GSRPD

October 4, 2019

Margherio Conference Center
Detroit, MI

23rd Annual Wayne State University School of Medicine

CHUAN-PU LEE, PH.D.
Endowed Graduate Student
Research Presentation Day

In Honor of C.P. Lee

Dr. Chuan-Pu Lee (known as “C.P. Lee” by her friends), passed away on July 20, 2016. C.P. Lee was the strongest advocate for graduate students of Wayne State University. She reminded students that diligence and determination were the only limits to achieving their success. C.P. Lee also generously offered pre- and post-doctoral travel awards to aid the cost of national and international conferences. Before her passing, C.P. Lee worked with the GSRPD committee to set up a cash prize endowment for 1st, 2nd and honorable mention presentations each year at GSRPD. Her life and memory will continue to serve graduate students through our newly titled event:
The Chuan-Pu Lee, PhD Endowed Graduate Student Research Presentation Day.

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Schedule of Events

Time	Event	Venue
8:00 – 8:30 am	Registration	Margherio Conference Center
8:00 – 9:00 am	Breakfast and Poster Setup	Breakfast - Margherio Conference Center Posters - Scott Hall Cafeteria
8:45 – 9:00 am	Welcome Remarks Dr. Linda Hazlett *Vice Dean of Research and Graduate Programs*	Margherio Conference Center
9:00 – 10:15 am	Oral Session I	Margherio Conference Center
10:15 – 11:20 am	Poster Session I	Scott Hall Cafeteria
11:20 – 12:35 pm	Oral Session II	Margherio Conference Center
12:35 – 1:25 pm	Lunch	Lunch - 1358 Scott Hall Seating – 1328 Scott Hall
1:25 – 2:30 pm	Poster Session II	Scott Hall Cafeteria
2:30 – 3:45 pm	Oral Session III	Margherio Conference Center
3:45 – 4:15 pm	Coffee Break	Outside Margherio
4:15 – 5:15 pm	Dr. Alejandro Sánchez Alvarado Keynote Lecture	Margherio Conference Center
5:15 – 5:30 pm	Awards Ceremony	

Welcome Message

Welcome to the 23rd Annual Graduate Student Research Presentation Day at the Wayne State University School of Medicine! GSRPD is a student-run event that showcases biomedical research across all biological disciplines. We are excited to have nearly 70 presentations given by graduate students from both the medical and main campuses at Wayne State University.
We are delighted to have you here with us today and hope you can see as many research presentations as possible. Additionally, many of our sponsors will have tables set up, so be sure to stop by and see the services and products they are offering to help with your research. We also encourage you to enter the raffle and have a chance to win some great prizes from local Detroit businesses.

Acknowledgments

We would like to thank all faculty members who volunteered their time. Furthermore, we extend our greatest appreciation to the Office of Graduate Scholars at the Wayne State University School of Medicine for their endless efforts to help execute the procedural aspects of this event. We also would like to thank the departments, organizations, and associations whose generous financial donations helped put on this student-run event. Lastly, we thank all the graduate students who presented their exciting research to the Wayne State community. GSRPD would not have been possible without Wayne State's finest researchers. We look forward to seeing you next year!
Special thanks to Dr. Daniel A. Walz, Deanna Dona, and Yanna Jones for all their support and help.

Cover image credit: Jordan Zhou
Image caption: Mouse placental labyrinth, Kang Chen Lab

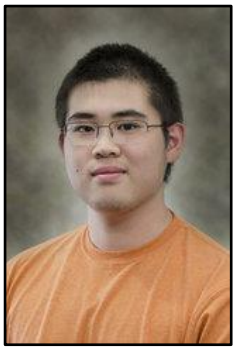
2019 Keynote Speaker:
Dr. Alejandro Sánchez Alvarado, PhD

Dr. Alejandro Sánchez Alvarado is a Scientific Director and investigator at Stowers Institute for Medical Research and the Howard Hughes Medical Institute. He received a bachelor's degree in molecular biology and chemistry from Vanderbilt University and a Ph.D. from University of Cincinnati Medical School. He completed postdoctoral training at Carnegie Institution of Washington under Donald D. Brown where he later became a staff associate. In 2002, Dr. Sánchez Alvarado joined the faculty of University of Utah School of Medicine where he held the H.A. and Edna Benning Presidential Endowed Chair until he joined Stowers Institute for Medical Research in 2011.

Dr. Sánchez Alvarado's lab studies processes of animal regeneration and is particularly interested in the molecular mechanisms by which organisms maintain the integrity of different tissues during the process of regeneration and growth. After initially directing effort towards the regeneration of tadpoles, his lab established the planarian *Schmidtea mediterranea* model for studying the molecular mechanics behind regeneration and has recently sequenced and annotated the *S. mediterranea* genome. They are also at the forefront of developing the tools and methods required for understanding animal regeneration leading to great insights into not only regeneration but also the development of higher organisms.

