Kim D, Liu Y, Benhamou RI, Sanchez H, Simón-Soro Á, Li Y, Hwang G, Fridman M, Andes DR, Koo H. Bacterial-derived exopolysaccharides enhance antifungal drug tolerance in a cross-kingdom oral biofilm. *ISME J*, 12(6):1427-1442 Jun 2018.
- Horev B, Klein MI, Hwang G, Koo H*, Benoit DSW*. pH-activated nanoparticles for targeted delivery and controlled drug release to disrupt oral biofilms. *ACS Nano*, 9(3):2390-404, 2015. *Co-senior authors. Highlighted in *Science* (2015)
- Hwang G, Marsh G, Gao L, Waugh R, Koo H. Binding Force Dynamics of *Streptococcus mutans*-glucosyltransferase B to *Candida albicans*. *J Dent Res*, 94(9):1310-7, Sept 2015.
- Song F, Koo H, Ren D. Effects of Material Properties on Bacterial Adhesion and Biofilm Formation. *J Dent Res*, 94(8):1027-34, Aug 2015.
- Fears KP, Gonzalez-Begne M, Love CT, Day DE, Koo H. Surface-induced changes in the conformation and glucan production of glucosyltransferase adsorbed on saliva-coated hydroxyapatite. *Langmuir*, 31(16):4654-62, Apr 2015.
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Research Overview

Delineation of mechanisms of resistance to tumor microenvironmental stress, with emphasis on the Unfolded Protein Response in cancer. Development of small molecule agents to target these mechanisms as novel targeted modalities. Development of novel radiosensitizers.

My laboratory is primarily interested in two broad areas:

1. To understand the mechanisms by which components of the microenvironment (e.g. hypoxia, low nutrient availability) interact with cellular survival/apoptotic pathways to produce a more resistant tumor phenotype. Once we understand the regulation and function of these survival pathways, we then design cell-based and assays to screen small molecule libraries for compounds that inhibit these processes and test them alone or in combination with genotoxic agents in several animal tumor models.
2. To increase the therapeutic effectiveness of ionizing radiation (IR) by either employing existing compounds with relatively safe toxicity profiles or employ screening strategies to identify novel and potent radiation sensitizers. We are also interested in developing novel delivery approaches for such compounds, such as biocompatible nanoparticles.

Selected Publications

Verginadis II, Kanade R, Bell B, Koduri S, Ben-Josef E, Koumenis C: A Novel Mouse Model to Study Image-Guided, Radiation-Induced Intestinal Injury and Preclinical Screening of Radioprotectors. *Cancer Res* 77(4): 908-17, Feb 15 2017.

Xu Z, Bu Y, Chitnis N, Koumenis C, Fuchs SY, Diehl JA: miR-216b regulation of c-Jun mediates GADD153/CHOP-dependent apoptosis. *Nat Commun* 7: 11422, May 13 2016.

Lehman SL, Cerniglia GJ, Johannes G, Ryeom S, Koumenis C: Translational upregulation of an individual p21Cip1 transcript variant by GCN2 regulates cell proliferation and survival under nutrient stress. *PLoS Genet* 11(6): e1005212, Jun 2015.

Dey S, Sayers CM, Lehman S, Cheng Y, Cerniglia G, Tuttle S, Feldman M, Zhang P, Fuchs S, Diehl AJ, Koumenis C: ATF4-dependent induction of heme oxygenase 1 prevents anoikis and promotes metastasis. *J Clin Invest* 125(7): 2592-608, Jul 1 2015.

Ma XH, Piao SF, Dey S, McAfee Q, Karakousis G, Villanueva J, Hart LS, Levi S, Hu J, Zhang G, Lazova R, Klump V, Pawelek JM, Xu X, Xu W, Schuchter LM, Davies MA, Herlyn M, Winkler J, Koumenis C, Amaravadi RK.: Targeting ER stress-induced autophagy overcomes BRAF inhibitor resistance in melanoma. *J Clin Invest* 124(3): 1406-17, Mar 2014.

- Sayers CM, Papandreou I, Guttman DM, Maas NL, Diehl JA, Witze ES, Koong AC, Koumenis C: Identification and characterization of a potent activator of p53-independent cellular senescence via a small-molecule screen for modifiers of the integrated stress response. *Mol Pharmacol* 83(3): 594-604, Mar 2013.
- Hart LS, Cunningham JT, Datta T, Dey S, Tameire F, Lehman SL, Qiu B, Zhang H, Cerniglia G, Bi M, Li Y, Gao Y, Liu H, Li C, Maity A, Thomas-Tikhonenko A, Perl AE, Koong A, Fuchs SY, Diehl JA, Mills IG, Ruggero D, Koumenis C: ER stress-mediated autophagy promotes Myc-dependent transformation and tumor growth. *J Clin Invest* 122(12): 4621-34, Dec 2012.
- Marotta D, Karar J, Jenkins WT, Kumanova M, Jenkins KW, Tobias JW, Baldwin D, Hatzigeorgiou A, Alexiou P, Evans SM, Alarcon R, Maity A, Koch C, Koumenis C: In vivo profiling of hypoxic gene expression in gliomas using the hypoxia marker EF5 and laser-capture microdissection. *Cancer Res* 71(3): 779-89, Feb 2011.
- Chitnis NS, Pytel D, Bobrovnikova-Marjon E, Pant D, Zheng H, Maas NL, Frederick B, Kushner JA, Chodosh LA, Koumenis C, Fuchs SY, Diehl JA: miR-211 is a pro-survival micro-RNA that regulates chop expression in a PERK-dependent manner. *Mol Cell* 48(3): 353-64, Nov 2012.
- Ye J, Kumanova M, Hart SL, Sloane K, Zhang H, De Panis DN, Bobrovnikova-Marjon E, Diehl A, Ron D, Koumenis C: The GCN2-ATF4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation. *EMBOJ* 29(12): 2082-96, Jun 2010.
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Research Overview

The Lazar laboratory is studying the transcriptional regulation of metabolism. We are particularly focused on the role played by nuclear receptors (NRs). In the absence of ligand, NRs bind to DNA and function as potent transcriptional repressors by recruiting corepressor complexes that include the chromatin modulating enzyme histone deacetylase 3 (HDAC3). We are studying the tissue-specific and physiological roles of the corepressor complexes using by combining genomic, genetic, proteomic, bioinformatic, and metabolic phenotyping approaches. We are especially interested in the circadian NR Rev-erb alpha, which utilizes the corepressor complex to potently repress transcription. Rev-erb alpha is a key repressive component of the circadian clock that coordinates metabolism and biological rhythms. We are also studying PPAR gamma, a nuclear receptor that is a master regulator of adipocyte (fat cell) differentiation. Ligands for PPAR gamma have potent antidiabetic activity, and thus PPAR gamma represents a key transcriptional link between obesity and diabetes. The molecular, cellular, and integrative biology of these factors are being studied in mice and humans. We also have discovered resistin, a novel hormone and target of PPAR gamma that is made by fat cells in rodents and by macrophages in humans, and are testing the hypothesis that resistin links metabolism to inflammation in human metabolic diseases.

Selected Publications

Guan D, Xiong Y, Borck PC, Jang C, Doulias PT, Papazyan R, Fang B, Jiang C, Zhang Y, Briggs ER, Hu W, Steger D, Ischiropoulos H, Rabinowitz JD, Lazar MA. Diet-Induced Circadian Enhancer Remodeling Synchronizes Opposing Hepatic Lipid Metabolic Processes. *Cell*. 174(4): 831-842.e12, Aug 2018.

Nelson VL, Nguyen HCB, Garcia-Cañaveras JC, Briggs ER, Ho WY, DiSpirito JR, Marinis JM, Hill DA, Lazar MA. PPAR γ is a nexus controlling alternative activation of macrophages via glutamine metabolism. *Genes Dev*. 32(15-16): 1035-1044, Aug 2018.

Zhang Y, Dallner OS, Nakadai T, Fayzikhodjaeva G, Lu YH, Lazar MA, Roeder RG, Friedman JM. A noncanonical PPAR γ /RXR α -binding sequence regulates leptin expression in response to changes in adipose tissue mass. *Proc Natl Acad Sci U S A* [Epub ahead of print], Jun 2018.

Lazar MA. Reversing the curse on PPAR γ . *J Clin Invest* 128(6): 2202-2204, Jun 2018.

Razzoli M, Emmett MJ, Lazar MA, Bartolomucci A. β -Adrenergic receptors control brown adipose UCP-1 tone and cold response without affecting its circadian rhythmicity. *FASEB J.* [Epub ahead of print], May 2018.

Borck PC, Batista TM, Vettorazzi JF, Soares GM, Lubaczeuski C, Guan D, Boschero AC, Vieira E, Lazar MA, Carneiro EM. Nighttime light exposure enhances Rev-erb α -targeting microRNAs and contributes to hepatic steatosis. *Metabolism* 85: 250-258, May 2018 Notes: pii: S0026-0495(18)30119-7.

Hill DA, Lim HW, Kim YH, Ho WY, Foong YH, Nelson VL, Nguyen HCB, Chegireddy K, Kim J, Habbertheuer A, Vallabhajosyula P, Kambayashi T, Won KJ, Lazar MA. Distinct macrophage populations direct inflammatory versus physiological changes in adipose tissue. *Proc Natl Acad Sci U S A.* 115(22): E5096-E5105, May 2018.

Kim YH, Marhon SA, Zhang Y, Steger DJ, Won KJ, Lazar MA. Rev-erb α dynamically modulates chromatin looping to control circadian gene transcription. *Science* 359(6381): 1274-1277, Mar 2018.

Jang JC, Li J, Gambini L, Batugedara HM, Sati S, Lazar MA, Fan L, Pellecchia M, Nair MG. Human resistin protects against endotoxic shock by blocking LPS-TLR4 interaction. *Proc Natl Acad Sci U S A* 114(48): E10399-E10408, Nov 2017.

Poleshko A, Shah PP, Gupta M, Babu A, Morley MP, Manderfield LJ, Ifkovits JL, Calderon D, Aghajanian H, Sierra-Pagán JE, Sun Z, Wang Q, Li L, Dubois NC, Morrissey EE, Lazar MA, Smith CL, Epstein JA, Jain R. Genome-Nuclear Lamina Interactions Regulate Cardiac Stem Cell Lineage Restriction. *Cell* 171(3): 573-587, Oct 2017.



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Research Overview

TDP-43 is the major component of pathologic inclusions in amyotrophic lateral sclerosis (ALS) and frontotemporal degeneration (FTD). TDP-43 is an RNA-binding protein which is known to regulate pre-mRNA splicing and mRNA stability. Mutations within the gene encoding FUS, another RNA-binding protein, cause ALS, and FUS-positive inclusions are seen in rare forms of FTD. Spinal muscular atrophy is caused by mutations in the gene encoding survival of motor neuron protein, an essential component of the spliceosome. Intronic hexanucleotide repeat expansions in *C9orf72* are the most common cause of ALS and FTD, implicating toxic RNA species in these clinically diverse yet mechanistically similar diseases. Clearly, ALS and FTD are RNA diseases. Our laboratory is interested in the function and dysfunction of TDP-43, FUS and *C9orf72*, and in identifying the basic molecular pathways which are relevant to human disease.

Selected Publications

Lee Edward B, Lee Virginia M-Y, Trojanowski John Q: Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration. *Nature reviews. Neuroscience* 13(1): 38-50, Nov 2011.

Igaz Lionel M*, Kwong Linda K*, Lee Edward B*, Chen-Plotkin Alice, Swanson Eric, Unger Travis, Malunda Joe, Xu Yan, Winton Matthew J, Trojanowski John Q, Lee Virginia M-Y: Dysregulation of the ALS-associated gene TDP-43 leads to neuronal death and degeneration in mice. *The Journal of clinical investigation* 121(2): 726-38, Feb 2011 Notes: *Lionel M Igaz, Linda K Kwong and Edward B Lee are co-lead authors.

Liu Elaine Y, Russ Jenny, Wu Kathryn, Neal Donald, Suh Eunran, McNally Anna G, Irwin David J, Van Deerlin Viviana M, Lee Edward B: *C9orf72* hypermethylation protects against repeat expansion-associated pathology in ALS/FTD. *Acta neuropathologica* 128(4): 525-41, Oct 2014.

Russ Jenny, Liu Elaine Y, Wu Kathryn, Neal Donald, Suh EunRan, Irwin David J, McMillan Corey T, Harms Matthew B, Cairns Nigel J, Wood Elisabeth M, Xie Sharon X, Elman Lauren, McCluskey Leo, Grossman Murray, Van Deerlin Viviana M, Lee Edward B: Hypermethylation of repeat expanded *C9orf72* is a clinical and molecular disease modifier. *Acta neuropathologica* 129(1): 39-52, Jan 2015.

McMillan Corey T, Russ Jenny, Wood Elisabeth M, Irwin David J, Grossman Murray, McCluskey Leo, Elman Lauren, Van Deerlin Vivanna, Lee Edward B: *C9orf72* promoter hypermethylation is neuroprotective: Neuroimaging and neuropathologic evidence. *Neurology* 84(16): 1622-30, Apr 2015.



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Research Overview

We study the physiology of the epithelial cells lining the upper airway (nose and sinuses) and the lower airway (lung) to understand how they sense and respond to pathogens. We combine biochemistry and molecular biology with real-time optical measurements of airway cell signaling and associated physiological responses, including ciliary beating, calcium signaling, fluid secretion, ion transport, nitric oxide production, and antimicrobial peptide secretion. Our goal is to better understand the cellular and molecular bases of airway diseases to identify novel molecular targets for new therapies.

There are two major diseases we focus on. The first is chronic rhinosinusitis (CRS), which affects 8-10% of the US population with direct healthcare costs of over 6 billion dollars annually. CRS has a major impact on individual quality of life as well as on public health; CRS accounts for 1 out of every 5 antibiotic prescriptions in adults in the US, making its treatment a major contributor to the emergence of antibiotic-resistant organisms. A continuing goal of our research is to identify new and better therapies to treat CRS and other airway diseases without the use of antibiotics, particularly through the stimulation of endogenous innate immune pathways. We also focus on cystic fibrosis (CF), the most common lethal genetic recessive disease in the US characterized by defective mucociliary transport due to altered ion transport and fluid secretion. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. Our goal is to better understand the molecular basis of CF and identify novel targets to restore or enhance airway function.

The close partnership we have with physicians at the Hospital of the University of Pennsylvania and the Philadelphia VA Medical Center allows ideas generated in our lab to be directly tested or evaluated in a real clinical setting, giving our research high translational potential.

Selected Publications

Freund, J.R., Mansfield, C.J., Doghramji, L.J., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Reed, D.R., Jiang, P., and Lee, R.J. Activation of Airway Epithelial Bitter Taste Receptors by *Pseudomonas aeruginosa* Quinolones Modulates Calcium, cyclic-AMP, and Nitric Oxide Signaling. *Journal of Biological Chemistry* 293: 9824-9840, June 2018 Notes: PMID:29748385; Selected as a JBC Recommended Read 7/7/2018.

McMahon, D.B., Workman, A.D., Kohanski, M.A., Carey, R.M., Freund, J.R., Hariri, B.M., Chen, B., Doghramji, L.J., Adappa, N.D., Palmer, J.N., Kennedy, D.W., and Lee, R.J. Protease-Activated Receptor 2 Activates Airway Apical Chloride Permeability and Increases Ciliary Beating. *The FASEB Journal* 32: 155-167, Jan 2018.

Hariri, B.M., McMahon, D.B., Chen, B., Adappa, N.D., Palmer, J.N., Kennedy, D.W., and Lee, R.J. Plant flavones enhance antimicrobial activity of respiratory epithelial cell secretions against *Pseudomonas aeruginosa* *PLOS One* 12(9): e0185203, Sept 2017.

Lee, R.J.,* Hariri, B.M., McMahon, D.B., Chen, B., Doghramji, L.D., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Jiang, P., Margolskee, R.F., Cohen, N.A.* Bacterial D-Amino Acids Suppress Sinonasal Innate Immunity

Through Sweet Taste Receptors in Solitary Chemosensory Cells. *Science Signaling* 10(495): eaam7703, Sept 2017. *Co-corresponding.

Hariri, B.M., McMahon, D.B., Chen, B., Freund, J.R., Mansfield, C.J., Doghramji, L.J., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Reed, D.R., Jiang, P., and Lee, R.J. Flavones Modulate Respiratory Epithelial Innate Immunity: Anti-Inflammatory Effects and Activation of the T2R14 Receptor. *Journal of Biological Chemistry* 292(20): 8484-8497, May 2017.

Lee, R.J. and Cohen, N.A. Bitter Taste Bodyguards. *Scientific American* 314(2): 38-43, Feb 2016.

Hariri, B.M., Payne, S.J., Chen, B., Mansfield, C., Doghramji, L.J., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Niv, M.Y., and Lee, R.J. In Vitro Effects of Anthocyanidins on Sinonasal Epithelial Nitric Oxide Production and Bacterial Physiology. *American Journal of Rhinology and Allergy* 30(4): 261-268, July 2016.

Lee RJ, Foskett JK: Ca²⁺ Signaling and Secretion in Airway Epithelia. *Cell Calcium* 55(6): 325-36, Jun 2014.

Lee, R.J., Kofonow, J.M., Rosen, P.L., Siebert, A.P., Chen, B., Doghramji, L., Xiong, G., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Kreindler, J.L., Margolskee, R.F., Cohen, N.A. Bitter and Sweet Taste Receptors Regulate Human Upper Respiratory Innate Immunity. *Journal of Clinical Investigation* 124(3): 1393-1405, Mar 2014.

Lee, R.J., Xiong, G., Kofonow, J.M., Chen, B., Lysenko, A., Jiang, P., Abraham, V., Doghramji, L., Adappa, N.D., Palmer, J.N., Kennedy, D.W., Beauchamp, G.K., Doulias, P.T., Ischiropoulos, H., Kreindler, J.L., Reed, D.R., Cohen, N.A. T2R38 Taste Receptor Polymorphisms Underlie Susceptibility to Upper Respiratory Infection. *Journal of Clinical Investigation* 122(11): 4145-59, Nov 2012.



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Research Overview

Dr. Lee's research focuses on disease proteins that form pathological inclusions in hereditary and sporadic Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS) and related neurodegenerative disorders of aging. Her work demonstrated that tau, alpha-synuclein and TDP-43 proteins form unique brain aggregates in neurodegenerative diseases and provided critical evidence that aggregation of brain proteins is a common mechanistic theme in diverse neurodegenerative diseases including AD, PD, FTLD, ALS and related disorders. Significantly, Dr. Lee's studies implicated the abnormal aggregation of tau, alpha-synuclein and TDP-43 in mechanisms that compromise neuronal viability. Most importantly, this research has opened up new avenues of research to identify targets for drug discovery to develop better treatments for these disorders.

Selected Publications

Cohen TJ, Hwang AW, Restrepo C, Yuan CX, Trojanowski JQ, Lee VM-Y. An acetylation switch controls TDP-43 function and aggregation propensity. *Nat Commun* 6: 5845, 2015.

Goosens J, Vanmechelen E, Trojanowski JW, Lee VM, Van Broeckhoven C, van der Zee J, Engelborghs S. TDP-43 as a possible biomarkers for frontotemporal lobar degeneration: a systematic review of existing antibodies. *Acta Neuropathol Commun.* 3: 15, 2015.

Porta S, Kwong LK, Trojanowski JQ, Lee VM. Drosha Inclusions Are New Components of Dipeptide-Repeat Protein Aggregates in FTLD-TDP and ALS C9orf72 Expansion Cases. *J Neuropathol Exp Neurol* 74: 380-387, 2015.

Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. *Nat Rev Neurosci* 16: 109-120, 2015.

Ballatore C, Gay B, Huang L, Robinson KH, James MJ, Trojanowski JQ, Lee VM-Y, Brunden KR, Smith AB 3rd. Evaluation of the cyclopentane-1,2-dione as a potential bio-isostere of the carboxylic acid functional group. *Bioorg Med Chem Lett* 24: 4171-4175, 2014.

- Crescenzi R, DeBrosse C, Nanga RP, Reddy S, Haris M, Hariharan H, Iba M, Lee VM-Y, Detre JA, Borthakur A, Reddy R. In vivo measurement of glutamate loss is associated with synapse loss in a mouse model of tauopathy. *Neuroimage* 101C: 185-192, 2014.
- Peeraer E, Bottelvergs A, Van Kolen K, Mahieu M, Duyschaever H, Verdonck L, Torremans A, Sluydts E, Van Acker N, Kemp JA, Brunden KR, Trojanowski JQ, Dewachter I, Lee VM-Y, Moechars D. Intracerebral injection of preformed synthetic tau fibrils initiates widespread tauopathy and neuronal loss in the brains of tau transgenic mice. *Neurobiol Dis* 73: 83-95, 2014.
- Boluda S, Toledo JB, Irwin DJ, Raible KM, Byrne MD, Lee EB, Lee VM-Y, Trojanowski JQ. A comparison of A β amyloid pathology staging systems and correlation with clinical diagnosis. *Acta Neuropath* 128: 543-550, 2014.
- Ballatore C, Smith AB 3rd, Lee VM-Y, Trojanowski JQ, Brunden KR. Aminothienopyridazines as imaging probes of tau pathology: a patent evaluation of WO2013090497. *Expert Opin Ther Pat* 24: 355-360, 2014.
- Tran HT, Chung CH, Luk KC, Iba M, Zhang B, Trojanowski JQ, Lee VM-Y. α -Synuclein immunotherapy blocks uptake and templated propagation of misfolded α -Synuclein and neurodegeneration. *Cell Reports* 72: 1-12, 2014.
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Research Overview

Heart Valve Disease: Research programs underway concerning the developmental basis for aortic valve disease, mechanistic studies of progression of calcific aortic stenosis, serotonin mechanisms in heart valve disease, and novel biomaterials for heart valve prostheses.

Gene delivery stents are an area of major interest: plasmid or viral vectors configured in sustained release preparations onto vascular stents for site specific vascular gene therapy.

Magnetic delivery of nanoparticles for pharmaceutical and cell therapy to treat arterial disease.

Selected Publications

Fishbein I, Guerrero DT, Alferiev IS, Foster JB, Minutolo NG, Chorny M, Monteys AM, Driesbaugh KH, Nagaswami C, Levy RJ: Stent-based delivery of adeno-associated viral vectors with sustained vascular transduction and iNOS-mediated inhibition of in-stent restenosis. *Gene Ther* Aug 2017.

Battig Mark R, Fishbein Ilia, Levy Robert J, Alferiev Ivan S, Guerrero David, Chorny Michael: Optimizing endothelial cell functionalization for cell therapy of vascular proliferative disease using a direct contact co-culture system. *Drug Deliv Transl Res* Jul 2017 Notes: NIHMS897618.

Lee Suengwon, Levy Robert J, Christian Abigail J, Hazen Stanley L, Frick Nathan E, Lai Eric K, Grau Juan B, Bavaria Joseph E, Ferrari Giovanni: Calcification and Oxidative Modifications Are Associated With Progressive Bioprosthetic Heart Valve Dysfunction. *J Am Heart Assoc* 6(5), May 2017.

Goldberg E, Grau JB, Fortier JH, Salvati E, Levy RJ, Ferrari G.: Serotonin and catecholamines in the development and progression of heart valve diseases. *Cardiovascular Research* 2017 Notes: in press.

Fishbein I, Welch, Guerrero DT, Alferiev IS, Adamo RF, Chorny M, Gupte RK, Tang Y, Levy RJ: Paraffin Processing of Stented Arteries Using a Post-Fixation Dissolution of Metallic and Polymeric Stents. *Cardiovascular Pathology* 25(6): 483-488, Aug 2016.

Slee JB, Alferiev IS, Nagaswami C, Weisel JW, Levy RJ, Fishbein I, Stachelek SJ: Enhanced biocompatibility of CD47-functionalized vascular stents. *Biomaterials* 87: 82-92, May 2016.

Adamo Richard F, Fishbein Ilia, Zhang Kehan, Wen Justin, Levy Robert J, Alferiev Ivan S, Chorny Michael: Magnetically enhanced cell delivery for accelerating recovery of the endothelium in injured arteries. *J Control Release* 222: 169-75, Jan 2016.

Christian AJ, Alferiev IS, Connolly JM, Ischiropoulos H, Levy RJ.: The effects of the covalent attachment of 3-(4-hydroxy-3,5-di-tertbutylphenyl) propyl amine to glutaraldehyde pre-treated bovine pericardium on structural degeneration, oxidative modification and calcification of rat subdermal implants. *J Biomed Mater Res A* 103(7): 2441-8, Jul 2015.

Alferiev Ivan S, Iyer Radhika, Croucher Jamie L, Adamo Richard F, Zhang Kehan, Mangino Jennifer L, Kolla Venkatadri, Fishbein Ilia, Brodeur Garrett M, Levy Robert J, Chorny Michael: Nanoparticle-mediated delivery of a rapidly activatable prodrug of SN-38 for neuroblastoma therapy. *Biomaterials* 51: 22-9, May 2015.

Iyer R, Croucher JL, Chorny M, Mangino JL, Alferiev IS, Levy RJ, Kolla V, Brodeur GM: Nanoparticle delivery of an SN38 conjugate is more effective than irinotecan in a mouse model of neuroblastoma. *Cancer Lett* 360(2): 205-12, Feb 2015.



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Research Overview

We are studying the biochemical and antigenic structure of nicotinic receptors from human muscle and Torpedo electric organ. We investigate pathological mechanisms and specific immunosuppressive therapy of experimental autoimmune myasthenia gravis in rats induced by immunization with purified receptor.

We are also studying the structure and function of neuronal nicotinic receptors. These studies primarily involve expression of cloned human receptors in *Xenopus* oocytes and permanently transfected cell lines.

We are also studying the effects of acute and chronic exposure to nicotine on various subtypes of nicotinic receptors. Understanding these effects is important for explaining both the effects of nicotine in tobacco and the effects of nicotinic drugs which are being developed. These structures should also reveal mechanisms through which nicotinic receptors could influence development and synaptic plasticity. Receptors are normally exposed to acetylcholine for milliseconds, but can be exposed to nicotine for hours. Nicotine, like any agonist, initially activates and then desensitizes receptors. On prolonged exposure it increases assembly of receptor subunits and decreases turnover of receptors in the surface membrane. It can be a full or partial agonist and block the cation channel. All of these effects vary depending on the receptor subtype. Combinations of these effects on various receptor subtypes in various regions are responsible for addiction to nicotine, tolerance to some of its effects, and mediating its many effects, which range from enhanced cognition to reduced anxiety and pain.

Selected Publications

Weltzin M, Cooper J, Lindstrom J, Lukas R, and Whiteaker P: Distinctive effects of nicotinic receptor intracellular loop mutations associated with nocturnal frontal lobe epilepsy. *Neuropharmacology* 102: 158-73, Mar 2016.

Lucero LM, Weltzin MM, Eaton JB, Cooper JF, Lindstrom JM, Lukas RJ, Whiteaker P: Differential $\alpha 4(+)/(-)\beta 2$ Agonist-binding Site Contributions to $\alpha 4\beta 2$ Nicotinic Acetylcholine Receptor Function within and between Isoforms. *Journal of Biological Chemistry* 291(5): 2444-59, Jan 2016.

Wang J, Kuryatov A, Jin Z, Norleans J, Kamenecka T, Kenny P, and Lindstrom J: A novel alpha 2/alpha 4 subtype-selective positive allosteric modulator of nicotinic acetylcholine receptors acting from the C-tail of an alpha subunit. *Journal of Biochemistry* 290(48): 28834-46, Nov 2015.

Kusner L, Losen M, Vincent A, Lindstrom J, Tzartos S, Lazaridis K, and Martinez-Martinez P: Guidelines for pre-clinical assessment of the acetylcholine receptor-specific passive transfer myasthenia gravis model - recommendations for methods and experimental designs. *Experimental Neurology* 270: 3-10, 2015.

- Wang J, Kuryatov A, Sriram A, Zhuang J, Kamenecka T, Kenny P, and Lindstrom J: An accessory agonist binding site promotes activation of alpha 4 beta 2* nicotinic acetylcholine receptors. *Journal of Biological Chemistry* 290: 13907-13918, 2015.
- Luo J and Lindstrom J: AChR-specific immunosuppressive therapy of myasthenia gravis. *Biochemical Pharmacology* 97: 609-619, 2015.
- Shorey-Kendrick L, Ford M, Allen D, Kuryatov A, Lindstrom J, Wilhelm L, Grant K, and Spindel E: Nicotinic receptors in nonhuman primates: analysis of genetic and functional conservation with humans. *Neuropharmacology* 96: 263-273, 2015.
- Hone A, McIntosh J, Azam L, Lindstrom J, Lucero L, Whiteaker P, Passas J, Blazquez J, and Albillos A: Alpha-Conotoxins identify the alpha 3 beta 4* subtype as the predominant nicotinic acetylcholine receptor expressed in human adrenal chromatin cells. *Molecular Pharmacology* 88: 881-893, 2015.
- Losen M, Martinez-Martinez P, Molenaar P, Lazaridis K, Tzartos S, Brenner T, Duan R, Luo J, Lindstrom J, and Kusner L: Standardization of the experimental autoimmune myasthenia gravis (EAMG) model by immunization of rats with *Torpedo californica* receptors - recommendations for methods and experimental designs. *Experimental Neurology* 270: 18-28, 2015.
- Wang J, Kuryatov A, and Lindstrom J: Expression of cloned alpha 6* nicotinic acetylcholine receptors. *Neuropharmacology* 96: 194-204, 2015.
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Research Overview

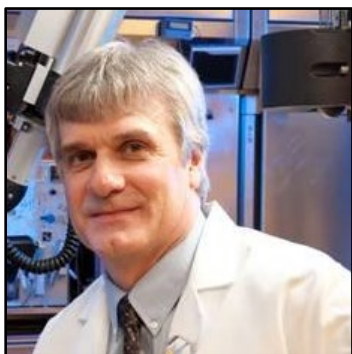
Excitotoxicity is a unique pathophysiological mechanism which is involved in cerebral ischemia, secondary damage in neuronal trauma, and neuronal damage from prolonged seizures. The deleterious effects from excitotoxicity result from calcium entry through a specific glutamate receptor, the N-methyl D-aspartate (NMDA) receptor. NMDA receptor antagonists act both as neuroprotective agents against excitotoxicity and as anticonvulsants in animals, but human clinical trials with the most potent agents have been complicated by side effects including psychosis. Much evidence indicates the presence of multiple types of NMDA receptors in the brain, and evidence from our laboratory suggests that different subtypes play different roles in physiological and excitotoxic processes. If one could develop therapeutic agents which are selective for the subtypes involved in excitotoxicity, one could more readily utilize NMDA receptor antagonists for treatment of human diseases.

We use a systematic approach to examine the subtype specific physiological and pharmacological properties of NMDA receptors. NMDA receptors are created in tissue culture expression systems, and their properties are studied biochemically, pharmacologically and physiologically to correlate receptor properties in these systems with such properties in vivo. We have previously shown that different NMDA receptor subtypes have distinct pharmacologies and produce different changes in intracellular calcium. In the near future we will extend these examinations of subtype specific properties to include the modulation of other intracellular messengers such as nitric oxide and examine the effect of such properties on excitotoxicity. Combined with our studies on the pharmacological specificity of NMDA receptor subtypes, this will facilitate the development of therapeutic agents directed to those NMDA receptors which play crucial roles in excitotoxicity.

Selected Publications

- Al-Saleem, F., Kaushik, R., Salovin, A.J., Lynch, D.R., Dessain, S.: Membrane-bound and soluble forms of an NMDA receptor extracellular domain retain epitopes targeted in auto-immune encephalitis. *BMC Biotechnology* 18.(1): 41, Jun 2018.
- Ejaz, R., Chen, S., Isaacs, C. J., Carnevale, A., Wilson, J., George, K., Delatycki, M. B., Perlman, S. L. Mathews, K. D., Wilmot, G. R., Hoyle, J. C., Subramony, S. H., Zesiewicz, T., Farmer, J. M., Lynch, D. R., Yoon, G. : Impact of mobility device use on quality of life in children with Friedreich ataxia. *J Child Neurol* 33(6): 397-404, May 2018.
- Salovin, A., Glanzman, J, Roslin, K., Armangue, T., Lynch, D.R., Panzer JA: Anti-NMDA Receptor Encephalitis and Non-Encephalitic HSV1 Infection. *Neurology: Neuroimmunology & Neuroinflammation* 5(4): e548, Apr 2018.

