SCHEDULE OF EVENTS

11:00 AM - 12:00 PM     COFFEE/OPENING REMARKS - BANQUET ROOM

Student Talks – Session 1

G Protein Coupled Receptor Kinase 2 (GRK2): A Novel target of allergy
- Monica Thapaliya/Ali Lab

Development of a phospholipase A2 activatable fluorophore for human and canine lung cancer imaging
- Michael C. Hart/Delikatny Lab

12:15 - 1:15 PM     LUNCH

1:15 - 2:15 PM     FACULTY TALKS

- Shaon Sengupta - Assistant Professor of Pediatrics
- David Cormode - Associate Professor of Radiology
- Aime Franco- Assistant Professor of Pediatrics

2:15 - 3:45 PM

Student Talks – Session 2

Epitope editing in hematopoietic cells to enable CD45-directed immune therapy
- Nils Wellhausen/June Lab

Exploring Prostaglandin-Independent Mechanisms of NSAID-Associated Enteropathy
- Kayla Barekat/FitzGerald Lab

Targeted delivery of fingolimod to the inflamed brain stabilizes the blood-brain barrier and reduces post-stroke vasogenic edema
- Michael Zaleski/Brenner Lab

3:45 – 4:45 PM     Student Poster Session/Coffee - Pre-Function Room
4:45 - 5:45 PM

Student Talks – Session 3
Using CD69 PET Imaging to Monitor Immunotherapy-Induced Immune Activation
- Kimberly J. Edwards/Sellmyer Lab

Glucose Challenge Uncovers Temporal Fungibility of Metabolic Homeostasis Throughout the Day
- Dania Malik/Weljie Lab

5:45 - 6:45 PM  Reception - Drafting Room

7:00 PM  Dinner - Banquet Room
<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Presentation Abstracts</td>
</tr>
<tr>
<td>Poster Session Abstracts</td>
</tr>
<tr>
<td>Pharmacology Student Profiles:</td>
</tr>
<tr>
<td>Recent Graduates</td>
</tr>
<tr>
<td>First Year Students</td>
</tr>
<tr>
<td>Student Biographies</td>
</tr>
<tr>
<td>Pharmacology Faculty Profiles</td>
</tr>
</tbody>
</table>
Special thanks to the 3rd and 4th year students for planning and organizing this year’s Pharmacology Student Symposium.

Left to right: Back Row – Nils Wellhausen, Zachary Lamplugh, Alex Benton, Conroy Field, Adrienne Jo, Ryan O’Connell; Front Row – Kyla Mace, Sonia Lombroso, Catherine Wingrove, Ambar Jimenez, Asmita Panthi, Bridget McVeigh

Left to right: Ryan Paulukinas, Eric Waite, Alexandra Vazquez, Alex Starr, Alyssa Weist, Veronika Yakovishina, Elizabeth Pruzinsky, Brandon Anderson, Kimberly Edwards, Daniel Park
Exploring Prostaglandin-Independent Mechanisms of NSAID-Associated Enteropathy

Kayla Barekat

Advisor: Garret FitzGerald, M.D., F.R.S.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used nonaddictive medications for the management of chronic pain and inflammation; however, these drugs are associated with many gastrointestinal (GI) and cardiovascular adverse events, including intestinal bleeding, ulceration, stenosis, myocardial infarction, and stroke. Traditional NSAIDs exert their effects by inhibiting both cyclooxygenases (COX) -1 and -2 to suppress prostaglandin synthesis and are estimated to cause intestinal ulceration in roughly 40% of patients. This toxicity was attributed to inhibition of COX-1-dependent synthesis of prostaglandin (PG) E$_2$ and prostacyclin (PGI$_2$) in gastrointestinal epithelial cells, which are involved in protection of the GI mucosal barrier, compounded by inhibition of COX-1-dependent thromboxane (Tx)A$_2$ formation by platelets, predisposing to hemorrhage. Yet inhibition or genetic deletion of COX-1 alone does not result in spontaneous GI lesions, and concomitant inactivation of COX-2 seemed necessary to cause GI damage in previous limited mouse models.

So under the assumption that NSAID enteropathy is an unavoidable consequence of simultaneously suppressing both COX enzymes, I had developed a novel mouse model of inducible COX-1 + COX-2 deletion to complement our lab’s chronic NSAID exposure model. These COX double-knockout mice exhibited substantially suppressed prostaglandin levels comparable to (and often lower than) those of wildtype mice treated with the nonselective NSAID naproxen. Yet surprisingly the COX double-knockouts never spontaneously developed any gastrointestinal damage when tracked for an entire year, whereas the naproxen mice consistently exhibit intestinal lesions and bleeding within 3 weeks. Moreover, upon administering naproxen to the COX double-knockout mice, they do develop enteropathy, despite lacking the intended drug target and exhibiting no change in prostaglandin levels from baseline. The same pattern is observed when these mice are treated with phenylpropionic acid, a compound that bears a similar structure to naproxen yet has no COX activity.

These results challenge the prevailing dogma that attributes NSAID enteropathy to prostaglandin inhibition, robustly demonstrating that prolonged suppression of prostaglandin synthesis alone is not sufficient to induce intestinal damage. Rather, mechanisms specific to the drug (including topical irritation of the intestinal epithelium, mitochondrial dysfunction, enterohepatic recirculation, and prolonged exposure to bile acids) appear to be required as the dominant insult. With a better understanding of how NSAIDs elicit intestinal damage, these studies ultimately aim to improve enteric NSAID tolerance in patients. They may afford insights that allow for the design of safer
pharmaceuticals or drug combinations that widen the therapeutic index of a commonly consumed class of drugs.
Using CD69 PET Imaging to Monitor Immunotherapy-Induced Immune Activation

Kimberly J. Edwards

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

**Introduction:** Preclinical evidence shows that immunologically active tumors, containing high levels of CD3⁺/CD8⁺ T cell infiltrates, correlate with favorable responses to immunotherapy. As a result, efforts have been made to image and monitor immune activity, particularly within the tumor microenvironment (TME). The proposed approach uses CD69, the canonical early-activation marker expressed in a variety of activated immune cells including cytotoxic T cells and NK cells, as a promising predictive marker of response to cancer immunotherapy.

**Hypothesis:** CD69 is an imaging biomarker of immune cell activation and CD69 PET is capable of characterizing and monitoring immune cell activation in the TME in response to checkpoint blockade therapy.

**Methods:** The PET imaging probe was produced by conjugating an anti-mouse CD69 monoclonal antibody (H1.2F3) to deferoxamine (DFO) and labeling with Zr-89 ([⁸⁹Zr]-DFO-H1.2F3). To test this probe in vitro, an uptake study was conducted using PMA/Ionomycin-stimulated primary mouse T cells and an untreated control. To model an in vivo system, the probe was tested within the context of a validated immunocompetent immune checkpoint inhibitor preclinical model. Adult, female, Balb/c mice bearing CT26 syngeneic tumors were injected with [⁸⁹Zr]-DFO-H1.2F3 on day 12 post tumor inoculation, and were then imaged or sacrificed for organ harvest on day 15 post tumor inoculation, i.e. 72 hours post radiotracer injection.

**Results:** The in vitro uptake study showed that [⁸⁹Zr]-DFO-H1.2F3 detects the 15.5-fold change in CD69 expression between unstimulated and stimulated T cells. The in vivo PET/CT imaging study showed increased uptake in tumors from responder mice, relative to tumors from nonresponders and untreated controls. Ex vivo biodistribution validation showed increased tumor uptake in responders (43.1 ± 12.8 %ID/g; n = 6) relative to that of nonresponder and untreated control cohorts (10.3 ± 1.2 %ID/g; n = 4, and 12.6 ± 1.8 %ID/g; n = 5, respectively). Autoradiography corroborated biodistribution analyses showing increased uptake (%ID/mm²) for responders relative to nonresponders and untreated control mice. Using chromogenic detection methods, immunohistochemistry staining detected increased expression of CD69, OX40, Granzyme B, ICOS and CD3 expression in tumor sections of responder mice relative to tumor sections from nonresponders and untreated controls.

**Conclusions:** This CD69 PET imaging approach detects CD69 expression with sufficient sensitivity to quantify immune cell activation in a syngeneic mouse immunotherapy model. It also has potential for predicting therapeutic immune response to novel immunotherapies.
Development of a phospholipase A2 activatable fluorophore for human and canine lung cancer imaging

Michael C. Hart

Advisor: Edward Delikatny, Ph.D.

Introduction: Lung cancer is the leading cause of cancer-related death in the United States. Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC) which are primarily treated by surgical resection of the disease. NSCLC resections rely on tissue palpation and visual inspection to identify margins. This nonspecific identification leads to roughly 40% of NSCLC patients experiencing disease recurrence. Thus, targeted imaging agents for the intraoperative detection of NSCLC would improve rates of curative resections. Cytosolic phospholipase A2 (cPLA2) is overexpressed and hyperactive in NSCLC. Our lab previously developed a PLA2 activatable fluorophore for triple-negative breast cancer (TNBC) imaging, DDAO-arachidonate (DDAO-A). Due to the high cPLA2 expression and mortality rate associated with NSCLC, we hypothesized that DDAO-arachidonate would be preferentially activated in human and canine lung cancer tissues when compared to normal lung tissues making it a promising agent for real-time guidance of NSCLC surgical resections.

Methods: Human (n=10) and canine (n=3) normal lung and lung tumor tissues were obtained from patients at the Hospital of the University of Pennsylvania and the School of Veterinary Medicine. Tissues were treated topically with DDAO-A, and fluorescence was measured after 15 min. Five KLN 205 tumor-bearing DBA/2 mice, a NSCLC model, were treated intratumorally with DDAO-A, a negative control probe called DDAO-palmitate (DDAO-P), or with DDAO-P chased by DDAO-A to rescue fluorescence activation. Tumors and flank muscle tissues were excised from all mice and imaged for ex vivo fluorescence.

Results: In 8 out of 10 human and in all canine specimens, tissues exhibited fluorescent tumor-to-normal ratios (TNRs) of 2:1 or higher demonstrating that DDAO-A is preferentially activated in lung tumor tissues. Mice treated with the negative control probe, DDAO-P, exhibited insignificant increases in tumor fluorescence. DDAO-A chase treatments and initial intratumoral injections resulted in significant increases in the signal-to-noise ratios (SNR) showing strong activation of DDAO-A in tumors with SNRs up to 9.47:1.

Conclusions: DDAO-A is preferentially activated by lung tumor tissues in mouse models and in human and canine specimens. TNRs of 2:1 and higher demonstrated tumor selectivity making the probe a promising candidate for the real-time guidance of surgical resections.
Glucose Challenge Uncovers Temporal Fungibility of Metabolic Homeostasis Throughout the Day

Dania Malik

Advisor: Aalim Weljie, Ph.D.

Rhythmicity is a feature of many behavioral and biological processes including metabolism. Although, previous work has well characterized steady state metabolic cycling, an understanding of how these metabolic changes arise is limited. Here, we demonstrate temporally dynamic metabolism of excess $^{13}\text{C}_6$-glucose in *Drosophila* using a purpose-built mass spectrometry workflow targeting 37 downstream metabolites across multiple pathways (glycolysis, TCA cycle, pentose phosphate pathway, and amino acid biosynthesis). Broad activity of downstream glucose pathways was observed in wild type shortly following lights on by sampling throughout the day using 4-hour resolution. In contrast to wild type, TCA cycle activity was generally more active in a hyperactive short sleep mutant (*fumin*) in a time-independent analysis. However, *fumin* demonstrated unique temporal patterns in glucose processing at dawn and dusk with pentose phosphate activity specifically observed at dusk. Moreover, an increase in the number of rhythmic (diurnal and ultradian) isotopologues and metabolite pools were observed in the mutant. Surprisingly, neither underlying feeding rhythms nor the presence of food was observed to drive rhythmicity of glucose processing across genotypes. This approach provides a mechanistic basis to deconvolute metabolic changes in *Drosophila* arising from decreased sleep, circadian processes, and environmental factors through the incorporation of additional sleep and clock mutants as well as controlled conditions in a high time resolution manner. Furthermore, the platform can also be applied to understanding altered metabolism in disease states in other model and human systems with potential to improve target selection as well as timing of therapeutic interventions.
G Protein Coupled Receptor Kinase 2 (GRK2): A Novel target of allergy

Monica Thapaliya

Advisor: Hydar Ali, Ph.D.

Aggregation of high affinity Immunoglobulin E (IgE) receptor (FcεRI) by allergen on mast cell results in the manifestation of allergic diseases such as allergic rhinitis, asthma, food allergy and eczema. While all mast cells are characterized by the presence of cell surface FcεRI, a subtype present in the human skin (but not lungs) also expresses a novel GPCR, MAS-related GPCR-X2 (MRGPRX2; mouse orthologue MrgprB2) which contributes to injection-site reactions. G-protein coupled receptor (GPCR) kinase 2 (GRK2), a crucial regulator of GPCR signaling, has been investigated as an attractive therapeutic target for cardiovascular and metabolic diseases. Several GRK2-targeted inhibition strategies have been reported including the use of direct pharmacological inhibitors such as paroxetine (widely prescribed antidepressant) and paroxetine based GRK2-specific inhibitors such as compound CCG258747. Plethora of studies have reported GRK2 in the regulation of vascular function, immunity, and inflammation, but its role in mast cell mediated allergy remains elusive. Utilizing shRNA-mediated knockdown and retroviral overexpression, it is reported that GRK2 regulates FcεRI in vitro, despite being a non-GPCR. However, the physiological relevance of this finding and the in vivo implication is not known. Thus, this study is aimed at elucidating the role of GRK2 in mast cell mediated allergic response in physiologically relevant murine system and to determine if GRK2 inhibitors, paroxetine and CCG258747 can be used to modulate FcεRI-mediated MC responses in vitro and in vivo.