Alvarado is a member of the National Academy of Science, the American Academy of Arts and Sciences, and the Latin American Academy of Sciences, a Kavli Fellow of the National Academy of Sciences USA, and a Fellow of the Marine Biological Laboratory in Woods Hole, MA. Additionally, he is the recipient of a National Institutes of Health MERIT award and the EE Just Medal for Scientific Achievement. He has served on numerous scientific advisory committees and boards including the National Advisory Council of the National Institute of General Medical Sciences, National Institutes of Health, and presently serves on the Board of Directors of American Century Investments.

GSRPD Committee 2019



Jordan Zhou

Committee Chair, Sponsors
Center for Molecular Medicine and Genetics
5th year PhD Candidate

Madison Peterson

Abstracts, Public Relations
Dept. of Biochemistry, Microbiology, and Immunology
3rd year PhD Candidate

Marissa Petitpas

Judges, Sponsors
Center for Molecular Medicine and Genetics
3rd year MS Student

Nathan Kelley

Judges
Dept. of Biochemistry, Microbiology, and Immunology
3rd year PhD Candidate

Shreya Banerjee

Abstracts, Judges
Dept. of Ophthalmology, Visual and Anatomical Sciences
3rd year PhD Student

Special thanks to our day-of volunteers:
Stephanie Gladyck (CMMG), Hasini Kalpage (CMMG), Ashley Kramer (OVAS), Taylor Vensko (BMI), Kendall Muzzarelli (BMI), Jonathan Greenberg (BMI), Vanessa Kamdoum (BMI), Bhavita Bhaya (BMI), and Jillian Green (BMI)

ORAL SESSION I

1. **The dopamine oxidation product HOCD may account for the dopaminergic selectivity of both Parkinsonism and manganism**

Praneet Kaur Marwah and David Njus
Dept. of Biological Sciences, Wayne State University, Detroit, MI

Parkinson's disease and manganism cause similar symptoms because both selectively target dopaminergic neurons. We have discovered a dopamine derivative, hypochlorite-oxidized cysteinyl-dopamine (HOCD), that is a potent redox cycler and may contribute to the oxidative stress observed in Parkinson's disease. HOCD is formed when cysteinyl-dopamine, the principal oxidation product of dopamine in vivo, is exposed to hypochlorite. Hypochlorite is produced by the enzyme myeloperoxidase, which is reportedly elevated in Parkinson's disease. Now we report that the two-equivalent redox cycling of HOCD is greatly amplified by $MnCl_2$, suggesting that HOCD may also contribute to the movement disorders associated with chronic manganese poisoning or manganism. Mn at micromolar concentrations accelerates the reoxidation of HOCD reduced by dithiothreitol, H_2 or NADH and NADH-quinone oxidoreductase (NQO1). Other metal ions including Cu, Fe, Co, and Zn do not have this effect. We suggest that HOCD may occur naturally at low concentrations in the substantia nigra. Its deleterious action may be elicited by complexing to Mn causing manganism or by an abnormal increase in its concentration contributing to Parkinson's disease.

2. **Regulation of traction force mediated by the calpain small subunit and galectin-3**

Imjoo Jang, Shalini Menon, Rabiah Nargis and Karen A. Beningo
Dept. of Biological Sciences, Wayne State University, Detroit, Michigan 48202

During cellular migration, traction forces are generated by the acto-myosin cytoskeleton and transmitted to the extracellular matrix. Although traction forces are critical for cell migration, the mechanism underlying the generation of these forces still remains unclear. We have previously demonstrated that calpain 4 (Capn4), the small regulatory subunit of the calpain 1 and 2 proteases, regulates the production of traction force in migrating mouse embryonic fibroblasts independent of the large subunit's catalytic activity. We further found that Capn4 is crucial for the tyrosine phosphorylation and secretion of galectin-3 (Gal3), a β-galactoside binding protein known to cluster and activate the cell surface receptors. Traction force microscopy indicates that extracellular Gal3 can rescue the magnitude of traction forces, which is defective in Capn4-deficient cells. We have determined that the influence of secreted Gal3 on the production of traction forces is mediated by c-Abl kinase, which is known to phosphorylate Gal3 on tyrosine residues. We also found that the phosphorylation of Gal3 on tyrosine 107 is essential for its secretion and the generation of traction forces. Our study also suggests the involvement of active β_1 integrin, but not FAK autophosphorylation, in the Gal3-mediated regulation of traction force. This study provides insight into the signaling pathway through which Capn4 and secreted Gal3 regulates the production of traction forces, thus regulating cell migration.