- Guo, L. Wang, Q. Weng, L. Hauser, L., Strawser, C. Rocha, A. Dancis, A., Mesaros, C. Lynch, D.R. Blair, I.: Liquid Chromatography-High Resolution Mass Spectrometry Analysis of Platelet Frataxin as a Protein Biomarker for the Rare Disease Friedreich's Ataxia. *Anal Chem* 90(3): 2216-2223, Feb 2018.
- Wang, Q., Guo, L., Strawser, C., Hauser, L., Hwang, W., Snyder, N.W., Lynch, D.R., Mesaros, C., Blair, I. : Low apolipoprotein A-I levels in Friedreich's ataxia and in frataxin-deficient cells: Implications for therapy *PLOS* 13(2): e0192779, Feb 2018.
- Sharma, R., Lee, M., Panzer, J., Lee, J. L., Felicori, L. F., Chandu, D., Rattelle, A., Ippolito, G., Cox, R., Lynch, D.R., Dessain, S.: Monoclonal antibodies from patients with anti-NMDA receptor encephalitis. *Annals of Clinical and Translational Neurology* 2018 Notes: in press.
- Nachun, D., Gao, F., Isaacs, C., Strawser, C., Yang, Z., Dokuru, D., Van Berlo, V., Sears, R., Farmer, J., Perlman, S., Lynch, D.R., Coppola, G.: Peripheral blood gene expression reveals an inflammatory transcriptomic signature in Friedreich's ataxia patients. *Hum Molec Genet* 2018 Notes: in press.
- Ali G Hamedani, Lauren Hauser, Susan Perlman, Katherine Mathews, George R Wilmot, Theresa Zesiewicz, S H Subramony, Tetsuo Ashizawa, Martin Delatycki, Alicia Brocht, and David R Lynch: Longitudinal analysis of contrast acuity in Friedreich ataxia. *Neurology Genetics* 2018 Notes: in press.
- Theresa Zesiewicz, Jason L. Salemi, Susan Perlman, Kelly L. Sullivan, Jessica D. Shaw, Yangxin Huang, Charles Isaacs, Clifton Gooch, David R. Lynch, Matthew B. Klein : Double-blind, Randomized, Controlled Trial of EPI-743 in Friedreich's Ataxia. *Neurodegenerative Disease Management* 2018 Notes: in press.
- McCormick, A., Shinnick, J., Schadt, K., Rodriguez, R., Addonizio, L., Hirano, M., Perlman, S., Lin, K.Y., Lynch, D.R.: Cardiac transplantation in Friedreich Ataxia: Extended follow-up. *J Neurol Sci.* 375: 471-473, Apr 2017
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Research Overview

Current studies focus on: 1) the role of specific neurotransmitter receptors in neurological and neuropsychiatric disorders, such as dopamine D3 receptors in the mediating the behavioral effects of psychostimulants and other abused substances; 2) study of the sigma-2 receptor/PGRMC1 as a molecular marker of cell proliferation and quiescence in tumor cells; 3) development of sigma-2 receptor ligands for the targeted delivery of cancer chemotherapeutics to tumors; 4) study of sigma-2 receptor agonists as potential chemosensitizers in the treatment of cancer; 5) development of molecular imaging agents to study the formation of reactive oxygen species/reactive nitrogen species; 6) development of molecular imaging agents to study the different pathways of programmed cell death; 7) development of PET radiotracers for imaging alpha synuclein deposits in Lewy bodies and Lewy neurites in neurodegenerative disorders.

Research Techniques

Organic synthesis; design and synthesis of small molecules targeting CNS receptors, proteins overexpressed in tumors, or mediators of oxidative stress; radiolabeling with positron-emitting radionuclides; small animal imaging studies with PET; radioligand binding studies; in vitro autoradiography; western blot analyses; cell culture of cancer cells, hippocampal neurons and microglia; microscopy; histology; radioimmunoassay; and HPLC analysis of metabolites.

Selected Publications

Sahlholm Kristoffer, Ielacqua Giovanna D, Xu Jinbin, Jones Lynne A, Schlegel Felix, Mach Robert H, Rudin Markus, Schroeter Aileen: The role of beta-arrestin2 in shaping fMRI BOLD responses to dopaminergic stimulation. *Psychopharmacology* 234(13): 2019-2030, Jul 2017.

Sellmyer Mark A, Lee Iljung, Hou Catherine, Weng Chi-Chang, Li Shihong, Lieberman Brian P, Zeng Chenbo, Mankoff David A, Mach Robert H: Bacterial infection imaging with [(18)F]fluoropropyl-trimethoprim. *Proceedings of the National Academy of Sciences of the United States of America* Jul 2017.

McDonald Elizabeth S, Mankoff Julia, Makvandi Mehran, Chu Wenhua, Chu Yunxiang, Mach Robert H, Zeng Chenbo: Sigma-2 ligands and PARP inhibitors synergistically trigger cell death in breast cancer cells. *Biochemical and biophysical research communications* 486(3): 788-795, May 2017.

Yang Dongzhi, Comeau Anthony, Bowen Wayne D, Mach Robert H, Ross Brian D, Hong Hao, Van Dort Marcian E: Design and Investigation of a [(18)F]-Labeled Benzamide Derivative as a High Affinity Dual Sigma

Receptor Subtype Radioligand for Prostate Tumor Imaging. *Molecular pharmaceuticals* 14(3): 770-780, Mar 2017.

Zhou Rong, Pantel Austin R, Li Shihong, Lieberman Brian P, Ploessl Karl, Choi Hoon, Blankemeyer Eric, Lee Hsiaoju, Kung Hank F, Mach Robert H, Mankoff David A: [(18)F](2S,4R)4-Fluoroglutamine PET Detects Glutamine Pool Size Changes in Triple-Negative Breast Cancer in Response to Glutaminase Inhibition. *Cancer research* 77(6): 1476-1484, Mar 2017.

Michel Loren S, Dyroff Samantha, Brooks Frank J, Spayd Katherine J, Lim Sora, Engle Jacquelyn T, Phillips Sharon, Tan Benjamin, Wang-Gillam Andrea, Bognar Christopher, Chu Wenhua, Zhou Dong, Mach Robert H, Laforest Richard, Chen Delphine L: PET of Poly (ADP-Ribose) Polymerase Activity in Cancer: Preclinical Assessment and First In-Human Studies. *Radiology* 282(2): 453-463, Feb 2017.

Zeng Chenbo, McDonald Elizabeth S, Mach Robert H: Molecular Probes for Imaging the Sigma-2 Receptor: In Vitro and In Vivo Imaging Studies. *Handbook of experimental pharmacology* Feb 2017.

Sander Effron Samuel, Makvandi Mehran, Lin Lilie, Xu Kuiying, Li Shihong, Lee Hsiaoju, Hou Catherine, Pryma Daniel A, Koch Cameron, Mach Robert H: PARP-1 Expression Quantified by [(18)F]FluorThanatrace: A Biomarker of Response to PARP Inhibition Adjuvant to Radiation Therapy. *Cancer biotherapy & radiopharmaceuticals* 32(1): 9-15, Feb 2017.

Hashim Yassar M, Vangveravong Suwanna, Sankpal Narendra V, Binder Pratibha S, Liu Jingxia, Goedegebuure S Peter, Mach Robert H, Spitzer Dirk, Hawkins William G: The Targeted SMAC Mimetic SW IV-134 is a strong enhancer of standard chemotherapy in pancreatic cancer. *Journal of experimental & clinical cancer research: CR* 36(1): 14, Jan 2017.

George Erin, Kim Hyoung, Krepler Clemens, Wenz Brandon, Makvandi Mehran, Tanyi Janos L, Brown Eric, Zhang Rugang, Brafford Patricia, Jean Stephanie, Mach Robert H, Lu Yiling, Mills Gordon B, Herlyn Meenhard, Morgan Mark, Zhang Xiaochen, Soslow Robert, Drapkin Ronny, Johnson Neil, Zheng Ying, Cotsarelis George, Nathanson Katherine L, Simpkins Fiona: A patient-derived-xenograft platform to study BRCA-deficient ovarian cancers. *JCI insight* 2(1): e89760, Jan 2017.



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Research Overview

The major focus of the laboratory is the process by which the binding of hormones to cell-surface receptors is translated into the regulation of target enzymes and ion channels. The Manning laboratory is specifically interested in pathways of transduction defined by heterotrimeric GTP-binding regulatory proteins (G proteins). Current studies include mapping linkages among receptors and G proteins in intact cells, defining post-translational modifications of G protein subunits that influence targeting and protein-protein interactions, and exploring the roles of novel G proteins. Considerable effort in the laboratory is devoted toward understanding the relevance of G proteins to the actions of the Hedgehog morphogens. We are currently pursuing noncanonical forms of signaling achieved by Hedgehogs using the Gi family of G proteins. We are also interested in the activation of the one or more forms of Gli transcription factors by ligands apart from Hedgehogs, and specifically through receptors that couple to the G12/13 family. Pursuit of these interests have required the development of methods to evaluate the communication of receptors with G proteins, with an emphasis placed on determinants of efficacy. The idea that ligands working through a single receptor can generate different signals (functional selectivity), or that these signals can be generated by a single ligand as function of ligand concentration, represents a common theme of the work.

Selected Publications

- Guo, X., N.A. Riobo-Del Galdo, E.J. Kim, G.R. Grant, and D.R. Manning: Overlap in signaling between Smoothed and the alpha subunit of the heterotrimeric G protein G13. PLOS ONE 2018.
- Shen, F, L Cheng, AE Douglas, NA Riobo, and DR Manning: Smoothed is a fully competent activator of the heterotrimeric G protein G(i). Mol Pharmacol 83: 691, 2013.
- Polizio, A.H., Chinchilla, P., Chen, X., Kim, S., Manning, D.R., Riobo, N.A.: *Heterotrimeric Gi proteins link Hedgehog signaling to activation of Rho small GTPases to promote fibroblast migration*. J. Biol. Chem. 286: 19589-19596, 2011.
- Douglas, A.E., Heim, J.A., Shen, F., Amada, L.L., Riobo, N.A., Fernandez-Zapico, M.E., Manning, D.R.: The alpha subunit of the G protein G13 regulates the activity of one or more Gli transcription factors independently of Smoothed. J Biol Chem 286: 30714, 2011.
- Crouthamel M, Abankwa D, Zhang L, Dilizio C, Manning DR, Hancock JF, Wedegaertner PB: *An N-terminal polybasic motif of G{alpha}q is required for signaling and influences membrane nanodomain distribution* Mol Pharmacol Page: In Press [Epub ahead of print] Jul 2010.
- Zhang L, Brass LF and Manning DR: *The Gq and G12 families of heterotrimeric G proteins report functional selectivity*. Mol Pharmacol 75: 235-241, 2009.
- Riobo NA, Saucy B, Dilizio C, Manning DR: *Activation of heterotrimeric G proteins by Smoothed*. Proc Natl

Acad Sci USA 103: 12607-12612, 2006.

Zhang L, DiLizio C, Kim D, Smyth EM, Manning DR: *The G12 family of G proteins as a reporter of thromboxane A2 receptor activity*. Molec Pharmacol 69: 1433-1440, 2006.

Windh RT and Manning DR: *Analysis of G protein activation in Sf9 and mammalian cells by agonist-promoted [³⁵S]GTP gamma S binding*. Methods in Enzymology 344: 3-14, 2002.



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Research Overview

Researchers in the Maris Laboratory are focused on understanding the underlying molecular and genetic mechanisms that contribute to the development and progression of pediatric neuroblastoma. Also, efforts in the Maris Laboratory are dedicated to the development of new molecular diagnostic tests and less toxic, targeted cancer therapies to treat relapsed or refractory neuroblastoma. The long-term goal of the work in this laboratory is to use a multidisciplinary approach to improve existing cure rates for children with neuroblastoma.

Selected Publications

- Ozkaynak MF, Gilman AL, London WB, Naranjo A, Diccianni MD, Tenney SC, Smith M, Seeger R, Reynolds CP, Smith LM, Shulkin BL, Parisi M, Maris JM, Park JR, Sondel PM, Yu AL: Corrigendum: A Comprehensive Safety Trial of Chimeric Antibody 14.18 With GM-CSF, IL-2, and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy: Children's Oncology Group Study ANBL0931. *Front Immunol* July 2018.
- Deveau P, Colmet Daage L, Oldridge D, Bernard V, Bellini A, Chicard M, Clement N, Lapouble E, Combaret V, Boland A, Meyer V, Deleuze JF, Janoueix-Lerosey I, Barillot E, Delattre O, Maris JM, Schleiermacher G, Boeva V: QuantumClone: clonal assessment of functional mutations in cancer based on a genotype-aware method for clonal reconstruction. *Bioinformatics* June 2018.
- Ozkaynak MF, Gilman AL, London WB, Naranjo A, Diccianni MB, Tenney SC, Smith M, Messer KS, Seeger R, Reynolds CP, Smith LM, Shulkin BL, Parisi M, Maris JM, Park JR, Sondel PM, Yu AL: A Comprehensive Safety Trial of Chimeric Antibody 14.18 With GM-CSF, IL-2, and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy: Children's Oncology Group Study ANBL0931. *Front Immunol* June 2018.
- Rajbhandari P, Lopez G, Capdevila C, Salvatori B, Yu J, Rodriguez-Barrueco R, Martinez D, Yarmarkovich M, Weichert-Leahey N, Abraham BJ, Alvarez MJ1, Iyer A1, Harenza JL, Oldridge D, De Preter K, Koster J, Asgharzadeh S, Seeger RC, Wei JS, Khan J, Vandesompele J, Mestdagh P, Versteeg R, Look AT, Young RA, Iavarone A, Lasorella A, Silva JM, Maris JM, Califano A: Cross-Cohort Analysis Identifies a TEAD4-MYCN Positive Feedback Loop as the Core Regulatory Element of High-Risk Neuroblastoma. *Cancer Discov* May 2018.
- Wei JS, Kuznetsov IB, Zhang S, Song YK, Asgharzadeh S, Sindiri S, Wen X, Patidar R, Nagraraj S, Walton A, Guidry Auvil JM, Gerhard DS, Yuksel A, Catchpole DR, Hewitt SM, Sondel PM, Seeger RC, Maris JM,

- Khan J: Clinically Relevant Cytotoxic Immune Cell Signatures and Clonal Expansion of T Cell Receptors in High-risk MYCN-not-amplified Human Neuroblastoma. *Clin Cancer Res*. May 2018.
- Ma X, Liu Y, Liu Y, Alexandrov LB, Edmonson MN, Gawad C, Zhou X, Li Y, Rusch MC, Easton J, Huether R, Gonzalez-Pena V, Wilkinson MR, Hermida LC, Davis S, Sioson E, Pounds S, Cao X, Ries RE, Wang Z, Chen X, Dong L, Diskin SJ, Smith MA, Guidry Auvil JM, Meltzer PS, Lau CC, Perlman EJ, Maris JM, Meshinchi S, Hunger SP, Gerhard DS, Zhang J: Pan-cancer genome and transcriptome analyses of 1,699 paediatric leukaemias and solid tumours. *Nature* Mar 2018.
- Depuydt P, Boeva V, Hocking TD, Cannoodt R, Ambros IM, Ambros PF, Asgharzadeh S, Attiyeh EF, Combaret V, Defferrari R, Fischer M, Hero B, Hogarty MD, Irwin MS, Koster J, Kreissman S, Ladenstein R, Lapouble E, Laureys G, London WB, Mazzocco K, Nakagawara A, Noguera R, Ohira M, Park JR, Pötschger U, Theissen J, Tonini GP, Valteau-Couanet D, Varesio L, Versteeg R, Speleman F, Maris JM, Schleiermacher G, De Preter K: Genomic Amplifications and Distal 6q Loss: Novel Markers for Poor Survival in High-risk Neuroblastoma Patients. *J Natl Cancer Inst*. Mar 2018.
- Matsuno Ryosuke, Gifford Andrew J, Fang Junming, Warren Mikako, Lukeis Robyn E, Trahair Toby, Sugimoto Tohru, Marachelian Araz, Asgharzadeh Shahab, Maris John M, Ikegaki Naohiko, Shimada Hiroyuki: Rare MYC-amplified Neuroblastoma With Large Cell Histology. *Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society Page: 1093526617749670*, Jan 2018.
- Deveau Paul, Colmet Daage Leo, Oldridge Derek, Bernard Virginie, Bellini Angela, Chicard Mathieu, Clement Nathalie, Lapouble Eve, Combaret Valerie, Boland Anne, Meyer Vincent, Deleuze Jean-Francois, Janoueix-Lerosey Isabelle, Barillot Emmanuel, Delattre Olivier, Maris John, Schleiermacher Gudrun, Boeva Valentina: QuantumClone: Clonal assessment of functional mutations in cancer based on a genotype-aware method for clonal reconstruction. *Bioinformatics (Oxford, England)* Jan 2018.
- de Alarcon Pedro A, Matthay Katherine K, London Wendy B, Naranjo Arlene, Tenney Sheena C, Panzer Jessica A, Hogarty Michael D, Park Julie R, Maris John M, Cohn Susan L: Intravenous immunoglobulin with prednisone and risk-adapted chemotherapy for children with opsoclonus myoclonus ataxia syndrome associated with neuroblastoma (ANBL00P3): a randomised, open-label, phase 3 trial. *The lancet child & adolescent health* 2(1): 25-34, Jan 2018.
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Research Overview

Eukaryotic cells are compartmentalized into distinct membrane-bound organelles and vesicular structures, each with its own characteristic function and set of protein constituents. Work in my laboratory is focused on understanding how integral membrane protein complexes are assembled and sorted to the appropriate compartments within the late secretory and endocytic pathways, how sorting and assembly contribute to the biogenesis of cell type-specific organelles, how these processes impact biological function in the pigmented, blood clotting, and immune systems, and how they are thwarted by generally rare genetic diseases.

Our primary focus over the past 20 years has been on melanosomes of pigmented cells. Melanosomes are unique lysosome-related organelles present only in cells that make melanin, the major synthesized pigment in mammals. Genetic defects in melanosome constituents or in their delivery to nascent melanosomes result in ocular or oculocutaneous albinism, characterized by lack of pigmentation in the eyes and or skin and concomitant visual impairment and susceptibility to skin and ocular cancers. Melanosomes are among a number of tissue-specific lysosome-related organelles that are malformed and dysfunctional in a group of rare heritable disorders, including Hermansky-Pudlak and Chediak-Higashi syndromes. In an effort to understand the molecular basis of these diseases, we are dissecting the molecular mechanisms that regulate how different stage melanosomes are formed and integrated with the endosomal pathway. We use biochemical, morphological, and genetic approaches to follow the fates of melanosome-specific and ubiquitous endosomal and lysosomal proteins within pigment cells from normal individuals or mice and disease models. Using these approaches, we are (1) outlining protein transport pathways that lead to the formation of these unusual organelles, (2) dissecting biochemical pathways that lead to their morphogenesis, and (3) defining how these processes are subverted by genetic disease. Current efforts focus on the molecular mechanisms by which factors that are deficient in patients and mouse models of the genetic disease, Hermansky-Pudlak syndrome, impact melanosome biogenesis. We are particularly interested in how these factors contribute to the formation and dynamics of tubular connections between endosomes and maturing melanosomes that facilitate cargo transport, as well as the formation of retrograde membrane carriers that retrieve unneeded proteins from melanosomes.

In addition to these studies, we are interested in the function of individual melanosome and lysosome components and how they impact melanogenesis. For example, melanosome precursors in pigment cells harbor internal fibrils upon which melanins deposit in later stages, the main component of which is a pigment cell-specific protein, PMEL. Fibrils formed by PMEL in vitro display features common with amyloid formed in disease states such as Alzheimer and Parkinson diseases. By dissecting how PMEL forms amyloid under physiological conditions, we hope to determine how the formation of "good" and "bad" amyloid differs and thus how the formation of "bad" amyloid might be controlled. Other melanosomal proteins are transporters that impact the intraluminal environment of melanosomes to alter the type and amount of melanin that is made. Together with our collaborators we are studying the biophysical function of these transporters and how they are linked to

features such as melanosome pH.

Because genetic diseases like Hermansky-Pudlak syndrome affect multiple organ systems, we study how similar sorting processes involved in melanosome biogenesis influence other organelles in different cell types. The first involves lysosome-related organelles in platelets called dense granules and alpha granules. When platelets are activated at sites of blood vessel damage, the contents of these granules are released, leading to optimal blood clot formation and platelet activation. Like melanosomes, dense granules are malformed in Hermansky-Pudlak syndrome, and in collaboration with the Poncz, Stalker and French laboratories at CHOP and Penn we are studying how dense granule contents are delivered within platelets and their precursors (megakaryocytes). Studies in collaboration with the Poncz and French labs also address the contents and secretion of alpha granules and their disruption in human bleeding disorders.

The second cellular system is the dendritic cell, a master regulator of T cell-mediated immunity. Patients with Hermansky-Pudlak syndrome type 2 have recurrent bacterial infections, and we have found that this is at least in part due to defects in the way that dendritic cells sense bacterial infection. Normally, ingested bacteria trigger signaling by innate immune receptors present on the membrane enclosing the bacteria (the phagosome) or in the cytoplasm; signaling by both sets of receptors is defective in dendritic cells from a mouse model of the disease due to (1) impaired recruitment of the receptors and their signaling platforms on phagosomes and (2) rapid clearing of cytoplasmic receptors by autophagy. Ongoing studies aim to dissect how phagosome membrane dynamics normally lead to signaling and how this is altered in disease states.

Selected Publications

Ripoll L, Heiligenstein X, Hurbain I, Domingues L, Figon F, Petersen KJ, Dennis MK, Houdusse A, Marks MS, Raposo G and Delevoye C: Myosin VI and actin dynamics induce membrane constriction and fission for recycling from melanosomes. *J. Cell Biol.* 217(8): 2709-2726, August 2018.

Crawford NG, Kelly DE, Hansen MEB, Beltrame MH, Fan S, Bowman SL, Jewett E, Ranciaro A, Thompson S, Lo Y, Pfeifer SP, Jensen JD, Campbell MC, Beggs W, Hormozdiari F, Mpoloka SW, Mokone GG, Nyambo T, Meskel DW, Belay G, Haut J, NISC Comparative Sequencing Program, Rothschild H, Zon L, Zhou Y, Kovacs MA, Xu M, Zhang T, Bishop K, Sinclair J, Rivas C, Elliot E, Choi J, Li SA, Hicks B, Burgess S, Abnet C, Watkins-Chow DE, Oceana E, Song YS, Eskin E, Brown KM, Marks MS, Loftus SK, Pavan WJ, Yeager M, Chanock S and Tishkoff S: Novel loci associated with skin pigmentation identified in African populations. *Science* 358(6365): eaan8433, November 2017.

Hanby HA, Bao J, Noh J-Y, Jarocho D, Poncz M, Weiss MJ and Marks MS: Platelet dense granules begin to selectively accumulate mepacrine during proplatelet formation. *Blood Advances* 1(19): 1478-1490, August 2017.

Dennis MK, Delevoye C, Acosta-Ruiz A, Hurbain I, Romao M, Hesketh GG, Goff PS, Sviderskaya EV, Bennett DC, Luzio JP, Galli T, Owen DJ, Raposo G, Marks MS: BLOC-1 and BLOC-3 regulate VAMP7 cycling to and from melanosomes via distinct tubular transport carriers. *J. Cell Biol.* 214(3): 293-308, August 2016.

Ho T, Watt B, Spruce LA, Seeholzer SH and Marks MS: The Kringle-Like Domain facilitates post-endoplasmic reticulum changes to PMEL oligomerization and disulfide bond configuration and promotes amyloid formation. *J. Biol. Chem.* 291(7): 3595-3612, February 2016.

Delevoye C, Heiligenstein X, Ripoll L, Gilles-Marsens F, Dennis MK, Linares RA, Derman L, Gokhale A, Morel E, Faundez V, Marks MS and Raposo G: BLOC-1 brings together the actin and microtubule cytoskeletons to generate recycling endosomes. *Curr. Biol.* 26(1): 1-13, January 2016.

*Dennis MK, *Mantegazza AR, Snir OL, Tenza D, Acosta-Ruiz A, Delevoye C, Zorger R, Sitaram A, de Jesus-Rojas W, Ravichandran K, Rux J, Sviderskaya EV, Bennett DC, Raposo G, Marks MS** and **Setty SRG: BLOC-2 targets recycling endosomal tubules to melanosomes for cargo delivery. *J. Cell Biol.* 209(4): 563-577, May 2015 Notes: *, ** Equal contributions. Marks MS is corresponding author.

Meng R, Wu J, Harper DC, Wang Y, Kowalska MA, Abrams CS, Brass LF, Poncz M, Stalker TJ, and Marks MS: Defective release of alpha-granule and lysosome contents from platelets in mouse Hermansky-Pudlak syndrome models. *Blood* 125(10): 1623-1632, March 2015.

Bellono N, Escobar IE, Lefkovith AJ, Marks MS and Oancea EV: An intracellular anion channel critical for pigmentation. *eLife* 3: e04543, December 2014.

Mantegazza AR, Zajac AL, Twelvetrees A, Holzbaur EL, Amigorena S and Marks MS: TLR-dependent phagosome tubulation in dendritic cells promotes phagosome cross-talk to optimize MHC-II antigen presentation. *Proc. Natl. Acad. Sci. U.S.A.* 111(43): 15508-15513, October 2014.



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Research Overview

Dave's research focuses on understanding the mechanical cues that regulate injury, repair, and growth in cells and tissues of the central nervous system. The process of mechanotransduction is critical in understanding the response of cells and tissues of the central nervous system (CNS) to traumatic injury. In this research area, experimental work is combined with mathematical modeling to provide a method to quantify the effect of physical forces on cell and tissue function. For example, some of the research combines finite element models of the brain with experimental work to estimate the tissue mechanical stress/strain associated with biological markers of injury. These models provide a starting point to relate traditional measures of stress to the microstructural constituents of the tissue. Structural models are being developed to link global mechanical deformations and the resulting deformation of cellular/subcellular microstructures in the CNS white matter. With the kinematic transformations between the macroscopic deformations and cellular components of the CNS white matter now better established, the research has expanded to determine the mechanism(s) by which a mechanical signal is converted into a biochemical signaling cascade for organotypic tissue, cultured neurons, and cultured axons. Clinical applications of his work include developing new testing standards to improve the safety of headgear and automotive restraint systems, and testing new techniques for repairing damaged tissues in the brain after injury.

Selected Publications

Cypin: A novel target for traumatic brain injury, Swiatkowski, P. | Sewell, E. | Sweet, E.S. | Dickson, S. | Swanson, R.A. | McEwan, S.A. | Cuccolo, N. | McDonnell, M.E. | Patel, M.V. | Varghese, N. | Morrison, B. | Reitz, A.B. | Meaney, D.F. | Firestein, B.L., *Neurobiology of Disease*, 2018

Mechanical disruption of the blood–brain barrier following experimental concussion, Johnson, V.E. | Weber, M.T. | Xiao, R. | Cullen, D.K. | Meaney, D.F. | Stewart, W. | Smith, D.H., *Acta Neuropathologica*, 2018

Reflections on 35 Years of Journal of Neurotrauma, Cohen, A. | Meaney, D.F. | Satin, L.S., Journal of Neurotrauma, 2018

Mechanoporation is a potential indicator of tissue strain and subsequent degeneration following experimental traumatic brain injury, LaPlaca, M.C. | Lessing, M.C. | Prado, G.R. | Zhou, R. | Tate, C.C. | Geddes-Klein, D. | Meaney, D.F. | Zhang, L., Clinical Biomechanics, 2018

Phosphodiesterase-4 inhibition restored hippocampal long term potentiation after primary blast, Vogel, E.W. | Morales, F.N. | Meaney, D.F. | Bass, C.R. | Morrison, B., Experimental Neurology, 2017



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Research Overview

My research uses physiological approaches to understand the mechanistic steps of disease. For example, the lab is currently investigating how elevated pressure leads to neuronal death, focusing on ATP release, pannexin hemichannels, P2X7 receptors, NMDA receptors and the neuroprotective actions of A3 adenosine receptors. The role of these components in cytokine release is also being probed. In addition, the lab is exploring the physiology of lysosomes, with investigations into the regulation of lysosomal pH in health and disease. Pharmacological and molecular manipulation of lysosomal Cl⁻ channels such as CFTR and CLC-7 is being used to reacidify lysosomes and improve degradative activity in aging and diseased cells.

Selected Publications

- Loov C, Mitchell CH, Simonsson M, Erlandsson A: Slow degradation in phagocytic astrocytes can be enhanced by lysosomal acidification. *Glia* 63(11): 1997-2009, 2015.
- Frost LS, Lopes VS, Bragin A, Reyes-Reveles J, Brancato J, Cohen A, Mitchell CH, Williams DS, Boesze-Battaglia K.: The contribution of melanoregulin to microtubule-associated protein 1 light chain 3 (LC3) associated phagocytosis in retinal pigment epithelium. *Molecular Neurobiology* 52(3): 1135-1151, 2015.
- Beckel JM, Daugherty SL, Tyagi P, Wolf-Johnston AS, Birder LA, Mitchell CH, de Groat WC: Pannexin 1 channels mediate the release of ATP into the lumen of the rat urinary bladder. *Journal of Physiology* 593(8): 1857-1871, 2015.
- Lu W, Hu HL, Sevigny J, Gabelt BT, Kaufman PL, Johnson EC, Morrison JC, Zode GS, Sheffield VC, Zhang XL, Laties AM, Mitchell CH: Rat, mouse, and primate models of chronic glaucoma show sustained elevation of extracellular ATP and altered purinergic signaling in the posterior eye. *Investigative Ophthalmology and Visual Science* 56(5): 3075-3083, 2015.
- Maguire SE, Rhoades S, Chen WF, Sengupta A, Yue ZF, Lim JC, Mitchell CH, Weljie AM, Sehgal A: Independent effects of gamma-aminobutyric acid transaminase (GABAT) on metabolic and sleep homeostasis. *Journal of Biological Chemistry* 290(33): 20407-20416, 2015.
- Lee JH, McBrayer MK, Wolfe DM, Haslett LJ, Kumar A, Sato Y, Lie PPY, Mohan P, Coffey EE, Kompella U, Mitchell CH, Lloyd-Evans E, Nixon RA: Presenilin 1 maintains lysosomal Ca²⁺ homeostasis via TRPML1 by regulating vATPase-mediated lysosome acidification. *Cell Reports* 12(9): 1430-1444, 2015.
- Tordoff MG, Aleman TR, Ellis HT, Ohmoto M, Matsumoto I, Shestopalov VI, Mitchell CH, Foskett JK, Poole RL:

- Normal taste acceptance and preference of PANX1 knockout mice. *Chemical Senses* 40(7): 453-459, 2015.
- Guha, S, Liu, J, Baltazar, G, Laties, AM, Mitchell, CH: Rescue of compromised lysosomes enhances degradation of photoreceptor outer segments and reduces lipofuscin-like autofluorescence in retinal pigmented epithelial cells. *Advances in Experimental Medicine and Biology* 801: 105-111, 2014.
- Beckel JM, Argall AJ, Lim JC, Xia J, Lu W, Coffey EE, Macarak EJ, Shahidulla M, Delamere NA, Zode GS, Sheffield VC, Shestopalov VI, Laties AM, Mitchell CH: Mechanosensitive release of ATP through pannexin channels and mechanosensitive upregulation of pannexin channels in optic nerve head astrocytes: a mechanism for purinergic involvement in chronic strain. *Glia* 62(9): 1486-1501, 2014.
- Coffey EE, Beckel JM, Laties AM, Mitchell CH: Lysosomal alkalization and dysfunction in human fibroblasts with the Alzheimer's disease-linked presenilin 1 A246E mutation can be reversed with cAMP. *Neuroscience* 263: 111-124, 2014.
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Research Overview

We are interested in understanding structure and function of Transient Receptor Potential (TRP) channels which have been implicated in a diverse range of cellular processes, including pain sensation, neuronal development, cardiovascular and renal pathophysiology, and cancer. Currently, the Moiseenkova-Bell laboratory has two main areas of research: First is to determine the structural basis of TRP channel activation, inhibition and desensitization mechanisms by utilizing cryo electron microscopy (cryo-EM). Second is to understand how TRP channels regulate cellular functions and the role of their dysregulation in human disease.

Recent Publications

Basak S., Gicheru Y., Samanta A., Molugu S.K., Huang W., de la Fuente M., Hughes T., Taylor D.J., Nieman M.T., Moiseenkova-Bell V.Y., Chakrapani S. : Cryo-EM structure of 5-HT_{3A} receptor in its resting conformation. *Nature Communications* 514: doi:10.1038/s41467-018-02997-4. February 2018.

Samanta A., Hughes T., Moiseenkova-Bell V.Y.: Transient Receptor Potential (TRP) Channels. *Subcell Biochemistry Membrane-bound Macromolecular Protein Complexes: Structure and Function*, Springer 87: 141-165, February 2018.

Hughes T.E.T., Lodowski D.T., Huynh K.W., del Rosario J., Yazici A., Kapoor A., Basak S., Samanta A., Chakrapani S., Zhou Z.H., Filizola M., Rohacs T., Han S., Moiseenkova-Bell V.Y. : Structural basis of the TRPV5 channel inhibition revealed by cryo-EM. *Nature Structural & Molecular Biology*. *Nature Structural & Molecular Biology*, 1: 53-60, January 2018.

Samanta A., Hughes T.E.T., Moiseenkova-Bell V.Y. : Cryo electron microscopy of TRP channels. *Methods in Molecular Biology*, Springer 2018 Notes: in press.

Samanta A., Kiselar J., Han S., Moiseenkova-Bell V.Y.: Structural insights into the molecular mechanism of mouse TRPA1 activation and inhibition. *J Gen Physiol*, 7;150(5):751-762, May 2018.

Arne J.M., Widjaja-Adhi M.A., Hughes T., Huynh K.W., Silvaroli J.A., Chelstowska S., Moiseenkova-Bell V.Y., Golczak M.: Allosteric modulation of the substrate specificity of acyl-CoA wax alcohol acyltransferase 2 (AWAT2). *Journal of Lipid Research* 58(4): 719-730, 2017 Notes: doi: 10.1194/jlr.M073692, Epub Jan 17 2017.

Huynh K.W., Cohen M.R., Jiang J., Samanta A., Lodowski D.T., Zhou Z.H., Moiseenkova-Bell V.Y.: Structure of the full-length TRPV2 channel by cryo-EM. *Nature Communications* 7: 11130, 2016 Notes: doi: 10.1038/ncomms11130.

Cohen M.R., Johnson W.M., Pilat J.M., Kiselar J., DeFrancesco-Lisowitz A., Zigmond R.E., Moiseenkova-Bell

V.Y.: NGF regulates TRPV2 via ERK signaling to enhance neurite outgrowth in developing neurons. *Molecular and Cellular Biology* 35(24): 4238-4252, 2015 Notes: Epub Sep 28 2015.