GRK2 global knockout is embryonic lethal. Thus, mast cell specific GRK2 knockout mice were generated via Cre-Lox breeding. Using primary lung mast cells from these mice, we found that both FcεRI-induced early mast cell response (degranulation via β-hexosaminidase release and Lysosomal-associated membrane protein 1 (LAMP-1) expression) and late mast cell response (cytokine/chemokine: IL6/IL13/CCL3/TNFα generation via ELISA) are significantly reduced in GRK2 knockout lung mast cells compared to control. Likewise, we found that both IgE-mediated passive cutaneous anaphylaxis and itch are also significantly reduced in GRK2 knockout mice compared to control, which suggests that GRK2 promotes FcεRI-mediated responses. Furthermore, we tested whether GRK2-inhibitors, paroxetine and CCG258747 can modulate these responses. Utilizing rat basophilic leukemia (RBL-2H3) cells and primary lung mast cells, we found that paroxetine and CCG258747 inhibit FcεRI-induced calcium mobilization and degranulation. Furthermore, intravenous administration of paroxetine in mice demonstrated substantial reduction of IgE-mediated passive cutaneous anaphylaxis. However, to our surprise we also found that both paroxetine and CCG258747 induce calcium mobilization and degranulation in RBL-2H3 cells stably expressing MRGPRX2 but not untransfected cells. Both
compounds also induced degranulation in mouse peritoneal mast cells derived from wild-type but not MrgprB2−/− mice. Additionally, intradermal administration of paroxetine also induced local increased vascular permeability in wild-type but not MrgprB2−/− mice. However, paroxetine failed to induce any systemic anaphylaxis in mice. Taken together, the data presented in this study suggests that GRK2 plays a positive regulatory role in mast cell mediated allergic reactions and that paroxetine based GRK2-inhibitors can be used to modulate IgE-mediated anaphylaxis. However, if these drugs are administered intradermally, injection site reaction may occur through the activation of cutaneous mast cells via MRGPRX2/MrgprB2.
Epitope editing in hematopoietic cells to enable CD45-directed immune therapy

Nils Wellhausen

Advisor: Carl June, M.D.

Targeted immunotherapies such as antibody-drug-conjugates or CAR-T cells constitute a significant advancement in cancer therapy. However, their use is limited to several well-known lineage markers for which the on-target off-tumor toxicities are clinically tolerated. Furthermore, targeted immunotherapy must be individually designed for every disease, leading to drug discovery and development inefficiencies. By targeting a pan-hematologic antigen, a single “drug” could be used for all hematologic indications, thereby accelerating clinical research. The widespread expression of CD45 on all nucleated hematopoietic cells makes it an attractive target for pan-hematologic cancer immune-based therapy. However, the long-term ablation of healthy hematopoietic cells expressing CD45 is expected to result in severe toxicity. Additionally, the expression of CD45 on human T cells makes anti-CD45 CAR-T cells vulnerable to fratricide, preventing their ex vivo expansion during CAR-T cell manufacturing.

We hypothesized that CD45 can be made druggable by combining potent anti-CD45 CAR-T cells with a hematopoietic stem cell (HSC) transplant in which the targeted CD45 epitope has been altered in both T-cells and HSCs in such a way that it is unrecognized by the anti-CD45 CAR-T cells while maintaining its surface expression, conformation, and enzymatic function. This would create, by a process of subtraction, a cancer-specific antigen in all residual host hematopoietic cells, paving the way to a profound, “sterilizing” ablation of residual host hematopoietic cells and re-engraftment of hematopoietic lineages by CD45-edited HSCs.

Here we mapped the amino acid residues on human CD45 that are required for binding by three different anti-CD45 clones using sequential domain truncation and alanine mutagenesis. We then devised CRISPR adenine base editing (ABE) to install a single mutation at the identified functionally redundant epitope on CD45 that is normally recognized by the antibodies. Using this approach in T cells, we have generated a CD45 molecule that is “invisible” to CAR-T cells made from these anti-CD45 clones, rendering them resistant to fratricide. We further show that these CD45-edited CAR45 T cells are effective against various types of blood cancer cell lines and primary patient acute myeloid leukemias both in vitro and in xenograft mouse models.

We will also present up-to-date results on hematopoietic engraftment of human CD45-edited CD34+ HSCs in immunodeficient mice, showing that CD45 editing levels are maintained in vivo comparable to input cells, thus indicating full preservation of functionality of the engineered cells.
Targeted delivery of fingolimod to the inflamed brain stabilizes the blood-brain barrier and reduces post-stroke vasogenic edema

Michael Zaleski

Advisor: Jacob Brenner, M.D., Ph.D.

Ischemic strokes occur when a brain artery is obstructed, resulting in neurological deficits, disability, and even death. Despite the emergence of endovascular thrombectomy as the standard of care, patient outcomes for ischemic stroke remain poor. One major reason for poor outcomes is ischemia reperfusion injury (IRI), which is exacerbated cellular damage that occurs after blood flow is restored to previously ischemic areas. In IRI, endothelial cells decrease their barrier function, allowing into the brain parenchyma both toxic plasma proteins and infiltrating leukocytes.

Fingolimod is a small molecule drug that has shown promise in small clinical trials for the treatment of ischemic stroke. Fingolimod is an S1PR (sphingosine-1 phosphate receptor) modulator that increases endothelial barrier function and can reduce brain edema in the context of IRI. However, the current administration and dosage form of fingolimod is not optimal for treatment of IRI. Fingolimod is administered orally and binds strongly to red blood cells (RBCs) and plasma proteins (<0.02% of drug unbound in whole blood), resulting in slow distribution to the brain.

To address this problem, we developed a liposomal formulation that stably encapsulates fingolimod and can be administered intravenously. We show that fingolimod-liposomes reduce partitioning of drug to RBCs and plasma proteins (82.0 ± 1.0% of free drug vs. 24.5 ± 0.9% of liposomal drug partitions into RBCs). Additionally, the liposomes can be targeted to the inflamed cerebral vasculature by coating liposomes with targeting moieties (e.g., antibodies) that bind to vascular cell adhesion molecule 1 (VCAM-1), a protein on endothelial cells upregulated during inflammation.

We show that fingolimod-loaded liposomes targeted to VCAM-1 significantly increases drug exposure in the brain compared to free drug (AUC_{brain} = 445 ± 11.5 ng/mL*hr for free drug vs. 645 ± 13.6 ng/mL*hr for VCAM-liposomes). We also show VCAM-targeted fingolimod liposomes completely ameliorate capillary leak in a mouse model of post-stroke vasogenic edema. In summary, VCAM-targeted liposomes are able to deliver fingolimod to endothelial cells of the brain in a mouse model of stroke, stabilize the endothelial barrier, and prevent capillary leak to the brain parenchyma. This drug delivery technology has the potential to limit ischemia reperfusion injury and improve outcomes in ischemic stroke.
Low-dose sodium iodate: a potential avenue for testing a wider range of retina-protective therapies

Brandon Anderson

Advisor: Joshua Dunaief, M.D., Ph.D.

Sodium iodate (NaIO$_3$) causes oxidative stress to the retina and is commonly used by vision scientists to test therapeutics intended to treat disorders like age-related macular degeneration (AMD). An important difference, however, between NaIO$_3$ and AMD is the time it takes to damage the retina. While AMD is a chronic disease that develops over years, NaIO$_3$ damages the retina within a week. Because of this, it is possible that some therapeutics that protect against a slower developing disease such as AMD would be unable to protect against the fast-acting NaIO$_3$; this may lead to incorrectly discarding these therapies. Decreasing the severity of NaIO$_3$’s damage by dropping the dose is a potential solution to this issue. In this study we used in vivo imaging and histology to compare different doses, sexes, and ages to characterize retinal damage caused by NaIO$_3$. 20 mg/kg NaIO$_3$ was the lowest dose needed to damage the retina and sometimes resulted in a phenotype similar to geographic atrophy, a common form of AMD. 25 mg/kg NaIO$_3$ in female mice led to the least amount of damage while still being consistent. Older (22-month) mouse retinas were affected differently than younger (3-month) mouse retinas.
Genetic activation of α-cell glucokinase in mice causes enhanced glucose-suppression of glucagon secretion during normal and diabetic states

Varun Bahl

Advisor: Klaus Kaestner, Ph.D.

While the molecular events controlling insulin secretion from β-cells have been documented in detail, the exact mechanisms governing glucagon release by α-cells are understood only partially. This is a critical knowledge gap, as the normal suppression of glucagon secretion by elevated glucose levels fails in Type 2 Diabetes (T2D) patients, contributing to hyperglycemia through stimulation of hepatic glucose production. A critical role of glycolytic flux in regulating glucagon secretion was supported by recent studies in which manipulation of the activity and expression of the glycolytic enzyme glucokinase altered the setpoint for glucose-suppression of glucagon secretion (GSGS). Given this precedent, we hypothesized that genetic activation of glucokinase specifically in α-cells would enhance GSGS and mitigate T2D hyperglucagonemia. To test this hypothesis, we derived an inducible, α-cell-specific glucokinase activating mutant mouse model (GckloxPGck*/loxPGck*; Gcg-CreERT2; referred to as “α-mutGCK”) in which the wild-type glucokinase gene (GCK) is conditionally replaced with a glucokinase mutant allele containing the ins454a activating mutation (Gck*), a mutation that increases the affinity of glucokinase for glucose by almost seven-fold. The effects of α-cell GCK activation on glucose homeostasis, and hormone secretion were assessed using both in vivo and ex vivo assays. Additionally, the effect of α-cell GCK activation on GSGS was investigated under diabetogenic conditions of high fat diet (HFD) feeding. Our study shows that α-mutGCK mice have enhanced GSGS in vivo and ex vivo, independent of alterations in insulin levels and secretion, or islet hormone content. α-mutGCK mice maintained on HFD displayed improvements in glucagonemia compared to controls, which developed the expected obesity, glucose intolerance, elevated fasting blood glucose, hyperinsulinemia, and hyperglucagonemia. Using our novel α-cell specific activation of GCK mouse model, we have provided additional support to demonstrate that the glycolytic enzyme glucokinase is a key determinant in glucose sensing within α-cells to regulate glucagon secretion.
Immunological Targeting of LOXHD1 for the Treatment of Ewing Sarcoma

Tatiana Blanchard

Advisor: Beatriz Carreno, Ph.D.

Ewing Sarcoma (ES) is the second most common bone cancer affecting children and young adults. Standard of care high-dose chemotherapy has yielded poor results for patients with recurrent disease with a 5-year overall survival of < 10%. Adoptive cellular therapy strategies utilizing T cells redirected against tumor-associated antigens, such as NY-ESO-1, have yielded promising results for the treatment of synovial sarcoma. 85% of ES cases are driven by a unique t(11:22)(q24;q12) translocation resulting in an EWSR1-FLI1 fusion. We discovered that EWSR1-FLI1 fusion drives aberrant expression of Lipoxygenase Homology Domains 1 (LOXHD1) and LOXHD1 may constitute as a unique target for harnessing immune responses against ES since its expression appears to be required for ES cell growth and tumorigenesis. The repertoire of LOXHD1-derived peptides presented by HLA-A*02:01 was evaluated in the SK-NM-C ES cell line by proteomics under non-inflammatory and inflammatory (+IFN-g) conditions. Proteomic analysis identified 6,718 and 7,887 peptides presented in the context of HLA-A*02:01 under non-inflammatory and inflammatory conditions, respectively. Of note, unique and shared LOXHD1-derived peptides were identified under these conditions and the immunogenicity of these peptides evaluated using CD8+T cells derived from healthy donors. Characterization of T cell responses to 4 peptides, 3 peptides under inflammatory and one expressed under both conditions is currently underway. TCRs directed at 2 of these peptides have been isolated and evaluated using gene-edited TCRab knock-out primary CD8+ T cells. Expression of these TCRs confers antigen specificity as determined by multimer staining and results in cytotoxic activity against a panel of unique ES human tumor cell lines. On-going efforts are directed at isolation of TCRs against the other 2 LOXHD1-derived peptides. Finally, a murine xenograft model using an ES cell line in NSG mice has been developed with the goal to evaluate the in vivo antitumor efficacy of LOXHD1-specific T cells. This study has identified LOXHD1 as a novel immunological target for ES.
Therapeutic Reversion of Point Mutations to Prevent Progression of Clonal Hematopoiesis

Dan Brown

Advisor: Sar Gill, M.D., Ph.D.