3. Global phosphorylation profiles of primary human skeletal muscle cells

Aktham Mestareehi, Berhane Seyoum, Xiangmin Zhang, and Zhengping Yi
Dept. of Pharmaceutical Sciences, Wayne State University School of Medicine, Detroit, Michigan

Diabetes is a group of metabolic diseases characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both. Insulin resistance is a main characteristic feature of type 2 diabetes. Skeletal muscle insulin resistance is considered to be the primary defect that is evident decades before β-cell failure and overt T2D. Skeletal muscle is the major site of insulin-stimulated glucose uptake (>70%) in the postprandial state in humans. Protein phosphorylation regulates many key cell signaling events, including insulin signaling. Abnormal protein phosphorylation has been implicated in the development of skeletal muscle insulin resistance and T2D. In the present study, human skeletal muscle biopsy was obtained from lean, insulin-sensitive and obese, insulin-resistant participants. The resulting peptides were analyzed by UPLC-ESI-MS/MS using an Orbitrap Fusion Lumos. We have identified >14,000 phosphorylation sites in 4,100 proteins, which is one of the largest catalogs of experimentally determined phosphorylation sites in primary human skeletal muscle cells. Among all phosphorylation sites identified, >9,000 were specifically localized and these localized phosphorylation sites are assigned to 3,700 proteins. We identified phosphorylation sites in 180 kinases/kinases subunits and 29 phosphatases subunits of protein phosphatase 2A. In summary, we have characterized the largest phosphoproteome of primary skeletal muscle cells derived from lean healthy insulin sensitive and obese insulin resistance participants and identified multiple biological processes, molecular functions, and pathways that are significantly enriched in the phosphoproteins.

4. Dysregulation of mitochondrial quality control mechanisms during in vitro ischemia-reperfusion injury

Anthony Anzell[1], Karin Przyklenk, PhD[2], and Thomas Sanderson, PhD[2],
[1]Dept. of Physiology and [2]Dept. of Emergency Medicine, Wayne State University School of Medicine, Detroit, MI, USA

Ischemic brain injury caused by cardiac arrest or stroke continue to be leading causes of death and disability in the U.S. While the restoration or reperfusion of blood flow is essential to salvage ischemic tissue, reperfusion paradoxically exacerbates damage via the excessive production of reactive oxygen species (ROS) from mitochondria. Mitochondria are the key regulators of cell fate during ischemia-reperfusion (I/R) injury. Therefore, stringent quality control mechanisms are critical to ensure a healthy mitochondrial network. The role of mitophagy during I/R injury still remains to be elucidated and previous studies are confounded by the dynamic nature of this process. Therefore, we characterized mitophagic flux utilizing primary cortical neurons isolated from mitochondrial quality control (mito-QC) reporter transgenic mice (C57BL/6-Gt(ROSA)26Sortm1(CAG-mCherry/GFP)Ganl/J) in an in vitro oxygen-glucose deprivation (OGD) system. The reporter allele contains a CAG promoter and mCherry-GFP-mtFIS1 fusion protein inserted into the Gt(ROSA)26Sor locus on chromosome 6. mCherry is stable in acidic pH (pKa 4.5) while GFP (pKa 5.9) is quenched in the acidic lysosomal environment, allowing identification of mitochondria inside autolysosomes. These novel findings provide key evidence for the role of mitophagy in neuronal death following I/R injury as well as further insight into the basic mechanisms of mitochondrial dysfunction that may play a role in a variety of neurodegenerative disease.

5. **Sex and exercise determine the progression of increased sympathetic activity over time: Implications for cardiovascular disease in sedentary individuals**
Paul Morrison and Patrick J. Mueller Ph.D.
Dept. of Physiology, Wayne State University School of Medicine, Detroit, MI, USA

Cardiovascular disease is the leading cause of death, and males have a higher risk of cardiovascular disease compared to women, at least prior to menopause. In many cardiovascular diseases, sympathetic nerve activity (SNA) is elevated, but the presence of female reproductive hormones may attenuate such increases. In 2009, Tan and colleagues reported a method by which sympathetic nerve frequencies could be estimated in human SNA recordings; however, the purpose of this study was to compare the progression of SNA in male and female rats over time. We hypothesized that increases in SNA action potential frequency in sedentary male rats would be offset by voluntary exercise or the presence of the estrous cycle in female rats. We recorded splanchnic SNA from 56 rats under Inactin anesthesia using Labchart software. Eight-week-old, male sedentary rats exhibited increased SNA action potential frequency compared to four-week-old rats (62.4 Â±5.8 Hz vs. 42.0 Â±6.3 Hz, respect. p=0.039). In contrast, SNA action potential frequency in eight-week-old, sedentary female rats was not significantly different from four-week-old rats (46.0 Â±4.3 Hz vs 54.6 Â±4.5 Hz respect. p=0.29). Interestingly, four weeks of voluntary wheel running offset increases in SNA in male rats (37.4 Â±6.1 Hz). Our results suggest maintaining a sedentary lifestyle promotes increases in SNA in males, with a protective effect of the onset of the estrous cycle in young females. Sex- and inactivity-dependent increases in SNA likely play an important role in the development and maintenance of cardiovascular disease.