Cohen M.R, Moiseenkova-Bell V.Y.: Structure of thermally activated TRP channels. *Current Topics in Membranes* 74: 181-211, 2014.

Huynh K.W., Cohen M.R., Moiseenkova-Bell V.Y.: Application of amphipols for structure-functional analysis of TRP channels. *Journal of Membrane Biology* 247(9-10): 843-851, 2014 Notes: Epub June 4 2014.



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Research Overview

Despite major enhancements in therapy over the past several decades, the cure rate for patients with high-risk neuroblastoma lags significantly behind that of other childhood cancers. My lab has unwaveringly focused on neuroblastoma and on the hypothesis that discovery of its hereditary basis will provide insights that are clinically actionable and improve outcomes. Our seminal discovery that gain-of-function mutations in the Anaplastic Lymphoma Kinase (ALK) oncogene are the cause of familial neuroblastoma (Nature, 2008) highlights the insights gained from a family-based study in a rare disease and the opportunities for targeting ALK in neuroblastoma and other human cancers driven by ALK. We have led collaborative investigations that demonstrated frequent ALK activating mutations in the more common sporadic cases, the development of molecular diagnostic tools, and preclinical studies to establish the role of ALK inhibitors in the treatment of neuroblastoma and other childhood cancers. This work led to the completion of a multi-institutional pediatric phase 1 trial of crizotinib (The Lancet Oncology, 2013), demonstrating rapid translation of preclinical molecular findings into the clinic. We have positioned ALK as the only mutated oncogene tractable for targeted therapy in neuroblastoma and subsequently showed that there is differential mutation-specific sensitivity to crizotinib that results from a relative increase in ATP-binding affinity (Science Translational Medicine, 2011), data that directly impacted the design of the pediatric phase 1 trial. Additionally, we have shown that ALK is a tractable target for immunotherapy (Oncogene, 2012), setting the stage for the development of antagonistic antibodies to maximize clinical benefit.

Selected Publications

Wood AC, Krytska K, Ryles HT, Infarinato NR, Sano R, Hansel TD, Hart LS, King FJ, Smith TR, Ainscow E, Grandinetti KB, Tuntland T, Kim S, Caponigro G, He YQ, Krupa S, Li N, Harris JL, Mossé YP. Dual ALK and CDK4/6 inhibition demonstrates synergy against neuroblastoma. *Clin Cancer Res.* 2017;23(11):2856-2868.

Infarinato NR, Park JH, Krytska K, Ryles HT, Sano R, Szigety KM, Li Y, Zou HY, Lee NV, Smeal T, Lemmon MA, Mossé YP. The ALK/ROS1 Inhibitor PF-06463922 Overcomes Primary Resistance to Crizotinib in ALK-Driven Neuroblastoma. *Cancer Discov.* 2015 Nov 10. [Epub ahead of print]

Mossé Yaël P, Laudenslager Marci, Longo Luca, Cole Kristina A, Wood Andrew, Attiyeh Edward F, Laquaglia Michael J, Sennett Rachel, Lynch Jill E, Perri Patrizia, Laureys Geneviève, Speleman Frank, Kim Cecilia, Hou Cuiping, Hakonarson Hakon, Torkamani Ali, Schork Nicholas J, Brodeur Garrett M, Tonini Gian P, Rappaport Eric, Devoto Marcella, Maris John M: Identification of ALK as a major familial neuroblastoma predisposition gene. *Nature* 455(7215): 930-5, Oct 2008.

Bresler Scott C, Wood Andrew C, Haglund Elizabeth A, Courtright Joshua, Belcastro Lili T, Plegaria Jefferson S, Cole Kristina, Toporovskaya Yana, Zhao Huaqing, Carpenter Erica L, Christensen James G, Maris John M, Lemmon Mark A, Mossé Yaël P: Differential inhibitor sensitivity of anaplastic lymphoma kinase variants found in neuroblastoma. *Science Translational Medicine* 3(108): 108ra114, Nov 2011.

- Mosse Yael P, Lim Megan S, Voss Stephan D, Wilner Keith, Ruffner Katherine, Laliberte Julie, Rolland Delphine, Balis Frank M, Maris John M, Weigel Brenda J, Ingle Ashish M, Ahern Charlotte, Adamson Peter C, Blaney Susan M: Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *The lancet oncology* 14(6): 472-80, May 2013.
- Carpenter E L, Haglund E A, Mace E M, Deng D, Martinez D, Wood A C, Chow A K, Weiser D A, Belcastro L T, Winter C, Bresler S C, Asgharzadeh S, Seeger R C, Zhao H, Guo R, Christensen J G, Orange J S, Pawel B R, Lemmon M A, Mosse Y P: Antibody targeting of anaplastic lymphoma kinase induces cytotoxicity of human neuroblastoma. *Oncogene* 31(46): 4859-67, Nov 2012.
- Mosse Yael P, Lipsitz Emily, Fox Elizabeth, Teachey David T, Maris John M, Weigel Brenda, Adamson Peter C, Ingle Mark A, Ahern Charlotte H, Blaney Susan M: Pediatric Phase I Trial and Pharmacokinetic Study of MLN8237, an Investigational Oral Selective Small-Molecule Inhibitor of Aurora Kinase A: A Children's Oncology Group Phase I Consortium Study. *Clinical Cancer Research* 18(21): 6058-64, Nov 2012.
- Carpenter Erica L, Mossé Yael P: Targeting ALK in neuroblastoma--preclinical and clinical advancements. *Nature Reviews Clinical Oncology* 9(7): 391-9, Jul 2012.
- Pugh Trevor J, Morozova Olena, Attiyeh Edward F, Asgharzadeh Shahab, Wei Jun S, Auclair Daniel, Carter Scott L, Cibulskis Kristian, Hanna Megan, Kiezun Adam, Kim Jaegil, Lawrence Michael S, Lichenstein Lee, McKenna Aaron, Pdamallu Chandra Sekhar, Ramos Alex H, Shefler Erica, Sivachenko Andrey, Sougnez Carrie, Stewart Chip, Ally Adrian, Birol Inanc, Chiu Readman, Corbett Richard D, Hirst Martin, Jackman Shaun D, Kamoh Baljit, Khodabakshi Alireza Hadj, Krzywinski Martin, Lo Allan, Moore Richard A, Mungall Karen L, Qian Jenny, Tam Angela, Thiessen Nina, Zhao Yongjun, Cole Kristina A, Diamond Maura, Diskin Sharon J, Mosse Yael P, Wood Andrew C, Ji Lingyun, Spoto Richard, Badgett Thomas, London Wendy B, Moyer Yvonne, Gastier-Foster Julie M, Smith Malcolm A, Auvil Jaime M Guidry, Gerhard Daniela S, Hogarty Michael D, Jones Steven J M, Lander Eric S, Gabriel Stacey B, Getz Gad, Seeger Robert C, Khan Javed, Marra Marco A, Meyerson Matthew, Maris John M: The genetic landscape of high-risk neuroblastoma. *Nature genetics* 45(3): 279-84, Mar 2013.
- Maris John M, Mosse Yael P, Bradfield Jonathan P, Hou Cuiping, Monni Stefano, Scott Richard H, Asgharzadeh Shahab, Attiyeh Edward F, Diskin Sharon J, Laudenslager Marci, Winter Cynthia, Cole Kristina A, Glessner Joseph T, Kim Cecilia, Frackelton Edward C, Casalunovo Tracy, Eckert Andrew W, Capasso Mario, Rappaport Eric F, McConville Carmel, London Wendy B, Seeger Robert C, Rahman Nazneen, Devoto Marcella, Grant Struan F A, Li Hongzhe, Hakonarson Hakon: Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. *The New England journal of medicine* 358(24): 2585-93, Jun 2008.
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Research Overview

The laboratory is focused on several projects. First is the targeting of drugs (enzymes either degrading or generating oxidants, fibrinolytics, interferon, antisense oligos and genes) to the pulmonary vascular endothelium. The purpose is to develop strategies for controlled site-specific delivery of a drug to the defined subcellular compartments of the pulmonary endothelium. For example, genetic material must be delivered into the nucleus, antioxidants must accumulate in the cytoplasm, and fibrinolytics must avoid internalization. We therefore study how carrier antibodies and their derivatives recognize endothelium, and characterize cellular trafficking and local effects of the targeted agents in cell cultures, perfused animal lungs and in intact animals. Our research includes identification of the molecules localized on the surface of endothelium useful as targets for drug delivery to either normal or pathologically challenged endothelium. Endothelium-specific antigens may serve as such targets. Affinity carriers that are currently explored in our laboratory include monoclonal antibodies (and their fragments) to: angiotensin-converting enzyme (ACE), thrombomodulin and surface adhesion molecules, ICAM, PECAM, P- and E-selectins. We have characterized carriers and their modifications providing: i) a drug with an affinity to endothelium (recognition and targeting) and, ii) drug delivery in a proper cellular compartment (sub-cellular addressing). Targeting to either surface (by non-internalizable carriers) or intracellularly has been documented in cell culture, perfused lungs and in rodents *in vivo*.

Secondly, we explore red blood cells (RBC) as natural carriers for drugs. We have developed an original methodology for effective conjugation of large amounts of a drug (e.g., fibrinolytic enzymes or receptors for plasminogen activators) on RBC, without loss of biocompatibility of the complex. Conjugation provides prolongation of half-life of plasminogen activators *in vivo* by orders of magnitude and offers specific transfer of the conjugated protein (tPA, uPA-receptor) to the pulmonary endothelium. Both mechanism of the transfer (tentatively via exchange of GPI-anchored membrane proteins between RBC and endothelium) and potential therapeutic applications of RBC-conjugated fibrinolytics (treatment/prevention of pulmonary embolism/deep vein thrombosis) are in the focus of the research. We also explore RBC as carriers for intracellular drug delivery in phagocyte cells in the reticuloendothelial tissue (liver and spleen) and endothelial cells.

Selected Publications

Brenner Jacob S, Pan Daniel C, Myerson Jacob W, Marcos-Contreras Oscar A, Villa Carlos H, Patel Priyal, Hekierski Hugh, Chatterjee Shampa, Tao Jian-Qin, Parhiz Hamideh, Bhamidipati Kartik, Uhler Thomas G, Hood Elizabeth D, Kiseleva Raisa Yu, Shuvaev Vladimir S, Shuvaeva Tea, Khoshnejad Makan, Johnston Ian, Gregory Jason V, Lahann Joerg, Wang Tao, Cantu Edward, Armstead William M, Mitragotri Samir,

Muzykantov Vladimir: Red blood cell-hitchhiking boosts delivery of nanocarriers to chosen organs by orders of magnitude. *Nat Commun* 9(1): 2684, Jul 2018.

Myerson Jacob W, Braender Bruce, Mcpherson Olivia, Glassman Patrick M, Kiseleva Raisa Y, Shuvaev Vladimir V, Marcos-Contreras Oscar, Grady Martha E, Lee Hyun-Su, Greineder Colin F, Stan Radu V, Composto Russell J, Eckmann David M, Muzykantov Vladimir R: Flexible Nanoparticles Reach Sterically Obscured Endothelial Targets Inaccessible to Rigid Nanoparticles. *Adv Mater* Page: e1802373, Jun 2018.

Khoshnejad Makan, Greineder Colin F, Pulsipher Katherine W, Villa Carlos H, Altun Burcin, Pan Daniel C, Tsourkas Andrew, Dmochowski Ivan J, Muzykantov Vladimir R: Ferritin Nanocages with Biologically Orthogonal Conjugation for Vascular Targeting and Imaging. *Bioconjug Chem* 29(4): 1209-1218, Apr 2018.

Villa Carlos H, Pan Daniel C, Johnston Ian H, Greineder Colin F, Walsh Landis R, Hood Elizabeth D, Cines Douglas B, Poncz Mortimer, Siegel Don L, Muzykantov Vladimir R: Biocompatible coupling of therapeutic fusion proteins to human erythrocytes. *Blood advances* 2(3): 165-176, Feb 2018.

Shuvaev Vladimir V, Kiseleva Raisa Yu, Arguiri Evguenia, Villa Carlos H, Muro Silvia, Christofidou-Solomidou Melpo, Stan Radu V, Muzykantov Vladimir R: Targeting superoxide dismutase to endothelial caveolae profoundly alleviates inflammation caused by endotoxin. *J Control Release* 272: 1-8, Feb 2018.

Khoshnejad Makan, Brenner Jacob S, Motley William, Parhiz Hamideh, Greineder Colin F, Villa Carlos H, Marcos-Contreras Oscar A, Tsourkas Andrew, Muzykantov Vladimir R: Molecular engineering of antibodies for site-specific covalent conjugation using CRISPR/Cas9. *Sci Rep* 8(1): 1760, Jan 2018.

Greineder Colin F, Villa Carlos H, Walsh Landis R, Kiseleva Raisa Y, Hood Elizabeth D, Khoshnejad Makan, Warden-Rothman Robert, Tsourkas Andrew, Muzykantov Vladimir R: Site-Specific Modification of Single-Chain Antibody Fragments for Bioconjugation and Vascular Immunotargeting. *Bioconjug Chem* 29(1): 56-66, Jan 2018.

Kiseleva Raisa Yu, Greineder C F, Villa C H, Marcos-Contreras O A, Hood E D, Shuvaev V V, DeLisser H M, Muzykantov V R: Vascular endothelial effects of collaborative binding to platelet/endothelial cell adhesion molecule-1 (PECAM-1). *Sci Rep* 8(1): 1510, Jan 2018.

Pan Daniel C, Myerson Jacob W, Brenner Jacob S, Patel Priyal N, Anselmo Aaron C, Mitragotri Samir, Muzykantov Vladimir: Nanoparticle Properties Modulate Their Attachment and Effect on Carrier Red Blood Cells. *Sci Rep* 8(1): 1615, Jan 2018.

Kartha Sonia, Yan Lesan, Weisshaar Christine L, Ita Meagan E, Shuvaev Vladimir V, Muzykantov Vladimir R, Tsourkas Andrew, Winkelstein Beth A, Cheng Zhiliang: Superoxide Dismutase-Loaded Porous Polymersomes as Highly Efficient Antioxidants for Treating Neuropathic Pain. *Adv Healthc Mater* 6(17), Sep 2017.



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Research Overview

Current Research Interests are focused on the health, genetic and behavioral aspects of performance in detection dogs. I have been following the health and behavior of the search dogs following the 9/11 response. We have established the AKC CAR Detection Dog DNA Bank to study the genetics of complex behavior. We have a DOD funded field study of the effect of different hydration strategies on performance, hydration, and inflammation in detection dogs. Opening Sept 11, 2012, the Penn Vet Working Dog Center will integrate the science and field experience to breed, select, raise and train dogs to use their noses to detect things (e.g. explosives, drugs, people, and even cancer and infectious diseases). The Penn Vet Working Dog Center will be a resource for behavioral, nutrition, development and conditioning studies in dogs being trained for detection work. In addition, the interactions between dogs and humans will be studied, focusing on 3 major groups of volunteers/interns working with the program: homeless youth, veterans, and parolees from prison dog raising programs. In addition, clinical research in emergency care of dogs and cats, sepsis and trauma continue to be of interest.

Selected Publications

Walton KL, Otto CM. Retrospective evaluation of feline rodenticide exposure and gastrointestinal decontamination: 146 cases (2000-2010). *J Vet Emerg Crit Care (San Antonio)*. 28(5):457-463, Sep 2018.

Hunt M, Otto CM, Serpell J, Alvarez J. Interactions between Handler Well-Being and Canine Health and Behavior in Search and Rescue Teams. *Anthrozoos* 25(3):323-335, 2012.

Bentley AM, Mayhew PD, Culp WT, Otto CM. Alterations in the Hemostatic Profiles of Dogs with Naturally Occurring Septic Peritonitis *J Vet Emerg Crit Care* 23(1):14–22, 2013

Wiley, CA, Ottoson MC, Garcia MM, Wiley LE, Otto, CM The seroprevalence of Canine Influenza Virus H3N8 in dogs participating in a flyball tournament in Pennsylvania in 2010: a follow-up study. *JVIM* 27(2):367-370. Article first published online: 20 FEB 2013 | DOI: 10.1111/jvim.12047

Mayhew PD, Savigny MR, Otto CM, Brown DC, Brooks MB, Bentley AM, Runge JJ, Callan MB. Evaluation of coagulation in dogs with partial or complete extra-hepatic biliary tract obstruction using thromboelastography. *JAVMA* 242(6):778-85, 2013 Mar 15.

Reineke EL, Walton K, Otto CM. Evaluation of oral versus intravenous administration of electrolyte solution in

dogs with sudden onset hemorrhagic diarrhea. J Am Vet Med Assoc 243:851–857, 2013.

Parr J, Otto CM. Emergency Visits and Occupational Hazards in German Shepherd Police Dogs (2008-2010) JVECC 23(6):591-597, 2013. Article first published online: 19 SEP 2013 | DOI: 10.1111/vec.12098

Ng Z, Pierce BJ, Otto CM, Buechner-Maxwell V, Siracusa C, Werre SR. The effect of dog–human interaction on cortisol and behavior in registered animal-assisted activity dogs. Applied Animal Behaviour Science 159:69-81, 2014 DOI: <http://dx.doi.org/10.1016/j.applanim.2014.07.009>

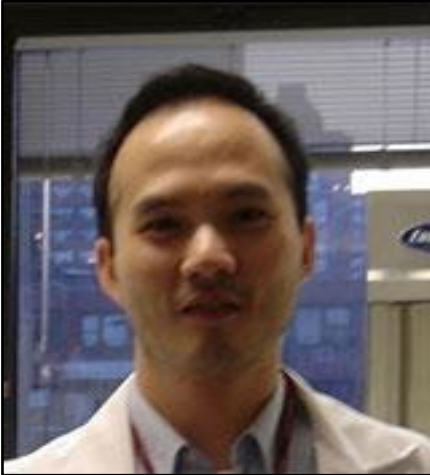
Hanel RM, Palmer L, Baker J, Brenner J, Crowe DT, Dorman D, Gicking JC.; Gilger B, Otto CM, Robertson SA, Rozanski E, Trumpatori B. Best practice recommendations for prehospital veterinary care of dogs and cats. J Vet Emerg Crit Care 2016;26(2):166-233.

Robinson, MA, Baumgardner, JE, Good, VP, Otto, CM: *Physiological and hypoxic O-2 tensions rapidly regulate NO production by stimulated macrophages*. American Journal Of Physiology-cell Physiology 294(4): C1079-C1087, APR 2008.

Otto, CM, Markstaller, K, Kajikawa, O, Karmrodt, J, Syring, RS, Pfeiffer, B, Good, VP, Frevert, CW, Baumgardner, JE: *Spatial and temporal heterogeneity of ventilator-associated lung injury after surfactant depletion*. Journal Of Applied Physiology 104(5): 1485-1494, MAY 2008.

Otto CM : *Clinical Trials in Spontaneous Disease in Dogs: A New Paradigm for Investigations of Sepsis*. J Vet Emerg Crit Care 17(4):359-367, 2007. 17(4): 359-367, Dec 2007.

Otto, CM, Downend, AB, Serpell, JA, Ziemer, LS, Saunders, HM: *Medical and behavioral surveillance of dogs deployed to the World Trade Center and the Pentagon from October 2001 to June 2002*. Journal Of The American Veterinary Medical Association 225(6): 861-867, SEP 15 2004.



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Research Overview

The laboratory's long term research goal is to develop a comprehensive understanding of Proteostasis and how alterations in this process contribute to normal biological and disease processes. Although much is known about the role of transcriptional and translational control of gene expression in various human disorders, the extent to which protein degradation contributes to disease processes remains vastly unexplored.

Key to understanding protein degradation is to elucidate the mechanisms by which the 26S proteasome is regulated in vivo. While it is known that regulation of proteasome activity is intrinsically linked to its local availability and protein-protein interaction profile, detailed mechanistic insights are still lacking. Further complicating things, we know virtually nothing of the intimate relationship that must exist between protein synthesis and degradation to regulate protein homeostasis, and the effects of environmental stresses on these processes. For example, dietary restriction, aging and environmental stresses have all been linked to proteasome deregulation through an unknown mechanism. Therefore, knowledge gained from our future endeavors will not only advance the basic understanding of protein homeostasis in the broader context of biology, but will also open up new therapeutic opportunities against those diseases that arise secondary to accumulation of misfolded "toxic" proteins such as cancer, amyotrophic lateral sclerosis (ALS), Retinitis Pigmentosa, and Alzheimer's and Parkinson's diseases. As a first step towards this goal, we will take advantage of the laboratory's unique set of skills in clinical medicine, biochemistry, cell & molecular biology, and Drosophila and Mouse genetics, to further extend these lines of work using a multi-pronged interdisciplinary approach.

Selected Publications

Cho-Park, P.F. and Steller H.: Proteasome regulation by ADP-ribosylation. *Cell* 153(3): 614-627, 2013.

Cho-Park, Y.A., Perez, D.L., Milligan, T.A., and Cho, P.F.: Radiographic evolution of a rapidly reversible leukoencephalopathy due to metronidazole. *Neurology: Clinical Practice* 3: 272-274, 2013.

Cho, P.F., Gamberi, C., Cho-Park, Y.A., Cho-Park, I.B., Lasko, P., and Sonenberg, N.: Cap-dependent translational inhibition establishes two opposing morphogen gradients in Drosophila embryos. *Curr Biol* 16(20): 2035-2041, 2006.

Bellsollell, L.*, Cho-Park, P.F.*, Poulin, F., Sonenberg, N., and Burley, S.K.: Two structurally atypical HEAT domains in the C-terminal portion of human eIF4G support binding to eIF4A and Mnk1. *Structure* 14(5): 913-923, 2006 Notes: *Equal contribution.

- Lasko, P., Cho-P., Poulin F., and Sonenberg, N.: Contrasting mechanisms of regulating translation of specific *Drosophila* germline mRNAs at the level of 5'-cap structure binding. *Biochem Soc Trans.* 33(Pt 6): 1544-1546, 2005.
- Cho, P.F., Poulin, F., Cho-Park, Y.A., Cho-Park, I.B., Chicoine, J.D., Lasko, P., and Sonenberg, N.: A new paradigm for translational control: inhibition via 5'-3' mRNA tethering by Bicoid and the eIF4E cognate 4EHP. *Cell* 121(3): 411-423, 2005.
- Boivin, D.B., James, F.O., Wu, A., Cho-Park, P.F., Xiong, H., and Sun Z.S.: Circadian clock genes oscillate in human peripheral blood mononuclear cells. *Blood* 102(12): 4143-4145, 2003.
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Research Overview

Steroid Hormone Transforming Aldo-Keto Reductases.

The aldo-keto reductase (AKR) superfamily contains mammalian hydroxysteroid dehydrogenases (HSDs). For each sex steroid there are a pair of HSDs, which by acting as reductases or oxidases can convert potent steroid hormones into their cognate inactive metabolites or vice versa. When found in steroid target tissues they can regulate the occupancy and trans-activation of steroid hormone receptors, providing a pre-receptor regulation of steroid hormone action. Many HSDs are considered therapeutic targets. For example, aldo-keto reductase AKR1C3 (type 5 17beta-hydroxysteroid dehydrogenase) catalyses the formation of the potent androgens, testosterone and 5alpha-dihydrotestosterone, in castrate resistant prostate cancer (CRPC). CRPC is dependent upon intratumoral androgen biosynthesis that reactivate the androgen receptor and is uniformly fatal. Structure-based inhibitor design is being used to develop selective AKR1C3 inhibitors for the treatment of CRPC. In another area structure-function studies on steroid 5beta-reductase (AKR1D1) are being pursued. This enzyme catalyzes a pivotal step in bile-acid biosynthesis and natural mutations are causal in bile-acid deficiency syndromes which are often neonatal fatal. In both areas we use the following techniques: site-directed mutagenesis, x-ray crystallography, transient and steady state kinetics, and transfection studies in prostate cancer cell lines.

Dihydrodiol Dehydrogenases and Polycyclic Aromatic Hydrocarbon (PAH) Activation

Dihydrodiol dehydrogenases are members of the AKR superfamily. They convert PAH-trans-dihydrodiols (proximate carcinogens) to reactive and redox active o-quinones. By entering into futile redox-cycles the o-quinones can amplify the production of reactive oxygen species (e.g., superoxide anion, hydrogen peroxide and hydroxyl radical). The pro-oxidant state may provide a mechanism by which PAH can act as complete carcinogens. Similar metabolic activation has been observed for the structurally related catechol estrogens and diethylstilbestrol. The cytotoxicity and genotoxicity of PAH o-quinones are being studied in human lung cells as it pertains to causality in human lung cancer. Methods include cell culture, high-resolution NMR, EPR, mass-spectrometry, PAH-DNA adduct chemistry, and mutagenesis paradigms.

Selected Publications

Zang T, Tamae D, Mesaros C, Wang Q, Huang M, Blair IA, Penning TM.: Simultaneous quantitation of nine hydroxy-androgens and their conjugates in human serum by stable isotope dilution liquid chromatography electrospray ionization tandem mass spectrometry. *J. Steroid Biochem. Mol. Biol.* 165: 7431-44, 2017.

- Mostaghel EA, Cho E, Zhang A, Alyamani M, Kaipainen A, Green S, Marck BT, Sharifi N, Wright JL, Gulati R, True LD, Loda M, Matsumoto AM, Tamae D, Penning TN, Balk SP, Kantoff PW, Nelson PS, Taplin ME, Montgomery RB. : Association of Tissue Abiraterone Levels and SLCO Genotype with Intraprostatic Steroids and Pathologic Response in Men with High-Risk Localized Prostate Cancer. *Clin. Cancer Res.* 23: 4592-4601, 2017.
- Huang M, Mesaros C, Hackfeld LC, Hodge RP, Zang T, Blair IA, Penning TM. : Potential Metabolic Activation of a Representative C4-Alkylated Polycyclic Aromatic Hydrocarbon Retene (1-Methyl-7-isopropylphenanthrene) Associated with the Deepwater Horizon Oil Spill in Human Hepatoma (HepG2) Cells. *Chem. Res. Toxicol.* 30: 1093-1101, 2017.
- Winterbottom CJ, Shah RJ, Patterson KC, Kreider ME, Panettieri RA Jr, Rivera-Lebron B, Miller WT, Litzky LA, Penning TM, Heinlen K, Jackson T, Localio AR, Christie JD.: Exposure to Ambient Particulate Matter is Associated With Accelerated Functional Decline in Idiopathic Pulmonary Fibrosis. *Chest* Page: doi: 10.1016/j.chest.2017.07.034. 2017.
- Zang, T., Taplin, M.E., Tamae, D., Xie, W., Mesaros, C., Zhang, Z., Bubley, G., Montgomery, B., Balk, S.P., Mostaghel, E.A., Blair, I.A. and Penning, T.M. : Testicular versus Adrenal Sources of Hydroxyandrogens in Prostate Cancer. *Endocr Relat Cancer.* 24: 393-404, 2017.
- Verma K, Zang T, Gupta N, Penning TM, Trippier PC. : Selective AKR1C3 Inhibitors Potentiate Chemotherapeutic Activity in Multiple Acute Myeloid Leukemia (AML) Cell Lines. *ACS Med. Chem. Lett. American Chemical Society*, 7: 774-9, 2016.
- Huang M, Mesaros C, Zhang S, Blair IA, Penning TM.: Potential Metabolic Activation of a Representative C2-Alkylated Polycyclic Aromatic Hydrocarbon 6-Ethylchrysene Associated with the Deepwater Horizon Oil Spill in Human Hepatoma (HepG2) Cells. *Chem. Res. Toxicol.* 29: 991-1002, 2016 Notes: ACS Editor's Choice.
- Zanetti KA, Wang Z, Aldrich M, Amos CI, Blot WJ, Bowman ED, Burdette L, Cai Q, Caporaso N, Chung CC, Gillanders EM, Haiman CA, Hansen HM, Henderson BE, Kolonel LN, Marchand LL, Li S, McNeill LH, Ryan BM, Schwartz AG, Sison JD, Spitz MR, Tucker M, Wenzlaff AS, Wiencke JK, Wilkens L, Wrensch MR, Wu X, Zheng W, Zhou W, Christiani D, Palmer JR, Penning TM, Rieber AG, Rosenberg L, Ruiz-Narvaez EA, Su L, Vachani A, Wei Y, Whitehead AS, Chanock SJ, Harris CC.: Genome-wide association study confirms lung cancer susceptibility loci on chromosomes 5p15 and 15q25 in an African-American population. *Lung Cancer.* 98: 33-42, 2016.
- Adeniji A, Uddin MJ, Zang T, Tamae D, Wangtrakuldee P, Marnett LJ, Penning TM.: Discovery of (R)-2-(6-Methoxynaphthalen-2-yl)butanoic Acid as a Potent and Selective Aldo-keto Reductase 1C3 Inhibitor. *J. Med. Chem. American Chemical Society*, 59, 2016.
- Huang M, Zhang L, Mesaros C, Hackfeld LC, Hodge RP, Blair IA, Penning TM.: Metabolism of an Alkylated Polycyclic Aromatic Hydrocarbon 5-Methylchrysene in Human Hepatoma (HepG2) Cells. *Chem. Res. Toxicol.* 28: 2045-58, 2015.
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Research Overview

Dr. Pierce's interest in the neuropharmacology of drugs of abuse began while he was an undergraduate student at the University of Kentucky. Working with Dr. Michael Bardo in the Psychology Department, Dr. Pierce studied the effects of amphetamine on the mesolimbic dopamine system. He continued to pursue his interest in the effects of psychostimulants on brain dopamine systems through graduate school at Indiana University, where he worked with Dr. George Rebec. Dr. Pierce received post-doctoral training from Dr. Peter Kalivas at Washington State University. Their work indicated that glutamate, in a complex interaction with limbic dopamine, plays an important role in both the development and long-term expression of behavioral sensitization to cocaine, an animal model of addiction. Dr. Pierce established an independent laboratory in the Department of Pharmacology at Boston University School of Medicine in 1997. Dr. Pierce joined the Department of Psychiatry's Center for Neurobiology and Behavior in October 2008.

Currently, there are no effective therapies for cocaine addiction, which directly affects over two million people in the United States alone. This reality is the driving force for Dr. Pierce's research program. The major hurdle for abstaining from abuse of cocaine is intense drug craving, which can be triggered months and even years following the cessation of drug use. The most widely accepted model of craving in animals involves self-administration followed by extinction and the subsequent reinstatement of drug seeking. Using this animal model, Dr. Pierce's research team pursues a strategy to identify novel neurobiological adaptations produced by cocaine. This information then can be used to formulate potential cocaine addiction therapies.

Selected Publications

White SL, Ortinski PI, Friedman SH, Zhang L, Neve RL, Kalb RG, Schmidt HD, Pierce RC. A Critical Role for the GluA1 Accessory Protein, SAP97, in Cocaine Seeking. *Neuropsychopharmacology*, February 2016. 152(1): 110-118.

Ortinski PI, Vassoler FM, Carlson GC, Pierce RC. *Temporally dependent changes in cocaine-induced synaptic plasticity in the nucleus accumbens shell are reversed by D1-like dopamine receptor stimulation.* *Neuropsychopharmacology*, March 2012.

Briand LA, Lee FS, Blendy JA, Pierce RC. *Enhanced extinction of cocaine seeking in brain-derived neurotrophic factor Val66Met knock-in mice.* *European Journal of Neuroscience*, March 2012. 35:932-9.

Schmidt HD, Sangrey GR, Darnell SB, Schassburger RL, Cha JH, Pierce RC, Sadri-Vakili G. *Increased BDNF expression in the ventral tegmental area during cocaine abstinence is associated with increased histone*

acetylation at BDNF exon I-containing promoters. Journal of Neurochemistry, January 2012. 120:202-209.

Iris Chen YI, Famous KR, Xu H, Choi JK, Mandeville J, Schmidt HD, Pierce RC, Jenkins BG. *Cocaine self-administration leads to alterations in limbic and motor circuitry*. European Journal of Neuroscience, September 2011. 34:800-815.

Yee J, Famous KR, Hopkins TJ, McMullen MC, Pierce RC, Schmidt HD. *Muscarinic acetylcholine receptors in the nucleus accumbens core and shell contribute to cocaine priming-induced reinstatement of drug seeking*. ^{SEP}European Journal of Pharmacology, January 2011. 650:596-604.



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Research Overview

My research efforts focus on the megakaryocyte-platelet-thrombus axis. The process by which hematopoietic stem cells differentiate into megakaryocytes, which then release platelets and the function of platelets in thrombosis and inflammation are the central foci of my laboratory. Many of the studies focus on the biology and pathobiology of the platelet-specific proteins, chemokines Platelet Factor 4 (PF4)/Platelet Basic Protein (PBP) and the integrin α IIb/ β 3 receptor.