Clonal hematopoiesis (CH) is characterized by the accumulation of somatic mutations that confer selective growth advantage to individual hematopoietic stem cells. The presence of CH mutations leads to an increased risk of hematologic malignancies and cardiovascular disease. CH-associated mutations are typically single nucleotide variations (SNV) in genes such as TET2, DNMT3A, and ASXL1. Thus, CH is a well-characterized pre-cancerous condition with a molecular pathogenesis that is partially understood, yet to date remains untreatable. We have employed adenine base editing to correct CH-associated point mutations in engineered K562 cell lines and patient-derived HSPC ex vivo. Specifically, we have targeted DNMT3A R882H and IDH1 R132H mutations. The overarching goal of this application is to demonstrate that base editing can specifically, reliably and durably correct SNV in CH-related genes and thereby turn back the clock on an otherwise progressive aging-related precancerous condition. The translational potential of this approach is supported by the use of relatively well-tolerated conditioning regimens in patients undergoing HSPC-based gene therapy for hemoglobinopathies, and is further aided by the recent development of non-genotoxic, well-tolerated conditioning regimens that could be used in otherwise frail or elderly patients.

The clinical significance of this work is underscored by the high frequency of CH in general population and by the increased risk of developing hematologic malignancies and cardiovascular disease in CH mutation carriers. While early studies using relatively insensitive next generation sequencing modalities identified CH in approximately 10% of 70y.o. individuals, more recent work using error-correct sequencing have observed mutations in DNMT3A or TET2 in up 95% of individuals tested. The presence of CH confers a hazard ratio of approximately 10-fold for subsequent hematologic malignancy, 2-3 fold for cardio/cerebrovascular disease and 1.4-fold for all-cause mortality. Notably, the risk of progression to hematologic malignancies and of other clinical sequelae increases with clone size, raising the possibility that CH may not need to be entirely eradicated to provide clinical benefit. Whether intervention to reduce CH clone size can mitigate the risk of HM or CD remains untested. CH-associated mutations were first described in patients with myeloid neoplasms. Mutations in DNMT3A, TET2 or ASXL1 are likely dominant (or ancestral) in some but not all cases of myelodysplastic syndromes (MDS). This is the therapeutic setting in which clinical proof-of-concept of this approach is most likely to
be first tested, given the more acceptable risk/benefit ratio in patients with advanced MDS.

Proof-of-concept work has demonstrated approximately 20% editing efficiency in DNMT3A R882H reversion, and 60% editing efficiency in IDH1 R132H reversion.
In vivo murine studies demonstrate that neutrophil activation by anti-NAP2 antibodies contributes to vaccine-induced immune thrombocytopenia and thrombosis (VITT).

Conroy Field

Advisor: Mortimer Poncz, M.D.

VITT involves thrombocytopenia and thrombosis post-initial anti-SARS-CoV-2 adenoviral vaccination. Most patients are found to have platelet-activating antibodies to the chemokine, platelet factor 4 (PF4) in the absence of heparin. VITT antibodies differ from those in heparin-induced thrombocytopenia (HIT), in which PF4 is bound to heparin. Distinct epitope sites on PF4 for VITT and HIT antibodies were defined (PMID34233346). We noted that the VITT antigenic site is conserved in mouse (m) PF4, and in the platelet-specific chemokine neutrophil-activating peptide 2 (NAP2), both human and mouse. We observed that VITT antibodies bind strongly to NAP2. In an active patient with VITT, we found that VITT antibodies circulate as immune complexes containing either PF4 or NAP2. Importantly, VITT antibodies plus NAP2 activates platelets. We tested in a passive-immunization murine model with VITT antibodies the ability to induce neutrophil-endothelial activation as an indicator of a prothrombotic state and identify the chemokines involved. We studied two systems: a femoral vein and a cremaster venule model, using confocal intravital imaging and labeled neutrophils. VITT antibodies were infused into mice transgenic for FcgRIIA and lacking PF4 (FcgRIIA+/mPF4−/−). This led to an immediately reduced neutrophil rolling by ~80% (14 to 3 μ/sec). Subsequent infusion of PF4 slowed neutrophil rolling by another ~80% (3 to .6 μ/sec). In contrast, VITT antibodies did not slow neutrophil speed in FcgRIIA+/mPF4−/−/mNAP2−/− mice. These data suggest that both NAP2 and PF4 contribute to thrombosis in VITT and may explain the pathogenesis of VITT in patients with no detectable anti-PF4 antibodies. VITT may be prothrombotic because it involves co-activation of neutrophils via NAP2 by way of CXCR2 and FcgRIIA. Targeting NAP2 pathobiology may enhance understanding of the pathogenesis of VITT and lead to new therapeutics.
Identifying tractable therapeutic targets in inhibitor-naïve and lorlatinib-resistant high-risk neuroblastoma

Mark Gerelus

Advisor: Yaël P. Mossé, M.D.

Neuroblastoma (NB), a predominantly pediatric extracranial cancer of neural crest cell origin, is a clinically and biologically heterogeneous disease, which poses a significant challenge to improving patient outcomes. Aberrations occur in the receptor tyrosine kinase (RTK) Anaplastic Lymphoma Kinase (ALK) in 14% of cases of high-risk NB (hrNB) and are substantially enriched for at time of relapse. ALK is the only tractable mutated oncogene in NB, and our lab has demonstrated that the next generation ALK inhibitor (ALKi) lorlatinib is a far more potent and superior inhibitor compared to earlier generations of ALK inhibitors, leading to the initiation of a multi-center clinical trial of lorlatinib in pediatrics with ALK-driven hrNB. Our published preclinical and unpublished preliminary clinical trial data argue that although targeted inhibition of mutant ALK with lorlatinib has achieved remarkable responses and shows signs of robust anti-tumor activity in the clinic, intrinsically resistant clones which exist due to intra-tumor heterogeneity are positively selected for by therapy. Additionally, the emergence of de novo oncogenic mutations can occur and result in relapse and resistance to lorlatinib therapy. Thus, an understanding of the development of resistance to lorlatinib on a biological level is vital, and there is a crucial need to elucidate mechanisms of resistance to discover new targeted therapeutic strategies to overcome the resistance observed in the clinic. We aim to leverage the use of small molecule inhibitors to specifically target proteins of the signaling pathways contributing to resistance. I hypothesize that inhibitor-naïve and lorlatinib-resistant hrNB are vulnerable to targeted small molecule inhibition as a therapeutic treatment strategy. There is a crucial need in the clinic to develop rational therapies using targeted small molecule inhibitors in both inhibitor-naïve and lorlatinib-resistant patient populations. Through generating and characterizing lorlatinib-resistant cell models to elucidate mechanisms of resistance to lorlatinib, we will provide crucial biological insights such that informed treatment decisions can be made to effectively combat and possibly prevent resistance to lorlatinib. Along with elucidating potential mechanisms of resistance in lorlatinib-resistant cell models created in vitro, this project explores the therapeutic potential of targeting the RAS/MAPK pathway in patient populations with RAS/MAPK alterations at diagnosis or upon therapy resistance.
Drug addiction is an urgent public health crisis affecting over 20.4 million Americans aged 12 or older and stress is a key risk factor in the initiation, maintenance, and relapse of addiction. Individual differences in response to stress are apparent as some individuals show resilience to stress, while others are susceptible. Additionally, women are twice as likely to suffer from stress-based psychiatric disorders, as well as show faster escalation of drug use and higher rates of relapse relative to men. Our lab has shown that orexin neuropeptides in the lateral hypothalamus mediate individual and sex differences in responses to stress. Specifically, female rats exhibited significantly increased orexin activation and expression compared to males. The delayed habituation exhibited by females is due, in part, to these elevations in orexins. In addition to regulating stress, orexins mediate the motivating properties of drugs of abuse. Here, we examined sex differences in Morphine Conditioned Place Preference (CPP), a standard pre-clinical behavioral paradigm to assess the rewarding effects of drugs of abuse. In this paradigm, morphine is paired with one side of a two contextually distinct compartments in the apparatus for four out of eight Conditioning Sessions, while vehicle (control) is paired with the alternate compartment in the remaining four sessions. On the Post-Conditioning Test, mice are given free access to both compartments and the duration spent in the morphine-paired side relative to the vehicle-paired side is measured. Significant increases in the time spent in the morphine-paired side following the conditioning is associated with the demonstration of morphine preference. We found that morphine-treated (10 mg/kg s.c.) male mice showed increased morphine preference whereas morphine-treated (10 mg/kg s.c.) females did not. In the next experiment, we tested the role of orexins initially in male mice. We administered the orexin-1 receptor (OX1R) antagonist SB-334867 (20 mg/kg i.p.) in morphine-treated (10 mg/kg s.c.) male mice either prior to the Conditioning Sessions or the Post-Conditioning Test to assess the role of OX1R in the acquisition and expression, respectively, in morphine preference. Morphine-treated male mice that were administered SB-334867 showed a trending decrease in the acquisition of morphine preference. These preliminary data demonstrate clear sex differences in the rewarding properties of morphine and suggest that orexins regulate these properties during Morphine CPP acquisition. Ongoing studies are assessing additional morphine doses and examining the role of orexins in females.
Glioma immunosuppression is driven by tumor stroma interaction with macrophages

Zachary Lamplugh

Advisor: Yi Fan, M.D., Ph.D.

Glioblastoma (GBM) is the most common and most lethal malignant primary brain tumor in humans. GBM tumors are immunologically “cold”, i.e., those tumors characterized with the lack or paucity of T cell infiltrates. GBM microenvironments contain a plethora of macrophages that undergo alternative, M2-like polarization to acquire immunosuppressive phenotypes, serving as one of the driving forces for tumor immune suppression and unsuccessful implementations of immunotherapies in GBM. Previous studies suggest that fibroblast activation protein (FAP)-positive fibroblasts contribute to immunosuppressive phenotypes, but its role in macrophage-mediated tumor immunosuppression remains largely unknown. Here, we identified a distinct population of FAP+ cells within mouse and human GBM tumors, which spatially regulates macrophage immunity. Our study using an endothelial lineage tracing mouse model with genetically engineered GBM tumors revealed that a subset of vascular endothelial cells within the GBM microenvironment underwent cell plasticity-mediated mesenchymal transformation and became FAP+. Consistent with these findings, our data showed that FAP+ cells were localized proximately to endothelial cells in human GBM. Importantly, these FAP+ cells derived from human GBM tumors induced M2 polarization of macrophages in-vitro. Furthermore, we revealed that FAP+ cell-derived decorin (DCN) induced M2 polarization in macrophages, leading to suppression of T-cell proliferation in-vitro. Thus, these characteristics of FAP+ cells that we have demonstrated here suggest these cells mediate immunosuppression within the glioma microenvironment and make for an ideal target to reverse GBM immunosuppression and improve the efficacy of immunotherapies.
Characterizing ALCAM as an oncoprotein and immunotherapeutic target in neuroblastoma

Jarrett Lindsay

Advisor: John Maris, M.D.

Neuroblastoma is a cancer arising from the developing sympathetic nervous system. Half of children diagnosed with neuroblastoma are considered high risk for death from the disease, with less than half of those patients surviving five years. ALCAM is a cell adhesion molecule that is overexpressed in neuroblastoma. ALCAM is a cancer stem cell marker in aggressive colorectal cancer and small cell lung cancer (SCLC), and in prostate cancer, proteolytic cleavage of ALCAM promotes bone metastasis. ALCAM also interacts with the immune system through its receptor CD6, which is expressed on developing and mature T cells, as well as NK cells. The ALCAM-CD6 interaction facilitates T cell adhesion in the immunological synapse and inhibits T cell activation. Thus, we hypothesize ALCAM is an oncoprotein necessary for immune evasion and metastasis, and is therefore an ideal immunotherapeutic target. To interrogate the effect of ALCAM in neuroblastoma chemotaxis, we generated ALCAM knockdown cell lines using a doxycycline-inducible CRISPR inhibition system. Using these cell lines, we performed scratch-wound assays using the Incucyte®S5X Live-Cell Monitoring System and found that ALCAM knockdown mediated significant reductions in wound healing compared to non-induced controls. Next, to characterize ALCAM as an immunotherapeutic target, we employed an ALCAM-targeting antibody-drug conjugate (CX-2009) that we obtained through a collaboration with CytomX® Therapeutics and found significant cytotoxicity in vitro and delayed tumor growth in vivo. Finally, to characterize the effects of the ALCAM-CD6 interaction on T cells, we activated human CD4+ and CD8+ T cells in the presence of ALCAM and found ALCAM inhibited IFN-γ, TNF-α, and CCL5 release after 24-48h, as well as inhibiting CD69 expression. Together, these data show ALCAM is a critical regulator of metastasis and immune evasion in neuroblastoma, and using the CX-2009 platform, is a tractable immunotherapeutic target.
Generating a *Drosophila* model of human hypersomnia informed by genetic findings

Kyla Mace

Advisor: Matthew Kayser, M.D., Ph.D.