ORAL SESSION II

6. **The role of tyrosine 67 phosphorylation of cytochrome *c* in respiration, apoptosis, and cancer**
Matthew Zurek and Maik Huettemann
Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI

Cytochrome *c* (Cyt *c*) has many functions and plays a fundamental role in cellular life and death decisions. Cyt *c* is well-known for its role in the electron transport chain (ETC) as an electron carrier between Complex III and Complex IV (COX), however its regulation is not well understood. Our lab has previously shown that Cyt *c* is regulated through tissue-specific post-translational modifications, particularly phosphorylations. To characterize these phosphorylation sites, specifically at residue tyrosine 67 (Y67), we use phosphomimetic glutamate mutant Cyt *c* grown in bacteria and perform assays pertaining to Cyt *c* 's role in the ETC. To understand the impact of phosphorylated Y67 and its implications in cancer, we test the protein's ability to be reduced, oxidized, the rate at which the heme group can be degraded, its superoxide scavagining capability, its caspase 3 activity, and COX activity. There is a significant decrease in the functionality of the phosphomimetic in caspase 3 activity as well as a reduction in its ability to scavenge reactive oxygen species (ROS). This suggests that when Cyt *c* is phosphorylated at this residue the cells can accumulate DNA damage from increased ROS and avoid apoptosis, both of which are attributes of cancer.

7. Identifying cell types contributing to brown adipose tissue neogenesis *in vivo* using single cell RNA sequencing

Rayanne B. Burl[1,2], Vanesa D. Ramseyer[1,2], Elizabeth A. Rondini[1,2], Roger Pique-Regi[1] and James G. Granneman[1,2]
[1]Center for Molecular Medicine and Genetics, Wayne State University, [2]Center for Integrative Metabolic and Endocrine Research, Wayne State University

The global incidence of obesity has reached epidemic proportions. One strategy to combat obesity is to increase the population of brown adipocytes, which burn fat. In order to exploit this therapeutic avenue, we need to understand the mechanisms by which mammals expand populations of brown adipocytes *in vivo*. The primary function of brown adipose tissue (BAT) is to increase heat production in response to cold, and cold stress is the primary means of inducing new populations of brown adipocytes *in vivo*. However, the cell types and mechanisms involved in this cold-induced neogenesis are poorly understood. Our goal is to determine the cell types involved in BAT neogenesis, decipher differentiation trajectories, and uncover how these cell types interact to promote new brown adipocyte differentiation. To do so, we used single cell RNA-sequencing (scRNA-seq) to identify the cell types present in BAT in a comprehensive and unbiased fashion. Single cell profiling over the course of cold-induced BAT neogenesis identified a distinct subpopulation of PDGFRα+ cells that proliferate and differentiate into new adipocytes. We also identified a dramatic shift in the expression profile of macrophages, as well as the appearance of a novel population of dendritic cells that arose from proliferation. Efforts are now focused on locating these cell types in the BAT neogenic zone and testing mechanisms for recruitment and differentiation.
Conclusions: These promising results suggest deep learning poses major efficiency and accuracy gains for cardiac substructure segmentation offering high potential for rapid implementation into clinical RTP for radical cardiac sparing.

8. Dynamic interactions of ABHD5 with PNPLA3 regulate triacylglycerol metabolism in brown adipocytes

Alexander Yang and Dr. James Granneman
Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI

Excessive fat accumulation in the liver can lead to liver failure and is a growing health concern. Hepatic steatosis, the first stage fatty liver disease (FLD), has been reported in one out of every three adults in the United States. Despite the clinical relevance of FLD, questions regarding its molecular pathogenesis remain unanswered. A genome wide study for genes linked to FLD demonstrated that the I148M variant of PNPLA3 is robustly associated with hepatic triglyceride (TG) content. However, the role of PNPLA3 in the liver and the mechanism for how the I148M variant promotes liver fat accumulation remain elusive. We have found PNPLA3 interacts with Î±/Î² hydrolase domain-containing 5 (ABHD5), the activator of the main TG lipase found in the liver, adipose triglyceride lipase (ATGL; officially PNPLA2). This interaction is dynamic and regulated by nutritional status in vitro and in vivo. Furthermore, the I148M variant increases PNPLA3 interaction with ABHD5 suggesting a gain of function. The I148M variant significantly increases the ability of PNPLA3 to prevent the interaction of ABHD5 with ATGL/PNPLA2. In brown adipocytes, equal overexpression of wild type (WT) PNPLA3 and the I148M variant results in similar suppression of ABHD5 dependent lipolysis. These data suggest that PNPLA3 binds ABHD5, thereby preventing ABHD5/PNPLA2- dependent lipolysis. In addition, we propose that the I148M PNPLA3 variant has increased stability, leading to greater suppression of ABHD5 dependent lipolysis and greater liver fat accumulation.