Selected Publications

- Tkaczynski Elizabeth, Arulsevan Abinaya, Tkaczynski John, Avery Stephen, Xiao Liqing, Torok-Storb Beverly, Abrams Kraig, Rao Narayanam V, Johnson Gregory, Kennedy Thomas P, Poncz Mortimer, Lambert Michele P: 2-O, 3-O desulfated heparin mitigates murine chemotherapy- and radiation-induced thrombocytopenia. *Blood advances* 2(7): 754-761, Apr 2018.
- Jarocho Danuta, Vo Karen K, Lyde Randolph B, Hayes Vincent, Camire Rodney M, Poncz Mortimer: Enhancing functional platelet release in vivo from in vitro-grown megakaryocytes using small molecule inhibitors. *Blood advances* 2(6): 597-606, Mar 2018.
- Villa Carlos H, Pan Daniel C, Johnston Ian H, Greineder Colin F, Walsh Landis R, Hood Elizabeth D, Cines Douglas B, Poncz Mortimer, Siegel Don L, Muzykantov Vladimir R: Biocompatible coupling of therapeutic fusion proteins to human erythrocytes. *Blood advances* 2(3): 165-176, Feb 2018.
- Johnston Ian, Hayes Vincent, Poncz Mortimer: Threading an elephant through the eye of a needle: Where are platelets made? *Cell research* May 2017.
- Sim Xiuli, Jarocho Danuta, Hayes Vincent, Hanby Hayley A, Marks Michael S, Camire Rodney M, French Deborah L, Poncz Mortimer, Gadue Paul: Identifying and enriching the platelet-producing human stem cell-derived megakaryocytes using factor V uptake. *Blood* Apr 2017.
- Vo Karen K, Jarocho Danuta J, Lyde Randolph B, Hayes Vincent, Thom Christopher S, Sullivan Spencer K, French Deborah L, Poncz Mortimer: FLI1 level during megakaryopoiesis affects thrombopoiesis and platelet biology. *Blood* Apr 2017.
- Hayes Vincent, Johnston Ian, Arepally Gowthami M, McKenzie Steven E, Cines Douglas B, Rauova Lubica, Poncz Mortimer: Endothelial antigen assembly leads to thrombotic complications in heparin-induced thrombocytopenia. *The Journal of clinical investigation* 127(3): 1090-1098, Mar 2017.
- Madeeva Daria, Cines Douglas B, Poncz Mortimer, Rauova Lubica: Role of monocytes and endothelial cells in heparin-induced thrombocytopenia. *Thrombosis and haemostasis* 116(5): 806-812, Oct 2016.

- Bdeir Khalil, Gollomp Kandace, Stasiak Marta, Mei Junjie, Papiewska-Pajak Izabela, Zhao Guohua, Worthen G Scott, Cines Douglas B, Poncz Mortimer, Kowalska M Anna: Platelet-specific Chemokines Contribute to the Pathogenesis of Acute Lung Injury. *American journal of respiratory cell and molecular biology* 56(2): 261-270, Oct 2016.
- Wang Qi, You Tao, Fan Hongqiong, Wang Yinyan, Chu Tinatian, Poncz Mortimer, Zhu Li: Rapamycin and bafilomycin A1 alter autophagy and megakaryopoiesis. *Platelets* 28(1): 1-8, Aug 2016.
- Khandelwal Sanjay, Lee Grace M, Hester C Garren, Poncz Mortimer, McKenzie Steven, Sachais Bruce S, Rauova Lubica, Kelsoe Garnett, Cines Douglas B, Frank Michael, Arepally Gowthami M: The antigenic complex in HIT binds to B-cells via complement and complement receptor 2 (CD21). *Blood* Jul 2016.
- Ostertag Eric M, Bdeir Khalil, Kacir Stephen, Thiboutot Michelle, Gulendran Gayathri, Yunk Lenka, Hayes Vincent M, Motto David G, Poncz Mortimer, Zheng X Long, Cines Douglas B, Siegel Don L: ADAMTS13 autoantibodies cloned from patients with acquired thrombotic thrombocytopenic purpura: 2. Pathogenicity in an animal model. *Transfusion* 56(7): 1775-85, Jul 2016.
- Greineder Colin F, Hood Elizabeth D, Yao Anning, Khoshnejad Makan, Brenner Jake S, Johnston Ian H, Poncz Mortimer, Gottstein Claudia, Muzykantov Vladimir R: Molecular engineering of high affinity single-chain antibody fragment for endothelial targeting of proteins and nanocarriers in rodents and humans. *Journal of controlled release : official journal of the Controlled Release Society* 226: 229-237, Feb 2016.
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Research Overview

The Powell Lab is actively investigating the application of immune-based therapy for cancer. Building on interrogations in basic T cell biology in the lab, bench-to-bedside translational immunology is being developed, with a strong focus on T cell-based therapy for ovarian cancer.

One obstacle to successful immunotherapy is the lack of highly avid, tumor-reactive T cells in multiple cancers. One current focus of the Powell lab is to generate/isolate high avidity, tumor-reactive T cells from heterogenous tumor infiltrating lymphocyte populations in traditionally "non-immunogenic" cancers utilizing novel culture conditions and T cell capture techniques. This in turn will permit downstream studies of T cell receptor (TCR) isolation, cancer antigen identification and molecular characterization of naturally occurring tumor-reactive T cells in human cancer.

A secondary field of study is the de novo generation of tumor-reactive T cells through genetic engineering methods. One approach relies on the isolation and cloning of T cell receptors (TCRs) that confer non-reactive T cells with specific and potent immune function following gene transfer via recombinant lentivirus or retrovirus. Another approach relies upon the use of chimeric antigen receptors (CARs) that confer T cells with the MHC-independent specificity of a tumor antigen-specific antibody and potent T cell activity delivered by TCR and costimulatory domains. The Powell Lab also employs the CAR approach to test the function of novel costimulatory signals in anti-tumor immunity.

Other current efforts include the exploration of immunomodulation to potentiate endogenous antitumor T cell responses, use of bispecific antibodies, pharmacological sensitization of tumor cells to immune attack, tumor vasculature targeting, preclinical validations, clinical translation and trial support.

Selected Publications

Song D, Ye Q, Santoro S, Fang C, Best A, Powell Jr. DJ. : Chimeric NKG2D CAR expressing T cell-mediated attack of human ovarian cancer is enhanced by HDAC inhibition. *Human Gene Therapy Jan 2013 Notes: 2013 Jan 8. [Epub ahead of print]*

Song, D., Ye, Q., Poussin, M., Harms, G.M., Figini, M., and Powell, D.J., Jr.: CD27 costimulation augments the survival and anti-tumor activity of redirected human T cells in vivo. *Blood 119(3): 696-706, Jan 2012.*

Urbanska, K. and Powell, D.J. Jr.: Development of a Novel Universal Immune Receptor for Antigen Targeting: to Infinity and Beyond. *Oncoimmunology 1(5): 777-779, Aug 2012.*

- Lanitis, E., Poussin, M., Hagemann, I.S., Coukos, G., Sandaltzopoulos, R., Scholler N. and Powell, D.J., Jr.: Redirected anti-tumor activity of primary human lymphocytes transduced with a fully-human anti-mesothelin chimeric receptor. *Molecular Therapy* 20(3): 633-43, Mar 2012.
- Rech, A.J., Mick, R., Martin, S., Recio, A., Aqui, N.A., Powell, D.J., Jr., Colligon, T.A., Trosko, J.A., Leinbach, L.I., Pletcher, C.H., Tweed, C.K., Demichele, A., Fox, K.R., Domchek, S.M., Riley, J.L., Vonderheide, R.H. : CD25 Blockade Depletes and Selectively Reprograms Regulatory T Cells in Concert with Immunotherapy in Cancer Patients. *Science Translational Medicine* 4(134): 134ra62, May 2012 Notes: doi: 10.1126/scitranslmed.3003330.
- Song, D., Ye, Q., Carpenito, C., Poussin, M., Wang, L-P., Ji, C., Figini, M., June, C.H., Coukos, G. and Powell, D.J., Jr.: In vivo persistence, tumor localization and anti-tumor activity of CIR engineered T cells is enhanced by costimulatory signaling through CD137 (4-1BB). *Cancer Research* 71(13): 4617-27. Jul 2011.
- Moon, E.K., Carpenito, C., Sun, J., Wang, L.C., Kapoor, V., Predina, J.D., Powell, D.J., Jr., Riley, J.L., June, C.H. and Albelda, S.M. : Expression of a Functional CCR2 Receptor Enhances Tumor Localization and Eradication by Human T Cells Expressing a Mesothelin-Specific Chimeric Antibody Receptor. *Clinical Cancer Research* 17(14): 4719-30, Jul 2011.
- Lanitis, E., Dangaj1, D., Hagemann, I.S., Song, D. Best, A., Sandaltzopoulos, R., Coukos, G. and Powell Jr., D.J. : Primary Human Ovarian Epithelial Cancer Cells Broadly Express HER2 at Immunologically-detectable Levels. *PLoS ONE* 7(11): e49829, Nov 2012 Notes: Epub 2012 Nov 26. doi: 10.1371/journal.pone.0049829.
- Ye, Q., Loisiou, M., Levine, B.L., Suhoski, M., Riley, J.L., June, C.H., Coukos, G. and Powell, D.J., Jr.: Engineered Artificial Antigen Presenting Cells Facilitate Direct and Efficient Expansion of Solid Tumor-Derived T lymphocytes *Journal of Translational Medicine* 9(131), Aug 2011 Notes: Epub doi: 10.1186/1479-5876-9-131.
- Chiang, C.L. Maier, D.A., Kandalaf, L.E., Brennan, A.L., Lanitis, E., Ye, Q. Levine, B.L., Czerniecki, B.J., Powell, D.J., Jr. and Coukos G.: Optimizing Parameters for Clinical-scale Production of High IL-12 Secreting Dendritic Cells Pulsed with Oxidized Whole Tumor Cell Lysate *Journal of Translational Medicine* 9(1): 198, Nov 2011.
- Chiang, C.L., Hagemann, A.R., Leskowitz, R., Mick, R., Garrabrant, T., Czerniecki, B.J., Kandalaf, L.E., Powell, D.J. Jr. and Coukos G.: Day-4 Myeloid Dendritic Cells Pulsed With Whole Tumor Lysate Are Highly Immunogenic and Elicit Potent Anti-Tumor Responses. *PLoS ONE* 6(12): e28732, Dec 2011 Notes: Epub 2011 Dec 14. doi: 10.1371/journal.pone.0028732.
- Dangaj, D., Abbott, K., Mookerjee, A., Zhao, A., Kirby, P.S., Sandaltzopoulos, R., Powell, D.J. Jr, Lamazière, A., Siegel, D.L., Wolf, C. and Scholler, N.: Mannose receptor (MR) engagement by mesothelin GPI anchor polarizes tumor-associated macrophages and is blocked by anti-MR human recombinant antibody. *PLoS One* 6(12): e28386, Dec 2011.
- Lanitis E., Smith J.B., Dangaj D., Flingai S., Poussin M., Xu S., Czerniecki B.J., Li Y.F., Robbins P.F. and Powell D.J. Jr.: A human ErbB2-specific TCR confers potent anti-tumor effector functions in genetically engineered primary cytotoxic lymphocytes *Human Gene Therapy* 25(8): 730-9, Aug 2014.
- Lynn RC, Poussin M, Kalota A, Feng Y, Low PS, Dimitrov DS, Powell DJ Jr.: Targeting of folate receptor-beta on acute myeloid leukemia blasts with chimeric antigen receptor expressing T-cells *Blood* 125(22): 3466-76, May 2015.
- David Bowtell, Steffen Böhm, Ahmed Ahmed, Paul-Joseph Aspuria, Robert C Bast, Jr, Valerie Beral, Jonathan S Berek, Mike Birrer, Sarah Blagden, Michael A Bookman, James Brenton, Katherine B Chiappinelli, Filipe Correia Martins, George Coukos, Ronny Drapkin, Richard Edmondson, Christina Fotopoulou, Hani Gabra, Jérôme Galon, Charlie Gourley, Valerie Heong, David Huntsman, Marcin Iwanicki, Beth Karlan, Allyson

Kaye, Ernst Lengyel, Douglas A Levine, Karen Lu, Iain McNeish, Usha Menon, Steve Narod, Brad H Nelson, Kenneth Nephew, Paul Pharoah, Daniel Powell, Pilar Ramos, Iris Romero, Clare Scott, Anil K Sood, Euan A Stronach, Frances Balkwill: Rethinking Ovarian Cancer II: A Roadmap for Reducing Mortality from High-grade Serous Ovarian Cancer. *Nature Reviews Cancer* 15(11): 668-79, Oct 2015.

Lynn RC, Feng Y, Schutsky K, Poussin M, Kalota A, Dimitrov DS, and Powell DJ Jr: High affinity FR β -specific CAR T cells eradicate AML and normal myeloid lineage without HSC toxicity *Leukemia* Feb 2016 Notes: Epub ahead of print. doi: 10.1038/leu.2016.35.



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Research Overview

This laboratory is studying the cellular and molecular basis of inflammation and fibrosis, with a particular focus on the role of stromal cells and extracellular matrix (ECM), in the context of chronic inflammatory diseases and cancer. The molecular pathways currently being studied include the adhesion receptor CD44 and its principle ligand, hyaluronan, and fibroblast activation protein (FAP), a stromal cell surface protease. Studies of CD44 and FAP are being conducted in mouse models of cancer, cardiovascular disease and pulmonary fibrosis using conditional CD44 knockout mice and FAP-null mice generated in the lab. Also, the FAP promoter has been exploited to generate mice that can be used to non-invasively image reactive stromal cells in fibrotic lesions and epithelial-derived tumors, to conditionally ablate reactive stromal cells, and to manipulate gene expression specifically in fibrotic lesions and tumor stromal cells. We are studying the impact of matrix modification on cell behavior directly through regulation of receptor mediated signal transduction as well as through modulation of tissue stiffness. We are also exploring the function of CD44 and FAP in human disease.

Selected Publications

Case, A., Brisson, B. K., Durham, A. C., Rosen, S., Monslow, J., Buza, E., Salah, P., Gillem, J., Ruthel, G., Veluvolu, S., Kristiansen, V., Puré, E., Brown, D. C., Sørenmo, K. U., Volk, S. W.: Identification of prognostic collagen signatures and potential therapeutic stromal targets in canine mammary gland carcinoma. *PLoS One* 12(7): e0180448, 2017.

Lo, A., Li, C. P., Buza, E. L., Blomberg, R., Govindaraju, P., Avery, D., Monslow, J., Hsiao, M., Puré, E.: Fibroblast activation protein augments progression and metastasis of pancreatic ductal adenocarcinoma. *JCI Insight* 2(19), 2017.

Katlinski, K. V., Gui, J., Katlinskaya, Y. V., Ortiz, A., Chakraborty, R., Bhattacharya, S., Carbone, C. J., Beiting,

- D. P., Gironde, M. A., Peck, A. R., Puré, E., Chatterji, P., Rustgi, A. K., Diehl, J. A., Koumenis, C., Rui, H., Fuchs, S. Y.: Inactivation of Interferon Receptor Promotes the Establishment of Immune Privileged Tumor Microenvironment. *Cancer Cell* 31(2): 194-207, 2017.
- Cuff, C., D. Kothapalli, I. Azonobi, S. Chun, Y. Zhang, R. Belkin, C. Yeh, A. Secreto, R.K. Assoian, D.J. Rader and E. Puré. 2001. The adhesion receptor CD44 promotes atherosclerosis by mediating inflammatory cell recruitment and vascular cell activation. *J. Clin. Invest.* 108:1031-1040. PMID: PMC200948
- Teder, P., R. W. Vandivier, D. Jiang, J. Liang, L. Cohn, E. Puré, P.M. Henson and P.W. Noble. 2002. Resolution of lung inflammation by CD44. *Science* 296:155-158. PMID: 11935029 [PubMed - indexed for MEDLINE]
- Zhao, L., J.A. Hall, N. Levenkova, M.K. Middleton, A.M. Zukas, E. Lee, D.J. Rader, J.J. Rux and E. Puré. 2007. CD44 regulates vascular gene expression in a pro-atherogenic environment. *Arterioscler. Thromb. and Vascular. Biol.* 27:886-892. PMID: 17272751 [PubMed - indexed for MEDLINE]
- Acharya, P.S., S. Majumdar, M. Jacob, J. Hayden, P. Mrass, W. Weninger, R.K. Assoian and E. Puré. 2008. Fibroblast migration is mediated by CD44-dependent TGF- β activation. *J. Cell Sci.* 121: 1393-1402. PMID: 18397995 [PubMed - indexed for MEDLINE]
- Zhao, L., E. Lee, A.M. Zukas, M.K. Middleton, M. Kinder, P.S. Acharya, R. Yahil, J.A. Hall, D.J. Rader and E. Puré. 2008. CD44 expressed on both bone marrow-derived and non-bone marrow-derived cells promotes atherosclerosis in apoE-deficient mice. *Arterioscler. Thromb. Vasc. Biol.* 28:1283-1289. PMID: 18420998 [PubMed - indexed for MEDLINE]
- Mrass, P., I. Kinjyo, S.L. Reiner, E. Puré and W. Weninger. 2008. CD44 mediates successful interstitial navigation by killer T cells and enables efficient antitumor immunity. *Immunity.* 29:971-985 (accompanying Preview). PMID: PMC2757129
- Santos, A.M., J. Jung, N Aziz, J.L. Kissil and E. Puré. 2009. Targeting fibroblast activation protein inhibits tumor stromagenesis and growth. *J Clin Invest.* 119:3613-3625. PMID 19920354 PMC 2786791
- Tchou, J., A.V. Kossenkov, L. Chang, C. Satija, M. Herlyn, L.C. Showe and E. Puré. 2012 Human breast cancer associated fibroblasts exhibit subtype specific gene expression profiles. *BMC Med. Genom.* 5:39. PMID: 22954256 PMID:PMC3505468
- Tchou, J., P.J. Zhang, Y.T. Bi., C. Satija, R. Majumdar, T.L. Stephen, H.Y. Chen, C. Mies, M. Herlyn, J. Conejo-Garcia, C.H. June and E. Puré. 2013. Fibroblast activation protein expression by stromal cells and tumor-associated macrophages in human breast cancer. *Human Pathology.* 44(11):2549-57. PMID:24074532 PMID: PMC4283499
- Wang, L.-C.S., A. Lo, J. Scholler, J. Sun, R.S. Majumdar, V. Kapoor, M. Antzis, C.E. Cotner, L.A. Johnson, A.C. Durham, C.C. Solomides, C.H. June, E. Puré, S.M. Albelda. 2013. Targeting fibroblast activation protein in tumor stroma with Chimeric Antigen Receptor T Cells can inhibit tumor growth and augment host immunity without severe toxicity. *Cancer Immunol Res.* 2(2):154-166 PMID: 24778279 PMID: PMC4007316
- Lo, A., L.-C.S. Wang, J. Scholler, J. Monslow, D. Avery, K. Newick, S. O'Brien, R.A. Evans, D.J. Bajor, C. Clendenin, A.C. Durham, E.L. Buza, R.H. Vonderheide, C.H. June, S.M. Albelda and E. Puré. 2015. Tumor-promoting desmoplasia is disrupted by depleting FAP-expressing stromal cells. *Cancer Research.* 75(14):2800-2810. PMID: 25979873 PMID: PMC4506263
- Fan, M.-H., Q. Zhu, H.-H. Li, H.-J. Ra, S. Majumdar, D.L. Gulick, J.A. Jerome, D.H. Madsen, M. Christofidou-Solomidou, D.W. Speicher, W.W. Bachovchin, C. Feghali-Bostwick, E. Puré. 2015. Fibroblast Activation Protein (FAP) Accelerates Collagen Degradation and Clearance from the Lung in Mice. *J. Biol. Chem.* Dec 9. pii: jbc.M115.701433. [Epub ahead of print] PMID:26663085

Puré, E. and A. Lo. 2016. Masters In Immunology: Can targeting stroma pave the way to enhanced antitumor immunity and immunotherapy of solid tumors? *Cancer Immunol Res*, 4; 269–78 Invited contribution.



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Research Overview

The Rader laboratory is focused on two major themes: 1) novel pathways regulating lipid and lipoprotein metabolism and atherosclerosis inspired by unbiased studies of human genetics; 2) factors regulating the structure and function of high density lipoproteins and the process of reverse cholesterol transport and their relationship to atherosclerosis. A variety of basic cell and molecular laboratory techniques, mouse models, and translational research approaches are used in addressing these questions. Some examples of ongoing projects are:

1. The roles of sortilin (gene SORT1) and tribbles-1 (gene TRIB1) in lipoprotein metabolism and atherosclerosis. Variants at the SORT1 locus are among the most strongly associated with LDL cholesterol and (coronary artery disease) in the human genome, and variants at the TRIB1 locus are significantly associated with all major plasma lipid traits and CAD. A variety of tissue-specific deleted mouse models, gene targeting in iPS cells with differentiation to hepatocytes, and cell biologic and biochemical approaches are being employed.
2. Functional genomics and mechanistic studies of a number of additional genes at loci significantly associated with lipid and metabolic traits, CAD, or other cardiovascular traits. Most of these genes harbor rare coding variants associated with these traits. In addition to elucidating fundamental mechanisms by which the protein influences relevant biology, the influence of specific mutations on protein structure and function are being explored.
3. Molecular regulation of HDL metabolism and reverse cholesterol transport using cells, mice, and humans.
4. Deep phenotyping of humans with low-frequency and rare variants in genes influencing lipid and cardiovascular traits, including the generation of iPS cells and differentiation to a variety of relevant cell types.

Selected Publications

Dron JS, Wang J, Low-Kam C, Khetarpal SA, Robinson JF, McIntyre AD, Ban MR, Cao H, Rhainds D, Dubé MP, Rader DJ, Lettre G, Tardif JC, Hegele RA: Polygenic determinants in extremes of high-density lipoprotein cholesterol. *J Lipid Res* Sep 2017 Notes: Epub ahead of print.

Zhao W, Rasheed A, Tikkanen E, Lee JJ, Butterworth AS, Howson JMM, Assimes TL, Chowdhury R, Orholm-Melander M, Damrauer S, Small A, Asma S, Imamura M, Yamauch T, Chambers JC, Chen P, Sapkota BR, Shah N, Jabeen S, Surendran P, Lu Y, Zhang W, Imran A, Abbas S, Majeed F, Trindade K, Qamar N, Mallick

NH, Yaqoob Z, Saghir T, Rizvi SNH, Memon A, Rasheed SZ, Memon FU, Mehmood K, Ahmed N, Qureshi IH, Tanveer-Us-Salam, Iqbal W, Malik U, Mehra N, Kuo JZ, Sheu WH, Guo X, Hsiung CA, Juang JJ, Taylor KD, Hung YJ, Lee WJ, Quertermous T, Lee IT, Hsu CC, Bottinger EP, Ralhan S, Teo YY, Wang TD, Alam DS, Di Angelantonio E, Epstein S, Nielsen SF, Nordestgaard BG, Tybjaerg-Hansen A, Young R; CHD Exome+ Consortium, Benn M, Frikke-Schmidt R, Kamstrup PR; EPIC-CVD Consortium; EPIC-Interact Consortium; Michigan Biobank, Jukema JW, Sattar N, Smit R, Chung RH, Liang KW, Anand S, Sanghera DK, Ripatti S, Loos RJF, Kooner JS, Tai ES, Rotter JI, Chen YI, Frossard P, Maeda S, Kadowaki T, Reilly M, Pare G, Melander O, Salomaa V, Rader DJ, Danesh J, Voight BF, Saleheen D. : Identification of new susceptibility loci for type 2 diabetes and shared etiological pathways with coronary heart disease. *Nat Genet* Sep 2017 Notes: Epub ahead of print.

Tuteja S, Wang L, Dunbar RL, Chen J, DerOhannessian S, Marcovina SM, Elam M, Lader E, Rader DJ: Genetic coding variants in the niacin receptor, hydroxyl-carboxylic acid receptor 2, and response to niacin therapy. *Pharmacogenet Genomics*. 27(8): 285-293, Aug 2017.

Bajaj A, Damrauer SM, Anderson AH, Xie D, Budoff MJ, Go AS, He J, Lash JP, Ojo A, Post WS, Rahman M, Reilly MP, Saleheen D, Townsend RR, Chen J, Rader DJ: Lipoprotein(a) and Risk of Myocardial Infarction and Death in Chronic Kidney Disease: Findings From the CRIC Study (Chronic Renal Insufficiency Cohort). *Arterioscler Thromb Vasc Biol* Aug 2017 Notes: Epub ahead of print.

Koekemoer AL, Codd V, Masca NGD, Nelson CP, Musameh MD, Kaess BM, Hengstenberg C, Rader DJ, Samani NJ : Large-Scale Analysis of Determinants, Stability, and Heritability of High-Density Lipoprotein Cholesterol Efflux Capacity. *Arterioscler Thromb Vasc Biol* Aug 2017 Notes: Epub ahead of print.

Khetarpal SA, Zeng X, Millar JS, Vitali C, Somasundara AVH, Zannoni P, Landro JA, Barucci N, Zavadski WJ, Sun Z, de Haard H, Toth IV, Peloso GM, Natarajan P, Cuchel M, Lund-Katz S, Phillips MC, Tall AR, Kathiresan S, DaSilva-Jardine P, Yates NA, Rader DJ : A human APOC3 missense variant and monoclonal antibody accelerate apoC-III clearance and lower triglyceride-rich lipoprotein levels. *Nat Med* Aug 2017 Notes: Epub ahead of print.

Small AM, Kiss DH, Zlatsin Y, Birtwell DL, Williams H, Guerraty MA, Han Y, Anwaruddin S, Holmes JH, Chirinos JA, Wilensky RL, Giri J, Rader DJ: Text mining applied to electronic cardiovascular procedure reports to identify patients with trileaflet aortic stenosis and coronary artery disease. *J Biomed Inform* 72: 77-84, Aug 2017.

Dunbar RL, Movva R, Bloedon LT, Duffy D, Norris RB, Navab M, Fogelman AM, Rader DJ.: Oral Apolipoprotein A-I Mimetic D-4F Lowers HDL-Inflammatory Index in High-Risk Patients: A First-in-Human Multiple-Dose, Randomized Controlled Trial. *Clin Transl Sci* Aug 2017 Notes: Epub ahead of print.

Döring Y, Noels H, van der Vorst EPC, Neideck C, Egea V, Drechsler M, Mandl M, Pawig LB, Jansen Y, Schröder K, Bidzhekov K, Megens RTA, Theelen W, Klinkhammer BM, Boor P, Schurgers LJ, van Gorp RH, Ries C, Kusters PJH, van der Wal AC, Hackeng TM, Gäbel G, Brandes RP, Soehnlein O, Lutgens E, Vestweber D, Teupser D, Holdt LM, Rader DJ, Saleheen D, Weber C: Vascular CXCR4 Limits Atherosclerosis by Maintaining Arterial Integrity: Evidence from Mouse and Human Studies. *Circulation*. 136(4): 388-403, Jul 2017.

Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, Abbas S, Majeed F, Akhtar S, Qamar N, Zaman KS, Yaqoob Z, Saghir T, Rizvi SN, Memon A, Mallick NH, Ishaq M, Rasheed SZ, Memon FU, Mahmood K, Ahmed N, Frossard P, Tsimikas S, Witztum JL, Marcovina S, Sandhu M, Rader DJ, Danesh J.: Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 5(7): 524-533, Jul 2017



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Research Overview

The primary mission of the Functional and Metabolic Imaging Group (FMIG) is the development and application of novel hyperpolarized MRI techniques to the diagnosis of various pulmonary and metabolic disorders. Hyperpolarization, the process of drastically increasing the population difference between nuclear spin states, provides a platform for imaging lung physiology and metabolic activity with spatial and temporal resolution unattainable with conventional MRI techniques, thus offering the potential for the earlier diagnosis of disease states and the precise monitoring of a patient's response to medical treatment. This core research theme is executed with an eye toward several ultimate goals: the identification of changes in pulmonary structure and function associated with disease, a more complete understanding of pathogenesis, and the establishment of a more sensitive testing environment to develop treatments for lung disease. To date, significant contributions in these areas include new imaging techniques for the comprehensive description of lung physiology and structure, accurate imaging of the regional pulmonary partial pressure of oxygen in both humans and large and small animals, highly developed imaging of regional ventilation, and a state-of-the-art mechanical ventilation device. Specifically, our research activities at FMIG is divided into four general branches: 1) The development of novel imaging techniques for the quantitative assessment of pulmonary structure and function: 2) The development of novel methods for real-time metabolic imaging: 3) The construction of novel polarization apparatuses: 4) The development and implementation of rapid imaging pulse sequences.

Selected Publications

Baron Ryan J, Hamedani Hooman, Kadlecsek Stephen J, Duncan Ian F, Xin Yi, Siddiqui Sarmad, Pourfathi Mehrdad, Cereda Maurizio, Rizi Rahim R: A Model for Predicting Future FEV1 Decline in Smokers Using Hyperpolarized He Magnetic Resonance Imaging. *Academic radiology* Aug 2018.

Ruppert Kai, Hamedani Hooman, Amzajerjian Faraz, Xin Yi, Duncan Ian F, Profka Harrilla, Siddiqui Sarmad, Pourfathi Mehrdad, Kadlecsek Stephen, Rizi Rahim R: Assessment of Pulmonary Gas Transport in Rabbits Using Hyperpolarized Xenon-129 Magnetic Resonance Imaging. *Scientific reports* 8(1): 7310, May 2018.

Cereda Maurizio, Xin Yi, Rizi Rahim R: Acute Respiratory Distress Syndrome - Can Data from the Sick Guide Care for the Healthy? *American journal of respiratory and critical care medicine* May 2018.

Ruppert Kai, Amzajerjian Faraz, Hamedani Hooman, Xin Yi, Loza Luis, Achekzai Tahmina, Duncan Ian F, Profka Harrilla, Siddiqui Sarmad, Pourfathi Mehrdad, Cereda Maurizio F, Kadlecsek Stephen, Rizi Rahim R: Rapid assessment of pulmonary gas transport with hyperpolarized 129Xe MRI using a 3D radial double golden-means acquisition with variable flip angles. *Magnetic resonance in medicine* Apr 2018.

- Pourfathi Mehrdad, Cereda Maurizio, Chatterjee Shampa, Xin Yi, Kadlecek Stephen, Duncan Ian, Hamedani Hooman, Siddiqui Sarmad, Profka Harrilla, Ehrich Jason, Ruppert Kai, Rizi Rahim R: Lung Metabolism and Inflammation during Mechanical Ventilation; An Imaging Approach. *Scientific reports* 8(1): 3525, Feb 2018.
- Xin Yi, Cereda Maurizio, Hamedani Hooman, Pourfathi Mehrdad, Siddiqui Sarmad, Meeder Natalie, Kadlecek Stephen, Duncan Ian, Profka Harrilla, Rajaei Jennia, Tustison Nicholas J, Gee James C, Kavanagh Brian P, Rizi Rahim R: Unstable Inflation Causing Injury: Insight from Prone Position and Paired CT Scans. *American journal of respiratory and critical care medicine* 198(2): 197-207, Feb 2018.
- Drachman Nicholas, Kadlecek Stephen, Pourfathi Mehrdad, Xin Yi, Profka Harilla, Rizi Rahim: In vivo pH mapping of injured lungs using hyperpolarized [1-(13) C]pyruvate. *Magnetic resonance in medicine* 78(3): 1121-1130, Sep 2017.
- Hamedani Hooman, Kadlecek Stephen, Xin Yi, Siddiqui Sarmad, Gatens Heather, Naji Joseph, Ishii Masaru, Cereda Maurizio, Rossman Milton, Rizi Rahim: A hybrid multibreath wash-in wash-out lung function quantification scheme in human subjects using hyperpolarized (3) He MRI for simultaneous assessment of specific ventilation, alveolar oxygen tension, oxygen uptake, and air trapping. *Magnetic resonance in medicine* 78(2): 611-624, Aug 2017.
- Drachman Nicholas, Kadlecek Stephen, Duncan Ian, Rizi Rahim: Quantifying reaction kinetics of the non-enzymatic decarboxylation of pyruvate and production of peroxy-monocarbonate with hyperpolarized (13)C-NMR. *Physical chemistry chemical physics : PCCP* 19(29): 19316-19325, Jul 2017.
- Cereda Maurizio, Xin Yi, Hamedani Hooman, Bellani Giacomo, Kadlecek Stephen, Clapp Justin, Guerra Luca, Meeder Natalie, Rajaei Jennia, Tustison Nicholas J, Gee James C, Kavanagh Brian P, Rizi Rahim R: Tidal changes on CT and progression of ARDS. *Thorax* Jun 2017.
- Xin Yi, Cereda Maurizio, Kadlecek Stephen, Emami Kiarash, Hamedani Hooman, Duncan Ian, Rajaei Jennia, Hughes Liam, Meeder Natalie, Naji Joseph, Profka Harrilla, Bolognese Brian J, Foley Joseph P, Podolin Patricia L, Rizi Rahim R: Hyperpolarized Gas Diffusion MRI of Biphasic Lung Inflation in Short and Long Term Emphysema Models. *American journal of physiology. Lung cellular and molecular physiology* 313(2): ajplung.00048.2017, May 2017.
- Siddiqui Sarmad, Kadlecek Stephen, Pourfathi Mehrdad, Xin Yi, Mannherz William, Hamedani Hooman, Drachman Nicholas, Ruppert Kai, Clapp Justin, Rizi Rahim: The use of hyperpolarized carbon-13 magnetic resonance for molecular imaging. *Advanced drug delivery reviews* 113: 3-23, Apr 2017.
- Pourfathi Mehrdad, Xin Yi, Kadlecek Stephen J, Cereda Maurizio F, Profka Harrilla, Hamedani Hooman, Siddiqui Sarmad M, Ruppert Kai, Drachman Nicholas A, Rajaei Jennia N, Rizi Rahim R: In vivo imaging of the progression of acute lung injury using hyperpolarized [1-(13) C] pyruvate. *Magnetic resonance in medicine* Jan 2017.
- Xu He N, Kadlecek Stephen, Shaghghi Hooraa, Zhao Huaqing, Profka Harilla, Pourfathi Mehrdad, Rizi Rahim, Li Lin Z: Differentiating inflamed and normal lungs by the apparent reaction rate constants of lactate dehydrogenase probed by hyperpolarized (13)C labeled pyruvate. *Quantitative imaging in medicine and surgery* 6(1): 57-66, Feb 2016.
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Research Overview

Glutamate and aspartate are the predominant excitatory neurotransmitters in the mammalian CNS. These two excitatory amino acids (EAAs) mediate most of the rapid depolarization that occurs in the CNS. In fact, the levels of these transmitters are 1000- to 10,000-fold higher than those of many other important neurotransmitters, including dopamine, serotonin, and acetylcholine. Paradoxically, these EAAs are also potent neurotoxins, both in vivo and in vitro. In fact, excessive activation of EAA receptors contributes to the neuronal degeneration observed after acute insults to the CNS, such as stroke and head trauma. We are interested in the normal physiology of EAAs and the role of these transmitters in neurodegeneration. Our laboratory has focused on understanding the regulation of extracellular levels of EAAs because it is this pool of EAAs that is toxic to neurons. Extracellular concentrations of glutamate and aspartate are normally maintained in the low micromolar range by a family of sodium-dependent high affinity transporters that are present on both neurons and glial cells. Our laboratory has developed evidence that neurons induce and maintain expression of one of the astrocytic transporters critical for limiting excitotoxicity. We have begun to define the mechanisms that contribute to this regulation. Our laboratory has also found that the function of several of the transporter subtypes can be rapidly (within minutes) altered by activation of certain kinases. This regulation is associated with a redistribution of these transporters to/or from the plasma membrane (see the image below). The long term goal of the laboratory is to develop new strategies for limiting glutamate-mediated damage by understanding the endogenous mechanisms that clear this excitotoxin.

