Cell Biology and Molecular Physiology Graduate Program

Rotation Projects 2020-2021

Welcome to the University of Pittsburgh School of Medicine Interdisciplinary Biomedical Graduate Program. Rotation opportunities available in the Cell Biology and Molecular Physiology (CBMP) Graduate Program are listed below. Faculty are drawn from both basic science and clinical departments. Research CBMP is focused on normal cellular biology and function, as well as disfunction in renal, liver, lung and heart disease, cancer, diabetes, ageing, and inherited disorders of developmental and reproductive functions. If you are interested in a rotation opportunity, speak to faculty at orientation or contact them by email.

Adam Kwiatkowski, Ph.D.
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Yiqin Du, M.D., Ph.D. (duy@upmc.edu)

Glaucoma is a major cause of irreversible blindness worldwide. It is caused by the abnormalities of the trabecular meshwork, the water draining system in our eye. Glaucoma damages the retina and optic nerve, which results in vision loss. Our group is working on developing novel treatments for glaucoma using stem cells to restore the trabecular meshwork function and to replace the damaged retina ganglion cells. We culture different stem cell types and use modern tools of cell biology, molecular biology, biochemistry, physiology, bioinformatics, imaging to study on cells, ex vivo organs, animal models to explore treatments and mechanisms for rescuing vision. Our current main projects are 1) We are exploring how stem cells and their trophic factors regenerate the trabecular meshwork tissue; 2) We induce 3-dimensional retinal organoids from iPSCs to generate retinal disease models and explore possible therapies using stem cells and/or secretome derived from stem cells.

Arjumand Ghazi, Ph.D. (arjumand.ghazi@chp.edu)

Molecular Genetics of Aging

We study the biology of aging using molecular genetic and genomic approaches in the model system, C. elegans. In particular, we focus on a group of transcription factors that modulate lipid homeostasis to coordinate the animal’s lifespan with its reproduction and immune status. The rotation projects will expand on our
recent studies on the mechanism of action of these factors.

1. The conserved role of TCER-1 in immunity and fertility: This project focuses on our discovery that a pro-longevity protein, TCER-1 (homolog of human transcription elongation factor, TCERG1), represses immunity, depending on the status of the animal’s fertility. We are beginning to explore the role of mouse TCERG1 in these processes. The rotation project will address TCER-1/TCERG1’s role in regulating splicing to modulate reproductive fitness and immune-resistance.

2. Role of smRNAs in Innate Immunity: We have recently discovered a role for smRNAs, especially endogenous siRNAs, in controlling immunity. This project involves exploration of immunity genes targeted by smRNAs in the host-pathogen combat.

3. Role of Peripheral Lipid Production and Breakdown in Aβ Pathology
This project is based on our discoveries on the role of lipid turnover in aging. It relies on a C. elegans model of the Alzheimer’s Disease protein, Aβ, to understand how lipid metabolism in non-neural tissues influences neurodegenerative disease development.

Gerry Hammond, Ph.D. (ghammond@pitt.edu)

Lipid signaling in cancer

Cancers arise from somatic mutations that uncouple tumor cells from physiological control, whilst also driving pathological proliferation and migration. The most common class of mutations, affecting more than half of all cancer cases studied, involves the up-regulation of a central lipid signaling pathway – the PI 3-kinase or PI3K pathway. The lipid products of this pathway activate downstream cellular programs promoting proliferation, survival and migration – all hallmarks of tumors.

I thus seems like a good idea to stop this pathway with PI3K inhibitors, and big pharma has many compounds approved or in late-stage clinical development. The huge caveat is that PI3K is crucial for other processes in the body – such as activation of the immune system, and the cellular response to insulin. So, PI3K blockers are not well tolerated. We need a more nuanced approach.