Idiopathic hypersomnia (IH) is characterized by excessive daytime sleepiness despite normal nighttime sleep and without any medical explanation. The pathophysiology of IH is poorly understood, impeded by the lack of animal models of the disorder. Recent work has identified single nucleotide polymorphisms associated with hypersomnia traits such as excessive daytime sleepiness, daytime naps, and long sleep duration. Using the fruit fly, a powerful model organism for studying sleep and circadian behavior, I sought to generate a model of hypersomnia informed by these human genetic findings to investigate its underlying molecular mechanisms. I completed a reverse-genetic knockdown screen of >180 *Drosophila* orthologs of putative hypersomnia trait-associated genes and identified genes whose knockdown in either neurons or glia produced long-sleeping flies. Through this screen, I found that neuronal knockdown of the axon guidance factor *beat-la* recapitulates several characteristics of human hypersomnia: compared to control animals, *beat-la* knockdown flies sleep more, are harder to wake from sleep, and fall back asleep more quickly after being woken. Developmental knockdown of *beat-la* is sufficient to increase adult sleep, suggesting a role in patterning adult neural circuits. I am working now to further define when, where, and how *beat-la* acts to regulate sleep, as well as a potential sleep regulatory role for its human homolog, *CADM2*. 
Neuronal and homeostatic regulation of sleep by the preoptic area and tuberomammillary nucleus

John Maurer

Advisor: Shinjae Chung, Ph.D.

While sleep is evolutionarily conserved across all animals studied, the precise function of sleep remains unknown. It is vital that organisms receive an adequate amount of sleep, as sleep deprivation has profound physiological effects. The preoptic area (POA) of the hypothalamus contains sleep-active GABAergic neurons and activation of their axons innervating the wake-active tuberomammillary nucleus histamine (TMNHIS) neurons are critical for sleep regulation. However, it is not yet understood exactly how the activity of POA GABAergic axonal projections to the TMN (POAGABA→TMN) changes in response to increased sleep need and whether they are necessary to integrate homeostatic pressure. Using fiber photometry in mice, we have found that TMNHIS neurons are most active at wake onset, but as mice transition from wake to NREM sleep the activity gradually decreases and continues to decrease until they reach their lowest activity during REM sleep. Conversely, fiber photometry also revealed that POAGABA→TMN neurons are sleep active, with most mice displaying the highest population activity during REM sleep. Following sleep deprivation, the sleep-active POAGABA→TMN neurons display elevated activity during sleep rebound across all sleep states, suggesting an important role of these neurons in regulating sleep homeostasis. Using optogenetics, we found that inhibition of TMNHIS neurons during sleep rebound produces a deeper quality of sleep, suggesting the inhibition of these neurons is a critical component of regulating sleep in response to sleep need. Future experiments aim to address whether inhibition of POAGABA→TMN neurons is necessary for sleep rebound and how individual POAGABA→TMN neurons respond to sleep loss. Together, these studies will identify novel circuit mechanisms by which the POA and TMN coordinate their activity during sleep/wake and periods of homeostatic sleep pressure.
Subcellular localization patterns and protein-protein interaction networks of wild-type human TRPML1 and mild and severe Mucolipidosis type IV-causing mutations

Bridget McVeigh

Advisor: Vera Moiseenkova-Bell, Ph.D.

Transient receptor potential mucolipin 1 (hTRPML1) is a ubiquitously expressed, nonselective, cation-permeable ion channel from the TRP channel super-family with polymodal activation and localization to the membranes of late endosomes and lysosomes (LEL), where it mediates calcium (Ca$^{2+}$) flux from the lysosomal lumen to the cytosol to coordinate membrane trafficking events, endocytosis, autophagy, and lysosomal biogenesis and exocytosis. Dysfunctional hTRPML1 activity underlies numerous neurodegenerative disorders due to the accumulation of lysosomal cargo, compromised heavy metal homeostasis, and reactive oxygen species formation, therefore it serves as a potential therapeutic target. Specifically, loss-of-function mutations in the TRPML1 gene, MCOLN1, causes Mucolipidosis type IV (MLIV) disease, an autosomal recessive neurodegenerative lysosomal storage disease. To further the current understanding of TRPML1 endogenous function, we studied the consequences of a mild (F408Δ) and severe (F465L) MLIV-causing mutations on wild-type hTRPML1 by exploiting the dual-function of APEX2, an ascorbate peroxidase, which was engineered as a tag to generate local contrast for transmission electron microscopy and to covalently biotinylate proximal proteins for proteomic screens. Our results identified TRPML1 localization patterns within intimate interorganelle contact sites and revealed previously known protein-protein interactors of TRPML1 as well as novel proteins that could provide insight into MLIV-disease progression and other neurodegenerative diseases with similar cellular pathogenesis.
Generating bispecific antibody DNA therapies for the immune targeting of carbonic anhydrase 9 in renal cell carcinoma

Ryan O’Connell

Advisor: David Weiner, Ph.D.

Renal cell carcinoma (RCC) is responsible for 90% of kidney cancers and stands as the 9th most common cancer in men and 14th most common cancer in women worldwide. Creating new, immune-based approaches to RCC therapy may provide patients with a path forward in managing their disease. Bispecific T cell engagers (BTEs) are promising antibody therapies equipped with dual specificity for cancer and T cell antigens, empowering them to direct and stimulate T-cell cytotoxic activity at the tumor site. Dramatic improvements to circulation time have been made by introducing an Fc region linked in a single-chain format to the canonical BTE molecule, and further improvements to potency and efficacy may yet be achieved with multivalent designs offering greater avidity. DNA-encoding such therapies as DNA-based BTEs (DBTEs) and administering them as plasmids for synthesis and secretion can offer even greater longevity of expression and a better safety profile. 90% of RCC cases involve significant overexpression of the tumor-associated antigen, carbonic anhydrase 9 (CA9), providing an ideal target for new innovation. However, no bispecific antibody therapies have been described for CA9, nor are there any bispecific antibody therapies in current clinical trials for RCC. Here we describe a panel of novel CA9-targeted DBTEs that includes canonical and half-life extended DBTEs, as well as a novel half-life/valency-enhanced (HLV) design with bivalency for CA9. We demonstrate 2.5-fold higher target cell binding to CA9-expressing cells with the HLV DBTE. We further illustrate the effective induction of cytotoxicity against RCC cell lines in vitro amongst all DBTEs, with the greatest potency achieved by the HLV DBTE at low, picomolar levels. We then use the canonical BTE to investigate pronounced T cell activation in vitro, before testing in vivo suggests extended expression with DNA and tumor control in a RCC xenograft, NSG mouse model. These data support further investigation of these DBTEs as potential therapies in RCC.
Alternative Splicing (AS) is an ubiquitous process in which a primary RNA transcript is processed by variable inclusion of exon and intron elements. This process is primarily regulated by functional cis-regulatory elements in the pre-mRNA and the trans-acting factors (RNA-binding proteins) that recognize and bind to these cis-elements to either promote or suppress the assembly of spliceosome at adjacent splice sites.

Studies have shown that, upon T-cell Receptor (TCR) activation, a significant number of genes associated with various signaling pathways, including the type-1 interferon (IFN) signaling pathway, are alternatively spliced. The underlying regulatory mechanisms of AS events of the IFN-signaling molecules and their impact on overall immune signaling network are yet to be fully understood.

Here we have identified and are studying an AS event of the Interferon Regulatory Factor-7 (IRF7), a master transcription factor in type-1 IFN signaling, that occurs upon activation of Jurkat cells, a model T-cell line. The observed splicing event, an alternative intron-1 usage in IRF7, adds a proline-rich 20aa region in the N-terminus adjacent to the DNA-binding domain and results in an alternate translation start site. Such splice-mediated alterations in the N-terminal end potentially have functional consequences. We have established that both IRF7 transcript variants, IRF7-canonical (Intron-1 skipped) and IRF7-alternative (Intron-1 retained) give rise to protein, and we are currently defining the isoform-specific functional differences; particularly their binding partners, stability, localization, DNA-binding activities, and eventually their roles in type-1 IFN response. Moreover, we are also interested in uncovering the underlying mechanistic basis of the IRF7 intron-1 retention, which looks interesting: the retained intron is short (85nt), GC-rich, has weak splice-sites, and contains GC-inverted repeats that fold transcript into RNA secondary structures. Such features in RNA are known to regulate splicing by altering the availability of cis-regulatory elements to the splicing machinery and trans-acting factors, which suggests that all or a combination of the IRF7 intron-1 features might contribute to the signal-induced intron-1 splicing event.

Together, defining the molecular mechanisms of the IRF7 intron-1 splicing event and functional differences of the splice variants will enhance our understanding on regulation of signal-induced splicing events, particularly intron-retention, and role of such events in modulating cellular type-1 IFN response.
Co-delivery of DNA-encoded bispecific T cell engagers (DBTEs) effectively controls heterogeneous GBM tumors and mitigates antigen escape

Daniel Park

Advisor: David Weiner, Ph.D.

Immunotherapy has revolutionized the cancer treatment, providing potential treatment options for hard-to-kill cancers such as glioblastoma multiforme (GBM). GBM is the most common and most aggressive brain cancer with a five-year survival rate of less than 5% and a median survival of 15 months. GBM displays a heterogeneous landscape of antigen expression including EGFR variant III (EGFRvIII) and HER2, which are expressed in up to 50% and 80% of GBM cases, respectively. This heterogeneity allows for tumor escape in single-agent immunotherapies which showed promising preclinical findings but have failed to demonstrate a significant clinical benefit beyond the standard of care in GBM patients thus far. An immunotherapeutic approach that targets multiple GBM antigens would show enhanced killing of heterogeneous tumors and mitigate antigen escape. To investigate this hypothesis, we developed and characterized EGFRvIII-targeted DNA-encoded bispecific T cell engager (EGFRvIII-DBTE) and studied it together with HER2-DBTE in a heterogeneous GBM model. We observed that EGFRvIII-DBTE was highly specific and capable of inducing cytotoxicity in EGFRvIII-expressing tumor cells. EGFRvIII-DBTE was well tolerated in NSG mice, displaying durable in vivo expression that lasted over 100 days with a single injection. In an intracranial GBM challenge, a single injection of EGFRvIII-DBTE exhibited robust tumor regression and clearance in NSG mice which was not observed with an empty vehicle control or irrelevant DBTE control. Finally, we developed a heterogeneous GBM challenge model using EGFRvIII-expressing U87 and HER2-expressing U251 cells and studied the efficacy of co-delivery of EGFRvIII-DBTE and HER2-DBTE in the challenge. We observed that co-administration of both DBTEs showed enhanced suppression of heterogeneous tumors and improved survival while single DBTE treatments showed modest tumor control. The brain sections of the challenged mice showed that the co-delivery of DBTEs mitigated antigen escape while single DBTE treatments allowed for antigen escape. These studies support that combined in vivo delivery of DBTEs targeting both EGFRvIII and HER2 can potentially improve outcomes of GBM immunotherapy and deserve additional study.
Insulin-induced AKR1C3 Metabolizes Classical and 11-oxygenated Androgens in a Model of PCOS Adipocytes

Ryan D. Paulukinas

Advisor: Trevor M. Penning, Ph.D.

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinopathy in reproductive-age women. PCOS patients commonly develop hyperandrogenism and this androgen excess (AE) is believed to drive the syndrome. PCOS women also characteristically develop insulin resistance (IR), which correlates with AE in PCOS women. Aldo-keto reductase family 1 member C3 (AKR1C3) catalyzes the conversion of peripheral androgens and is induced by insulin in adipocytes. Classically, AKR1C3 converts Δ4-androstene-3,17-dione (4AD) to testosterone (T) and 5α-androstane-3,17-dione (5AD) to 5α-dihydrotestosterone (DHT). As a result, androgen conversion in adipocytes may contribute to the AE of PCOS women. Additionally, the 11-oxygenated androgens of adrenal origin were reported as the dominant androgens of PCOS and may be an alternative source of AE. AKR1C3 can also convert 11-keto-Δ4-androstene-3,17-dione (11K-4AD) to 11-ketotestosterone (11K-T) and 11-keto-5α-androstane-3,17-dione (11K-5AD) to 11-keto-5α-dihydrotestosterone (11K-DHT). T, DHT, 11K-T and 11K-DHT are potent agonists for the androgen receptor (AR). Therefore, overexpression of AKR1C3 by insulin could increase AR activation through production of both classical and 11-keto potent androgens. We hypothesize that AKR1C3 induced by insulin will produce 11K-T and 11K-DHT in a model of PCOS adipocytes. We developed a stable-isotope-dilution liquid chromatography high resolution mass spectrometric assay (SID-LC-HRMS) for the quantification of both classical and 11-oxygenated androgens in differentiated Simpson-Golabi-Behmel Syndrome adipocytes. Cells were treated with 4AD, 11K-4AD, or 11β-hydroxy-Δ4-androstene-3,17-dione (11β-OH-4AD), the adrenal precursor to 11K-4AD. Androgens were derivatized with Girard P to enhance sensitivity and specificity. Analyte peaks were quantified using calibration curves of analyte to internal standard ratios versus pg of authentic standard. Our data suggests that 11β-OH-4AD is converted to 11K-4AD, which is then converted by insulin-induced AKR1C3 to 11K-T. The conversion of 11K-4AD to 11K-T was AKR1C3 dependent since a panel of AKR1C3 inhibitors blocked 11K-T formation. We found that 11K-T is inactivated to the less potent 11β-hydroxytestosterone (11β-OH-T) by 11β-hydroxy steroid dehydrogenase type 1 (HSD11B1). This suggests that HSD11B1 protects the AR from over-activation by converting potent 11-keto androgens to their less potent 11β-hydroxy counterparts. Both classical and 11-oxygenated androgens may be sources of AE in PCOS by their intracrine formation in adipocytes. Our work elucidates the role of AKR1C3 in the formation of both
classical and 11-keto potent androgens in a model of PCOS adipocytes and supports AKR1C3 as a potential therapeutic target in mitigating the AE of PCOS.
Receptor Interacting Protein 140 (RIP140) modulates cardiac hypertrophic remodeling and muscle endurance fitness

Elizabeth Pruzinsky

Advisor: Daniel Kelly, M.D.