Selected Publications

Port R.G., Gajewski C., Krizman E., Dow H.C., Hirano S., Brodtkin E.S., Carlson G.C., Robinson M.B., Roberts T.P.L., and Siegel S.J. : Protocadherin10 alters γ oscillations, amino acid levels, and their coupling: Baclofen partially restores oscillatory defects. *Neurobiology of Disease* 108: 324-338. 2017.

Lee M.C., Martinez-Lozano, Z., Krizman E., and Robinson M.B.: Endothelia induce expression of GLT-1 in astrocytes. *Journal of Neurochemistry* 143: 489-506, 2017.

Sengupta S., Yang G., O'Donnell J.C., Hinson M.D., McCormack S.E., Falk M.J., La P., Robinson M.B., Williams M.L., Yohannes M.T., Polyak E., Nakamaru-Ogiso E., and Dennery P.A: The circadian gene *Rev-erb α* improves cellular bioenergetics and provides preconditioning for protection against oxidative stress. *Free Radical Biology and Medicine* 93: 177-189. 2016.

- Ghosh Mausam, Lane Meredith, Krizman Elizabeth, Sattler Rita, Rothstein Jeffrey D, Robinson Michael B: Transcription Factor Pax6 Contributes to Induction of GLT-1 Expression in Astrocytes Through an Interaction with a Distal Enhancer Element. *Journal of Neurochemistry* doi: 10.1111/jnc.13406, 2016.
- O'Donnell J.C., Jackson J.G., and Robinson M.B. : Transient oxygen glucose deprivation causes a delayed loss of mitochondria and increases spontaneous calcium signaling in astrocytic processes. *Journal of Neuroscience* 36: 7109-7127. 2016.
- Wood K.H., Johnson B.S., Welsh S.A., Lee J.Y., Cui Y., Krizman E., Brodtkin E.S., Blendy J.A., Robinson M.B., Bartolomei M.S., and Zhou Z. : Tagging methyl-CpG-binding domain proteins reveals different spatiotemporal expression and supports distinct functions. *Epigenomics* 8: 455-473. 2016.
- Jackson J.G. and Robinson M.B. : Reciprocal regulation of mitochondrial dynamics and calcium signaling in astrocyte processes. *Journal of Neuroscience* 35: 15199-213, 2015.
- Jackson M.B., O'Donnell J.C., Krizman E., and Robinson M.B. : Displacing hexokinase from mitochondrial voltage-dependent anion channel impairs GLT1-mediated glutamate uptake but does not disrupt interactions between GLT-1 and mitochondrial proteins. *Journal of Neuroscience Research* 93: 999-1008, 2015.
- Raju Karthik, Doulias Paschalis-Thomas, Evans Perry, Krizman Elizabeth N, Jackson Joshua G, Horyn Oksana, Daikhin Yevgeny, Nissim Ilana, Yudkoff Marc, Nissim Itzhak, Sharp Kim A, Robinson Michael B, Ischiropoulos Harry: Regulation of brain glutamate metabolism by nitric oxide and S-nitrosylation. *Science signaling* 8(384): ra68, 2015.
- Jackson J.G., O'Donnell J.C., Takano H., Coulter D.A., and Robinson M.B.: Neuronal activity and glutamate uptake decrease mitochondrial mobility and position mitochondria near glutamate transporters. *Journal of Neuroscience* 34: 1613-1624, 2014.
- Jager J., O'Brien W.T., Manlove J., Krizman, E.N., Fang B., Gerhart-Hines Z., Robinson M.B., and Lazar M.A.: Behavioral changes and dopaminergic dysregulation in mice lacking the nuclear receptor Rev-erb α . *Molecular Endocrinology* 28: 490-498, 2014.
- Lane M.C., Jackson J.G., Krizman E.N., Rothstein J.D., Porter B.E., and Robinson M.B. : Genetic deletion of the neuronal glutamate transporter, EAAC1, results in decreased neuronal death after pilocarpine-induced status epilepticus. *Neurochemistry International* 73: 152-158, 2013.
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Research Overview

The main goal of our laboratory is to understand the neurobiological basis for drug addiction. We use a multidisciplinary approach that incorporates behavioral pharmacology and molecular biology techniques to identify novel neuroadaptations produced by chronic drug exposure. Our research program is broadly divided into three areas of focus:

1. Our lab is interested in understanding the biological mechanisms underlying nicotine addiction. Drug self-administration is a clinically relevant animal model that can be used to investigate the effects of potential smoking cessation medications in moderating nicotine reinforcement. Recent experiments aim to examine the role of acetylcholinesterase and nicotinic acetylcholine receptors in nicotine reinforcement and reinstatement.
2. Another focus of the laboratory is to integrate behavioral pharmacology and neuroscience with molecular techniques that probe drug-induced neuroadaptations at the genomic level. Specifically, our research aims to investigate the epigenetic mechanisms underlying drug craving and relapse. It is now clear that chronic exposure to drugs of abuse alters gene expression in limbic nuclei that underlies the neuronal and behavioral plasticity associated with drug taking and seeking. Our research is aimed at determining how drug-induced chromatin remodeling leads to alterations in growth factor expression following chronic cocaine.
3. Our previous studies have demonstrated that alterations in dopamine and glutamate transmission play a critical role in drug-taking and –seeking behaviors. Thus, one focus of our research program is to determine the molecular mechanisms that regulate plasticity in dopamine and glutamate systems and contribute to drug-seeking behavior. In collaboration with Dr. Chris Pierce, we are studying the role of protein kinase C (PKC) in cocaine priming-induced reinstatement, an animal model of relapse in human cocaine addicts. These studies also aim to understand how chronic cocaine exposure affects AMPA receptor trafficking in the nucleus accumbens.

Selected Publications

Guercio, L. A., Hofmann, M. E., Swinford-Jackson, S. E., Sigman, J. S., Wimmer, M. E., Dell'Acqua, M. L., ... Pierce, R. C. (2018). A-Kinase Anchoring Protein 150 (AKAP150) promotes cocaine reinstatement by increasing AMPA Receptor transmission in the accumbens shell. *Neuropsychopharmacology*, 43(6), 1395-1404.

- Ashare, R.L., Kimmey, B.A., Rupprecht, L.E., Bowers, M.E., Hayes, M.R., & Schmidt, H.D. (2017). Repeated administration of an acetylcholinesterase inhibitor attenuates nicotine taking in rats and smoking behavior in human smokers. *Translational Psychiatry*, 7(3), e1072.
- Van Nest, D., Hernandez, N. S., Kranzler, H. R., Pierce, R. C., & Schmidt, H. D. (2017). Effects of LY466195, a selective kainate receptor antagonist, on ethanol preference and drinking in rats. *Neuroscience Letters*, 639, 8-12.
- Alhadeff, A. L., Mergler, B. D., Zimmer, D. J., Turner, C. A., Reiner, D. J., Schmidt, H. D., ... Hayes, M. R. (2017). Endogenous glucagon-like peptide-1 receptor signaling in the nucleus tractus solitarius is required for food intake control. *Neuropsychopharmacology*, 42(7), 1471-1479.
- Maurer, J. J., Sandager-Nielsen, K., & Schmidt, H. D. (2017). Attenuation of nicotine taking and seeking in rats by the stoichiometry-selective alpha4beta2 nicotinic acetylcholine receptor positive allosteric modulator NS9283. *Psychopharmacology(Berl)*, 234(3), 475-484.
- Fowler, C. D., Gipson, C. D., Kleykamp, B. A., Rupprecht, L. E., Harrell, P. T., Rees, V. W., ... De Biasi, M. (2017). Basic science and public policy: Informed regulation for nicotine and tobacco products. *Nicotine & Tobacco Research*, published online 8/3/2017.
- Hernandez, N. S., O'Donovan, B., Ortinski, P. I., & Schmidt, H. D. (2017). Activation of glucagon-like peptide-1 receptors in the nucleus accumbens attenuates cocaine seeking in rats. *Addiction Biology*, published online 12/11/2017.
- Schmidt, H. D. (2017). Cocaine rearranges the neuronal epigenome. *Biological Psychiatry*, 82(11), 776-778.
- Mietlicki-Baase, E. G., McGrath, L. E., Koch-Laskowski, K., Krawczyk, J., Reiner, D. J., Pham, T., ... Hayes, M. R. (2017). Amylin receptor activation in the ventral tegmental area reduces motivated ingestive behavior. *Neuropharmacology*, 123, 67-79.
- Reiner, D. J., Mietlicki-Baase, E. G., Olivos, D. R., McGrath, L. E., Zimmer, D. J., Koch-Laskowski, K., ... Hayes, M. R. (2017). Amylin acts in the lateral dorsal tegmental nucleus to regulate energy balance through gamma-aminobutyric acid signaling. *Biological Psychiatry*, 82(11), 828-838.
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Research Overview

Obesity is the predominant risk factor for an expanding array of diseases including: type 2 diabetes, heart disease, stroke and cancer. Our lab investigates the transcriptional pathways that control the development, differentiation and function of adipose cells in normal development and in obesity. We are particularly interested in early determination and specification events; this involves the commitment of mesenchymal stem cells to a preadipocyte cell fate. We are also exploring pathways that determine the fate (and thus the function) of different types of fat cells.

Mammals have two main subtypes of adipose tissue, white and brown. White adipose tissue is specialized for energy storage, whereas brown adipose expends chemical energy in the form of heat. White adipose tissue is found in the subcutaneous layer and in distinct intra-abdominal depots. Excess abdominal adiposity is associated with metabolic dysfunction, insulin resistance and heart disease. By contrast, expansion of subcutaneous fat is not correlated with insulin resistance or metabolic disease.

Brown fat can counteract obesity by safely burning off excess energy. Increased brown adipose function promotes a lean and healthy phenotype. Conversely, animals lacking brown adipose develop obesity and type 2 diabetes. Recent PET-based imaging studies suggests that the amount of activated brown adipose in humans is inversely correlated with body mass index and age. These results suggest that brown adipose plays an important and unappreciated role in human energy balance. Moreover, drug or cell-based approaches that increase the amount or function of brown adipose could provide novel therapies for obesity and its metabolic complications.

Selected Publications

Shapira SN, Lim HW, Rajakumari S, Sakers AP, Ishibashi J, Harms MJ, Won KJ, Seale P. EBF2 transcriptionally regulates brown adipogenesis via the histone reader DPF3 and the BAF chromatin remodeling complex. *Genes Dev.* 31(7):660-673, 2017.

Kissig M, Ishibashi J, Harms MJ, Lim HW, Stine RR, Won KJ, Seale P. PRDM16 represses the type I interferon response in adipocytes to promote mitochondrial and thermogenic programming. *EMBO J.* 36(11):1528-1542, 2017.

Gupta RK, Arany Z, Seale P, Mepani RJ, Ye L, Conroe HM, Roby YA, Kulaga H, Reed RR, Spiegelman BM: Transcriptional Control of Preadipocyte Determination by Zfp423. *Nature* 25(464): 619-23, March 2010.

- Kajimura S, Seale P, Kubota K, Lunsford E, Frangioni JV, Gygi SP, Spiegelman BM: Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. *Nature* 460(7259): 1154-8, Aug 27 2009.
- Seale P, Kajimura S, Spiegelman BM: Transcriptional control of brown adipocyte development and physiological function--of mice and men. *Genes Dev* 23(7): 788-97, Apr 1 2009.
- Seale P, Lazar MA: Brown fat in humans: turning up the heat on obesity. *Diabetes* 58(7): 1482-4, Jul 2009.
- Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scimè A, Devarakonda S, Conroe HM, Erdjument-Bromage H, Tempst P, Rudnicki MA, Beier DR, Spiegelman BM: PRDM16 controls a brown fat/skeletal muscle switch. *Nature* 454(7207): 961-7, Aug 21 2008.
- Kajimura S, Seale P, Tomaru T, Erdjument-Bromage H, Cooper MP, Ruas JL, Chin S, Tempst P, Lazar MA, Spiegelman BM: Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex. *Genes Dev* 22(10): 1397-409, May 15 2008.
- Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D, Spiegelman BM: Transcriptional control of brown fat determination by PRDM16. *Cell Metab* 6(1): 38-54, Jul 2007.
- Handschin C, Kobayashi YM, Chin S, Seale P, Campbell KP, Spiegelman BM: PGC-1alpha regulates the neuromuscular junction program and ameliorates Duchenne muscular dystrophy. *Genes Dev* 21(7): 770-83, Apr 1 2007.
- Uldry M, Yang W, St-Pierre J, Lin J, Seale P, Spiegelman BM: Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. *Cell Metab* 3(5): 333-41, May 2006.
- Seale P, Ishibashi J, Holterman C, Rudnicki MA: Muscle satellite cell-specific genes identified by genetic profiling of MyoD-deficient myogenic cell. *Dev Biol* 275(2): 287-300, Nov 15 2004.
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Research Overview

The laboratory seeks to understand the molecular and cellular networks that drive behavior, in particular rhythmic behaviors such as sleep. Our studies are done largely with the fruit fly, *Drosophila melanogaster*, but we also translate our findings to mammalian models, especially mice. The major goals are to elucidate the mechanisms that confer a circadian (~24-hour) periodicity on much of behavior and physiology as well as understand how and why the drive to sleep is generated.

Circadian (~24-hour) clocks endogenous to most organisms drive daily rhythms of sleep:wake and of most physiological processes. Any kind of desynchrony between endogenous clocks and the environment, as is caused by travel to a different time zone or by shift work, results in a multitude of physiological disturbances. Likewise, sleep disruption, which is common in modern society, results in severe metabolic and cognitive deficits.

Our research has provided insight into mechanisms of the circadian clock, how clocks synchronize to light and how clocks interact with body systems to drive rhythms of behavior and physiology. Building upon a *Drosophila* model for sleep that we developed several years ago, we have also identified genes and circuits that underlie the homeostatic drive for sleep. Ongoing studies are revealing new mechanisms and cellular functions for sleep. Together our studies are providing a comprehensive understanding of how internal clocks drive body rhythms, how and why a sleep state occurs, and the extent to which clocks and sleep impact general physiology and aging.

Selected Publications

- King AN, Sehgal A. Molecular and circuit mechanisms mediating circadian clock output in the *Drosophila* brain. *Eur J Neurosci*. [Epub ahead of print] Jul 2018.
- Bai L, Lee Y, Hsu CT, Williams JA, Cavanaugh D, Zheng X, Stein C, Haynes P, Wang H, Gutmann DH, Sehgal A. A Conserved Circadian Function for the Neurofibromatosis 1 Gene. *Cell Rep*. 22(13):3416-3426. Mar 2018.
- Dubowy, C., Moravcevic, K., Yue, Z., Wan, J. Y., Van Dongen, H. P., & Sehgal, A. (2016). Genetic Dissociation of Daily Sleep and Sleep Following Thermogenetic Sleep Deprivation in *Drosophila*. *Sleep*, 39(5), 1083-1095. doi:10.5665/sleep.5760
- Erion, R., King, A. N., Wu, G., Hogenesch, J. B., & Sehgal, A. (2016). Neural clocks and Neuropeptide F/Y regulate circadian gene expression in a peripheral metabolic tissue. *Elife*, 5. doi:10.7554/eLife.13552
- Garbe, D. S., Vigderman, A. S., Moscato, E., Dove, A. E., Vecsey, C. G., Kayser, M. S., & Sehgal, A. (2016). Changes in Female *Drosophila* Sleep following Mating Are Mediated by SPSN-SAG Neurons. *J Biol Rhythms*. doi:10.1177/0748730416668048
- Monyak, R. E., Emerson, D., Schoenfeld, B. P., Zheng, X., Chambers, D. B., Rosenfelt, C., . . . Jongens, T. A. (2016). Insulin signaling misregulation underlies circadian and cognitive deficits in a *Drosophila fragile X*



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Research Overview

The lab mission is to develop molecular and cellular solutions addressing important challenges in biomedical science and clinical medicine. We create small molecules, engineered proteins and cell-based tools that can "light up" and control in vivo biology using principles of chemical and synthetic biology. When possible, our technologies are translated to the clinic using nuclear medicine and molecular imaging techniques. For example, our group recently pioneered the development, preclinical testing, and human application of a new class of positron emission tomography (PET) radiotracers based on the small molecule antibiotic trimethoprim. These molecules have diverse applications in our broad fields of investigation including cancer biology, immunology, and infectious disease. If you have any questions about who we are and what we do, don't hesitate to reach out to us.

Selected Publications

- Makvandi, M., Sellmyer, M. A. & Mach, R. H. Inflammation and DNA damage: Probing pathways to cancer and neurodegeneration. *Drug Discov Today Technol*, 2017, 25, 37–43.
- Sellmyer, M. A.,* I. Lee, C. Hou, C. C. Weng, S. Li, B. P. Lieberman, C. Zeng, D. A. Mankoff and R. H. Mach.* Bacterial infection imaging with [¹⁸F]fluoropropyl-trimethoprim. *Proc. Natl. Acad. Sci.*, 2017 114(31): 8372-8377.* co-corresponding authorship
- Sellmyer, M.A.,* Lee, I., Hou, C., Lieberman, B.P., Zeng, C., Mankoff, D.A., Mach, R.H.* Quantitative PET reporter gene imaging with [¹¹C]trimethoprim. *Molecular Therapy*, 2017, 25, 120–126. *co-corresponding authorship
- Jones, J., Li, D., Hui, E., Sellmyer, M.A., Prescher, J.A. Visualizing cell proximity with genetically encoded bioluminescent reporters. *ACS Chemical Biology* 2015 doi:10.1021/cb500777
- Sellmyer, M.A., Bronsart, L., Imoto, H., Contag, C.H., Wandless T.J., Prescher, J.A. Visualizing Cellular Interactions with a Generalized Proximity Reporter. *Proc. Natl. Acad. Sci.*, 2013, 110, 8567-8572.

- Sellmyer, M. A., Desser, T. S., Maturen, K. E., Jeffrey, R. B., Kamaya, A. Physiologic, Histologic, and Imaging Features of Retained Products of Conception. *Radiographics* 2013, 33, 781–796.
- Sellmyer, M.A., Chun, L.C., Egeler, E.L., Rakhit, R., Wandless, T.J. Intracellular context affects levels of a chemically dependent destabilizing domain. *PLoS ONE*, 2012, 7, e43297.
- Kwan, M.D., * Sellmyer, M.A.,* Quarto, N., Ho, A.M., Wandless, T.J., Longaker, M.T. Chemical control of FGF-2 release for promoting calvarial healing with adipose stem cells. *J. Biol. Chem.*, 2011, 286, 11307–11313
*Co-first authorship.
- Sellmyer, M.A., Thorne, S.H., Banaszynski, L.A., Contag, C.H., Wandless, T.J. A general method for conditional regulation of protein stability in living animals. *CSH Protocols*, 2009, doi: 10.1101/pdb.prot5173.
- Banaszynski, L. A.,* Sellmyer, M. A.,* Contag, C. H., Wandless, T. J., Thorne, S. H. Chemical control of protein stability and function in living animals. *Nature Medicine*, 2008, (14) 10, 1123-1127. *Co-first authorship.
- Sellmyer, M.A., Stankunas, K., Briesewitz, R., Crabtree, G.R., Wandless, T.J. Engineering Small Molecule Specificity in Nearly Identical Cellular Environments. *Biog. Med. Chem. Lett.*, 2007, 17, 2703-5.
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Research Overview

My lab is interested in uncovering innate immune mechanisms used by the host to defend itself against bacterial pathogens and how bacterial pathogens evade host immunity to cause disease.

We utilize the intracellular bacterial pathogen *Legionella pneumophila*, causative agent of the severe pneumonia Legionnaires' disease, as our primary model. *Legionella* has evolved numerous mechanisms for modulating eukaryotic processes in order to facilitate its survival and replication within host cells. The ease with which *Legionella* can be genetically manipulated provides a powerful system for dissecting immune responses to bacteria that differ in defined virulence properties and for elucidating mechanisms of bacterial pathogenesis.

A major focus of our lab is to understand how the immune system distinguishes between virulent and avirulent bacteria and tailors appropriate antimicrobial responses. One key immune pathway involves the inflammasome, a multi-protein cytosolic complex that activates the host proteases caspase-1 and caspase-11 upon cytosolic detection of bacterial products. These caspases mediate the release of IL-1 family cytokines and other inflammatory factors critical for host defense, but overexuberant activation can lead to pathological outcomes such as septic shock. We are currently pursuing how mouse and human inflammasomes differentially respond to bacterial infection.

We are also interested in elucidating how the immune system successfully overcomes the ability of pathogens to suppress critical immune functions. We recently found that infected macrophages circumvent *Legionella*'s ability to block host translation by selectively synthesizing and releasing key cytokines. These cytokines then instruct bystander immune cells to generate an effective immune response. We are defining additional mechanisms that facilitate communication between infected and bystander cells and promote antimicrobial defense.

We also study the evolutionarily related pathogen *Coxiella burnetii*, and other bacterial pathogens, with the goal of identifying shared and unique features of innate immunity and bacterial virulence. Insight into these areas will advance our understanding of bacterial pathogenesis, how the innate immune system distinguishes between virulent and avirulent bacteria and initiates antimicrobial immunity, and will ultimately aid in the design of effective antimicrobial therapies and vaccines.

Selected Publications

- Reyes Ruiz, V.M., Ramirez, J., Naseer, N., Palacio, N.M., Siddarthan, I.J., Yan, B.M., Boyer, M.A., Pensinger, D.A., Sauer, J-D., and Shin, S.: Broad detection of bacterial type III secretion system and flagellin proteins by the human NAIP/NLRC4 inflammasome. *Proceedings of the National Academy of Sciences* 114(50): 13242-13247, 2017.
- Casson, C.N.*, Doerner, J.L.*, Copenhaver, A.M., Ramirez, J., Holmgren, A.M., Boyer, M.A., Siddarthan, I.J., Rouhanifard, S.H., Raj, A., and Shin, S.: Neutrophils and Ly6Chi monocytes collaborate in generating an optimal cytokine response that protects against pulmonary *Legionella pneumophila* infection. *PLOS Pathogens* 13(4): e1006309, 2017 Notes: *co-first authors; listed in alphabetical order.
- Holmgren, A.M., McConkey, C., and Shin, S.: Outrunning the red queen: Bystander activation as a means of outpacing pathogen subversion. *Cellular and Molecular Immunology* 14(1): 14-21, 2017.
- Bradley, W.P., Boyer, M.A., Nguyen, H.T., Birdwell, L.D., Yu, J., Ribeiro, J.M., Weiss, S.R., Zamboni, D.S., Roy, C.R., and Shin, S.: Primary role for TLR-driven TNF rather than cytosolic immune detection in restricting *Coxiella burnetii* phase II replication within mouse macrophages. *Infection and Immunity* 84(4): 998-1015, 2016.
- Copenhaver, A.M., Casson, C.N., Nguyen, H.T., Duda, M.M., and Shin, S.: IL-1R signaling enables bystander cells to overcome bacterial blockade of host protein synthesis. *Proceedings of the National Academy of Sciences* 112(24): 7557-62, 2015.
- Casson, C.N., Yu, J., Reyes, V.M., Taschuk, F.O., Yadav, A., Copenhaver, A.M., Nguyen, H.T., Collman, R.G., and Shin, S.: Human caspase-4 mediates non-canonical inflammasome activation against Gram-negative bacterial pathogens. *Proceedings of the National Academy of Sciences* 112(21): 6683-93, 2015.
- Shin, S. and Brodsky, I.E.: The inflammasome: Learning from bacterial evasion strategies. *Seminars in Immunology pii: : S1044-5323(15)00014-7*, 2015.
- Copenhaver, A.M., Casson, C.N., Nguyen, H.T., Fung, T.C., Duda, M.M., Roy, C.R., and Shin, S. : Alveolar macrophages and neutrophils are the primary reservoir for *Legionella pneumophila* and mediate cytosolic surveillance of type IV secretion. *Infection and Immunity* 82(10): 4325-36, 2014.
- Philip, N.H., Dillon, C.P., Snyder, A.G., Fitzgerald, P., Wynosky-Dolfi, M.A., Zwack, E.E., Hu, B., Fitzgerald, L., Mauldin, E.A., Copenhaver, A.M., Shin, S., Wei, L., Parker, M., Zhang, J., Oberst, A., Green, D.R., and Brodsky, I. : Caspase-8 mediates caspase-1 processing and innate immune defense in response to bacterial blockade of NF- κ B and MAPK signaling. *Proceedings of the National Academy of Sciences* 111(20): 7385-90, 2014.
- Casson, C.N., Copenhaver, A.M., Zwack, E.E., Nguyen, H.T., Strowig, T., Javdan, B., Bradley, W.P., Fung, T.C., Flavell, R.A., Brodsky, I.E.*, and Shin, S.*: Caspase-11 activation in response to bacterial secretion systems that access the host cytosol. *PLOS Pathogens* 9(6): e1003400, 2013 Notes: *co-corresponding authors.
- Casson, C.N. and Shin, S. : Inflammasome-mediated cell death in response to bacterial pathogens that access the host cytosol: lessons from *Legionella pneumophila*. *Frontiers in Cellular and Infection Microbiology* 3: 111, 2013.
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Research Overview

Life demands that proteins fold into elaborate structures to perform the overwhelming majority of biological functions. We investigate how components of the proteostasis (protein homeostasis) network enable cells to achieve successful protein folding. In particular, we seek to understand how cells prevent, reverse, or even promote the formation of diverse misfolded conformers, encompassing: prions, amyloids, fibrillar structures, amorphous aggregates and toxic soluble oligomers.

Amyloid fibers are self-templating protein conformers. They self-replicate their specific 'cross-beta' conformation at their growing ends, by converting other copies of the same protein to the 'cross-beta' amyloid form. When amyloid fibers grow and divide with high efficiency they can be infectious, and are then termed prions (Cushman et al., 2010; Shorter & Lindquist, 2005; Shorter, 2010). Cells have evolved a sophisticated machinery to alleviate such aberrant protein aggregation. For example, protein disaggregases resolve protein aggregates, molecular chaperones prevent protein aggregation, osmolytes act as chemical chaperones, and degradation systems eliminate misfolded proteins (Shorter, 2008; Vashist et al. 2010).

Nonetheless, these safeguards can be breached, especially as organisms age, and the consequences are often fatal. Prion and amyloid formation are associated with some of the most devastating neurodegenerative diseases confronting humankind, including Alzheimer's disease, Parkinson's disease, variant Creutzfeldt-Jakob disease, and Huntington's disease (Cushman et al., 2010; Jackrel & Shorter, 2011). Yet, surprisingly, it is becoming increasingly clear that prions and amyloids are not always a problem. In fact, several have been harnessed during evolution for adaptive purposes and feature in some of the most revolutionary new concepts in biology and evolution, including protein-based genetic elements, long-term memory formation, melanosome biogenesis, evolutionary capacitance and the revelation of cryptic genetic variation (Shorter & Lindquist, 2005; Watt et al., 2009; Shorter, 2010). We employ biochemistry and genetics to understand the enigmatic mechanistic interfaces that exist between protein disaggregases, molecular chaperones, small molecules and amyloid/prion fibers or other misfolded species, and how these interfaces can be manipulated to divert pathogenic and promote beneficial phenotypic trajectories. Specifically, we are taking five broad approaches:

1. Defining the structural and mechanistic basis for Hsp104 function.
2. Applying Hsp104 to disease-associated protein misfolding and aggregation.
3. Defining the metazoan disaggregase machinery.
4. Defining how small molecules modulate amyloid folding trajectories.
5. Defining the misfolding trajectories of RNA-binding proteins bearing prion-like domains in amyotrophic lateral sclerosis and other neurodegenerative disorders.

Selected Publications

- Guo, L.[^], H.J. Kim[^], H. Wang[^], J. Monaghan[°], F. Freyermuth[°], J.C. Sung[°], K. O'Donovan, C.M. Fare, Z. Diaz, N. Singh, Z.C. Zhang, M. Coughlin, E.A. Sweeny, M.E. DeSantis, M.E. Jackrel, C.B. Rodell, J.A. Burdick, O.D. King, A.D. Gitler, C. Lagier-Tourenne, U.B. Pandey, Y.M. Chook, J.P. Taylor^{*}, and J. Shorter^{*}. : Nuclear-import receptors reverse aberrant phase transitions of RNA-binding proteins with prion-like domains. *Cell* 173(3): 677-692, April 2018 Notes: [^]Co-first author. [°]Co-second author. ^{*}Co-corresponding author.
- Boeynaems, S., S. Alberti, N.L. Fawzi, T. Mittag, M. Polymenidou, F. Rousseau, J. Schymkowitz, J. Shorter, B. Wolozin, L. Van Den Bosch, P. Tompa, and M. Fuxreiter. : Protein phase separation: a new phase in cell biology. *Trends Cell Biol.* 28(6): 420-435, June 2018.
- Gates, S.N., A.L. Yokom, J. Lin, M.E. Jackrel, A.N. Rizo, N.M. Kendzersky, C.E. Buell, E.A. Sweeny, K.L. Mack, E. Chuang, M.P. Torrente, M. Su, J. Shorter, and D.R. Southworth. : Ratchet-like polypeptide translocation mechanism of the AAA+ disaggregase Hsp104. *Science* 357(6348): 273-279, July 2017.
- March, Z. M., O.D. King^{*}, and J. Shorter^{*}: Prion-like domains as epigenetic regulators, scaffolds for subcellular organization, and drivers of neurodegenerative disease. *Brain Res.* 1647: 9-18, September 2016 Notes: ^{*}Co-corresponding author.
- Sweeny, E.A., M.E. Jackrel, M.S. Go, M.A. Sochor, B.M. Razzo, M.E. DeSantis, K. Gupta, and J. Shorter^{*}: The Hsp104 N-terminal domain enables disaggregase plasticity and potentiation. *Mol. Cell* 57(5): 836–849, March 2015 Notes: ^{*}Corresponding author.
- Jackrel, M.E., M.E. DeSantis, B.A. Martinez, L.M. Castellano, R.M. Stewart, K.A. Caldwell, G.A. Caldwell, and J. Shorter^{*}: Potentiated Hsp104 variants antagonize diverse proteotoxic misfolding events. *Cell* 156: 170-182, January 2014 Notes: ^{*}Corresponding author.
- Li, Y.R.^{*}, O.D. King, J. Shorter^{*}, and A.D. Gitler^{*}.: Stress granules as crucibles of ALS pathogenesis. *J. Cell Biol.* 201: 361-372, April 2013 Notes: ^{*} Co-corresponding author.
- Kim[^], H.J., N.C.Kim[^], Y.D. Wang[^], E.A. Scarborough[^], J. Moore[^], Z. Diaz[^], K.S. MacLea, B. Freibaum, S. Li, A. Molliex, A.P. Kanagaraj, R. Carter, K.B. Boylan, A.M. Wojtas, R. Rademakers, J.L. Pinkus, S.A. Greenberg, J.Q. Trojanowski, B.J. Traynor, B.N. Smith, S. Topp, A.S. Gkazi, J. Miller, C.E. Shaw, M. Kottlors, J. Kirschner, A. Pestronk, Y.R. Li, A.F. Ford, A.D. Gitler, M. Benatar, O.D. King, V.E. Kimonis, E.D. Ross, C.C. Weihl, J. Shorter^{*}, and J.P. Taylor^{*}.: Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. *Nature* 495: 467–473, March 2013 Notes: [^]Co-first author. ^{*}Co-corresponding author.
- DeSantis, M.E., E.H. Leung, E.A. Sweeny, M.E. Jackrel, M. Cushman-Nick, A. Neuhaus-Follini, S. Vashist, M.A. Sochor, M.N. Knight and J. Shorter^{*}: Operational Plasticity Enables Hsp104 to Disaggregate Diverse Amyloid and Non-Amyloid Clients. *Cell* 151: 778-793, Nov 2012 Notes: ^{*}Corresponding author. See also Preview: Hsp104 gives clients the individual attention they need. Murray, A.N, and J.W. Kelly. *Cell.* 151: 695-697.
- Duennwald, M.L, A. Echeverria, and J. Shorter^{*}.: Small Heat Shock Proteins Potentiate Amyloid Dissolution by Protein Disaggregases from Yeast and Humans. *PLoS Biol.* 9(6): e1001346, June 2012 Notes: ^{*}Corresponding author.
- Sun, Z.[^], Z. Diaz[^], X. Fang, M.P. Hart, A. Chesi, J. Shorter^{*} and A.D. Gitler^{*}: Molecular determinants and genetic modifiers of aggregation and toxicity for the ALS disease protein FUS/TLS. *PLoS Biol.* 9(4): e1000614, April 2011 Notes: [^]Co-first author. ^{*}Co-corresponding author.