9. Gene-environment interactions in iPSC-derived cardiomyocytes

AS Findley[1], AL Richards[1], K Rhodes[2], MC Ward[2], CA Kalita[1], A Alazizi[1], X Wen[3], DE Lanfear[4], R Pique-Regi[1], Y Gilad[2], F Luca[1]

[1]Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI; [2]Department of Human Genetics, University of Chicago, Chicago, IL; [3]Department of Biostatistics, University of Michigan, Ann Arbor, MI; [4]Center for Individualized and Genomic Medicine Research, Henry Ford Hospital, Detroit, MI

Genetic and environmental factors have been implicated in the development of cardiomyopathy. We have established a cell culture model to explore gene-environment interactions (GxE) in cardiomyocytes (CMs). We reprogrammed lymphoblastoid cell lines from 6 individuals into induced pluripotent stem cells (iPSCs), which were further differentiated into CMs. We exposed all cell lines to 28 treatments, including hormones, vitamins, and drugs. Twelve treatments induced a significant response for hundreds of genes in at least one cell type. We identified 4,835 genes expressed in all cell types and that show evidence of treatment-cell type interactions as measured by likelihood ratio test in DESeq2 (FDR < 10%). Using a random effects model accounting for interactions with cell-type and treatment, while taking advantage of experimental replication and accounting for other technical variables, we estimate that 64% of interindividual variation is explained by interactions with cell-type, while 34% of variation is due to interactions with treatments (potential GxE). To identify SNPs which could be responsible for these interactions in the CMs, we performed allele-specific expression (ASE) analysis. We identified 3,933 unique SNPs across all cell types displaying ASE, corresponding to 1,993 genes. When contrasting each treatment to the appropriate control, we identified 62 instances of conditional ASE (cASE) at 43 unique SNPs in 38 genes (FDR < 20%). One of these genes is TSPAN17, which plays a role in cardiovascular development. This and other examples show that genetic interactions with environmental exposures (treatments) have a strong contribution to inter-individual variation in health and disease.

10. Transcriptional signatures of psychosocial experiences reveal GxE effects in leukocyte gene expression of children with asthma

Justyna A. Resztak[1], Allison K. Farrell[2], Henriette E. Mair-Meijers[1], Adnan Alazizi[1], Samuele Zilioli[2], Richard B. Slatcher[2], Roger Pique-Regi[1], Francesca Luca[1]

[1]Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI

[2]Department of Psychology, Wayne State University, Detroit, MI

One of the ways psychosocial stress affects health is through altering cortisol levels that in turn affect gene expression in immune and inflammation-related pathways exacerbating the severity of symptoms of diseases such as asthma. Allergic asthma is a chronic disease characterized by inflammation of the airways and hyperreactivity to allergens, with higher severity and morbidity in disadvantaged populations. Genetic studies have identified transcriptional dysregulation in immune cells in blood circulation as an important component underlying asthma heritability. To identify transcriptional signatures of psychosocial experiences that may affect asthma symptoms, we analyzed 23 psychosocial variables and 16 asthma traits in leukocytes from an ethnically-diverse sample of 119 youth from Detroit, MI. We identified significant transcriptional signatures of 9 psychosocial and 4 asthma variables. We found considerable sharing of transcriptional signatures between asthma and psychosocial experiences: e.g, the transcriptional signature of self-disclosure was significantly associated with those of several measures of asthma: lung functioning (normalized FEV1, r=.30, p=.001), nightly asthma symptoms (r=.22, p=.02) and asthma severity (r= .38, p<.001). Using eQTL mapping on an expanded sample of 149 individuals, we identified 4669 eGenes (FDR = 10%), 1355 of which have not previously been detected in GTEx blood data. Using the transcriptional signatures as environmental proxies, we identified 117 interaction eQTLs, including 93 with psychosocial environments, demonstrating that negative psychosocial experiences in humans can contribute to interindividual variation in gene expression. These results demonstrate that social genomics approaches in humans can uncover potential molecular mechanisms underlying health disparities.