The main source of ATP produced in striated muscle is driven by fatty acid oxidation. During the development of heart failure, the capacity for myocardial fatty acid oxidation and oxidative phosphorylation is reduced, leading to an energy-starved heart. Similar metabolic derangements occur in skeletal muscle during heart failure and with detraining associated with chronic disease states. Receptor Interacting Protein 140 (RIP140) is a nuclear receptor co-regulator that has been shown to repress genes involved in oxidative metabolism. To investigate the role of RIP140 in heart and skeletal muscle, striated muscle-specific RIP140 KO mice (str-RIP140−/−) were generated and characterized. RNA-sequencing revealed broad upregulation of cardiac and skeletal muscle genes involved in mitochondrial oxidative metabolism including fatty acid oxidation, oxidative phosphorylation, and branched-chain amino acid degradation. In a model of chronic progressive left ventricular pressure overload, str-RIP140−/− mice were resistant to the development of cardiac hypertrophy and left ventricular diastolic dysfunction. In addition, str-RIP140−/− mice display a remarkable endurance performance phenotype. Specifically, str-RIP140−/− mice run significantly longer on an endurance treadmill regimen and have increased VO₂max. Respiratory Exchange Ratio (RER) is significantly decreased during exercise in str-RIP140−/− mice, indicative of increased utilization of fatty acids. Lastly, str-RIP140−/− mice are resistant to aging-related diminution in exercise performance. We conclude that genetic RIP140 loss-of-function offers protection against pathologic cardiac hypertrophic growth/dysfunction and enhances skeletal muscle oxidative capacity and endurance performance in pre-clinical models. These results suggest that RIP140 could prove to be a target for novel metabolic therapies aimed at cardiac and skeletal muscle diseases. This work was supported by NIH grants R01DK045416 (D.P.K.), R01HL128349 (D.P.K.) and 5T32AR053461-15 (E. P.).
Investigating the Influence of Periconceptional Exposure to Phthalate on DNA Methylation and Disease Risk by Dissecting Windows of Susceptibility

Nicole M. Robles-Matos

Advisor: Marisa S. Bartolomei, Ph.D.

Environmental exposure to endocrine disrupting chemicals (EDCs) during fetal and placental development may perturb placental function, a critical determinant of fetal health outcomes throughout pregnancy and post-natal diseases. EDCs in maternal blood can cross into the placenta to disrupt placental growth and vascularization which correlated with low birth weight and increase risk of obesity and diabetes later in life. One EDC strongly associated with these developmental changes is Di-(2-ethylhexyl)-phthalate (DEHP). DEHP is often used in the production of plastics and it is ubiquitous in the environment present in food containers, children’s toys, and medical devices. DEHP functions as an anti-androgen in the fetal and placental endocrine systems and interferes with the action of several hormones. As a result, DEHP exposure during pregnancy and/or lactation may result in metabolic and neurological deficits later in life. How these early life challenges elicit lasting effects throughout post-natal life, however, remains unclear. Epigenetic dysregulation has been proposed as a potential mechanism playing a key role in gene-environment interactions. One epigenetic factor, DNA methylation, is particularly vulnerable to environmental exposures as it changes dynamically during fetal development. Offspring phenotypes often depend on the timing of the exposure, thus, we hypothesize that preconception exposure to DEHP alone, similar to a preconception-gestation exposure, disrupts global DNA methylation patterns and growth of the embryo and the placenta. To test this hypothesis, F0 dams were exposed to two doses of DEHP-containing feed (Lower: 50 ug/kg/d, Upper: 10 mg/kg/d) starting two weeks prior to conception until (1) gestational day 0.5 or (2) embryonic day (E) 12.5. At E12.5, fetal and placental weights and fetus:placenta (F:P) ratio were measured. Global DNA methylation was assessed on E12.5 placentas using a LUMinometric Methylation Assay (LUMA). We found that upper-DEHP exposure during preconception-gestation exposure window is associated with a reduction in fetal weight and F:P ratio compared to controls. To correlate these findings with molecular changes, our global methylation analysis revealed a significant hypomethylation of E12.5 female placentas exposed to upper-DEHP during preconception and preconception-gestation windows. Finally, we found a reduction in the number of blood vessels on the labyrinth zone of E12.5 placentas using CD34 histological analysis. Our data suggests that DEHP affects the fetus and the placenta in a dose- and sex-specific manner.
Mutated FUS imparts a loss-of-function mechanism that can be restored through inhibiting ADP-ribosylation

Laura Romano

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

An ongoing debate in the field of neurodegenerative disease is whether disease-causing mutations impart a gain-of-function or loss-of-function to the mutated protein. It is generally recognized that both gain- and loss-of functions occur to the mutated protein, with both mechanisms contributing roles to the manifestation of disease. Here, we have identified a loss-of-function mechanism for the RNA-binding protein, fused in sarcoma (FUS). Mutations in the FUS gene have been shown to be causative for neurodegenerative disease like amyotrophic lateral sclerosis (ALS). We identified a FUS mutation that abrogates interaction with proteasome regulator of 31 kDa (PI31). Loss of this interaction leads to aberrant translation of glutamate dehydrogenase 2 (GLUD2) mRNA, as shown in vitro and with ALS patient-derived fibroblasts. Furthermore, we identified Tankyrse-mediated ADP-ribosylation of PI31 as a posttranslational modification that mimics the FUS mutant to weaken the FUS-PI31 interaction. XAV939, a small-molecule inhibitor of Tankyrase, reduces glutamate dehydrogenase 2 protein levels and therefore has therapeutic potential to restore the loss-of-function imparted by our FUS mutant.
CB2-Selective Cannabinoids as Modulators of HIV-1 Infection & Activation in Brain-Resident Myeloid Cells

Alexander Starr

Advisor: Kelly Jordan-Sciutto, Ph.D.

In the CNS, Human Immunodeficiency Virus-1 (HIV) infects both brain-resident macrophages and microglia, resulting in pro-inflammatory activation and a viral reservoir that persists despite anti-retroviral treatment. Given that neurons cannot be infected with HIV, it is likely that indirect, myeloid-cell mediated neurotoxicity contributes to the mood, memory, and cognitive deficits collectively referred to as HIV-associated neurocognitive disorders (HAND). Here, after characterizing the expression of endocannabinoid components in our human, in vitro myeloid cell models, we examine the effects of the CB2-specific agonist, JWH-133, on HIV infection kinetics and glutamate uptake. Findings indicate that CB2 agonists attenuate viral replication in a time- and dose-specific manner, and they have no impact on HIV-driven alterations in glutamate uptake. This confirms a role for CB2 signaling in the myeloid cell antiviral response and implies that previously reported neuroprotective effects of cannabinoids in the context of HAND are not glutamate-dependent.
Examining dendritic cell heterogeneity in the tumor microenvironment

Jerrick To

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

Dendritic cells (DCs) are key antigen-presenting cells comprising of functionally and phenotypically distinct subsets. DCs are rare in tumors where their heterogeneity remains unclear. To overcome the limitations of surface marker-based analyses, we utilized genetically engineered DC-reporter mice (Zbtb46-GFP) to isolate tissue and tumor DCs and performed single-cell RNA sequencing (scRNA-seq). Through the scRNA-seq approach, the major ontological DC subsets (CD103+ DC1 and CD11b+ DC2) were identified along with two activated DC subsets. One activated subset displayed a hallmark DC migratory program (migratory DC or mDC) and showed superior T cell stimulatory properties. Notably, tumors also harbored a distinct subset of activated DCs that lack a migratory program, instead displaying signature of interferon exposure (interferon-DCs or IFN-DC). IFN-DCs were proficient in antigen-presentation, supported T cell proliferation, and expressed T cell-recruiting chemokines. Using a combination of genetic, pharmacologic, and computational approaches, we further show that both type I and II interferons can regulate IFN-DCs from DC2s in the tumor microenvironment. Taken together, our findings illuminate DC heterogeneity in tumors and suggest a ‘division of labor’ amongst activated DCs, whereby mDCs migrate to and drive T cell priming in draining lymph nodes while IFN-DCs help recruit T cells and regulate their function within the tumor microenvironment. Finally, analysis of DCs from an aggregated human mononuclear phagocyte scRNA-seq dataset revealed a similar split in migratory or interferon-signaling modules among human tumor DCs.
Hepatocellular Carcinoma (HCC) is the most prevalent type of liver cancer and the third leading cause of cancer deaths worldwide. Unlike most other cancer types, the incidence rate for HCC continues to rise with over 800,000 cases diagnosed annually worldwide. The first-line treatment for HCC has long been the multi-kinase inhibitor sorafenib, which extends survival by only three months on average. We have completed a CRISPR activation screen in mice livers of genes that are upregulated in human HCC. We found that upregulated Clk2 expression can drive hyperproliferation in the mouse liver. CLK2 is a gene involved in splicing that has been found to be a driver in several solid cancers, and early work with inhibitors looks promising. This study has the potential to impact on the care of patients with HCC in the US and worldwide.
Investigating the Role of β-cell Senescence in Type 2 Diabetes Pathology

Eric Waite

Advisor: Klaus Kaestner, Ph.D.

The risk of developing Type 2 Diabetes (T2D) increases with age, but little is known about the underlying disease mechanisms that contribute to this phenomenon. One of the hallmarks of aging is the accumulation senescent cells. Senescent cells display a complex phenotype characterized by permanent growth arrest, macromolecular damage, metabolic derangement, and a pro-inflammatory secretory phenotype, and have been shown to drive age-related phenotypes in a subset of organs. Consequently, the discovery of β-cells with a senescent-like signature triggered excitement about the possibility of targeting this senescent β-cell subpopulation to potentially delay T2D onset or treat existing disease. While it appears that the incidence of β-cell senescence increases with both age and T2D in humans and animal models, the existing data are preliminary, inconsistent, and require additional confirmation. Previous work has relied on organism-wide transgene-mediated senescent cell ablation (senolysis) and the systemic administration of putative senolytic small molecules that result in the ablation of numerous senescent and non-senescent cell populations, producing confounding effects when attempting to investigate specific senescent cell populations. These investigations found that organism-wide senolysis improved glucose homeostasis and β-cell function and identity. To complicate matters, others have found that overexpressing p16\textsuperscript{Ink4a}, a cell cycle inhibitor and marker and effector of cellular senescence, in β-cells enhances glucose stimulated insulin secretion, seemingly beneficial in a diabetic state. Therefore, cell type-specific senescent cell ablation is a critical next step in validating senescent cells as valid therapeutic targets not just in T2D, but in many other disease contexts. The novel, cell type-specific senolysis mouse model proposed here, the ‘SenKiller’ mouse, will employ a fragment of the p16\textsuperscript{Ink4a} promoter, the same fragment employed by the organism-wide transgenic models mentioned above, a lox-stop-lox cassette harboring an mCherry fluorescent reporter, and an EGFP-tagged diphtheria toxin receptor (DTR-EGFP) to effect cell death following Cre-mediated recombination and diphtheria toxin (DT) administration. In combination with the multitude of available cell-type specific Cre-driver lines, the SenKiller mouse will be an important tool for investigating the role of senescence in T2D and, more broadly, in mammalian physiology and pathology. In this proposal, an extensively validated β-cell specific Cre-line will be used in conjunction with the SenKiller mouse to generate double-transgenics so that while all senescent, p16\textsuperscript{+} cells in the mouse will express mCherry, only senescent, p16\textsuperscript{+} β-cells will express the DTR-EGFP transgene. A high fat diet will be used to model T2D and senescent, p16\textsuperscript{+} β-cells will be ablated with DT both during disease progression and
after glucose intolerance has already been established. The experiments proposed here will unequivocally determine if the specific elimination of senescent β-cells is a viable therapeutic approach for the treatment or prevention of T2D.
Regulation of sleep and wake by corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus

Alyssa Wiest

Advisor: Shinjae Chung, Ph.D.