Johnson, B.S., D. Snead, J.J. Lee, J. M. McCaffery, J. Shorter* and A.D. Gitler* : TDP-43 is intrinsically aggregation-prone, and amyotrophic lateral sclerosis-linked mutations accelerate aggregation and increase toxicity. *J. Biol. Chem.* 284(30): 20329-39, July 2009 Notes: * Co-corresponding author.



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Research Overview

The principal goal of our research program is to elucidate the underlying molecular mechanisms that link fetal growth retardation to the later development of obesity and type 2 diabetes in adulthood. We currently have 3 major projects and several smaller projects. The first project focuses on the relationship between oxidative stress and β -cell dysfunction and insulin resistance. We have developed a model of fetal growth retardation in the rodent (mice and rats) which leads to the later development of diabetes and obesity in adult animals. We have established that fetal growth retardation induces progressive mitochondrial dysfunction, oxidative stress, mtDNA mutations, and electron transport defects. These defects cause abnormal β -cell function and development, and hepatic and muscle insulin resistance. Oxidative stress decreases transcription of key genes related to β -cell development, induces modifications of proteins of the Krebs cycle in the liver, and muscle. Pdx-1 is a critical transcription factor that regulates β -cell function and development. Transcription of this gene is permanently down-regulated in β -cells of IUGR rats leading to a gradual reduction in β -cell function and β -cell replication. We have determined that oxidative stress induced by uteroplacental insufficiency in IUGR fetal pancreas induces aberrant methylation and chromatin remodeling at the Pdx-1 promoter, which in turn induces transcription silencing. The focus of the second project is to determine whether the effects of an aberrant intrauterine milieu can be reversed after birth, we have designed a number of therapeutic modalities including diet modifications and antioxidant treatment. In collaboration with Dr. Doris Stoffers, we have successfully prevented the development of diabetes in IUGR rats with several of these treatments. Administration of a pancreatic β -cell trophic factor, Exendin-4, during the neonatal period dramatically prevents the development of diabetes in our model. Neonatal Exendin-4 treatment prevents the progressive reduction in β -cell mass that is observed in IUGR rats over time. Expression of Pdx-1 is restored to normal levels, and islet β -cell proliferation rates are normalized by the neonatal Exendin-4 treatment. Of major clinical significance is our finding that Exendin-4 treatment in the newborn period prevents the onset of obesity in IUGR rats. This surprising finding has stimulated a new direction for this project and we are currently determining the mechanisms by which Exendin-4 treatment reverses epigenetic modifications such as DNA methylation and histone modifications of key genes related to β -cell development. The third project is focused on the effects of obesity during pregnancy and the long-term outcome in the offspring. The specific aims of this project are to determine the window of susceptibility of the developing organism to the effects of obesity during gestation, determining whether regulation of the adipogenic pathway is altered in offspring, and defining the molecular mechanisms responsible for enhanced adipogenesis observed in offspring of obese mothers.

Selected Publications

Rashid CS, Bansal A, Simmons RA. Oxidative Stress, Intrauterine Growth Restriction, and Developmental Programming of Type 2 Diabetes. *Physiology (Bethesda)*. 1;33(5):348-359, Sept 2018.

- Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, Aagaard K, Thornburg KL, Catalano PM, Galan HL, Hay WW Jr, Frias AE, Shankar K, Simmons RA, Moses RG, Sacks DA, Loeken MR. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol*. pii: S0002-9378(18)30529-5. doi: 10.1016/j.ajog.2018.06.013. [Epub ahead of print] Jun 2018.
- Tran P, Kennedy B, Pisansky M, Won KJ, Gewirtz J, Simmons RA*, Georgieff M*. Prenatal choline supplementation diminishes early-life iron deficiency induced reprogramming of molecular networks associated with behavioral abnormalities in the adult rat hippocampus. *J Nutr*, in press, 2016.* Co-senior authors
- Tran PV, Kennedy BC, Lien YC, Simmons RA, Georgieff MK. Fetal iron deficiency induces chromatin remodeling at the *Bdnf* locus in adult rat hippocampus. *Am J Physiol Regul Integr Comp Physiol*. 308:R276-82, 2015. PMID:PMC4329464
- Susiarjo M, Xin F, Bansal A, Stefaniak M, Li C, Simmons RA*, Barolomei MS. Bisphenol A exposure disrupts metabolic health across multiple generations in the mouse. *Co-senior authors. *Endocrinology*, 2015 156: 2049-2058. PMID:PMC4430620.
- Simmons RA, Rando OJ. I'm eating for two: Parental dietary effects on offspring metabolism. *Cell*, 161:93-105, 2015. PMID:PMC4465102.
- Jaekle-Santos LJ, Li C, Doulias PT, Ischiropoulos H, Worthen GS, Simmons RA. Neutralizing Th2 inflammation in neonatal islets prevents β -cell failure in adult IUGR rats. *Diabetes*. 63:1672-84, 2014. PMID: PMC3994952.
- Sasson IE, Vitins AP, Mainigi MA, Moley KH, Simmons RA. Pre-gestational versus gestational exposure to maternal obesity differentially programs the offspring. *Diabetologia*, 58:615-624, 2015. PMID: PMC4452998
- Thompson RF, Fazzari MJ, Niu H, Barzilai N, Simmons RA*, Greally JM*: Experimental intrauterine growth restriction induces alterations in DNA methylation and gene expression in pancreatic islets of rats. *J Biol Chem* 285:15111-15118, 2010. *Co-senior authors. PMID: PMC2865297.
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Research Overview

My research is focused on complement-mediated inflammatory, autoimmune and thrombotic vasculopathy disorders. By creating gene targeted mice, we establish mouse models of human diseases to understand disease pathogenesis and to test novel anti-complement therapies. We are also interested in the interaction of complement with other innate immune pathways such as the Toll-like receptors and with the adaptive immune system. Our long term goal is to advance basic complement immunology and to help develop new therapies for complement-mediated human diseases.

Selected Publications

Song D, Mohammed I, Bhuyan R, Miwa T, Williams AL, Gullipalli D, Sato S, Song Y, Dunaief JL, Song WC. Retinal Basal Lamina Deposits in Complement fH/fP Mouse Model of Dense Deposit Disease. *Invest Ophthalmol Vis Sci.* 2;59(8):3405-3415, Jul 2018.

Ueda Yoshiyasu, Mohammed Imran, Song Delu, Gullipalli Damodar, Zhou Lin, Sato Sayaka, Wang Yuan, Gupta Shuchi, Cheng Zhongjian, Wang Hong, Bao Jialing, Mao Yingying, Brass Lawrence, Zheng X Long, Miwa Takashi, Palmer Matthew, Dunaief Joshua, Song Wen-Chao: Murine systemic thrombophilia and hemolytic uremic syndrome from a factor H point mutation. *Blood* 129(9): 1184-1196, Mar 2017.

Williams Allison Leshner, Gullipalli Damodar, Ueda Yoshiyasu, Sato Sayaka, Zhou Lin, Miwa Takashi, Tung Kenneth S, Song Wen-Chao: C5 inhibition prevents renal failure in a mouse model of lethal C3 glomerulopathy. *Kidney international* 91(6): 1386-1397, Jun 2017.

Facciabene Andrea, De Sanctis Francesco, Pierini Stefano, Reis Edimara S, Balint Klara, Facciponte John, Rueter Jens, Kagabu Masahiro, Magotti Paola, Lanitis Evripidis, DeAngelis Robert A, Buckanovich Ronald J, Song Wenchao C, Lambris John D, Coukos George: Local endothelial complement activation reverses endothelial quiescence, enabling t-cell homing, and tumor control during t-cell immunotherapy. *Oncoimmunology* 6(9): e1326442, 2017.

Song Delu, Sulewski Michael E, Wang Chenguang, Song Jiantao, Bhuyan Rupak, Sterling Jacob, Clark Esther, Song Wen-Chao, Dunaief Joshua L: Complement C5a receptor knockout has diminished light-induced microglia/macrophage retinal migration. *Molecular vision* 23: 210-218, 2017.

Bergfeld Arne, Dasari Prasad, Werner Sandra, Hughes Timothy R, Song Wen-Chao, Hortschansky Peter, Brakhage Axel A, Hünig Thomas, Zipfel Peter F, Beyersdorf Niklas: Direct Binding of the pH-Regulated

Protein 1 (Pra1) from *Candida albicans* Inhibits Cytokine Secretion by Mouse CD4(+) T Cells. *Frontiers in microbiology* 8: 844, 2017.

Song Delu, Wilson Brooks, Zhao Liangliang, Bhuyan Rupak, Bandyopadhyay Mausumi, Lyubarsky Arkady, Yu Chen, Li Yafeng, Kanu Levi, Miwa Takashi, Song Wen-Chao, Finnemann Silvia C, Rohrer Bärbel, Dunaief Joshua L: Retinal Pre-Conditioning by CD59a Knockout Protects against Light-Induced Photoreceptor Degeneration. *PloS one* 11(11): e0166348, 2016.

Ueda Yoshiyasu, Gullipalli Damodar, Song Wen-Chao: Modeling complement-driven diseases in transgenic mice: Values and limitations. *Immunobiology* 221(10): 1080-90, Oct 2016.

Wang Yuan, Miwa Takashi, Ducka-Kokalari Blerina, Redai Imre G, Sato Sayaka, Gullipalli Damodar, Zangrilli James G, Haczku Angela, Song Wen-Chao: Properdin Contributes to Allergic Airway Inflammation through Local C3a Generation. *Journal of immunology (Baltimore, Md. : 1950)* 195(3): 1171-81, Aug 2015.

Song Di, Yu Xiao-Juan, Wang Feng-Mei, Xu Bing-Ning, He Ying-Dong, Chen Qian, Wang Su-Xia, Yu Feng, Song Wen-Chao, Zhao Ming-Hui: Overactivation of Complement Alternative Pathway in Postpartum Atypical Hemolytic Uremic Syndrome Patients with Renal Involvement. *American journal of reproductive immunology (New York, N.Y. : 1989)* 74(4): 345-56, Oct 2015.

Miao Jing, Leshner Allison M, Miwa Takashi, Sato Sayaka, Gullipalli Damodar, Song Wen-Chao: Tissue-specific deletion of *Crry* from mouse proximal tubular epithelial cells increases susceptibility to renal ischemia-reperfusion injury. *Kidney international* 86(4): 726-37, Oct 2014.



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Research Overview

I have been involved with investigations in the field of thrombosis and hemostasis since joining the Brass lab at the University of Pennsylvania as a post-doctoral fellow in 2003. Since that time, the goal of my research studies has been to gain a better understanding of the mechanisms responsible for hemostasis and thrombosis, with a particular emphasis on how multiple signaling inputs present at a site of vascular injury are integrated to regulate platelet activation *in vivo*. The following is a brief summary of major ongoing projects performed in association with members of the Brass lab.

Project 1: Spatio-temporal regulation of platelet activation following vascular injury *in vivo*

We recently determined that hemostatic plugs formed following vascular injury *in vivo* are composed of discrete regions with variable degrees of platelet activation. Ongoing studies are investigating how multiple components of the platelet signaling network are integrated to produce this heterogeneous hemostatic plug architecture. To accomplish these goals, we make extensive use of multiple systems for examination of thrombosis *in vitro* and *in vivo*, including a spinning disk confocal intravital microscopy system for visualization of thrombosis in the microcirculation of mice. Intravital microscopy approaches also involve the use of established and novel fluorescent probes for visualizing various aspects of the hemostatic response *in vivo*, including fluorescently labeled antibodies, fluorescent biochemical activity sensors and genetically encoded fluorescent indicators.

Project 2: The influence of local microenvironments on hemostasis and thrombosis *in vivo*

In conjunction with the studies in Project 1, we have become interested in how local microenvironments within a platelet aggregate help to shape the movement and overall distribution of soluble plasma components that regulate platelet activation and coagulation. These studies couple *in vivo* imaging approaches measuring solute transport with *in vitro* and computational approaches to model and analyze the physical characteristics of the microenvironment between adjacent platelets as they become tightly packed in a hemostatic plug.

Project 3: Platelet function in the setting of trauma and other pathologic states

Platelet function is known to be perturbed in a number of pathologic settings and may contribute to the morbidity and mortality associated with these pathologies. One example is in the setting of trauma, where a subset of severe trauma patients develop a coagulopathic state characterized by abnormal blood clotting and excessive hemorrhage. We are using animal models to study platelet function in the setting of trauma-induced coagulopathy as part of a multi-institution consortium funded by the NHLBI (TACTIC).

Project 4: The role of junctional adhesion molecules in platelet biology

Another longstanding research project involves examination of the role of a family of cell adhesion molecules found on the surface of platelets, including ESAM and JAM-A, which are found at the tight junctions of other cell types (e.g. endothelial cells and epithelial cells). As platelets do not form tight junctions the role of these proteins in platelet biology is rather unclear, but they appear to be negative regulators of platelet plug formation in vivo as genetic deletion of these proteins in mice leads to a pro-thrombotic phenotype. Current studies are investigating the mechanisms by which this family of proteins influences platelet functions, as well as their role in platelet-leukocyte and platelet-endothelial cell crosstalk.

Selected Publications

- Shen J, Sampietro S, Wu J, Tang J, Gupta S, Matzko CN, Tang C, Yu Y, Brass LF, Zhu L, Stalker TJ. Coordination of platelet agonist signaling during the hemostatic response in vivo. *Blood Adv.* 1(27):2767-2775, Dec 2017.
- Welsh JD, Stalker TJ, Voronov R, Muthard RW, Tomaiuolo M, Diamond SL, Brass LF.: *A systems approach to hemostasis: 1. The interdependence of thrombus architecture and agonist movements in the gaps between platelets.* *Blood* 124(11): 1808-15, Sep 11 2014.
- Tomaiuolo M, Stalker TJ, Welsh JD, Diamond SL, Sinno T, Brass LF.: *A systems approach to hemostasis: 2. Computational analysis of molecular transport in the thrombus microenvironment.* *Blood* 124(11): 1816-23, Sep 11 2014.
- Stalker TJ, Welsh JD, Tomaiuolo M, Wu J, Colace TV, Diamond SL, Brass LF.: *A systems approach to hemostasis: 3. Thrombus consolidation regulates intrathrombus solute transport and local thrombin activity.* *Blood* 124(11): 1824-31, Sept 11 2014.
- Min S, Suzuki, A, Stalker, TJ, Zhao, L, Wang, Y, McKennan, C, Riese, M, Guzman, J, Zhang, S, Lian, L, Joshi, R, Meng, R, Seeholzer, SH, Choi, J, Koretzky, G, Marks, MS, Abrams, CS. : *Loss of PIKfyve in platelets causes a lysosomal disease leading to inflammation and thrombosis in mice.* *Nature Communications* 5: 4691, Sept 2 2014.
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Research Overview

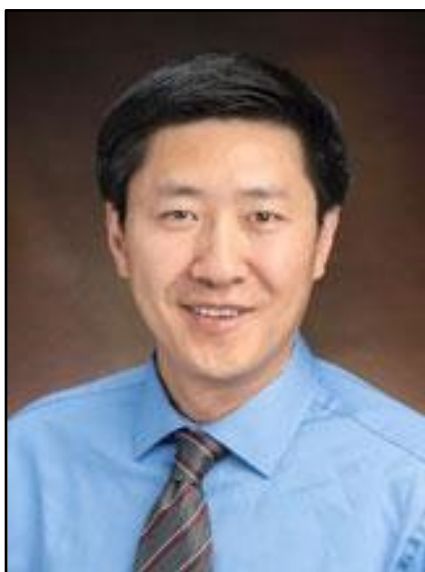
Research in our laboratory focuses on the embryonic development and adult regeneration of the endocrine pancreas, and the relationship of defects in these pathways to the pathophysiology of diabetes mellitus, a disease caused by a deficiency in the production or action of insulin. The beta cells of the endocrine pancreas are the only source of insulin production in the body- therefore the regulation of beta cell mass is pivotal to the development of diabetes and successful therapies aimed at correcting diabetes must impact beta cell growth and/or function. Further support for this focus derives from genetic studies linking monogenic forms of human diabetes to mutations in transcription factors that regulate the development of beta cell mass. A model example is the homeobox transcription factor, IPF-1/PDX-1, that plays critical roles in embryonic pancreas development and in differentiated islet beta cell function in the adult endocrine pancreas. Using cutting edge molecular methods, yeast two hybrid libraries, transgenic and knock-out mice, cDNA microarray, chromatin immunoprecipitation, human genetics, and genomic and proteomic approaches, our current projects include:

1. Characterization of a novel PDX C-terminus Interacting Factor, PCIF1, identified in a yeast two-hybrid screen. PCIF1 is a novel nuclear factor that recruits Pdx1 into a cullin3 based E3 ubiquitin ligase for polyubiquitination and proteasomal degradation. Biochemical, molecular, in vivo and human genetics approaches are being applied to elucidate the role of this novel regulatory molecule.
2. Examining the molecular mechanisms by which the incretin hormone GLP-1 stimulates expansion of beta cell mass, with a particular emphasis on signal transduction and the identification of molecular mechanisms whereby GLP-1 promotes beta cell regeneration and regulates PDX expression.
3. Elucidating molecular mechanisms underlying islet compensation for diet-induced insulin resistance.
4. Identifying targets of Pdx1, Pbx and Meis homeodomain factors in the pancreatic β cell.

Selected Publications

Juliana CA, Yang J, Cannon CE, Good AL, Haemmerle MW, Stoffers DA. A PDX1-ATF transcriptional complex governs β cell survival during stress. *Mol Metab.* pii: S2212-8778(18)30517-9. doi: 10.1016/j.molmet.2018.07.007. [Epub ahead of print] Aug 2018.

- Loyd C, Liu Y, Kim T, Holleman C, Galloway J, Bethea M, Ediger BN, Swain TA, Tang Y, Stoffers DA, Rowe GC, Young M, Steele C, Habegger KM, Hunter, CS : LDB1 Regulates Energy Homeostasis During Diet-Induced Obesity *Endocrinology* 158 (5): 1289-1297, May 2017
- Remsberg JR, Ediger BN, Ho WY, Damle M, Li Z, Teng C, Lanzillotta C, Stoffers DA, and Lazar MA: Deletion of Histone Deacetylase 3 in Adult Beta Cells Improves Glucose Tolerance via Increased Insulin Secretion *Molecular Metabolism* 6(1): 30-37, Nov 2017.
- Rozo AV, Babu DA, Suen PA, Groff DN, Seeley RJ, Simmons RA, Seale P, Ahima RS and Stoffers DA: Neonatal GLP1R activation limits adult adiposity by durably altering hypothalamic architecture. *Molecular Metabolism* 6(7): 748-759, May 2017.
- Melissa A. Burmeister, Jennifer E. Ayala, Hannah Smouse, Adriana LandivarRocha, Jacob D. Brown, Daniel J. Drucker, Doris A. Stoffers, Darleen A. Sandoval, Randy J. Seeley and Julio E. Ayala : The Hypothalamic Glucagon-Like Peptide-1 (GLP-1) Receptor (GLP-1R) is Sufficient but Not Necessary for the Regulation of Energy Balance and Glucose Homeostasis in Mice. *Diabetes* 66(2): 372-384, Feb 2017.
- Stanescu DE, Yu R, Won KJ, Stoffers DA: Single cell transcriptomic profiling of mouse pancreatic progenitors *Physiological Genomics* 49(2): 105-114, Feb 2017.
- Juliana CA, Yang J, Rozo AV, Good A, Groff DN, Wang SZ, Green MR and Stoffers DA: ATF5 regulates β cell survival during stress *Proceedings of the National Academy of Sciences USA* 114(6): 1341-1346, Feb 2017.
- Ediger BN, Hee-Woong L, Juliana CA, Groff DN, Williams L, Dominguez G, Liu JH, Taylor B, Walp E, Kamesawaran V, Yang J, Liu C, Hunter C, Kaestner KH, Naji A, Li C, Sander M, Stein R, Sussel L, Won KJ, May CS, Stoffers DA: LIM-Domain-Binding 1 maintains the terminally-differentiated state of pancreatic β -cells. *Journal of Clinical Investigation* 127(1): 215-229, Jan 2017.
- Melissa Burmeister, Jacob Brown, Jennifer Ayala, Doris Stoffers, Darleen Sandoval, Randy Seeley, and Julio Ayala: The Glucagon-Like Peptide-1 Receptor in the Ventromedial Hypothalamus Reduces Short-Term Food Intake in Male Mice by Regulating Nutrient Sensor Activity. *American Journal of Physiology* in press 2017.
- Peter Kropp, Jennifer Dunn, Bethany Carboneau, Doris Stoffers, and Maureen Gannon : Cooperative function of Pdx1 and Oc1 in multipotent pancreatic progenitors impacts postnatal islet maturation and adaptability. *American Journal of Physiology-Endocrinology and Metabolism* under review 2017.
- Henley K@, Stanescu D@, Kropp PA, Wright CVE, Won KJ, Stoffers DA*, Gannon M* *,@equal contribution: Threshold-dependent cooperative function of Pdx1 and Oc1 within pancreatic progenitors establishes competency for later β -cell maturation. *Cell Reports* 15(12): 2637-50, Jun 2016.
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Research Overview

Gene expression variation plays a major role in driving phenotypic variation. Our lab is interested in Systems Biology of gene regulation. The advent of various bulk and single-cell omics technologies increasingly allows us to interrogate the status of a cell's components and to determine how, when, and where these molecules interact with each other. By combining omics experiments and computational modeling, we are studying gene regulatory networks in several model systems.

I. Model gene regulatory networks in development and disease

We are studying gene regulatory networks controlling development and differentiation of hematopoietic stem cells, T cells, and oncogenesis. Specific projects include:

1. Identify and characterize keys transcription factors and enhancers that control cell/tissue-specific gene expression.
2. Understand how 3-dimensional genome organization controls cell/tissue-specific gene expression.
3. Understand how mutations in regulatory DNA sequences contribute to pathogenesis.

II. Discover molecular networks as biomarkers for human diseases

Molecular networks are increasingly serving as tools to unravel the basis of human diseases. We are developing network-based approaches to identifying disease-related sub-networks that can serve as biomarkers for the diagnosis and prognosis of diseases and as candidates for novel therapeutics.

Selected Publications

Gao L, Uzun Y, Gao P, He B, Ma X, Wang J, Han S, Tan K.: Identifying noncoding risk variants using disease-relevant gene regulatory networks Nature Communications Feb 2018.

Tober J, Maijenburg MW, Y, Gao L, Hadland BK, Gao P, Clarke R, Bernstein I, Keller G, Tan K*, Speck NA*.: Maturation of hematopoietic stem cells from prehematopoietic stem cells is accompanied by up-regulation of PD-L1. Journal of Experimental Medicine Dec 2017.

- Yu W, He B, Tan K: Identifying topologically associating domains and subdomains by Gaussian mixture model and proportion test. *Nature Communications* 8(1): 535, Sept 2017.
- Li Y, Gao L, Hadland B, Tan K*, Speck NA*: CD27 marks murine embryonic hematopoietic stem cells and type II pre-hematopoietic stem cells. *Blood* 130(3): 372-376, July 2017.
- He B, Xing S, Chen C, Gao P, Teng L, Shan Q, Gullicksrud JA, Martin MD, Yu S, Harty JT, Badovinac VP, Tan K*, Xue HH*: CD8⁺ T cells utilize highly dynamic enhancer repertoires and regulatory circuitry in response to infections. *Immunity* 45(6): 1341-1354, Dec 2016.
- He, B and Tan K: Understanding transcriptional regulatory networks using computational models. *Current Opinion in Genes & Development* 37: 101-108, Mar 2016.
- Gao Z, Chen C, He B, Tan K* and Lu C*: A microfluidic device for profiling genome-wide histone modifications using 100 cells. *Nature Methods* 12(10): 959-962, Oct 2015.
- Cai X, Gao L, Teng L, Ge J, Oo Z, Kumar A, Gilliland GD, Mason PJ, Tan K and Speck NA.: Runx1 deficiency decreases ribosome biogenesis and confers stress resistance to hematopoietic stem and progenitor Cells. *Cell Stem Cell* 17(2): 165-77, Aug 2015.
- Teng L, He B, Wang J, and Tan K. : 4DGenome: a comprehensive database of chromatin interactions. *Bioinformatics* 31(15): 2560-4, Aug 2015.
- Ma X, Gao Long, Lee CF, Gao P, Karamanlidis G, Garcia-Menendez L, Tian R and Tan K: Revealing pathway dynamics in heart diseases by analyzing multiple differential networks. *PLoS Computational Biology* 11(6): e1004332, Jun 2015.
- He B, Chen C, Teng L, and Tan K.: Global view of enhancer-promoter interactome in human cells. *Proc Natl Acad Sci* 111(21): E2191-9, May 2014.
- Steinke FC, Yu S, Zhou X, He B, Yang W, Zhou B, Kawamoto H, Zhu J, Tan K and Xue HH.: TCF-1 and LEF-1 act upstream of Th-POK to promote the CD4(+) T cell fate and interact with Runx3 to silence Cd4 in CD8(+) T cells. *Nature Immunology* 15(7): 646-56, Jul 2014.
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Research Overview

Broadly, the lab studies the development and physiology of the mammalian brain. One goal is to define the systems that contribute to specific behaviors, and to understand the mechanisms that underlie these behaviors. Such knowledge may ultimately permit the prevention and treatment of mental illness. Gene-targeting allows the analysis of specific genetic alterations in the context of the whole organism. The ability to add, delete or modify genes is particularly useful in the analysis of complex organ systems such as the brain, where half of all genes are thought to be uniquely expressed.

The lab focuses on the adrenergic nervous system in which norepinephrine (NE) and epinephrine are the classic neurotransmitters. By genetically eliminating the biosynthetic enzyme for NE, dopamine beta-hydroxylase (DBH), mutant mice (Dbh^{-/-}) that completely lack NE and epinephrine were created. These mice are conditional mutants in that NE can be restored to the adrenergic terminals by supplying a synthetic amino acid precursor of NE, L-DOPS. The lab is pursuing several fundamental observations that resulted from the creation of these mutant mice. These include the roles of NE in learning and memory, as well as the neuronal physiology and signaling that underlie these effects. They also include the role of NE in the effects of stress. For each of these, potentially important interactions with other transmitters and hormones is also being explored. Finally, Dr. Thomas is pursuing several novel genetic approaches for producing complementary models to the Dbh^{-/-} mice toward a more complete understanding of CNS adrenergic function.

Selected Publications

Ross JA, Reyes BAS, Thomas SA, Van Bockstaele EJ. Localization of endogenous amyloid- β to the coeruleo-cortical pathway: consequences of noradrenergic depletion. *Brain Struct Funct*, 223(1):267-284, Jan 2018.

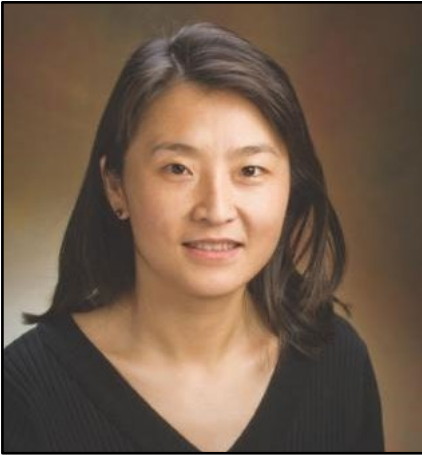
Young, MB and Thomas, SA: M1-muscarinic Receptors Promote Fear Memory Consolidation via Phospholipase C and the M-current. *J Neurosci* 34: 1570-1578, 2014.

Zhang L, Ouyang M, Ganellin CR and Thomas, SA: The slow afterhyperpolarization: a target of beta1-adrenergic signaling in hippocampus-dependent memory retrieval. *J Neurosci* 33: 5006-16, 2013.

Ouyang, Y., Young, M.B., Lestini, M.M., Schutsky, K. and Thomas, S.A.: Redundant catecholamine signaling consolidates fear memory via phospholipase C. *J Neurosci* 32: 1932-41, 2012.

Schutsky, K., Ouyang, M., Castelino, C. B., Zhang, L. and Thomas, S. A.: Stress and glucocorticoids impair memory retrieval via β 2-adrenergic, Gi/o-coupled suppression of cAMP signaling. *J Neurosci* 31: 14172-14181, 2011.

- Schutsky, K., Ouyang, M. and Thomas, S. A.: Xamoterol impairs hippocampus-dependent emotional memory retrieval via Gi/o-coupled β 2-adrenergic signaling. *Learning & Memory* 18: 598-604, 2011.
- Murchison, C. F., Schutsky, K., Jin, S.-H. and Thomas, S. A.: Norepinephrine and β 1-adrenergic signaling facilitate activation of hippocampal CA1 pyramidal neurons during contextual memory retrieval. *Neuroscience* 181: 109-116, 2011.
- Ouyang M, Zhang L, Zhu JJ, Schwede F, Thomas SA: Epac is required for hippocampus-dependent memory retrieval. *Proc Natl Acad Sci USA* 105: 11993-11997, 2008.
- Ouyang M and Thomas SA: A requirement for memory retrieval during and after long-term extinction learning. *Proc Natl Acad Sci USA* 102: 9347-9352, 2005.
- Murchison CF, Zhang X-Y, Zhang W-P, Ouyang M, Lee A, Thomas S: A distinct role for norepinephrine in memory retrieval. *Cell* 117: 131-143, 2004.
- Cryan JF, O'Leary OF, Jin S-H, Friedland JC, Ouyang M, Hirsch BR, Page ME, Dalvi A, Lucki, I Thomas SA: Norepinephrine-deficient mice lack responses to antidepressant drugs, including SSRIs. *Proc Natl Acad Sci USA* 101: 8186-8191, 2004.
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Research Overview

Our lab focuses on molecular hematology-oncology with an emphasis on studying signal transduction in normal blood cell development and hematological malignancies. We use genetically-engineered mouse models, bone marrow transplantation, tissue culture cells, gene transcriptional profiling, protein complex purification and mass spectrometric identification, coupled with extensive usage of molecular, cellular, and biochemical technologies.

Hundreds of billions of blood cells have to be replenished everyday. Cytokines and cytokine receptors play important roles in blood cell formation, a process known as hematopoiesis. The amplitude and duration of cytokine receptor signaling is a highly regulated process that is crucial for cytokine-governed hematopoiesis. Dysregulation of these complex signaling networks can predispose to myeloproliferative diseases and myeloid leukemia.

We previously identified the adaptor protein, Lnk, as a novel negative regulator of cytokine receptor signaling. Lnk deficiency in mice results in an enhanced proliferative capacity of hematopoietic stem cells (HSCs) and progenitor cells of multiple lineages. Lnk loss-of-function leads to hyper-sensitivity to thrombopoietin (Tpo) and erythropoietin (Epo), which regulate platelet and red blood cell formation, respectively. Our results also implicate a new mechanism for rapidly downmodulating cytokine signaling: Lnk negatively regulates cytokine receptor induced JAK2 activity in a phosphorylation-dependent manner. We are interested in:

1. Elucidating molecular mechanisms of Lnk regulatory functions in cytokine receptor signaling
2. Understanding both normal and oncogenic cytokine receptor signaling processes that control hematopoietic stem and progenitor cell numbers and development in vivo
3. Undertaking studies to identify novel signaling components in the receptor/JAK2 signaling complex that lead to oncogenic transformation, as JAK2 is the central kinase governing many cytokine receptor signaling, and has been found mutated in some patients with myeloproliferative diseases.
4. Understanding ubiquitination and de-ubiquitination in regulation of cytokine signaling and hematopoietic stem cell expansion.
5. Investigating cytokine signaling in Acute Lymphoblastic Leukemia.