ORAL SESSION III

11. Ablation of TRPV1 responsive Type III and IV afferents attenuates cardiovascular responses to muscle metaboreflex activation

Joseph 'JT' Mannozzi and Donal O'Leary
Dept. of Physiology, Wayne State University School of Medicine, Detroit, MI

Profound vasoconstriction in heart failure is a major contributor to exercise intolerance and is thought to be in part due to muscle metaboreflex activation. Muscle metaboreflex pressor characteristics are altered in heart failure from sympathetic mediated increases in cardiac output and contractility to enhanced peripheral vasoconstriction even within the active skeletal muscle. These responses are a result of activation of type III and IV afferents in ischemic active skeletal muscle, some of which contain transient receptor potential vanilloid 1 (TRPV1) channels. Intrathecal, epicardial, and systemic administration of an ultra-potent analog of capsaicin known as Resiniferatoxin (RTX) has shown the capability of attenuating TRPV1 mediated responses to cardiac sympathetic afferent activation and relief of nociceptive pain. In this study we observed in healthy chronically instrumented conscious canines that administration of intrathecal RTX attenuates muscle metaboreflex activation initiated by partial reductions in hindlimb blood flow at a workload of 3.2 Km/h. Attenuation of the muscle metaboreflex was observed via reductions in known reflex increases of Cardiac Output (1.29 +- 0.2 L/min to 0.40 +- 0.2 L/min) and Mean Arterial Pressure (24 +- 4.5 mmHg to 8 +- 7.8 mmHg). We conclude that intrathecal administration of RTX at the level of L4-L6 of the spinal cord in chronically instrumented conscious canines attenuates muscle metaboreflex activation. Furthermore, we believe that application of RTX in heart failure will attenuate the profound vasoconstrictor responses elicited by muscle metaboreflex activation and likely improve cardiovascular performance thereby improving exercise tolerance.

12. Cardiac substructure segmentation with deep learning for improved cardiac sparing

Eric Morris and Carri Glide-Hurst
Dept. of Radiation Oncology, Wayne State University School of Medicine, Detroit, MI 48201

Purpose: Radiation dose to cardiac substructures may yield radiation-induced heart disease. However, substructures are not considered in radiation therapy planning (RTP) due to poor visualization on computed tomography (CT). Thus, we developed a novel deep learning pipeline leveraging magnetic resonance imaging (MRI) and CT for state-of-theart segmentation requiring only non-contrast CT inputs. **Materials/Methods:** Thirty-six left-sided whole-breast cancer patients underwent cardiac T2 MRI and CTsimulation. A rigid cardiac-confined MR/CT registration enabled ground-truth delineations of 12 substructures (chambers, great vessels, coronary arteries (CA), etc.). Paired MRI/CT data for 25 patients were placed into separate image channels to train a 3dimensional Neural Network (3D U-Net) using all substructures simultaneously. Deep supervision and a Dice-weighted multiclass loss function were applied. Segmentation results were assessed for 11 test CTs pre/post augmentation and post-processing using 3D conditional random fields (CRF). **Results:** The model stabilized in ~19 hours after 200 epochs (training error<0.001). Augmentation and CRF increased Dice similarity coefficient (DSC) ~5% and ~1% across substructures, respectively. Deep learning provided accurate segmentations DSC>80.0% in the chambers and vessels. Mean distance to agreement (MDA) across 12 substructures was<2.0mm (great vessel MDA=1.24±0.31mm). Compared to previous multi-atlas method, MDA improved ~1.4mm while DSC improved 3-7% (chambers) and 28-38% (CA). For four patients, deep learning yielded CA contours, whereas the atlas-based segmentation failed. Contour generation takes ~5s (<1% of multi-atlas time).

13. RBMS3 promotes the epithelial-to-mesenchymal transition in breast cancer via direct regulation of the transcription factor PRRX1

James Block and Guojun Wu
Dept. of Cancer Biology, Wayne State University School of Medicine, Detroit, MI

The epithelial-to-mesenchymal transition (EMT) has been proposed as a mechanism by which cancer cells invade surrounding tissue and metastasize. To identify novel regulators of EMT, we performed an integrative analysis of multiple RNA sequencing studies of different EMT model systems. From this analysis, RNA binding motif single-stranded interacting protein 3 (RBMS3), a regulator of mRNA stability, was identified as a conserved target of multiple EMT programs. RBMS3 expression was significantly correlated with the expression of EMT-associated genes in both breast cancer cell lines and in patient-derived tumor samples. Survival analysis by a multivariate Cox proportional hazards model demonstrated that RBMS3 was a significant independent predictor of worse overall survival in breast cancer. By ectopically expressing RBMS3 in human mammary (HMLE) cells, we determined that RBMS3 is sufficient to cause EMT-like changes in morphology, protein expression and cell invasion and migration. Knockdown of RBMS3 in two triple-negative breast cancer cell lines, SUM-159 and MDA-MB-231, caused a partial reversion in EMT marker expression and significantly decreased migratory and invasive capacity. Mechanistically, RBMS3 specifically upregulated the EMT-promoting transcription factor PRRX1 via direct binding and stabilization of PRRX1 mRNA. Knocking down PRRX1 in the HMLE/RBMS3 model caused a full reversion to the epithelial phenotype, and re-expressing PRRX1 in MDA-MB-231/shRBMS3 cells partially rescued the effect of RBMS3 knockdown. These results suggest that RBMS3 requires PRRX1 activation to regulate EMT. In conclusion, this study identifies RBMS3 as a necessary and sufficient regulator of EMT via direct regulation of PRRX1 expression.