Sleep is an evolutionarily conserved behavior that is widely observed across the animal kingdom. It is characterized by transitions between different vigilance states: wake, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. As sleep has many beneficial and restorative effects, good quality sleep is important for mental and physical health. Stress is known to be a major cause of disrupted sleep and chronic sleep disruption can lead to an increased risk of developing psychiatric disorders. The paraventricular nucleus of the hypothalamus (PVN) contains corticotropin-releasing hormone (CRH-PVN) neurons that have been shown to be activated by many different stressors, including social defeat and restraint stress. While known as a crucial center for sleep regulation, the preoptic area of the hypothalamus contains a population of glutamatergic, wake-promoting neurons (VGLUT-POA) that are activated by stress and encode negative valence. We hypothesized that extended activation of these two populations of wake-promoting, stress-active neurons would result in sleep disturbances like those seen after acute stress. When mice are subjected to acute restraint stress, they experience a decrease in NREM and REM sleep and increase in wake percentage within the first few hours following the stress. When these two populations are activated for an extended period, each produces a distinct sleep phenotype. During the one-hour stimulation period, both CRH-PVN and VGLUT-POA mice stayed awake for an average of 72% and 78% of the hour, respectively. During the two-hour period immediately following the stimulation, CRH-PVN mice showed a significant increase in REM sleep percentage due to a significantly increased frequency when compared to baseline recordings. VGLUT-POA mice showed an increase in wake percentage and decrease in NREM and REM sleep percentages compared to baseline recordings, similar to acute restraint stress. Extended activation of two populations of wake-promoting, stress-active neurons produces two distinctly different sleep phenotypes.
Characterizing the immunomodulatory and oncogenic roles of B7-H3 in neuroblastoma

Catherine L. Wingrove

Advisor: John Maris, M.D.

Neuroblastoma is a tumor of the developing sympathetic nervous system and the most commonly diagnosed extracranial solid tumor of childhood. About half of patients have high-risk disease characterized by widespread metastases upon diagnosis, with amplification of the MYCN oncogene being a seminal cancer driver in 20% of cases. Despite intensive chemotherapy regimens and recent advances in immunotherapy, less than half of high-risk patients are cured, and relapsed disease is uniformly fatal. Therefore, there is an unmet need for the development of new therapies for high-risk neuroblastoma. B7-H3, encoded by the CD276 gene, is a type 1 transmembrane protein in the B7 family of immunoregulatory proteins and is highly expressed in many adult and pediatric cancers, including neuroblastoma. Preclinical success of several immunotherapeutic strategies directed toward B7-H3, including CAR-T cells and antibody drug conjugates, suggest that B7-H3 is a targetable tumor-associated antigen. B7-H3 has been shown to have both stimulatory and inhibitory effects on T and NK cells. Thus, the nature of this protein is controversial and likely cell-context dependent. To determine the effects of B7-H3 on T cell function, we activated CD4+/CD8+ T cells in the presence of immobilized B7-H3. In this tumor-free context, B7-H3 inhibits CD3/CD28-mediated T cell activation. To probe the effects of B7-H3 in a tumor-specific context, we used CRISPRi and CRISPR/Cas9 gene editing to deplete B7-H3 from neuroblastoma cell lines. CAR-T cells specific for neuroblastoma-specific PHOX2B peptides released more IFN-γ when targeting SKNAS isogenic B7-H3-depleted tumor cells. Finally, we investigated secretion of the immunosuppressive cytokine, TGF-β, and found that B7-H3 depleted cells secrete less TGF-β than controls. Altogether, our data suggest that B7-H3 expressed on neuroblastoma cells may regulate the secretion of immunosuppressive cytokines and functions as a coinhibitory ligand to modulate T cell activity.
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 present in 14% of patients with the most aggressive form of the disease, positioning ALK as a promising target for NB therapy. The first generation ALK inhibitor, crizotinib has shown limited anti-tumor activity in patients with ALK driven relapsed NB leading to opening of new clinical trial with highly potent third generation ALK inhibitor, lorlatinib. The analysis of ALK variant mutations using circulating tumor DNA throughout the trial has shown rise in secondary ALK mutations (G1202R and L1196M) in addition to primary driving ALK mutations (F1174L and R1275Q). More importantly the secondary ALK mutations coocurred with patients disease progression.

To understand if the secondary ALK mutations cause resistance to Lorlatinib, we employed in silico methods to analyze ALK binding pocket structure as well lorlatinib binding thermodynamics and kinetics. The lorlatinib binding thermodynamic studies showed that acquisition of secondary mutations reduces the energy of binding except in the case of F1174L+G1202R mutation. However, structural analysis of the drug binding pocket showed that throughout simulation the mutated Arg 1202 adapts conformation which occludes binding pocket and prevents lorlatinib binding. Furthermore, kinetic model of lorlatinib binding which accounts for ALK open and closed binding pocket conformations (controlled by Arg 1202 residue position), showed increase in drug IC50. Taken together, the structural and thermodynamic data suggest that secondary ALK mutations cause resistance to lorlatinib by decreasing energy of drug binding or causing binding pocket structural conformation where the mutated Arg 1202 residue occludes binding pocket.
Recent Graduates

**Kryshawna Beard**
Mentor: David Meaney, PhD
Evaluating brain derived extracellular vesicles as diagnostic biomarkers of traumatic brain injury
Post PhD Plans: Academic editor in clinical medicine for Research Square Company

**Keith Campagno**
Mentor: Claire Mitchell, PhD
P2X7 Receptor Stimulation and Elevated Intraocular Pressure Rapidly Alter Microglia Morphology, State Markers, and Cytokine Release
Post PhD Plans: Intern, Project Development Regulatory, Genentech

**Suhee Chang**
Mentor: Marisa Bartolomei, PhD
The Developmental Role of H19 and IGF2 in Mouse and Human
Post PhD Plans: Postdoc; Johns Hopkins University, Jeff Coller’s lab studying tRNA suppressors on premature termination codons.

**Ryan Cupo**
Mentor: James Shorter, PhD
Discovery of a Human Mitochondrial Protein Disagggregase, SKD3
Post PhD Plans: Postdoc; Dr. Richard Youle at the National Institute of Neurological Disease and Stroke in the National Institutes of Health (NIH).
Emily Fabyanic
Mentor: Hao Wu, PhD
*Development of Single-Cell Transcriptomic and Epigenomic Sequencing Technologies to Assess Cell-Type-Specific Gene Regulatory Programs in Mammalian Brains*

Post PhD Plans: Next Generation Sequencing Scientist, Spark Therapeutics

Daniel Jacome
Mentor: Mark Sellymer, MD, PhD
*Imaging and Manipulating Cells and Their Interactions with Trimethoprim-Based Tools*

Post PhD Plans: Senior Consultant at Trinity Life Sciences

Claire Meurice
Mentor: Kelly Jordan-Sciutto, PhD
*Development and Validation of a Novel E2F1 Mouse Model to Evaluate the Cell-Type Specific Contribution of E2F1 to Age-Associated Neurodegeneration*

Post PhD Plans: Postdoctoral Fellow at Sanofi

Rebecca Myers
Mentor: Peter Klein, MD, PhD
*APC and GSK-3 Regulate Hippo Signaling Through Ajuba*

Post PhD Plans: Medical Writer for PRECISIONscientia

Theresa Patten
Mentor: Mariella De Biasi, PhD
*Development of a Mouse Model to Study E-Cigarettes and the Role of a Fruit Flavorant on Adolescent Nicotine Reward*

Post PhD Plans: Post-doc; Dr. Amita Sehgal's; Pennsylvania School of Medicine, investigating the underlying mechanisms of homeostatic sleep in Drosophila melanogaster.
Natalia Amaris Quijano Carde

Mentor: Mariella De Biasi, PhD  
*Preclinical Investigations of Genetic Correlates of Alcohol Use Disorder*  
Post PhD Plans: Post-doc., Clinical Pharmacology and Pharmacometrics supporting the Oncology and Neuroscience therapeutic areas, Janssen R&D.

Andrea Rodriguez Rios (Guzman)

Mentor: Edward J. (Jim) Delikatny, PhD  
*Development of a pH-Sensitive Probe for In Vivo Cerenkov Imaging of the Tumor Microenvironment*  
Post PhD Plans: Medical Writer at PrecisionScientia

Ryan von Kleeck

Mentor: Richard Assoian, PhD  
*Mechanisms of Early Arterial Stiffening and Reduced Smooth Muscle Contractility in the Premature Aging Disease Hutchinson-Gilford Progeria Syndrome aging disease Hutchinson-Gilford Progeria Syndrome.*  
Post PhD Plans: In-vivo research group at Vesigen Therapeutics in Cambridge, MA focusing on understanding how extracellular vesicles can be used to deliver therapeutic technologies for various diseases.

Khadija Wilson

Mentor: Ben Garcia, PhD, FRSC  
*Elucidating the Pathological Mechanism of Histone H3.3 Mutations in Neurodevelopment*  
Post PhD Plans: Technical Specialist at Sterne, Kessler, Goldstein & Fox, P.L.L.C.
First Year Students

Kobe Abney
School: SPELMAN COLLEGE

Laboratory Rotations
(1) Eddie Lee
(2) Jake Brenner
(3) Rebecca Simmons

Nicole Carrillo Vallejo
School: COLLEGE OF WILLIAM AND MARY

Laboratory Rotations
(1) Andrew Tsourkas
(2) Mark Sellmyer
(3) Jake Brenner

Samuelle Delcy
School: CUNY BROOKLYN COLLEGE

Laboratory Rotations
(1) Akiva Cohen
(2) D. Kacy Cullen

Thesis Lab: Cohen Lab
Carolann Espy
School: GEORGIA INSTITUTE OF TECHNOLOGY
Laboratory Rotations
(1) Jake Brenner  
(2) Jim Shorter  
(3) Joe Zhou

Christine Faunce
School: VIRGINIA TECH
Laboratory Rotations
(1) Megan Matthews  
(2) Shelley Berger  
(3) Ronen Marmorstein

Julia Rocereta
School: MUHLENBERG COLLEGE
Laboratory Rotations
(1) Vera Moiseenkov-Bell  
(2) Roderic Eckenhoff  
(3) Melike Lakadamyali
Thesis Lab: Moiseenkov-Bell

Galina Rozenberg
School: OHIO STATE UNIVERSITY
Laboratory Rotations
(1) Kelly Jordan-Sciutto  
(2) Garret FitzGerald  
(3) Maayan Levy
Junyoung Shin

School: MASSACHUSETTS COLLEGE OF PHARMACY AND HEALTH SCIENCES

Laboratory Rotations
(1) Xiaolu Yang
(2) Yi Fan
(3) Patrick Grohar

Emma Tyner

School: PACIFIC UNION COLLEGE

Laboratory Rotations
(1) D. Kacy Cullen
(2) Julie Blendy
(3) Heath Schmidt

Alaina Wojciechowski

School: UNIVERSITY AT BUFFALO (SUNY)

Laboratory Rotations
(1) Shelley Berger
(2) Duniaef
(3) Eddie Lee

Thesis Lab: Dunaief Lab
Current Students

Brandon Anderson

School: Brigham Young University

Email: Brandon.Anderson@pennmedicine.upenn.edu

Laboratory Rotations
(1) Roderic Eckenhoff
(2) Josh Dunaief
(3) Kelly Jordan Sciutto

Doctoral Thesis
Advisor: Dunaief
Protecting the retina by removing ferrous iron through chemical chelation or viral gene transfer of the ferroxidase ceruloplasmin

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)

Email: kbarekat@pennmedicine.upenn.edu

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
Alexander Benton

School: WASHINGTON UNIVERSITY

Email: abbenton@pennmedicine.upenn.edu

Laboratory Rotations
1. Daniel Powell
2. Marco Ruella

Doctoral Thesis
Advisor: Daniel Powell
Site-Specific Integration of CAR T Constructs Targeting Solid Tumors by Homology Directed Repair Using CRISPR/Cas9

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@pennmedicine.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)


Publications


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
Awarded a Predoctoral Training Grant in Pharmacology, T32GM008076. July 2018-July 2019
Christina Brown
School: Coe College
Email: cvbrown@pennmedicine.upenn.edu

Laboratory Rotations
(1) Avery Posey
(2) Patrick Grohar
(3) Yi Fan

Doctoral Thesis
Advisor: Avery Posey

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
Sofia Castelli
School: Drexel University
Email: sofiacas@pennmedicine.upenn.edu

Laboratory Rotations
1. Daniel Powell
2. David Weiner
3. Carl June

Doctoral Thesis
Advisor: Carl June
Mechanism of action of chimeric cytokine receptors to potentiate CAR T cell therapy through IL-9 signaling

Nohelly Derosiers
School: CUNY THE CITY COLLEGE OF NY
Email: nohellyd@pennmedicine.upenn.edu

Laboratory Rotations
1. D. Kacy Cullen
2. Yi Fan
3. Avery Posey

Doctoral Thesis
Advisor: Avery Posey
Investigating the Role of ST6Gal-1 in CD8+ T-cell Stemness and Survival
Kimberly Edwards
School: Mount Holyoke
Email: edwardkj@pennmedicine.upenn.edu

Laboratory Rotations
1. Dmitriy Gabrilovich
2. Mark Sellmyer
3. Robert Mach

Doctoral Thesis
Advisor: Mark Sellmyer
Assessing Immune Cell Activation and Function with Novel PET Imaging Probes

Julia Ferrante
School: Villanova University
Email: jrferran@pennmedicine.upenn.edu

Laboratory Rotations
1. Julie Blendy
2. Heath Schmidt
3. Josh Duniaef

Doctoral Thesis
Advisor: Julie Blendy
Characterizing the role of reactive microglia in Neonatal Opioid Withdrawal Syndrome
Conroy Field

School: University of Delaware

Email: fieldco@pennmedicine.upenn.edu

Laboratory Rotations
1. Mark Kahn
2. Mortimer Poncz
3. Rodney Camire

Doctoral Thesis
Advisor: Mortimer Poncz
Neutrophil role in venous thrombosis: studies in heparin-induced thrombocytopenia and beyond

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@pennmedicine.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.