Selected Publications

- Lv Kaosheng, Jiang Jing, Donaghy Ryan, Riling Christopher R, Cheng Ying, Chandra Vemika, Rozenova Krasimira, An Wei, Mohapatra Bhopal C, Goetz Benjamin T, Pillai Vinodh, Han Xu, Todd Emily A, Jeschke Grace R, Langdon Wallace Y, Kumar Suresh, Hexner Elizabeth O, Band Hamid, Tong Wei: CBL family E3 ubiquitin ligases control JAK2 ubiquitination and stability in hematopoietic stem cells and myeloid malignancies. *Genes & development* 31(10): 1007-1023, May 2017.
- Giani Felix C, Fiorini Claudia, Wakabayashi Aoi, Ludwig Leif S, Salem Rany M, Jobaliya Chintan D, Regan Stephanie N, Ulirsch Jacob C, Liang Ge, Steinberg-Shemer Orna, Guo Michael H, Esko Tõnu, Tong Wei, Brugnara Carlo, Hirschhorn Joel N, Weiss Mitchell J, Zon Leonard I, Chou Stella T, French Deborah L, Musunuru Kiran, Sankaran Vijay G: Targeted Application of Human Genetic Variation Can Improve Red Blood Cell Production from Stem Cells. *Cell stem cell* 18(1): 73-8, Jan 2016.
- Cheng Ying, Chikwava Kudakwashe, Wu Chao, Zhang Haibing, Bhagat Anchit, Pei Dehua, Choi John K, Tong Wei: LNK/SH2B3 regulates IL-7 receptor signaling in normal and malignant B-progenitors. *The Journal of clinical investigation* 126(4): 1267-81, Apr 2016.
- Jiang Qinqin, Paramasivam Manikandan, Aressy Bernadette, Wu Junmin, Bellani Marina, Tong Wei, Seidman Michael M, Greenberg Roger A: MERIT40 cooperates with BRCA2 to resolve DNA interstrand cross-links. *Genes & development* 29(18): 1955-68, Sep 2015.
- Rozenova Krasimira, Jiang Jing, Donaghy Ryan, Aressy Bernadette, Greenberg Roger A, Tong Wei: MERIT40 deficiency expands hematopoietic stem cell pools by regulating thrombopoietin receptor signaling. *Blood* 125(11): 1730-8, Mar 2015.
- Jiang Jing, Balcerek Joanna, Rozenova Krasimira, Cheng Ying, Bersenev Alexey, Wu Chao, Song Yiwen, Tong Wei: 14-3-3 regulates the LNK/JAK2 pathway in mouse hematopoietic stem and progenitor cells. *The Journal of clinical investigation* 122(6): 2079-91, Jun 2012.
- Bersenev Alexey, Rozenova Krasimira, Balcerek Joanna, Jiang Jing, Wu Chao, Tong Wei: Lnk deficiency partially mitigates hematopoietic stem cell aging. *Aging cell* 11(6): 949-59, Dec 2012.
- Bersenev Alexey, Wu Chao, Balcerek Joanna, Jing Jiang, Kundu Mondira, Blobel Gerd A, Chikwava Kudakwashe R, Tong Wei: Lnk constrains myeloproliferative diseases in mice. *The Journal of clinical investigation* 120(6): 2058-69, Jun 2010.
- Huang Jian, Zhang Yi, Bersenev Alexey, O'Brien W Timothy, Tong Wei, Emerson Stephen G, Klein Peter S: Pivotal role for glycogen synthase kinase-3 in hematopoietic stem cell homeostasis in mice. *The Journal of clinical investigation* 119(12): 3519-29, Dec 2009.
- Scott Linda M, Tong Wei, Levine Ross L, Scott Mike A, Beer Philip A, Stratton Michael R, Futreal P Andrew, Erber Wendy N, McMullin Mary Frances, Harrison Claire N, Warren Alan J, Gilliland D Gary, Lodish Harvey F, Green Anthony R: JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *The New England journal of medicine* 356(5): 459-68, Feb 2007.
- Bersenev Alexey, Wu Chao, Balcerek Joanna, Tong Wei: Lnk controls mouse hematopoietic stem cell self-renewal and quiescence through direct interactions with JAK2. *The Journal of clinical investigation* 118(8): 2832-44, Aug 2008.
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Research Overview

Developing targeted imaging and therapeutic agents designed to improve the detection and treatment of cancer. Specific research interests include (i) developing new nanoformulations that are capable of carrying extremely high payloads of drugs, radiosensitizing agents, and/or contrast agents; (ii) investigating new targeting strategies that maximize specificity and sensitivity; and (iii) developing new bioconjugation techniques that enable the highly efficient, site-specific labeling of antibodies and other targeting ligands and that allow for the rapid production of bispecific antibodies.

Recent Publications

Thawani Jayesh P, Amirshaghghi Ahmad, Yan Lesan, Stein Joel M, Liu Jessica, Tsourkas Andrew: Photoacoustic-Guided Surgery with Indocyanine Green-Coated Superparamagnetic Iron Oxide Nanoparticle Clusters. *Small* (Weinheim an der Bergstrasse, Germany) 13(37), Oct 2017.

Kartha Sonia, Yan Lesan, Weisshaar Christine L, Ita Meagan E, Shuvaev Vladimir V, Muzykantov Vladimir R, Tsourkas Andrew, Winkelstein Beth A, Cheng Zhiliang: Superoxide Dismutase-Loaded Porous Polymersomes as Highly Efficient Antioxidants for Treating Neuropathic Pain. *Advanced healthcare materials* 6(17), Sep 2017.

Yan Lesan, Miller Joann, Yuan Min, Liu Jessica F, Busch Theresa M, Tsourkas Andrew, Cheng Zhiliang: Improved Photodynamic Therapy Efficacy of Protoporphyrin IX-Loaded Polymeric Micelles Using Erlotinib Pretreatment. *Biomacromolecules* 18(6): 1836-1844, Jun 2017.

Wang Hejia Henry, Altun Burcin, Nwe Kido, Tsourkas Andrew: Proximity-Based Sortase-Mediated Ligation. *Angewandte Chemie (International ed. in English)* 56(19): 5349-5352, May 2017.

Karunamuni Roshan, Naha Pratap C, Lau Kristen C, Al-Zaki Ajlan, Popov Anatoliy V, Delikatny Edward J, Tsourkas Andrew, Cormode David P, Maidment Andrew D A: Development of silica-encapsulated silver nanoparticles as contrast agents intended for dual-energy mammography. *European radiology* 26(9): 3301-9, Sep 2016.

Nwe Kido, Huang Ching-Hui, Qu Feini, Warden-Rothman Robert, Zhang Clare Y, Mauck Robert L, Tsourkas Andrew: Cationic gadolinium chelate for magnetic resonance imaging of cartilaginous defects. *Contrast media & molecular imaging* 11(3): 229-35, May 2016.

Sun Lova, Joh Daniel Y, Al-Zaki Ajlan, Stangl Melissa, Murty Surya, Davis James J, Baumann Brian C, Alonso-Basanta Michelle, Kaol Gary D, Tsourkas Andrew, Dorsey Jay F: Theranostic Application of Mixed Gold and

Superparamagnetic Iron Oxide Nanoparticle Micelles in Glioblastoma Multiforme. *Journal of biomedical nanotechnology* 12(2): 347-56, Feb 2016.

Al Zaki Aylan, Hui James Z, Higbee Elizabeth, Tsourkas Andrew: Biodistribution, Clearance, and Toxicology of Polymeric Micelles Loaded with 0.9 or 5 nm Gold Nanoparticles. *Journal of biomedical nanotechnology* 11(10): 1836-46, Oct 2015.

Hui James Z, Tamsen Shereen, Song Yang, Tsourkas Andrew: LASIC: Light Activated Site-Specific Conjugation of Native IgGs. *Bioconjugate chemistry* 26(8): 1456-60, Aug 2015.

McQuade Casey, Al Zaki Aylan, Desai Yaanik, Vido Michael, Sakhuja Timothy, Cheng Zhiliang, Hickey Robert J, Joh Daniel, Park So-Jung, Kao Gary, Dorsey Jay F, Tsourkas Andrew: A multifunctional nanoplatfrom for imaging, radiotherapy, and the prediction of therapeutic response. *Small (Weinheim an der Bergstrasse, Germany)* 11(7): 834-43, Feb 2015.



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Research Overview

The long-term goal of my lab is to determine the mechanisms that transform adult stem cells into the cell of origin for many types of cancer. In particular, we study the epigenetic mechanisms that drive tumor initiation and progression upon loss of major tumor suppressor genes such as the Rb genes family.

This family, which includes Rb, p130 and p107, plays a central role in the regulation of cell cycle activity by sequestering E2F transcription factors. Cellular exposure to mitotic stimuli leads to the functional inactivation of Rb family proteins. Consequently, E2F factors are released and transactivate a large set of genes that collectively promote the progression through cell cycle. Genetic and epigenetic events targeting various components of the Rb pathway have been identified in the vast majority of cancers. A common and important consequence of these events is the permanent inactivation of Rb family, therefore establishing Rb family genes as major tumor suppressor genes. However, besides aberrant proliferation, the mechanisms that drive tumorigenesis upon Rb family inactivation remain mostly unknown.

To determine these mechanisms and identify critical drivers of tumorigenesis for translational purposes, we have generated new mouse models that recapitulate the acute Rb family inactivation observed in cancer and have chosen hematopoiesis and the liver as experimental systems. Our recent data (Cell Stem Cell 2008, JEM 2011 & 2013) have demonstrated that stem cells, in contrast to terminally differentiated cells, are particularly sensitive to Rb family loss. Indeed, Rb family deficient stem cells rapidly exhibit a complex phenotype including proliferation, biased differentiation and tumorigenesis. Complementary molecular approaches have started to unravel new and surprising means for E2F factors, including the recruitment of complex epigenetic mechanisms, to activate important oncogenic features that drive tumor progression.

Our current research effort aims at identifying these epigenetic mechanisms and developing compound-based strategies to inactivate them and impair tumor development. To this end, we are developing several mouse models and using a combination of bioinformatic analysis, as well as in vitro, ex vivo and in vivo approaches.

Selected Publications

Eunsun Kim, Ying Cheng, Elisabeth Bolton-Gillespie, Xiongwei Cai, Connie Ma, Amy Tarangelo, Linh Le, Madhumita Jambhekar, Pichai Raman, Katharina E Hayer, Gerald Wertheim, Nancy A. Speck, Wei Tong and Patrick Viatour: Rb family proteins enforce the homeostasis of quiescent hematopoietic stem cells by repressing Socs3 expression. *Journal of Experimental Medicine*. 214(7): 1901-12, Jul 2017.

- Amy Tarangelo, Nathanael Lo, Rebecca Teng, Eunsun Kim, Linh Le, Deborah Watson, Emma E. Furth, Pichai Raman, Ursula Ehmer and Patrick Viatour: Recruitment of Pontin/Reptin by E2f1 amplifies E2f transcriptional response during cancer progression. *Nature Communications*. Nature Publishing Group (eds.). 2015.
- Garfin P, Min D, Bryson J, Serwold T, Edris B, Blackburn CC, Richie E, Weinberg K, Manley N, Sage J and Viatour P: Inactivation of the RB family prevents thymus involution and promotes thymic function by direct control of Foxn1 expression. *Journal of Experimental Medicine* 210 (6): 1087-97, 2013.
- Viatour P and Sage J: Newly identified aspects of tumor suppression by Rb. *Disease Models and Mechanisms* 4 (5), 2011.
- Viatour P, Saddic L, Elhmer U, Lin C, Dorrell C, Andersen JB, Schaffer B, Ostermeier A, Vogel H, Sylvester KG, Thorgeirsson SS, Grompe M, and Sage J.: Notch signaling suppresses hepatocellular carcinoma initiated from mouse adult liver progenitors following inactivation of the Rb family. *Journal of Experimental Medicine* 208 (10): 1963-76, 2011.
- Viatour P, Somerville TC, Venkatasubrahmanyam S, Kogan S, McLaughlin ME, Weissman IL, Butte AJ, Passegue E and Sage J.: Hematopoietic stem cell quiescence is maintained by compound contributions of the retinoblastoma gene family. *Cell Stem Cell* 3(4): 416-428, 2008.
- Kotake Y, Cao R, Viatour P, Sage J, Zhang Y, Xiong Y.: pRb family proteins are required for H3K27 trimethylation and Polycomb repression complexes binding to and silencing p16INK4alpha tumor suppressor gene. *Genes and Development* 21(1): 49-54, 2007.
- Viatour P, Merville MP, Bours V and Chariot A.: Phosphorylation of NF- κ B/I κ B proteins: implications in cancer and inflammation. *Trends in Biochemical Sciences* 30(1): 43-52, 2005.
- Viatour P, Dejardin E, Warnier M, Lair F, Claudio E, Bureau F, Marine JC, Merville MP, Maurer U, Green DR, Piette J, Siebenlist U, Bours V and Chariot A.: GSK3-mediated BCL-3 phosphorylation modulates its degradation and its oncogenicity. *Molecular Cell* 16(1): 35-45, 2004.
- Viatour P, Bentires-Alj M, Chariot A, Deregowski V, de Leval L, Merville MP and Bours V.: NF-kappaB2/p100 induces Bcl-2 expression. *Leukemia* 17(7): 1349-1356, 2003.
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Research Overview

The central aim in my lab is to understand the genetic, biological, and evolutionary basis of metabolic and cardiovascular phenotypes in human populations. To build this understanding, the lab constructs computational and statistical tools grounded in principles of population biology and quantitative genetics. These tools are then applied to genetic data collected across thousands of whole human genomes.

My research has answered population genetic questions about recent demographic and selective events in human populations, and work to develop new statistics to identify selective pressures is ongoing. Recent work in the lab has focused on statistical models which capture variability in the rate of mutation in the human genome.

I have an active interest in mapping risk alleles for common diseases, particularly type-2 diabetes and coronary heart disease, but perhaps more importantly, to identify the causal variant, gene, and mechanism that influences risk to these diseases from existing non-coding associations identified by genome-wide association studies.

I continue to utilize the framework of Mendelian Randomization, to perform causal inference studies between genetically-heritable biomarkers and complex diseases. Work in the lab is toward applications, but also development of novel methodologies.

In the coming years, the lab activities will focus on several key areas of interest, which includes:

- Developing statistical models to capture variability in the rate of mutation in human genomes, with application to identifying de novo mutations and rare variation related to human disease
- Computational methods and functional characterization of the causal variants and genes related to non-coding associations for type 2 diabetes and heart disease
- Developing informational and statistical tools which interrogate human genetic association data together with other sources of 'omics data to construct credibly actionable information on pathways responsible for disease susceptibility
- Population genetic methods to identify loci in the human genome which are targets of natural selective pressures, and to further identify the causal variants and genes responsible
- Genomics in Arachnids to understand the structure and function of spider silk genes

Selected Publications

Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart AF, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buyschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. : Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *The Lancet* 380(9841): 572-580, Aug 2012.

Aggarwala V and Voight BF: An expanded sequence context model broadly explains variability in polymorphism levels across the human genome. *Nature Genetics* 48(4): 349–355, Apr 2016 Notes: doi: 10.1038/ng.3511.

Babb PL, Lahens NF, Correa-Garhwal SM, Nicholson DN, Kim EJ, Hogenesch JB, Kuntner M, Higgins L, Hayashi CY, Agnarsson I, Voight BF.: The *Nephila clavipes* genome highlights the diversity of spider silk genes and their complex expression. *Nature Genetics* 49(6): 895-903, June 2017.

Siewert KM and Voight BF: Detecting Long-term Balancing Selection using Allele Frequency Correlation. *Mol. Biol. Evol* Jul 2017 Notes: doi: doi/10.1093/molbev/msx209/3988103.

Voight BF, Kudaravalli S, Wen X, Pritchard JK: A map of recent positive selection in the human genome. *PLoS Biology* 4(3): e72, Mar 2006.

Aikens RC, Zhao W, Saleheen D, Reilly MP, Epstein SE, Tikkanen E, Salomaa V, Voight BF.: Systolic Blood Pressure and Risk of Type 2 Diabetes: a Mendelian Randomization Study. *Diabetes* 66(2): 543-550, Feb 2017.

Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, Young R, Shah N, Samuel M, Sheikh N, Mucksavage ML, Shah O, Li J, Morley M, Laser A, Mallick NH, Zaman KS, Ishaq M, Rasheed SZ, Memon FU, Ahmed F, Hanif B, Lakhani MS, Fahim M, Ishaq M, Shardha NK, Ahmed N, Mahmood K, Iqbal W, Akhtar S, Raheel R, O'Donnell CJ, Hengstenberg C, März W, Kathiresan S, Samani N, Goel A, Hopewell JC, Chambers J, Cheng YC, Sharma P, Yang Q, Rosand J, Boncoraglio GB, Kazmi SU, Hakonarson H, Köttgen A, Kalogeropoulos A, Frossard P, Kamal A, Dichgans M, Cappola T, Reilly MP, Danesh J, Rader DJ, Voight BF, Saleheen D.: Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study. *J Am Coll Cardiol* 67(4): 407-16, Feb 2016.

Aggarwala V, Ganguly A, Voight BF: De novo mutational profile in RB1 clarified using a mutation rate modeling algorithm. *BMC Genomics* 18(1): 155, Feb 2017.

Voight BF, Scott LJ, Steinthorsdottir V, Morris AP, Dina C, Welch RP, Zeggini E, Huth C, Aulchenko YS, Thorleifsson G, McCulloch LJ, Ferreira T, Grallert H, Amin N, Wu G, Willer CJ, Raychaudhuri S, McCarroll SA, Langenberg C, Hofmann OM, Dupuis J, Qi L, Segrè AV, van Hoek M, Navarro P, Ardlie K, Balkau B, Benediktsson R, Bennett AJ, Blagieva R, Boerwinkle E, Bonnycastle LL, Bengtsson Boström K, Bravenboer B, Bumpstead S, Burt NP, Charpentier G, Chines PS, Cornelis M, Couper DJ, Crawford G, Doney AS, Elliott KS, Elliott AL, Erdos MR, Fox CS, Franklin CS, Ganser M, Gieger C, Grarup N, Green T, Griffin S, Groves

CJ, Guiducci C, Hadjadj S, Hassanali N, Herder C, Isomaa B, Jackson AU, Johnson PR, Jørgensen T, Kao WH, Klopp N, Kong A, Kraft P, Kuusisto J, Lauritzen T, Li M, Lieverse A, Lindgren CM, Lyssenko V, Marre M, Meitinger T, Midthjell K, Morken MA, Narisu N, Nilsson P, Owen KR, Payne F, Perry JR, Petersen AK, Platou C, Proença C, Prokopenko I, Rathmann W, Rayner NW, Robertson NR, Rocheleau G, Roden M, Sampson MJ, Saxena R, Shields BM, Shrader P, Sigurdsson G, Sparsø T, Strassburger K, Stringham HM, Sun Q, Swift AJ, Thorand B, Tichet J, Tuomi T, van Dam RM, van Haeften TW, van Herpt T, van Vliet-Ostaptchouk JV, Walters GB, Weedon MN, Wijmenga C, Witteman J, Bergman RN, Cauchi S, Collins FS, Gloyn AL, Gyllenstein U, Hansen T, Hide WA, Hitman GA, Hofman A, Hunter DJ, Hveem K, Laakso M, Mohlke KL, Morris AD, Palmer CN, Pramstaller PP, Rudan I, Sijbrands E, Stein LD, Tuomilehto J, Uitterlinden A, Walker M, Wareham NJ, Watanabe RM, Abecasis GR, Boehm BO, Campbell H, Daly MJ, Hattersley AT, Hu FB, Meigs JB, Pankow JS, Pedersen O, Wichmann HE, Barroso I, Florez JC, Frayling TM, Groop L, Sladek R, Thorsteinsdottir U, Wilson JF, Illig T, Froguel P, van Duijn CM, Stefansson K, Altshuler D, Boehnke M, McCarthy MI; MAGIC investigators; GIANT Consortium.: Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. *Nature Genetics* 42(7): 579-89, Jul 2010.

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S: Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science (New York, N.Y.)* 316(5829): 1331-6, Jun 2007.



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Research Overview

Our lab is conducting exciting research on the genetics of liver repopulation and hepatocellular carcinoma (HCC). We have developed two highly innovative *in vivo* genetic screening paradigms to elucidate genetic pathways involved in carcinogenesis and liver repopulation in the setting of toxic injury. We aim to discover pathways that lead to drug sensitivity and resistance in HCC. One of our assays involves CRISPR activation screening *in vivo* in the liver, the first-ever use of this type of screening in live mice.

Selected Publications

Shoshkes-Carmel M, Wang YJ, Wangensteen KJ, Tóth B, Kondo A, Massassa EE, Itzkovitz S, Kaestner KH. Subepithelial telocytes are an important source of Wnts that supports intestinal crypts. *Nature*. 2018 May 2. [Epub ahead of print]

Mahmud N, Wangensteen KJ. Endoscopic Band Ligation to Treat a Massive Hemorrhoidal Hemorrhage Following a Transrectal Ultrasound-Guided Prostate Biopsy. *Ann Coloproctol*. 2018 Feb;34(1):47-51.

Wang AW*, Wangensteen KJ*, Wang YJ, Zahm AM, Moss NG, Erez N, Kaestner KH. TRAP-seq identifies cystine/glutamate antiporter as a driver of recovery from liver injury. *The Journal of clinical investigation*. 2018 Mar. [Epub ahead of print]. * co-first authors.

Wang Min-Jun, Chen Fei, Liu Qing-Gui, Liu Chang-Cheng, Yao Hao, Yu Bing, Zhang Hai-Bin, Yan He-Xin, Ye Yibiao, Chen Tao, Wangensteen Kirk J, Wang Xin, Hu Yi-Ping, He Zhi-Ying. Insulin-like growth factor 2 is a key mitogen driving liver repopulation in mice. *Cell death & disease*. 9(2): 26, Jan 2018.

Wangensteen KJ, Wang YJ, Dou Z, Wang AW, Mosleh-Shirazi E, Horlbeck MA, Gilbert LA, Weissman JS, Berger SL, Kaestner KH. Combinatorial genetics in liver repopulation and carcinogenesis with a novel *in vivo* CRISPR activation platform. *Hepatology*. 2017 Nov 1. [Epub ahead of print]

Dou Z, Ghosh K, Vizioli MG, Zhu J, Sen P, Wangensteen KJ, Simithy J, Lan Y, Lin Y, Zhou Z, Capell BC, Xu C, Xu M, Kieckhaefer JE, Jiang T, Shoshkes-Carmel M, Tanim KMAA, Barber GN, Seykora JT, Millar SE, Kaestner KH, Garcia BA, Adams PD, Berger SL. Cytoplasmic chromatin triggers inflammation in senescence and cancer. *Nature*. 2017 Oct 19;550(7676):402-406.

Shin S*, Wangensteen KJ*, Teta-Bissett M*, Wang YJ, Mosleh-Shirazi E, Buza EL, Greenbaum LE, Kaestner KH. Genetic lineage tracing analysis of the cell of origin of hepatotoxin-induced liver tumors in mice. *Hepatology*. 2016 Oct;64(4):1163-1177. * co-first authors

De Luca-Johnson J, Wangensteen KJ, Hanson J, Krawitt E, Wilcox R. Natural History of Patients Presenting with Autoimmune Hepatitis and Coincident Nonalcoholic Fatty Liver Disease. *Dig Dis Sci*. 2016 Sep;61(9):2710-20.



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Research Overview

We are interested in the neural and homeostatic mechanisms controlling REM sleep and the functional role of this brain state in emotional memories and behaviors. We study REM sleep and its functional roles in the mouse model. Our lab employs a wide range of methods including optogenetics, in vivo electrophysiology, calcium imaging, viral tracing and quantitative modeling to disentangle the neural and homeostatic mechanisms controlling REM sleep. We further seek to develop a circuit-based understanding of how REM sleep affects emotional behaviors in health and disease.

Selected Publications

- Chung S, Weber F, Zhong P, Tan CL, Nguyen TN, Beier KT, Hörmann N, Chang WC, Zhang Z, Do JP, Yao S: Identification of preoptic sleep neurons using retrograde labelling and gene profiling. *Nature* May 2017.
- Weber F, Dan Y : Circuit-based interrogation of sleep control. *Nature* 538: 51-59, Oct 2016.
- Weber F, Chung S, Beier KT, Xu M, Luo L, Dan Y: Control of REM sleep by ventral medulla GABAergic neurons. *Nature* 526(7573): 435-8, Oct 2015.
- Weber F, Machens CK: Sensory Coding, Efficiency. *Encyclopedia of Computational Neuroscience*. D. Jaeger, R. Jung (eds.). Springer Press, 2015.
- Joesch M, Weber F, Eichner H, Borst A: Functional specialization of parallel motion detection circuits in the fly. *The Journal of Neuroscience* 33(3): 902-5, Jan 2013 Notes: Joesch M and Weber F are co-first authors.
- Weber F, Machens CK, Borst A: Disentangling the functional consequences of the connectivity between optic-flow processing neurons. *Nature Neuroscience* 15(3): 441-8, Mar 2012.
- Borst A, Weber F: Neural action fields for optic flow based navigation: a simulation study of the fly lobula plate network. *PloS one* 6(1): e16303, Jan 2011.
- Weber F, Machens CK, Borst A: Spatiotemporal response properties of optic-flow processing neurons. *Neuron* 67(4): 629-42, Aug 2010 Notes: Evaluated by F1000, <http://f1000.com/prime/5133958>.
- Weber F, Eichner H, Cuntz H, Borst A: Eigenanalysis of a Neural Network for Optic Flow Processing. *New Journal of Physics* 10: 015013, 2008.





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Research Overview

Dr. Weiner's research focus is in the area of Molecular Immunology. His group has focused extensively on the development of gene-based vaccines, immune therapies and molecular interventions for the treatment of human and animal disease. His laboratory is one of the founders of the field of DNA vaccines, and importantly, was the first to move DNA vaccines to human clinical studies establishing their initial safety and immunogenicity opening up this area for clinical development. First study in HIV immune therapy conducted in 1995, and first immune therapy for cancer (CTCL) in 1995. The first DNA trial in normal healthy HIV+ patients occurred in 1997.

Other clinical trials of DNA, conducted in collaboration with the HIV Vaccine Trials Network (HVTN) are: HVTN 070, study of DNA vaccine against HIB including cytokine genes, and HVTN 080, study of DNA vaccine for HIV by adaptive electroporation with IL12. In 2009, collaboration with a biotechnology company resulted in VGX 3100, a study of a DNA vaccine for cervical cancer and immune therapy.

His group was the first to show that a DNA based approach could impact an HIV model challenge in nonhuman primates. Based on these accomplishments Dr. Weiner contributed to the initial 'Points to Consider' guidance document for the FDA on moving gene based approaches through the Clinic. He has created many new technologies for treatment of human disease and has been awarded more than 50 patents on his laboratory's work. His lab is instrumental in the recent resurgence of interest in the DNA vaccine field due to the lab and collaborators developing new vectors and delivery approaches that improved their immune potency in humans. He is very active in teaching and training of students and fellows and junior faculty. He chairs the popular Gene Therapy and Vaccines Program at the University of Pennsylvania, and co directs the Tumor Virology Program of the Abramson Cancer Center at the University of Pennsylvania.

Selected Publications

Duperret EK, Liu S, Paik MJ, Trautz A, Stoltz R, Liu X, Ze K, Perales-Puchalt A, Reed C, Yan J, Xu X, Weiner DB. A designer cross-reactive DNA immunotherapeutic vaccine that targets multiple MAGE-A family members simultaneously for cancer therapy. *Clin Cancer Res.* pii: clincanres.1013.2018. doi: 10.1158/1078-0432.CCR-18-1013. [Epub ahead of print] Sep 2018.

Morrow Matthew P, Yan Jian, Pankhong Panyupa, Shedlock Devon J, Lewis Mark G, Talbott Kendra, Toporovski Roberta, Khan Amir S, Sardesai Niranjana Y, Weiner David B: *IL-28B/IFN-lambda3 Drives Granzyme B Loading and Significantly Increases CTL Killing Activity in Macaques.* *Molecular therapy : the journal of the American Society of Gene Therapy* 18(9): 1714-23, Sep 2010.

Morrow Matthew P, Yan Jian, Pankhong Panyupa, Ferraro Bernadette, Lewis Mark G, Khan Amir S, Sardesai Niranjana Y, Weiner David B: *Unique Th1/Th2 Phenotypes Induced During Priming and Memory Phases Using IL-12 or IL-28B Vaccine Adjuvants in rhesus macaques.* *Clinical and vaccine immunology : CVI* Aug 2010.

Hirao Lauren A, Wu Ling, Satishchandran Abhishek, Khan Amir S, Draghia-Akli Ruxandra, Finnefrock Adam C, Bett Andrew J, Betts Michael R, Casimiro Danilo R, Sardesai Niranjana Y, Kim J Joseph, Shiver John W, Weiner David B: *Comparative analysis of immune responses induced by vaccination with SIV antigens by recombinant Ad5 vector or plasmid DNA in rhesus macaques*. *Molecular therapy : the journal of the American Society of Gene Therapy* 18(8): 1568-76, Aug 2010.

Shedlock Devon J, Talbott Kendra T, Morrow Matthew P, Ferraro Bernadette, Hokey David A, Muthumani Karupiah, Weiner David B: *Ki-67 staining for determination of rhesus macaque T cell proliferative responses ex vivo*. *Cytometry. Part A : the journal of the International Society for Analytical Cytology* 77(3): 275-84, Mar 2010.

Muthumani Karupiah, Lambert Vance M, Kawalekar Omkar, Heller Richard, Kim J Joseph, Weiner David B, Ugen Kenneth E: *Anti-cancer activity of the HIV accessory molecule viral protein R (Vpr): Delivery as a DNA expression plasmid or biologically active peptides*. *Vaccine* 28(8): 2005-10, Feb 2010.



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Research Overview

The Weljie Lab is located in the Department of Systems Pharmacology and Translational Therapeutics within the Perelman School of Medicine at the University of Pennsylvania. Our lab is at the forefront of metabolomics technologies to examine biological problems in a translational medicine context, particularly related to sleep and circadian rhythms.

Metabolomics is a growing sub-field of systems biology centered on the study of small biological molecules in biological fluids and tissues. Recent research suggests that analysis of metabolite concentrations in living systems is useful in disease diagnosis, prognosis, and predicting drug efficacy in a personalized medicine context.

There is an intrinsic link between metabolism and function of the innate circadian clock system in numerous organisms and disease states, but the exact mechanism by which the clock controls mammalian metabolism is poorly understood. Our work seeks to fill this knowledge gap along with a particular emphasis on understanding the relationship of the clock with cancer and environmental health.

Selected Publications

Tambellini Nicolas P, Zarembek Vanina, Krishnaiah Saikumari, Turner Raymond J, Weljie Aalim M: Primary Metabolism and Medium-Chain Fatty Acid Alterations Precede Long-Chain Fatty Acid Changes Impacting Neutral Lipid Metabolism in Response to an Anticancer Lysophosphatidylcholine Analogue in Yeast. *Journal of proteome research* 16(10): 3741-3752, Oct 2017.

Sengupta Arjun, Rhoades Seth D, Kim Eun Ji, Nayak Soumyashant, Grant Gregory R, Meerlo Peter, Weljie Aalim M: Sleep restriction induced energy, methylation and lipogenesis metabolic switches in rat liver. *The international journal of biochemistry & cell biology* Aug 2017.

Sivanand Sharanya, Rhoades Seth, Jiang Qinqin, Lee Joyce V, Benci Joseph, Zhang Jingwen, Yuan Salina, Viney Isabella, Zhao Steven, Carrer Alessandro, Bennett Michael J, Minn Andy J, Weljie Aalim M, Greenberg Roger A, Wellen Kathryn E: Nuclear Acetyl-CoA Production by ACLY Promotes Homologous Recombination. *Molecular cell* 67(2): 252-265.e6, Jul 2017.

Banoei Mohammad M, Vogel Hans J, Weljie Aalim M, Kumar Anand, Yende Sachin, Angus Derek C, Winston Brent W: Plasma metabolomics for the diagnosis and prognosis of H1N1 influenza pneumonia. *Critical care (London, England)* 21(1): 97, Apr 2017.

Lu Danny, Weljie Aalim, de Leon Alexander R, McConnell Yarrow, Bathe Oliver F, Kopciuk Karen: Performance of variable selection methods using stability-based selection. *BMC research notes* 10(1): 143, Apr 2017.

- Krishnaiah Saikumari Y, Wu Gang, Altman Brian J, Grove Jacqueline, Rhoades Seth D, Coldren Faith, Venkataraman Anand, Olarerin-George Anthony O, Francey Lauren J, Mukherjee Sarmistha, Girish Saiveda, Selby Christopher P, Cal Sibel, Er Ubeydullah, Sianati Bahareh, Sengupta Arjun, Anafi Ron C, Kavakli I Halil, Sancar Aziz, Baur Joseph A, Dang Chi V, Hogenesch John B, Weljie Aalim M: Clock Regulation of Metabolites Reveals Coupling between Transcription and Metabolism. *Cell metabolism* 25(4): 961-974.e4, Apr 2017.
- Rhoades Seth D, Sengupta Arjun, Weljie Aalim M: Time is ripe: maturation of metabolomics in chronobiology. *Current opinion in biotechnology* 43: 70-76, Feb 2017.
- Vysochan Anna, Sengupta Arjun, Weljie Aalim M, Alwine James C, Yu Yongjun: ACSS2-mediated acetyl-CoA synthesis from acetate is necessary for human cytomegalovirus infection. *Proceedings of the National Academy of Sciences of the United States of America* Feb 2017.
- McConnell Yarrow J, Farshidfar Farshad, Weljie Aalim M, Kopciuk Karen A, Dixon Elijah, Ball Chad G, Sutherland Francis R, Vogel Hans J, Bathe Oliver F: Distinguishing Benign from Malignant Pancreatic and Periampullary Lesions Using Combined Use of ¹H-NMR Spectroscopy and Gas Chromatography-Mass Spectrometry. *Metabolites* 7(1), Jan 2017.
- Kim Dongyeop, Sengupta Arjun, Niepa Tagbo H R, Lee Byung-Hoo, Weljie Aalim, Freitas-Blanco Veronica S, Murata Ramiro M, Stebe Kathleen J, Lee Daeyeon, Koo Hyun: *Candida albicans* stimulates *Streptococcus mutans* microcolony development via cross-kingdom biofilm-derived metabolites. *Scientific reports* 7: 41332, Jan 2017.
- Sarfaraz M Omair, Myers Robert P, Coffin Carla S, Gao Zu-Hua, Shaheen Abdel Aziz M, Crotty Pam M, Zhang Ping, Vogel Hans J, Weljie Aalim M: A quantitative metabolomics profiling approach for the noninvasive assessment of liver histology in patients with chronic hepatitis C. *Clinical and translational medicine* 5(1): 33, Dec 2016.
- Zhao Steven, Torres AnnMarie, Henry Ryan A, Trefely Sophie, Wallace Martina, Lee Joyce V, Carrer Alessandro, Sengupta Arjun, Campbell Sydney L, Kuo Yin-Ming, Frey Alexander J, Meurs Noah, Viola John M, Blair Ian A, Weljie Aalim M, Metallo Christian M, Snyder Nathaniel W, Andrews Andrew J, Wellen Kathryn E: ATP-Citrate Lyase Controls a Glucose-to-Acetate Metabolic Switch. *Cell reports* 17(4): 1037-1052, Oct 2016.
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Research Overview

My research focuses on the mechanism of hepatic fibrosis. Liver fibrosis results from the deposition of excess, abnormal extracellular matrix by myofibroblasts derived from non-fibrogenic cells that undergo “activation” in the context of chronic liver injury. Fibrosis in the bile duct is a similar matrix-driven process, although the identity of the myofibroblast populations and the chronic vs. acute nature of the injury are not known.