14. Converting autoreactive T cells into suppressor cells to ameliorate pathology in preclinical models of multiple sclerosis

Kaitlyn Gordon and Eric Sebzda
Dept. of Biochemistry, Microbiology and Immunology, Wayne State University School of Medicine, Detroit, MI

Multiple sclerosis (MS) is an aggressive neurodegenerative disease that results from the immune system eating away at the protective covering of nerves. The disease affects approximately 1 million people across the United States and about 2.5 million worldwide. Unfortunately, the debilitating disease leads to severe paralysis and cures presently do not exist. Current treatments consist of palliative care with efforts to slow symptomology. Most treatments globally suppress immune functions so as to reduce neuronal degradation; however, this leaves patients susceptible to opportunistic infections and other serious health issues. Therefore, discovering new treatments that target autoimmune lymphocytes while sparing normal immune responses is a medical priority. We have recently discovered a unique combination of FDA-approved drugs that theoretically convert autoreactive T cells into a suppressive lymphocyte population. T cells orchestrate the pathology associated with MS and thus eliminating this autoreactive cell type may safely cure this disease. Therefore, we are currently testing this combination drug therapy on mouse models of MS, termed experimental autoimmune encephalitis (EAE). These models replicate both a relapsing-remitting and a secondary progressive form of MS, which together represents 85% of MS patients. Preliminary data indicates that this treatment works on secondary progressive MS; future studies will determine if combination drug therapy also lessens pathology in relapsing-remitting MS. We are also currently studying the cellular mechanisms responsible for disease amelioration. Seeing as these individual drugs are safely tolerated in humans, successful completion of these studies may ultimately lead to clinical trials.

15. Identification of factors that enable long-term *Vibrio cholerae* colonization of zebrafish

Madison Peterson[1], Geoffrey B. Severin[2], Christopher R. Rhoades[2], Christopher M. Waters[2], and Jeffrey H. Withey[1]

[1]Dept. of Biochemistry, Microbiology, and Immunology, Wayne State University School of Medicine, Detroit, MI; [2]Dept. of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI

The Gram negative, aquatic bacterium, *Vibrio cholerae* (VC) is attributed with causing the acute diarrheal disease cholera, which affects millions of people globally each year. Of over 155 VC serogroups identified, only the O1 and O139 serogroups cause pandemic outbreaks. Within the O1 serogroup, two biotypes, Classical and El Tor, are responsible for all seven cholera pandemics since 1817 with El Tor responsible for the ongoing seventh pandemics. Current literature supports the hypothesis that various fish can act as reservoirs and vectors of VC. VC studies in a zebrafish model have demonstrated resilience of El Tor biotype. Classical infections were cleared within 72 hours, while El Tor infections persisted through 6 days. Colonization beyond this timepoint has not previously been studied, leaving any effects of long-term colonization by El Tor, and the factors involved, unknown. Using the zebrafish as a model organism, cholera disease hallmarks and intestinal colonization levels were monitored after infection with VC El Tor to determine the timeline of disease persistence. A panel approach was taken to quantify diarrhea, and VC colonization levels were determined by plating intestinal homogenates of infected fish. Knockout strains were generated to evaluate whether target genes were essential for environmental persistence. Infection with El Tor biotype consistently resulted in prolonged colonization of the zebrafish intestine compared to infection with Classical biotype. Key genetic regions of VC El Tor genome were identified as critical for persistence. Identification of the specific genes responsible for persistence is critical for characterizing the pathogenicity of this bacterium.

A little something
to keep you engaged...

POSTER SESSION I

1. Valproate activates endoplasmic reticulum stress elements in human embryonic kidney cells

Mahmoud Suliman[*1], Iris D. Zelnik [*2], Michael W. Schmidtke [*1], Anthony H. Futerman[*2], Miriam L. Greenberg [*1]

[1]Dept. of Biological Sciences, Wayne State University, Detroit, MI; [2]Weizmann Institute of Science, Rehovot, Israel.