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.

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

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.

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

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

Email: sghura@pennmedicine.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@pennmedicine.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


Poster Presentations


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.


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)
Nicolas Gonzalez

School: UNIVERSITY OF CALIFORNIA- SANTA CRUZ

Email: nidgonza@pennmedicine.upenn.edu

Laboratory Rotations
1. Nikolaus Sgourakis
2. Michael Milone
3. Wei Tong

Doctoral Thesis
Advisor: Michael Milone
*Characterization of the bone marrow microenvironment that promotes decreased CAR-T cell efficacy in multiple myeloma*

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*
Adrienne Jo
School: CLAREMONT MCKENNA COLLEGE
Email: ajo97@pennmedicine.upenn.edu

Laboratory rotations
1. Mariella De Biasi
2. Kelly Jordan Sciutto
3. Seema Bhatnagar

Doctoral Thesis
Advisor: Seema Bhatnagar
*Individual- and Sex-related Differences in the Effects of Orexins on Stress-induced Drug-motivated Behaviors*

Nathan Kendsersky
School: University of Pittsburgh
B.S. Molecular Biology, Minors in Chemistry and Music (2016)
Email: namich@pennmedicine.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


Zachary Lamplugh

School: SYRACUSE UNIVERSITY

Email: zlamp@pennmedicine.upenn.edu

Laboratory Rotations
1. Yi Fan
2. Ellen Pure
3. Michael Milone

Doctoral Thesis
Advisor: Yi Fan
Reprogramming glioma microenvironment for CAR T immunotherapy

Diane Lee

School: UNIVERSITY OF CALIFORNIA - IRVINE

Email: diane531@pennmedicine.upenn.edu
Laboratory Rotations
1. Akilesh Reddy
2. Hao Wu
3. Benjamin Voight

Doctoral Thesis
Advisor: Benjamin Voight
_Determining the genetic influence of diet on type 2 diabetes and the role of liver in insulin resistance-mediated diabetes_

Grace Lee

School: TRINITY UNIVERSITY
Email: gracesun@pennmedicine.upenn.edu

Laboratory Rotations
1. Joe Zhao
2. Colin Conine
3. Elizabeth Heller

Doctoral Thesis
Advisor: Colin Conine
_Determining the role of sperm microRNAs in early development and epigenetic inheritance in mice_

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*

---

**Sonia Lombroso**

School: WESLEYAN UNIVERSITY

Email: lombroso@pennmedicine.upenn.edu

**Laboratory Rotations**
1. Chris Bennett
2. Shelley Berger
3. Elizabeth Heller

---

**Doctoral Thesis**
Advisor: Chris Bennett
*Discovering Regulators of Macrophage Identity in the Brain*

---

**Kyla Mace**

School: UNIVERSITY NORTH CAROLINA - CHAPEL HILL

Email: kmace@pennmedicine.upenn.edu

**Laboratory Rotations**
1. Julie Blendy
2. Heath Schmidt
3. Matthew Kayser

---

**Doctoral Thesis**
Advisor: Matthew Kayser
*Hypersomnia as a disorder of persistent juvenile sleep*
Dania Malik

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

Email: daniam@pennmedicine.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

Awards
NIH Pharmacology T32 Training Grant (2017, 2018)

Bridget McVeigh

School: UNIVERSITY OF SCRANTON

Email: mcveighb@pennmedicine.upenn.edu

Laboratory Rotations
  1. Vera Moiseenkova-Bell
  2. Kevin Foskett
Doctoral Thesis
Advisor: Vera Moiseenkova-Bell
Subcellular localization patterns and protein-protein interaction networks of wild-type human TRPML1 and mild and severe Mucolipidosis type IV-causing mutations

John Maurer

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

Email: jmau@pennmedicine.upenn.edu

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

Zoey Miller

School: DICKINSON COLLEGE

Email: zoeym@pennmedicine.upenn.edu

Laboratory Rotations
1. Donita Brady
2. Sara Cherry
3. Robert Lee
Doctoral Thesis
Advisor: Robert Lee
*Understanding the Role of Bitter Taste Receptors in Head and Neck Squamous Cell Carcinomas*

**Ryan O’Connell**

School: STONY BROOK UNIVERSITY SUNY

Email: ryanoc7@pennmedicine.upenn.edu

Laboratory Rotations

1. Daniel Rader
2. David Weiner

Doctoral Thesis
Advisor: David Weiner
*Targeting carbonic anhydrase 9 for immune therapy in advanced renal cell carcinoma by monoclonal antibodies and DNA-encoded, T-cell engaging bispecifics*

**Sofya Osharovich**

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

Email: sofyaosh@pennmedicine.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

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

**Asmita Panthi**
School: SOUTH CAROLINA STATE UNIVERSITY
Email: apanthi@pennmedicine.upenn.edu

**Laboratory Rotations**
1. Junwei Shi
2. Jim Shorter
3. Karin Eisinger

**Doctoral Thesis**
Advisor: Kristen Lynch
*Defining the novel regulatory networks, mechanisms, and functions of IRF7 alternative splicing in coregulating innate and adaptive immune responses*

**Daniel Park**
School: Rutgers University, Camden
Email: danipark@pennmedicine.upenn.edu

**Laboratory Rotations**
1. Margaret Chou
2. Michael Farwell
3. David Weiner

**Doctoral Thesis**
Advisor: David Weiner
Evaluating pharmacokinetic profile and T-cell-mediated cytotoxicity of DNA-encoded bispecific antibody in a mouse GBM model

**Ryan Paulukinas**

School: University of the Sciences

Email: Ryan.Paulukinas@pennmedicine.upenn.edu

**Laboratory Rotations**
1. Margaret Chou
2. Trevor Penning
3. Garret FitzGerald

**Doctoral Thesis**
Advisor: Trevor Penning
*The Androgenic Impact of AKR1C3 and the 11-Oxygenated Androgens on PCOS*

**Ross Pirnie**

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

Email: rpirnie@pennmedicine.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

Elizabeth Pruzinsky
School: Drexel University
Email: Elizabeth.Pruzinsky@pennmedicine.upenn.edu

Laboratory Rotations
1. Kirk Wangensteen
2. Yael Mosse
3. Doris Stoffers
4. Daniel Kelly

Doctoral Thesis
Advisor: Daniel Kelly
The role of the nuclear receptor co-repressor RIP140 in the control of muscle fitness

Nicole Robles-Matos
School: University of Puerto Rico, Rio Piedras
B.S. Chemistry (2017)
Email: nroble@pennmedicine.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

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**Laura Romano**
School: Rutgers University  
B.S. Biochemistry (2015)

Email: lromano@pennmedicine.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

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**Chris Roselle**
School: Ithaca College  
BS Biochemistry (2008)

School: Lehigh University  
MS Chemistry (2015)

E-mail: croselle@pennmedicine.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 Δ133p53 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 Δ133p53α 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)


Lauren Shaw

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

Email: lashaw@pennmedicine.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.
Redirecting gene-engineered T-cells through attachment of targeting ligands to universal immune receptors

Doctoral Thesis
Dr. Daniel Powell, Development of universal immune receptors
Prithvi Sinha
School: Johns Hopkins University
Email: prsinha@pennmedicine.upenn.edu

Laboratory Rotations
1. Costas Koumenis
2. Margaret Chou
3. Yi Fan

Doctoral Thesis
Advisor: Yi Fan
*Vascular niche macrophages regulate tumor immunity and induce γδT cell exhaustion in Glioblastoma*

Heather Sosnoski
School: SYRACUSE UNIVERSITY
Email: hsosnosk@pennmedicine.upenn.edu

Laboratory Rotations
1. Yael Mosse
2. Avery Posey
3. Wenchao Song

Doctoral Thesis
Advisor: Avery Posey
*Utilization of Chimeric Autoantibody Receptor T-Cells for Targeted Treatment of Anti-Neutrophil Cytoplasmic Antibody Vasculitis*
Alexander Starr

School: New York University

Email: Alexander.Starr@pennmedicine.upenn.edu

Laboratory Rotations
1. Kelly Jordan Sciutto
2. Frances Jensen
3. Jim Shorter

Doctoral Thesis
Advisor: Kelly Jordan Sciutto

Modulation of the NLRP3 inflammasome by cannabinoids in hiPSC models of HAND

Monica Thapaliya

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

Email: thmonica@pennmedicine.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.
Investigating the role of GRK2 in mast cell mediated allergy and pseudoallergy.
Jerrick To

College of Wooster
B.A. Biochemistry and Molecular Biology (2017)

Email: totsun@pennmedicine.upenn.edu

Laboratory Rotations
(1) Saar Gill, M.D., Ph.D.
Development of anti-IL1RAP CAR T Cells
(2) Dmitry Gabrilovich, 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.

Alexandra Vazquez

School: University of Puerto Rico, Rio Piedras Campus

Email: Alexandra.Vazquez-Salgado@pennmedicine.upenn.edu

Laboratory Rotations
1. Doris Stoffers
2. Peter Klein
3. Kirk Wangensteen

Doctoral Thesis
Advisor: Kirk Wangensteen
Identifying and Characterizing Novel Druggable Targets in Hepatocellular Carcinoma
Eliana von Krusenstiern
School: HAVERFORD COLLEGE
Email: elianav@pennmedicine.upenn.edu

Laboratory Rotations
1. Kelly Jordan Sciutto/Judith Grinspan
2. Katie Bar
3. Jim Delikatny

Doctoral Thesis
Advisor: Kelly Jordan Sciutto/Judith Grinspan
*Role of Stress Granule Sequestration of Myelin mRNAs in the Dysregulation of Oligodendrocyte Maturation*

Eric Waite
School: University of Maryland, College Park
Email: Eric.Waite@pennmedicine.upenn.edu

Laboratory Rotations
1. Margaret Chou
2. John Maris
3. Klaus Kaestner

Doctoral Thesis
Advisor: Klaus Kaestner
*The role of β-cell senescence in the pathology of diabetes*
Katherine Webb

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

Email: katwebb@pennmedicine.upenn.edu

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

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Catherine Wingrove

School: HOPE COLLEGE

Email: catwin@pennmedicine.upenn.edu

Laboratory Rotations
1. Daniel Powell
2. John Maris
3. Margaret Chou

Doctoral Thesis
Advisor: John Maris
*Defining the mechanisms of B7-H3 overexpression and role in immune evasion in neuroblastoma*
Gabriela Witek

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

E-mail: gwitek@pennmedicine.upenn.edu

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

Johnathan Wong

School: LOUISIANA TECH UNIVERSITY

E-mail: jhwong@pennmedicine.upenn.edu

Laboratory Rotations
1. Kelly Jordan Sciutto
2. David Lynch
3. Josh Duniaef

Doctoral Thesis
Advisor: Kelly Jordan Sciutto
Investigating the Regulatory Role of Copper in Myelination
Michael Zaleski

School: NOTRE DAME UNIVERSITY

E-mail: Michael.Zaleski@pennmedicine.upenn.edu

Laboratory Rotations
1. Paul Axelsen
2. Jake Brenner
3. Mehran Mekvandi

Doctoral Thesis
Advisor: Jake Brenner
Nanoparticle surface chemistry and complement activation: enabling the development of new nanomedicines
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


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


Davis PD, Raffen R, Dul LJ, Vogen MS, Williamson KE, Stevens JF, Argon Y.: Inhibition of amyloid fiber


William M. Armstead, Ph.D.
Research Professor, Department of Anesthesia and Critical Care
3 John Morgan Building
Phone: 215-573-3674
Fax: 215-349-5078
Email: armsteaw@uphs.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p10266

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, photothermal 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.


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


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 knockouts/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


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 [Ca2+]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


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


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.


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


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


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


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


Ian A. Blair, Ph.D.
A.N. Richards Professor of Pharmacology, Department of Pharmacology; Director, Center for Cancer Pharmacology; Scientific Director, Abramson Cancer Center Proteomics Facility; Penn Genomics Frontiers Institute Proteomics Facility Director, Systems Biology, Institute for Translational Medicine and Therapeutics; Director, Molecular Profiling Core, Center of Excellence in Environmental Toxicology

854 Biomedical Research Building II/III
Phone: 215-573-9880
Fax: 215-573-9889
Email: ianblair@mail.med.upenn.edu
http://www.med.upenn.edu/blairlab/index.shtml

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


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


**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**


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).


Lawrence Brass, M.D., Ph.D.