We are investigating the mechanisms of fibrosis in three ways: a) by studying the matrix, mechanical, and soluble factors that influence fibrosis, including the activation of myofibroblast precursor populations; b) by identifying new fibrogenic cell populations and new means of studying previously identified cells; and c) by applying the results of our experiments with isolated cells to whole animal models and to the study of human diseases, including hepatocellular carcinoma and biliary fibrosis.

We have demonstrated in rat models of fibrosis that increased liver stiffness precedes matrix deposition and that fibrosis and liver stiffness are not linearly related. The early increases in liver stiffness are important because hepatic stellate cells and portal fibroblasts, the major myofibroblast precursors of the liver, require increased stiffness to become fibrogenic. Our recent work has examined liver mechanics in more detail, and we have attempted to determine the components of the liver responsible for various mechanical properties. We have found that livers strain soften and compression stiffen, in contrast to biopolymers like collagen. Our work suggests that proteoglycans and other matrix components as well as cell-matrix interactions are the reason for these mechanical properties. Our theory collaborators have developed a new constitutive model for the tissue that is in good agreement with our data.

This work led to an ongoing project examining the mechanics of the cirrhotic liver and their impact on the development of hepatocellular carcinoma (HCC). Using a variety of matrices, animal models, and human and animal cells, we are studying the impact of various mechanical properties on liver cell behavior with the goal of understanding the remarkable propensity of HCC to develop in a highly mechanically abnormal environment.

We have not studied liver mechanics in isolation, but also study various matrix components, including fibronectin splice variants and proteoglycans, and are examining their effects on liver cell function, fibrosis, and liver mechanics.

Human model diseases of interest to our studies of the mechanism of fibrosis include biliary atresia. We are part of an international group that has recently identified a plant toxin that causes biliary atresia. We have developed model mammalian cell systems to study its mechanism of action and are testing structurally similar compounds in an attempt to identify critical structural groups, which may lead us to compounds of relevance to

humans. Additionally, as part of a general interest in biliary fibrosis, we are studying potential myofibroblast precursor populations in the extrahepatic bile duct, the impact of acute vs. chronic cholangiocyte injury, mechanisms of liver fibrosis post bile duct obstruction, and differences between intra- and extra-hepatic cholangiocytes.

Overall, our goal is to develop a unified and comprehensive model of liver fibrosis that incorporates multiple cell types, soluble and secreted factors, matrix proteins, and local and regional mechanical factors.

Selected Publications

Muir AB, Dods K, Henry SJ, Benitez AJ, Lee D, Whelan KA, DeMarshall M, Hammer DA, Falk G, Wells RG, Spergel J, Nakagawa H, Wang ML: Eosinophilic esophagitis associated chemical and mechanical microenvironment shapes esophageal fibroblast behavior. *J Pediatr Gastroenterol Nutr* 63(2): 200-9, Aug 2016.

Waisbourd-Zinman O, Koh H, Tsai S, Lavrut P-M, Dang C, Zhao X, Pack M, Cave J, Hawes M, Koo KA, Porter JR, Wells RG: The toxin bilitresone causes mouse extrahepatic cholangiocyte damage and fibrosis via decreased glutathione and SOX17. *Hepatology* 64(3): 880-93, May 2016.

Koo K, Waisbourd-Zinman O, Wells R, Pack M, Porter JR: Reactivity of Bilitresone, a Natural Biliary Toxin, with Glutathione, Histamine and Amino Acids. *Chemical Research in Toxicology* 29(2): 142-9, Feb 2016.

Maryna Perepelyuk, LiKang Chin, Xuan Cao, Anne van Oosten, Vivek B. Shenoy, Paul A. Janmey, Rebecca G. Wells: Normal and Fibrotic Rat Livers Demonstrate Shear Strain Softening and Compression Stiffening: a Model for Soft Tissue Mechanics. *PLOS One* 11(1): e0146588, Jan 2016.

Steven Caliari, Maryna Perepelyuk, Brian Cosgrove, Shannon Tsai, Gi Yun Lee, Robert Mauck, Rebecca Wells, and Jason Burdick: Stiffening hydrogels for investigating the dynamics of hepatic stellate cell mechanotransduction during myofibroblast activation. *Scientific Reports* 6: 21387, Jan 2016.

Bridget Sackey-Aboagye, Abby L. Olsen, Sarmistha M. Mukherjee, Alexander Ventriglia, Yasuyuki Yokosaki, Linda E. Greenbaum, Gi Yun Lee, Hani Naga and Rebecca G. Wells : Fibronectin extra domain A promotes liver sinusoid repair following hepatectomy *PLOS One* in press, 2016.

Caliari SR, Perepelyuk M, Soulas EM, Lee GY, Wells RG, Burdick JA: Gradually softening hydrogels for modeling hepatic stellate cell behavior during fibrosis regression. *Integrative Biology* in press 2016.

Zhao X, Lorent K, Wilkins B, Marchione DM, Gillespie K, Waisbourd-Zinman O, So J, Koo KA, Shin D, Porter JR, Wells RG, Blair I, Pack M: Glutathione antioxidant pathway activity and reserve determine toxicity and specificity of the biliary toxin bilitresone in zebrafish. *Hepatology* in press 2016.

Koo K, Lorent K, Gong W, Windsor P, Whittaker S, Pack M, Wells RG, Porter J: Bilitresone, A Reactive Natural Toxin from *Dysphania glomulifera* and *D. littoralis*: Discovery of the Toxic Moiety 1,2-Diaryl-2-Propenone. *Chemical Research in Toxicology* 28(8): 1519-1521, Aug 2015.

Iheda-Stansbury K, Ames J, Chokshi M, Aiad N, Sanyal S, Kawabata KC, Levental I, Sundararaghavan HG, Burdick JA, Janmey P, Miyazono K, Wells RG, Jones PL: Role played by Prx1-dependent extracellular matrix properties in vascular smooth muscle development in the embryonic lungs. *Pulmonary Circulation* 5(2): 382-397, Jun 2015.



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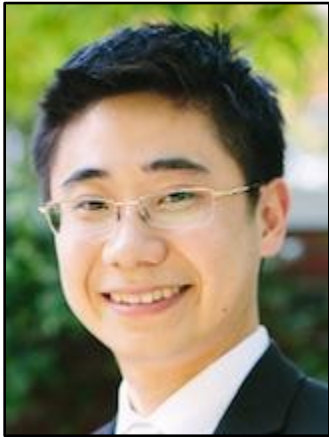
Research Overview

1. Biosynthetic control and molecular genetics of major acute phase proteins
2. Mechanisms and mediators of inflammation
3. Inherited defects of folate metabolism and their role in hyper-homocysteinemia, cardiovascular disease, neural tube defects, and other pathological conditions
4. Pharmacogenetics of commonly prescribed drugs that target, or interact with, components controlling homocysteine and folate metabolism

Selected Publications

- Bagley SJ, Vitale S, Zhang S, Aggarwal C, Evans TL, Alley EW, Cohen RB, Langer CJ, Blair IA, Vachani A, Whitehead AS. Pretreatment Red Blood Cell Total Folate Concentration Is Associated With Response to Pemetrexed in Stage IV Nonsquamous Non-Small-cell Lung Cancer. *Clin Lung Cancer*. 18(2):e143-e149. Mar 2017.
- Summers CM, Mitchell LE, Stanislawski-Sachadyn A, Baido SF, Blair IA, Von Feldt JM, Whitehead AS. Genetic and lifestyle variables associated with homocysteine concentrations and the distribution of folate derivatives in healthy premenopausal women. *Birth Defects Res A Clin Mol Teratol*. 2010 Jun 11. [Epub ahead of print]
- Hammons AL, Summers CM, Woodside JV, McNulty H, Strain JJ, Young IS, Murray L, Boreham CA, Scott JM, Mitchell LE, Whitehead AS. Folate/homocysteine phenotypes and MTHFR 677C>T genotypes are associated with serum levels of monocyte chemoattractant protein-1. *Clin Immunol*. 2009 Oct;133(1):132-7.
- Edgar KS, Woodside JV, Skidmore P, Cardwell C, Farell K, McKinley MC, Young IS, Whitehead AS, Gey KF, Yarnell JW, Evans A. Thiol and cardiovascular risk factor status in a male northern Irish population. *Int J Vitam Nutr Res*. 2008 Jul-Sep;78(4-5):208-16.
- Lu ZY, Jensen LE, Huang Y, Kealey C, Blair IA, Whitehead AS. The up-regulation of monocyte chemoattractant protein-1 (MCP-1) in Ea.hy 926 endothelial cells under long-term low folate stress is mediated by the p38 MAPK pathway. *Atherosclerosis*. 2009 Jul;205(1):48-54.
- Lu ZY, Morales M, Khartulyari S, Mei M, Murphy KM, Stanislawski-Sachadyn A, Summers CM, Huang Y, Von Feldt JM, Blair IA, Mitchell LE, Whitehead AS. Genetic and biochemical determinants of serum concentrations of monocyte chemoattractant protein-1, a potential neural tube defect risk factor. *Birth Defects Res A Clin Mol Teratol*. 2008 Oct;82(10):736-41.

Gibson A, Woodside JV, Young IS, Sharpe PC, Mercer C, Patterson CC, McKinley MC, Kluijtmans LA, Whitehead AS, Evans A. Alcohol increases homocysteine and reduces B vitamin concentration in healthy male volunteers--a randomized, crossover intervention study. *QJM*. 2008 Nov;101(11):881-7.



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Research Overview

DNA cytosine methylation (5-methylcytosine) is an evolutionarily conserved epigenetic mark and has a profound impact on transcription, development and genome stability. Historically, 5-methylcytosine (5mC) is considered as a highly stable chemical modification that is mainly required for long-term epigenetic memory. The recent discovery that ten-eleven translocation (TET) proteins can iteratively oxidize 5mC in the mammalian genome represents a paradigm shift in our understanding of how 5mC may be enzymatically reversed. It also raises the possibility that three oxidized 5mC bases generated by TET may act as a new class of epigenetic modifications.

Interestingly, key epigenetic enzymes such as TET family of DNA deoxygenase and JmjC-domain-containing histone demethylase directly utilize oxygen and some major metabolites as their cofactors to modify epigenetic marks on DNA or histone, supporting the notion that cells in multicellular organisms can rapidly adapt to changing environmental inputs or metabolic states by dynamically modifying their epigenome and gene expression programs.

Our laboratory uses high-throughput sequencing technologies, bioinformatics, mammalian genetic models, as well as synthetic biology tools to investigate the mechanisms by which proteins that write, read and erase DNA and histone modifications contribute to mammalian development and relevant human diseases. To achieve this goal, we are also interested in developing new genomic sequencing and programmable epigenome-modifying methods to precisely map and manipulate these DNA modifications in the complex mammalian genome.

Selected Publications

Emily Schutsky, Jamie DeNizio, Peng Hu, Monica Yun Liu, Christopher Nabel, Emily Fabyanic, Young Hwang, Frederic Bushman, Hao Wu ‡, Rahul Kohli ‡ (‡, co-corresponding): Nondestructive, base-resolution sequencing of 5-hydroxymethylcytosine using a DNA deaminase. *Nature Biotechnology* 2018 (In press).

Peng Hu*, Jian Liu*, Juanjuan Zhao*, Benjamin Wilkins, Katherine Lupino, Hao Wu ‡, Liming Pei ‡ (‡, co-corresponding): Single-nucleus transcriptomic survey of cell diversity and functional maturation in the postnatal mammalian hearts. *Genes & Development* 2018 (in press).

- Peng Hu*, Emily Fabyanic*, Deborah Y. Kwon, Sheng Tang, Zhaolan Zhou, Hao Wu: Dissecting Cell-Type Composition and Activity-Dependent Transcriptional State in Mammalian Brains by Massively Parallel Single-Nucleus RNA-Seq. *Molecular Cell* 68(5):1006-1015, Dec 2017.
- Hao Wu, Xiaoji Wu, Yi Zhang: Base-resolution profiling of active DNA demethylation using MAB-seq and caMAB-seq. *Nature Protocol* 11(6): 1081-1100, Jun 2016.
- Hao Wu, Yi Zhang: Charting oxidized methylcytosines at base resolution. *Nature Structural & Molecular Biology* 22(9): 656-661, Sep 2015.
- Hao Wu, Yi Zhang: Reversing DNA methylation: mechanisms, genomics, and biological functions. *Cell* 156(1-2): 45-68, Jan 2014.
- Hao Wu*, Xiaoji Wu*, Li Shen, Yi Zhang: Single-base resolution analysis of active DNA demethylation using methylase-assisted bisulfite sequencing. *Nature Biotechnology* 32(12): 1231-1240, Dec 2014.
- Soh Boon-Seng, Wu Hao, Chien Kenneth R: Cardiac regenerative medicine 2.0. *Nature biotechnology* 31(3): 209-11, Mar 2013.
- Shen Li*, Wu Hao*, Diep Dinh, Yamaguchi Shinpei, D'Alessio Ana C, Fung Ho-Lim, Zhang Kun, Zhang Yi: Genome-wide analysis reveals TET- and TDG-dependent 5-methylcytosine oxidation dynamics. *Cell* 153(3): 692-706, Apr 2013.
- Xu Huansheng, Yi B Alexander, Wu Hao, Bock Christoph, Gu Hongcang, Lui Kathy O, Park Joo-Hye C, Shao Ying, Riley Alyssa K, Domian Ibrahim J, Hu Erding, Willette Robert, Lepore John, Meissner Alexander, Wang Zhong, Chien Kenneth R: Highly efficient derivation of ventricular cardiomyocytes from induced pluripotent stem cells with a distinct epigenetic signature. *Cell research* 22(1): 142-54, Jan 2012.
- Wu Hao, Zhang Yi: Early embryos reprogram DNA methylation in two steps. *Cell stem cell* 10(5): 487-9, May 2012.
- Wu Hao, D'Alessio Ana C, Ito Shinsuke, Xia Kai, Wang Zhibin, Cui Kairong, Zhao Keji, Sun Yi Eve, Zhang Yi: Dual functions of Tet1 in transcriptional regulation in mouse embryonic stem cells. *Nature* 473(7347): 389-93, May 2011.
- Wu Hao, Zhang Yi: Tet1 and 5-hydroxymethylation: a genome-wide view in mouse embryonic stem cells. *Cell cycle (Georgetown, Tex.)* 10(15): 2428-36, Aug 2011.
- Tao Jifang*, Wu Hao*, Lin Quan, Wei Weizheng, Lu Xiao-Hong, Cattle Jeffrey P, Ao Yan, Olsen Richard W, Yang X William, Mody Istvan, Sofroniew Michael V, Sun Yi E: Deletion of astroglial Dicer causes non-cell-autonomous neuronal dysfunction and degeneration. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 31(22): 8306-19, Jun 2011.
- Wu Hao, Zhang Yi: Mechanisms and functions of Tet protein-mediated 5-methylcytosine oxidation. *Genes & development* 25(23): 2436-52, Dec 2011.
- Wu Hao, D'Alessio Ana C, Ito Shinsuke, Wang Zhibin, Cui Kairong, Zhao Keji, Sun Yi Eve, Zhang Yi: Genome-wide analysis of 5-hydroxymethylcytosine distribution reveals its dual function in transcriptional regulation in mouse embryonic stem cells. *Genes & development* 25(7): 679-84, Apr 2011.
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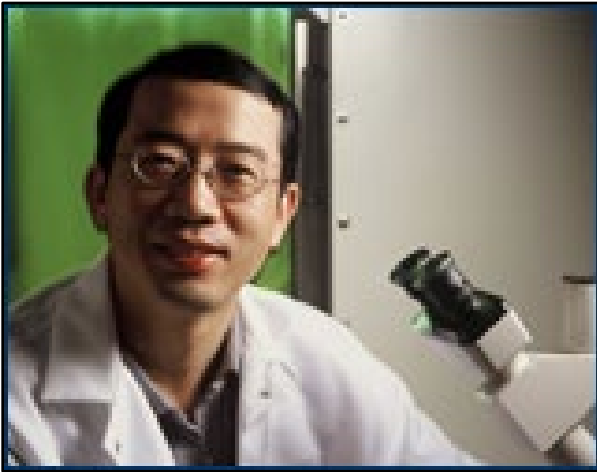
Research Overview

The research programs in the Wu laboratory focus on the mutualistic interactions between the gut microbiota and the host with a particular focus on metabolism. Growing evidence suggests that diet impacts upon both the structure and function of the gut microbiota that, in turn, influences the host in fundamental ways. Current areas of investigation include the effect of diet on the composition of the gut microbiota and its subsequent effect on host metabolism related to nitrogen balance as well as its impact on metabolic pathways in the intestinal epithelium, principally fatty acid oxidation. Through a UH3 roadmap initiate grant, he is helping to direct a project investigating the impact of diet on the composition of the gut microbiome and its relationship to therapeutic responses associated with the treatment of patients with Crohn's disease using an elemental diet. Finally, Dr. Wu is leading a multidisciplinary group of investigators using phosphorescent nanoprobe technology to examine the dynamic oxygen equilibrium between the host and the gut microbiota at the intestinal mucosal interface.

Selected Publications

- Ni J, Shen TCD, Chen EZ, Bittinger K, Bailey A, Roggiani M, Sirota-Madi A, Friedman ES, Chau L, Lin A, Nissim I, Scott J, Lauder A, Hoffman C, Rivas G, Albenberg L, Baldassano RN, Braun J, Xavier RJ, Clish CB, Yudkoff M, Li H, Goulian M, Bushman FD, Lewis JD, Wu GD.: A Role for Bacterial Urease in Crohn's Disease and Gut Dysbiosis. *Science Translational Medicine* 2017.
- Shen TC, Chehoud C, Ni J, Hsu E, Chen YY, Bailey A, Laughlin A, Bittinger K, Bushman FD, Wu GD: Dietary Regulation of the Gut Microbiota Engineered by a Minimal Defined Bacterial Consortium. *PLoS One* 11: e0155620, May 2016.
- Sartor RB, Wu GD: Roles for Intestinal Bacteria, Viruses, and Fungi in Pathogenesis of Inflammatory Bowel Diseases and Therapeutic Approaches. *Gastroenterology* 2016.
- Yang Y, Owyang C, Wu GD: East Meets West: The Increasing Incidence of Inflammatory Bowel Disease in Asia as a Paradigm for Environmental Effects on the Pathogenesis of Immune-Mediated Disease. *Gastroenterology* 2016.
- Lewis JD, Chen EZ, Baldassano RN, Otley AR, Griffiths AM, Lee D, Bittinger K, Bailey A, Friedman ES, Hoffmann C, Albenberg L, Sinha R, Compher C, Gilroy E, Nessel L, Grant A, Chehoud C, Li H, Wu GD, Bushman FD.: Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's Disease. *Cell Host Microbe* 18(4): 489-500, October 2015.
- Kelsen J, Bittinger K, Pauly-Hubbard H, Posivak L, Grunberg S, Baldassano R, Lewis JD, Wu GD, Bushman FD: Alterations of the subgingival microbiota in pediatric Crohn's disease studied longitudinally in discovery and validation cohorts. *Inflammatory Bowel Disease* Epub ahead of print, August 2015.

- Lee D, Baldassano RN, Otley AR, Albenberg L, Griffiths AM, Compher C, Chen EZ, Li H, Gilroy E, Nessel L, Grant A, Chehoud C, Bushman FD, Wu GD, Lewis JD: Comparative effectiveness of nutritional and biological therapy in North American children with active Crohn's Disease. *Inflammatory Bowel Disease* 21(8): 1786-93, August 2015.
- Chehoud C, Albenberg LG, Judge C, Hoffmann C, Grunberg S, Bittinger K, Baldassano RN, Lewis JD, Bushman FD, Wu GD: Fungal signature in the gut microbiota of pediatric patients with inflammatory bowel disease. *Inflammatory bowel diseases* 21(8): 1948-56, August 2015.
- Shen TC, Albenberg L, Bittinger K, Chehoud C, Chen YY, Judge CA, Chau L, Ni J, Sheng M, Lin A, Wilkins BJ, Buza EL, Lewis JD, Daikhin Y, Nissim I, Yudkoff M, Bushman FD, Wu GD: Engineering the gut microbiota to treat hyperammonemia. *Journal of Clinical Investigation* 125(7): 2841-50, July 2015.
- Bryson AL, Hwang Y, Sherrill-Mix S, Wu GD, Lewis JD, Black L, Clark TA, Bushman FD: Covalent modification of bacteriophage T4 DNA inhibits CRISPR-Cas9. *mBio* 6(3): 00648-15, June 2015.
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Research Overview

The Yang Lab studies the molecular and cellular mechanisms that protect against major diseases, including cancer and neurodegeneration. Our current projects are focused on three areas: 1) apoptosis pathways, 2) the tumor suppressor p53, and 3) the cellular systems that degrade misfolded proteins. Our experimental strategies include molecular and cell biology techniques, biochemical techniques, metabolic analysis, cell culture, genomics, mouse disease models, and human patient samples.

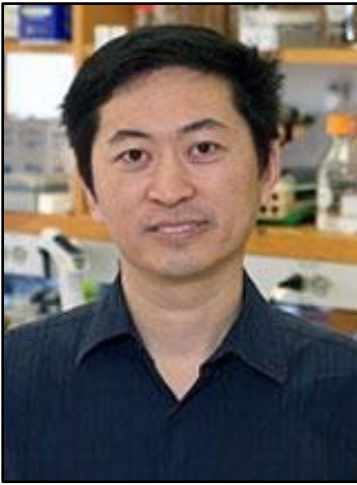
Apoptosis is a physiological process of cell auto-destruction that eliminates unwanted, damaged, or harmful cells. Dysregulation of apoptosis is associated with many diseases such as cancer, neurodegeneration, and immunodeficiency. Apoptosis is executed by the caspase family of cysteine proteases. We previously pioneered a paradigm for the activation of caspases, whereby initiator caspase activation is controlled by oligomerization. We are investigating the regulation of caspase activation in various apoptosis pathways. Paradoxically, some caspases are also involved in cell proliferation. We are studying the proliferative role of caspases to better understand the interplay between cellular life and death processes.

p53 plays a preeminent role in blocking tumor formation and is the single most frequently mutated gene in human tumors. p53 is activated by various tumor-promoting stresses and effectuates a range of anti-proliferative and repair responses. We are investigating the regulation and functions of p53, as well as its structural homologue p73. We previously identified a complex that stabilizes the principal p53 antagonist Mdm2 and are now examining how this complex controls p53 activation. We also revealed a role for p53 family proteins in modulating cellular metabolism, particularly the production of NADPH, the reducing equivalent required for biosynthesis and anti-oxidant defense. We are further studying how these proteins act as both sentinels and regulators for metabolism, coordinating metabolism with cell fate decision, and how these functions may be compromised in tumor cells. We are also investigating other metabolic alterations in tumor cells that enable their survival, proliferation, and metastasis.

Proteins are the most abundant macromolecules in the cell and are critical to virtually all physiological processes. However, proteins are prone to misfolding, and accumulation of misfolded proteins is genetically and pathologically linked to neurodegenerative diseases and cancer. Cells ultimately rely on degradative systems to maintain protein quality. We recently identified a cellular system that selectively degrades misfolded proteins through sequential SUMOylation and ubiquitination, and protects against neurodegeneration. We are further defining the mechanism of this novel protein quality control system, as well as its dysregulation in human diseases.

Selected Publications

- Chen L., Brewer M., Guo L., Wang R., Jiang P., Yang X.: Enhanced Degradation of Misfolded Proteins Promotes Tumorigenesis. *Cell Reports* 18(13): 3143-3154, March 2017.
- Guo L., Giasson B.I., Glavis-Bloom A., Brewer M.D., Shorter J., Gitler A.D., and Yang X.: A cellular system that degrades misfolded proteins and protects against neurodegeneration. *Mol Cell* 55: 15-30, 2014 Notes: Cover story and commented on in this issue.
- Du W., Jiang P., Mancuso A., Stonestrom A., Brewer M.D., Minn A.J., Mak T.W., Wu M., and Yang X.: TAp73 enhances the pentose phosphate pathway and supports cell proliferation. *Nat Cell Bio* 15: 991-1000, 2013 Notes: Cover story and commented on in this issue.
- Jiang P., Du W., Mancuso A., Wellen K. and Yang X.: Reciprocal regulation of p53 and malic enzymes modulates metabolism and senescence. *Nature* 493: 689-93, 2013.
- Jiang P., Du W., Wang X., Mancuso A., Gao X., Wu M., and Yang X.: p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat Cell Biol.* 13: 310-18, 2011 Notes: cover story and commented on in this issue.
- Chu Y. and Yang X.: SUMO E3 activity of TRIM proteins. *Oncogene* 30: 1108-16, 2011.
- Mei Y., Yong J., Liu H., Shi Y., Meinkoth J., Dreyfuss G., and Yang X.: tRNA binds to cytochrome c and inhibits caspase activation. *Mol Cell* 37: 668-78, 2010 Notes: Cover story and commented on in this issue. Highlighted in Science Signaling and Chemical & Engineering News.
- Kawadler H., Riley J. L., and Yang X.: The paracaspase MALT1 control caspase-8 activation during lymphocyte proliferation. *Mol Cell* 31: 415-21, 2008 Notes: Highlighted in Science Signaling.
- Tang J., Qu L., Zhang J., Wang W., Michaelson J. S., Degenhardt Y., El-Deiry W.S., and Yang X.: Critical role for Daxx in regulating Mdm2. *Nat Cell Biol.* 8: 855-62, 2006 Notes: Commented on in this issue.
- Hu S., Du M.-Q., Park S.-M., Alcivar A., Qu L., Gupta S., Tang J., Baens M., Ye H., Lee T., Marynen P., Riley J.L., and Yang X.: cIAP2 is a ubiquitin protein ligase for BCL10 and is dysregulated in mucosa-associated lymphoid tissue lymphomas. *J Clin Invest.* 116: 174-81, 2006 Notes: Commented in this issue.
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Research Overview

A fundamental question in Genetics and Neuroscience is how the brain executes genetic programs while maintaining the ability to adapt to the environment. The underlying molecular mechanisms are not well understood, but epigenetic regulation, mediated by DNA methylation and chromatin organization, provides an intricate platform bridging genetics and the environment, and allows for the integration of intrinsic and environmental signals into the genome and subsequent translation of the genome into stable yet adaptive functions in the brain. Impaired epigenetic regulation has been implicated in many neurodevelopmental and neuropsychiatric disorders.

The Zhou laboratory is interested in understanding the epigenetic mechanisms that integrate environmental factors with genetic code to govern brain development and function, elucidating the pathophysiology of specific neurodevelopmental disorders with known genetic causes such as Rett syndrome and CDKL5 deficiency, and illuminating the pathogenesis of selective neuropsychiatric disorders with complex genetic traits such as autism and major depression. We use a variety of cutting-edge genomic technologies, together with cellular and physiological assays in genetically modified mice, to pursue our interests. We aim to ultimately translate our findings into therapeutic development to improve the treatment for neurodevelopmental and neuropsychiatric disorders.

1. Defining the stress-induced epigenetic code underlying depressive-like behaviors

The genetic underpinnings of neuropsychiatric disorders are highly complex, involving multifaceted interactions between risk genes and the environment. It is known that environmental factors such as adverse early life events or chronic traumatic experience confer significantly greater susceptibility to psychiatric conditions later in life. However, the pathogenic mechanisms by which environmental factors interact with genetic programs in the nervous system to trigger psychiatric illness remain poorly understood. Thus, we have developed novel genetically modified mice, and plan to employ the next-generation sequencing and single cell sequencing technologies to identify the stress-induced epigenetic modifications from neuronal cell types of interest, to employ CRISPR-mediated genomic and epigenomic editing techniques to evaluate the causal relationship between stress-induced epigenetic changes and maladaptive behaviors, and to elucidate the key signaling pathways that mediate gene-environment interactions in the brain.

2. Elucidating the molecular basis of Rett Syndrome

Rett Syndrome (RTT) is a neurodevelopmental disorder characterized by developmental regression, motor dysfunction, and cognitive deficits. The majority of RTT cases are associated with mutations on an X-

linked gene encoding MeCP2, a methyl-CpG binding protein involved in organizing chromatin and modulating gene expression. To understand the molecular pathogenesis of RTT, we have developed mouse models recapitulating RTT-associated mutations. We found that mice with RTT-associated missense mutations, such as R106W, T158M and T158A, develop RTT-like phenotypes and show deficits in neural circuitry. These mutations decrease the binding of MeCP2 to methylated DNA and concomitantly reduce MeCP2 protein stability, leading to gene expression and cellular morphological changes in a neuronal cell type-specific manner (Ref). We aim to define the role of methyl-DNA binding of MeCP2 in protein stability, delineate the cellular origin of impaired neural circuitry, and elucidate the mechanisms by which MeCP2 modulates neuronal cell-type specific function.

3. Understanding the pathogenic mechanisms of CDKL5 deficiency

CDKL5 deficiency is a disorder caused by genetic defects in the the X-linked gene encoding cyclin-dependent kinase-like 5 (CDKL5). Patients with CDKL5 dysfunction show early onset intractable seizures and severe neurodevelopmental impairment, and are frequently diagnosed with a number of disorders including Infantile Spasms, West Syndrome, Lennox-Gastaut, atypical Rett Syndrome, and autism. To gain insight into the pathogenic mechanisms underlying CDKL5-related disorders, we have developed mouse models in which the CDKL5 gene is ablated or modified. We found that loss of functional CDKL5 disrupts multiple signal transduction pathways, impairs hippocampal event-related potentials, and leads to autistic-like phenotypes in mice. We plan to identify the molecular targets of CDKL5, dissect the signaling cascades responsible for cardinal autistic-like phenotypes, and investigate the neural mechanisms by which CDKL5 dysfunction leads to early onset seizures and cognitive deficits.

4. Exploring the coding and decoding of the methylome in neurons

Cytosine methylation (5mC), mostly at CpG dinucleotides in mammals, is a central epigenetic mark essential for development. While we can now profile genome-wide DNA methylation at single-base resolution (sequencing methylome), how the methylome is established and maintained, and how the cell interprets the methylome to affect gene expression and chromatin structure remain poorly understood. Moreover, recent studies have challenged the stability of the methylome in postmitotic neurons and have coupled changes in DNA methylation at specific loci to adaptive behaviors. We are interested in understanding how DNA methylation is coded and decoded genome-wide but with locus-specificity in neurons. Given the high abundance of hydroxymethylcytosine (5hmC) in the brain, we set up to address the functional significance of 5mC and 5hmC in neural development, the role of the methylome in the establishment of neuronal identity, and the molecular mechanisms by which the methylome modulates genome function in the brain.

Selected Publications

Goffin D, Allen M#, Zhang L#, Amorim M#, Wang IT#, Reyes A, Mercado-Berton A, Ong C, Cohen S, Hu L, Blendy JA, Carlson G, Siegel S, Greenberg ME and Zhou Z: Rett syndrome mutation MeCP2 T158A disrupts DNA binding, protein stability and ERP responses. *Nature Neuroscience* 15(2): 274-283, 2012.

Wang IT, Allen M, Goffin D, Zhu X, Fairless AH, Brodtkin ES, Siegel SJ, Marsh ED, Blendy JA and Zhou Z: Loss of CDKL5 disrupts kinome profile and event-related potentials leading to autistic-like phenotypes in mice. *Proc Natl Acad Sci USA* 109(52): 21516-21521, 2012.

Goffin D, Brodtkin ES, Blendy JA, Siegel SJ and Zhou Z: Cellular origins of auditory event-related potential deficits in Rett syndrome. *Nature Neuroscience* 17(6): 804-806, 2014.

Wood KH, Johnson BS, Welsh SA, Lee JY, Cui Y, Krizman E, Brodtkin ES, Blendy JA, Robinson MB, Bartolomei MS and Zhou Z: Tagging of Methyl-CpG-binding Domain Proteins Reveals Different Spatiotemporal Expression and Supports Distinct Functions. *Epigenomics* 4: 455-473, 2016.

Fasolino M, Liu S, Wang Y and Zhou Z: Distinct cellular and molecular environments support aging-related DNA methylation changes in the substantia nigra. *Epigenomics* 9(1): 21-31, 2017.

- Lamonica JM, Kwon DY, Goffin D, Fenik P, Johnson BS, Cui Y, Guo H, Veasey S and Zhou Z: Elevating expression of MeCP2 T158M rescues DNA binding and Rett syndrome–like phenotypes. *Journal of Clinical Investigation* 127(5): 1889-1904, 2017.
- Kwon DY, Zhao YT, Lamonica JM and Zhou Z: Locus-specific histone deacetylation using a synthetic CRISPR-Cas9-based HDAC. *Nature Communications* 8: 15315. doi: 10.1038/ncomms15315, 2017.
- Tang S, Wang I-T, Yue C, Takano H, Terzic B, Pance K, Lee JY, Cui Y, Coulter DA* and Zhou Z* : Loss of CDKL5 in glutamatergic neurons disrupts hippocampal microcircuitry and leads to memory impairment in mice. *Journal of Neuroscience* 37(31): 7420-7437, 2017.
- Johnson BS#, Zhao Y#, Fasolino M#, Lamonica JM, Kim YJ, Georgakilas G, Wood KH, Bu D, Cui Y, Goffin A, Vahedi G, Kim TH and Zhou Z : Biotin tagging of MeCP2 in mice reveals contextual insights into the Rett syndrome transcriptome. *Nature Medicine*, 23(10): 1203-1214, 2017.
- Zhao YT, Kwon DY, Johnson BS, Fasolino M, Lamonica JM, Kim YJ, Zhao BS, He C, Vahedi G, Kim TH and Zhou Z*: Long genes linked to autism harbor broad enhancer-like chromatin domains. *Genome Research* 2018 Notes: doi: 10.1101/gr.233775.117.
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