We are studying the lipid products of PI3K. We have discovered that a homeostatic mechanism generated by two types of lipid kinase controls the abundance of PIP2, the lipid substrate lipid for PI 3-kianses. The balance of these two kinases controls the levels of PIP2 like the turns of a thermostat (see the diagram), tuning the strength of PI3K signals. We know that many tumors have the thermostat turned too far in favor of PIP2 and PI3K; therefore, we suspect that modulating the activity or localization of these proteins in cells could be a novel approach to treat cancer.
We are aiming to take these synthetic biology approaches to demonstrate how fine-tuning PIP2 homeostasis in living cells impacts PI3K signal strength, and whether this inhibits tumor cell proliferation. This will be an essential first step towards developing a new class of anti-cancer drug.

Todd Lamitina, Ph.D. (stl52@pitt.edu)

Cellular stress responses allow cells to adapt and thrive in fluctuating environments. These adaptive mechanisms are often referred to as the ‘general stress response’. However, nothing could be further from the truth. Each environmental stress presents unique challenges to cell physiology. As a result, cells have developed many stress response pathways that restore cellular homeostasis by activating distinct target genes. In many cases, studies of these pathways have led to the discovery of new signaling paradigms (i.e. the MAP kinase cascade, endoplasmic reticulum-associated degradation, etc). Often, these signaling mechanisms play critical roles in various human diseases, such as neurodegenerative disease like ALS and Huntington’s disease, which are thought to lead to disruptions in protein folding pathways. Despite the fundamentally important nature of stress response pathways and their links to human disease, the molecular nature of some stress response pathways are still mysterious.

In the Lamitina lab, we utilize genetic and cell biological approaches in the nematode model system *C. elegans* to uncover the molecular pathways controlling one of the most ancient but poorly understood stress pathways, the osmotic stress response. In addition, we have recently leveraged the genetic strengths of the worm to develop new models for both ALS and Huntington’s disease.

Potential rotation projects in each of these areas could include:
• Unbiased genetic screening to discover new genes required for the osmotic stress response
• Characterizing unique mutations in an RNA processing complex essential for activation of the osmotic stress response
• Using CRISPR/Cas9 and in vivo imaging approaches to interrogate the role of an evolutionarily conserved nuclear protein degradation pathway essential for toxicity in the most common genetic form of ALS and frontotemporal dementia

Partha Roy, Ph.D. (par19@pitt.edu)

Research Interests: Cancer (breast, renal) Biology, Cell Migration, Metastasis, Angiogenesis, Cell signaling
Directed cell migration plays an important role in embryonic development, wound healing, angiogenesis, immune response, cancer invasion and metastasis. Dynamic reorganization of actin cytoskeleton, a key aspect of cell migration, is regulated by the concerted actions of various classes of actin-binding proteins (ABPs), and some of these ABPs are fundamental drivers of actin-based cell motility. Altered expressions and activities of fundamental drivers of cell migration lead to aberrant cell motility in pathologic scenarios. Our main research interests are to: a) gain novel insights on how dysregulation of fundamental drivers of cell migration contributes to metastatic progression of solid cancers and pathological angiogenesis; and b) develop translational strategies exploiting the pathways of dysregulation as a means to suppress metastatic phenotype of cancer cells and angiogenesis-dependent pathology.

Rotation projects:
1) Role of profilin family of actin-binding proteins in renal cancer – fundamental mechanisms of what dysregulates profilin expression in renal cancer, role of profilin dysregulation in modulation of tumor microenvironment and tumor progression.
2) Profilin-dependent regulation of tumor cell migration through hijacking of phosphoinositide signaling – fundamental understanding of how profilin regulates membrane phosphoinositide turnover and in turn utilizes the actions of other cytoskeletal proteins (lamellipodin, Mena/VASP) to control tumor cell invasion.
3) Role of MRTF family transcriptional factors in breast cancer – characterization of isoform-specific functions of MRTF in tumor cell phenotypes, therapeutic targeting of MRTF pathway in hormone receptor positive vs negative metastatic breast cancer.
4) Crosstalk of actin cytoskeleton and mitochondria - mechanistic studies of how actin dynamics regulates mitochondrial morphogenesis and function, ultimately impacting energy-dependent biological processes (e.g. neovascularization).