Professor of Medicine, Division of Hematology & Oncology
Professor of Systems Pharmacology and Translational Therapeutics
Associate Dean, Combined Degree and Physician Scholars Programs,
University of Pennsylvania, School of Medicine
Director, Penn MSTP

815 Biomedical Research Building II/III
Phone: 215-573-3540
Email: brass@mail.med.upenn.edu
Lab web site: http://www.med.upenn.edu/brasslab/
Faculty listing: http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p15732

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


Rodney M. Camire, Ph.D.
Associate Professor, Department of Pediatrics
5018 Colket Translational Research Building
Phone: 215-590-9968
Fax: 215-590-3660
Email: rcamire@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g5165284/p32208

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
Beatriz M. Carreno, Ph.D.
Research Associate Professor of Pathology and Laboratory Medicine

PCAM South Tower, 8th Floor
Email: bcarreno@exchange.upenn.edu

Selected Publications


Carreno, B.M.: Building Cancer Vaccines From Tumor Mutations. NPR, Science Friday April 2015 Notes: 


Lewis A. Chodosh, M.D., Ph.D.
Professor, Departments of Cancer Biology and Medicine
Chair, Department of Cancer Biology
Associate Director for Basic Science, Abramson Cancer Center
Co-Director, 2-PREVENT Breast Cancer Translational Center of Excellence
614 Biomedical Research Building II/III
Phone: 215-898-1321
Fax: 215-573-6725
Email: chodosh@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p20564

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


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


Shinjae Chung, Ph.D.
Assistant Professor of Neuroscience
Smilow Center for Translational Research, Room 10-133
Philadelphia, PA 19151
Office: 215-746-1122
Email: shinjaec@pennmedicine.upenn.edu
https://chunglab.med.upenn.edu/

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


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.


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D. Kacy Cullen, Ph.D.
Research Associate Professor Of Neurosurgery
105 Hayden Hall / 3320 Smith Walk
Philadelphia, PA 19104
Office: 215-746-8176
Fax: 215-573-3808
Email: dkacy@mail.med.upenn.edu

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


Mariella De Biasi, Ph.D.
Associate Professor of Neuroscience in Psychiatry
Email: marielde@mail.med.upenn.edu
https://www.med.upenn.edu/apps/faculty/index.php/g275/p8658175

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 α3, α5, and β4 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


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


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

Jim Delikatny, Ph.D.
Research Professor, Department of Radiology
317 Anatomy-Chemistry Building
Phone: 215-898-3105
Email: delikatn@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g275/p15538

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


Dennis E. Discher, Ph.D.
Robert D. Bent Professor of Chemical & Biomolecular Engineering
Director of National Cancer Institute-funded Physical Sciences in Oncology Center @ Penn
129 Towne Building
Phone: 215-898-4809
Email: discher@seas.upenn.edu
http://www.seas.upenn.edu/~discher/

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


Joshua L. Dunaief, MD, PhD
Adele Niessen Professor of Ophthalmology

305B Stellar Chance
Philadelphia, PA 19104-6100

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


James H. Eberwine, Ph.D.
Elmer Holmes Bobst Professor of Pharmacology
38 John Morgan Building
Office: (215) 898-0420
Fax: (215) 573-7188
Email: eberwine@upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g275/p5441

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


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


Description of Research Expertise

I am 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


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 proteosomal 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 succesfully 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**


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Michael Farwell, M.D.
Assistant Professor of Radiology at the Hospital of the University of Pennsylvania

Hospital of the University of Pennsylvania
Department of Radiology
Division of Nuclear Medicine and Clinical Molecular Imaging
Office: 215-662-7750
Fax: 215-349-5843
Email: michael.farwell@uphs.upenn.edu

Selected Publications


Jeffrey Field, Ph.D.  
Professor, Department of Pharmacology  
1313 BRB 2-3  
Phone: 215-898-1912  
Fax: 215-573-0200  
Email: jfield@upenn.edu  
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p16384

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


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.


Dmitry I. Gabrilovich, M.D., Ph.D.
Wistar Institute Professor of Pathology and Laboratory Medicine

Phone: 215-495-6955
Email: dgabrilovich@wistar.org
https://www.wistar.org/our-science/scientists/dmitry-gabrilovich-md-phd

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-kB, 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.

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Recent Publications


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**


Saar I Gill, MD, PhD
Assistant Professor Of Medicine At The Hospital Of The University Of Pennsylvania
Smilow Translational Research Center 8-101
Philadelphia, PA 19104
Office: (215) 573-4015
Lab: (215) 573-4015
Email: saar.gill@uphs.upenn.edu

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


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


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


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


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


Chang-Gyu Hahn, M.D., Ph.D.
Associate Professor of Psychiatry

2003 Translational Research Laboratories
Phone: 215-898-8793
Fax: 215-573-2041
Lab: 215-746-0684
Email: hahnnc@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g275/p18424

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


Malay Haldar, MD, PhD
Assistant Professor of Pathology and Laboratory Medicine

413 BRB II/III, 421 Curie Blvd
Philadelphia, PA 19104
Office: 2155739704
Fax: 2157465511
Email: mhaldar@mail.med.upenn.edu
https://www.med.upenn.edu/apps/faculty/index.php/g275/p8840134

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


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.


Elizabeth A Heller, PhD
Assistant Professor of Pharmacology

10-115 Smilow Center for Translational Research
3400 Civic Center Boulevard, Building 421
Philadelphia, PA 19104
Office: 215 573-7038
Email: eheller@mail.med.upenn.edu

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


Marilyn Howarth, M.D.
Adjunct Associate Professor of Emergency Medicine
Director, Community Outreach and Engagement Core, Center of Excellence in Environmental Toxicology Perelman School of Medicine
Department: Emergency Medicine

1316a Biomedical Research Building II/III
Phone: (215) 898-6221
Email: marilyn.howarth@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20001020/c2045/p10762

Clinical Expertise
Occupational and Environmental Exposure Assessment
Community Exposure Assessment

Selected Publications


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


Research Interests


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


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. Neurtransmitter 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:

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 talampanel 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 talampanel 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 date 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.


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:


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 HIVE, 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 2a 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


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,
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


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 GKLF 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


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


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 isoforms 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


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


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


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 gabbling 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


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


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


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


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 \textit{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 \textit{C9orf72}, and in identifying the basic molecular pathways which are relevant to human disease.

\section*{Selected Publications}


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


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


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


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


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


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.

Robert H. Mach, Ph.D.  
Britton Chance Professor of Psychology in Radiology

Chemistry Building, Room 283  
231 S. 34th St  
Philadelphia, PA 19104  
Phone: 215-746-8233  
Email: rmach@mail.med.upenn.edu  
https://www.med.upenn.edu/apps/faculty/index.php/g275/p8658246

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


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


John Matthew Maris, M.D.
Professor of Pediatrics
4399 Colket Translational Research Building
Phone: 215-590-5244
Fax: 267-426-0685
Email: maris@email.chop.edu
https://www.chop.edu/cccr/labs/john-maris-laboratory

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


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 pigmentary, 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 intralumenal 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**


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


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

Claire H. Mitchell, Ph.D.
Professor of Anatomy & Cell Biology

431 Levy Building
Phone: 215-573-2176
Email: chm@mail.med.upenn.edu
https://www.med.upenn.edu/physiol/faculty_mitchell.html

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


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.
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


Yael P. Mosse, M.D.

Associate Professor of Pediatrics

Colket Translational Research Building, Office 3056
Phone: 215-590-0965
Email: mosse@email.chop.edu
http://www.research.chop.edu/people/yael-p-mosse

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


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


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


Robinson, MA, Baumgardner, JE, Good, VP, Otto, CM: Physiological and hypoxic O-2 tensions rapidly regulate


Park F. Cho-Park, MD, PhD
Assistant Professor of Pharmacology
Smilow Center for Translational Research
Room 10-104, Building 421
Office: 215-573-1190
Fax: 215-573-9135
Email: pacho@pennmedicine.upenn.edu
https://cho-park.org/

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

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


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


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.


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.


Mortimer Poncz, M.D.
Professor of Pediatrics

317 Abramson Research Center
Phone: 215-590-3574
Fax: 215-426-5476
Email: poncz@email.chop.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p5429

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 alphallb/beta3 receptor.

Selected Publications


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 highlyavid, 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


Ellen Puré, Ph.D.
Professor of Pharmacology

3800 Spruce Street
216E Vet
Phone: 215-573.9406
Email: epure@vet.upenn.edu
https://www.med.upenn.edu/apps/faculty/index.php/g20000343/p2386

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


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


Rahim R. Rizi, Ph.D.
Professor of Radiology

1 Silverstein, 3400 Spruce Street
Phone: 215-615-2426
Fax: 215-349-5115
Email: rizi@uphs.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p13700

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


Michael B. Robinson, Ph.D.
Professor of Pediatrics

502D Abramson Research Building
Phone: 215-590-2205
Fax: 215-590-3779
Email: Robinson@pennmedicine.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p9046

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/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


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


Patrick Seale, Ph.D.
Associate Professor of Cell and Developmental Biology

Institute for Diabetes, Obesity and Metabolism, Room 105
Smilow Center for Translational Research, 12th Floor
Phone: 215-573-8856
Fax: 215-898-5408
Email: sealep@pennmedicine.upenn.edu
http://www.med.upenn.edu/sealelab/index.html

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 preadipose 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


Amita Sehgal, Ph.D.
John Herr Musser Professor of Neuroscience
10-135 Smilow Center for Translational Research
Email: amita@pennmedicine.upenn.edu
http://www.med.upenn.edu/sehgal/index.shtml

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
Mark Sellmyer, M.D., Ph.D.
Assistant Professor of Radiology
Stellar-Chance Labs 813A
Phone: 215-573-3212
Email: mark.sellmyer@uphs.upenn.edu
https://www.med.upenn.edu/sellmyerlab/

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


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


James Shorter, Ph.D.
Professor of Biochemistry and Biophysics

805B Stellar-Chance Laboratories
Phone: 215-573-4256
Fax: 215-898-4217
Email: jshorter@mail.med.upenn.edu
http://www.med.upenn.edu/shorterlab/index.html

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.
3. Defining the metazoan disaggregate 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


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 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


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. PMCID:PMC4329464


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. PMCID:PMC4452998.

Wenchao Song, Ph.D.
Professor of Pharmacology

1254 BRB II/III
Phone: 215-573-6641
Fax: 215-746-8941
Email: songwe@upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p5289

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


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


Doris A. Stoffers, M.D., Ph.D.
Sylvan H. Eisman Professor of Medicine
Smilow Center for Translational Research, Room 12-124
Phone: 215-573-5413
Fax: 215-898-5408
Email: stoffers@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p3556

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


Kai Tan, PhD  
Associate Professor of Pediatrics

4004 Colket Translational Research Bldg.  
Philadelphia, PA 19104  
Office: 267-425-0050  
Lab: 267-425-0058  
Email: tank1@email.chop.edu  
http://tanlab4genereregulation.org/

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


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


Wei Tong, Ph.D.  
Assistant Professor of Pediatrics

310D Abramson Research Center  
Phone: 267-426-0930  
Fax: 267-426-5476  
Email: tongw@email.chop.edu  
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p8146029

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


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

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.

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

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

Bersenev Alexey, Rozenova Krasimira, Balcerek Joanna, Jiang Jing, Wu Chao, Tong Wei: Lnk deficiency

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

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

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

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):
Andrew Tsourkas, Ph.D.
Professor of Bioengineering

210 S. 33rd Street,
240 Skirkanich Hall
Email: atsourk@seas.upenn.edu
https://www.seas.upenn.edu/~atsourk/index.html

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


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


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


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


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


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


Shedlock Devon J, Talbott Kendra T, Morrow Matthew P, Ferraro Bernadette, Hokey David A, Muthumani Karuppih, Weiner David B: Ki-67 staining for determination of rhesus macaque T cell proliferative responses

Aalim M. Weljie, Ph.D.
Research Assistant Professor of Pharmacology

10-113 Translational Research Center
Phone: 215-573-8085
Email: aalim@upenn.edu
https://www.med.upenn.edu/weljielab/

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


Rebecca Wells, M.D.
Professor of Medicine

905 BRB II/III
Phone: 215-573-1860
Fax: 215-573-2024
Email: rgwells@mail.med.upenn.edu
http://www.wellslab.com/

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


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 fibrosis regression. Scientific Reports 6: 21387, Jan 2016.


Alexander S. Whitehead, D.Phil.
Professor, Department of Pharmacology

159 Johnson Pavilion
Phone: 215-898-2332
Fax: 215-573-9135
Email: aswhiteh@mail.med.upenn.edu
http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p17480

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


Hao Wu, Ph.D.
Assistant Professor of Genetics
547A Clinical Research Building
Office: 215-573-9360
Email: haowu2@pennmedicine.upenn.edu
https://www.med.upenn.edu/apps/faculty/index.php?q=275/p8878781

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 deoxygenate 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).


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


Xiaolu Yang, Ph.D.
Professor of Cancer Biology

650 BRB II/III
Phone: 215-573-6739
Fax: 215-573-6725
Email: xyang@pennmedicine.upenn.edu
https://www.med.upenn.edu/yanglab/

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


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 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.

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