Arohan Subramanya, M.D. (ars129@pitt.edu)

Phase transitions in the WNK signaling pathway.

Our laboratory studies biological processes that regulate cell size and coordinate electrolyte transport in the kidney tubule. A main area of focus concerns With-No-Lysine (WNK) kinases, a family of serine threonine kinases that sense chloride and activate during hyperosmotic stress. Recently, we discovered that WNK kinases activate through a process called liquid-liquid phase separation. During cell shrinkage, the WNKs crowd and condense into membraneless liquid droplets, resulting in kinase trans-autoactivation within a
concentrated space. Following activation, the kinases leave the droplets, triggering downstream phosphorylation and activation of a salt transporter, thereby rescuing cell volume. Our evolutionary analyses indicate that the ability of WNK kinases to phase separate is an ancient property that can be traced back to unicellular protists. However, later on in evolution, organisms with kidneys leveraged the crowding-induced phase behavior of WNK kinases to regulate blood potassium levels by controlling the rate of urinary potassium excretion.

We seek to understand how liquid phase transitions in the WNK signaling pathway (1) control cell volume and (2) coordinate renal potassium secretion. To this end, the student will have the opportunity to participate in cell and/or kidney-based studies using diverse approaches that we have already established in the lab. Some of these methods include a variety of live cell imaging techniques (spinning disc and resonant scanning multicolor confocal microscopy, FLIM-FRET, FRAP, cell volume measurements), proximity proteomics, gene editing, in vitro droplet assays with purified WNK kinases, and studies in kidneys from potassium-stressed genetically modified mice expressing mutant WNKs with altered phase behavior. Thus, the rotation will provide a unique opportunity for cell biology graduate students to explore the biological relevance of liquid phase condensation within a well-defined physiological framework.

Ora Weisz, Ph.D. (weisz@pitt.edu)

The Weisz lab uses imaging, biochemical, genomic, and modeling approaches to study the regulation of membrane traffic in the kidney proximal tubule. Cells in this nephron segment have a highly developed apical endocytic pathway that functions to recover proteins, vitamins, and other filtered molecules from tubule lumen. Defects in the function of this pathway cause tubular proteinuria that can lead to end stage kidney disease. Current projects in the lab are focused on identifying the compartments and machinery that mediate apical endocytosis in these highly specialized cells, creating an integrated model for protein recovery along the entire tubule, and discovering the roles in proximal tubule cell function of proteins whose mutations result in genetic proteinuric disease.

Bokai Zhu, Ph.D. (bzhu@pitt.edu)

Dr. Zhu's lab discovered a cell-autonomous mammalian 12h-clock that runs independently from the circadian clock to regulate 12h oscillations of gene expression and metabolism. Genes under strong 12h-clock regulation in the liver are enriched in the whole central dogma information flow process (ranging from pre-mRNA splicing, polyadenylation, RNA decay,
protein translation, translocation across ER membrane, protein folding and processing in the ER and protein transport from ER to Golgi) in an XBP1s-dependent manner. Cell-autonomous 12h rhythms of gene expression can be entrained by ER and metabolic stress cues in vitro. Intriguingly, the mammalian 12h transcriptome is also highly conserved in marine animals possessing a circatidal clock, therefore implying that mammalian 12h-clock may evolve from the ancient circatidal clock. Dr. Zhu's lab is currently investigating the regulation as well as the physiological/pathological functions of the 12h-clock, with an emphasis on its roles in maintaining hepatic metabolic homeostasis and preventing aging-associated diseases. A combination of state-of-the-art computational, biochemical, genetic, cellular, imaging and genomic approaches is currently utilized in the lab. Current rotations projects include:
1. Developing novel 12h-clock reporters
2. Transcriptional and post-transcriptional regulation of the mammalian 12h-clock
3. Metabolic regulation of mammalian 12h-clock
4. 12h-clock regulation of liver metabolism and aging