Bipolar disorder is a chronic mood disorder characterized by recurring cycles of mania and depression. It affects 2% of the population worldwide and is associated with a high rate of suicide. VPA is among the main drugs that are used to treat bipolar disorder. However, the molecular mechanism by which VPA exerts its therapeutic effect is not fully understood, and it has several side effects, such as weight gain, hair loss, teratogenicity, and hepatoxicity. Therefore, determining the therapeutic mechanism of VPA will identify specific targets for drug development that avoid the harmful side effects. Previous studies in our lab using yeast as a model organism demonstrated that VPA-mediated inositol depletion activates the unfolded protein response (UPR) by up-regulating ceramide synthesis. This is significant because deficiency in UPR activation was demonstrated in lymphocytes from bipolar disorder patients. This study tests the hypothesis that VPA exerts its mechanism of action by activating the UPR pathway. We demonstrate that VPA activates endoplasmic reticulum stress elements ERSE-I and ERSE-II and increases the protein levels of the abundant endoplasmic reticulum chaperone GRP78 in human embryonic kidney (HEK293T) cells. Furthermore, lipidomic analysis of HEK293T cells treated with VPA identified an increase in certain species of ceramides and their corresponding sphingomyelins. Future experiments will determine if VPA activates the UPR pathway by increasing these species of ceramides. These findings may identify a new mechanism whereby VPA exerts its mechanism of action.

3. The role of the vibrational stark effect with 2-(Trifluoro)methylbenzimidazole: A study using liquid Raman spectroscopy

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One major gap in today's literature regarding 2-(trifluoro)methylbenzimidazole (TFMBI) is the reason in which the dielectric constant of crystallized changes with varying temperatures. The dielectric constant is an indicator of the magnitude of the microscopic electric field that is produced by a material. It was hypothesized that the vibrational Stark effect, where an external electric field shifts peaks on a spectrum, was responsible for the change in dielectric constant. In order to test this hypothesis, solution Raman spectroscopy was conducted. Five solvents with varying dielectric constants were used to dissolve TFMBI: dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), methanol, ethanol, and acetone. Raman spectroscopy was conducted with these solutions in hopes of seeing a trend in the shift of Raman peaks characteristic to TFMBI. After comparing the Raman peaks in specific areas of the spectra, it was determined that there was still uncertainty as to whether the vibrational Stark effect was responsible for the change in dielectric constant due to the absence of a defining trend in the shift of peaks. Further studies must be conducted in order to fully understand why the dielectric constant changes. Characterizing TFMBI will help eventually implement this organic molecule and its derivatives into consumer lighting products that are more energy efficient.

5. Hormonal regulation of glycine decarboxylase and its impact on cellular physiology

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Type 2 diabetes (T2D) is accompanied by alterations in amino acid metabolism. Interestingly, in both humans and rodents, circulating glycine levels are significantly reduced in obesity, glucose intolerance and T2D. The glycine cleavage system (GCS) is the only biochemical route that degrades glycine in humans and loss-of-function mutations of GCS cause hyperglycinemia. Here, we show that the expression of the rate-limiting enzyme of GCS, Glycine Decarboxylase (GLDC), is upregulated in livers of mouse models of diabetes and diet-induced obesity. GLDC mRNA was stimulated during fasting, an energy-deprivation state. Surprisingly, we found this gene to be regulated by both- glucagon and insulin, two antagonistic hormones. In rat primary hepatocytes, GLDC expression was strongly stimulated by glucagon and cAMP, and mildly with insulin. In a rat hepatoma cell line, insulin strongly stimulated GLDC expression as compared to cAMP. We identified the cAMP-response element binding protein 1 (Creb1) and insulin responsive transcription factor Sterol regulatory element binding protein 1c (Srebp-1c) as the primary mediators of this glucagon and insulin stimulatory effect, respectively. We also observed that altering GLDC expression levels strongly affected intracellular glutathione levels and levels of reactive oxygen species (ROS). GLDC mediates the cAMP-dependent increase in cellular glutathione levels. Our findings suggest a working model in which cAMP-mediated regulation of GLDC might be a compensatory mechanism to increase glutathione production as a defense against diabetes-induced oxidative stress.

7. Assessment of benthic macroinvertebrates and primary productivity in streams with green infrastructure components in Detroit-Metro area

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Urbanization often has negative impacts on hydrology, water quality and food webs in freshwater systems. Green Infrastructure (GI) can serve multiple purposes, including reducing flooding enters and preventing pollution in streams and lakes. The objective of this work is to determine what type of GI can help mitigate some of the impacts of urbanization, including improved water quality, increased biodiversity of benthic macroinvertebrates and primary productivity. Two types of GI were compared, including natural vegetation in (1) recreational parks and (2) near roads with open canopy cover and sources of water retention (including stormwater infrastructure) across three urban streams (Clinton, Huron and Rouge). Five sites were selected in each stream for each of the two categories. Chlorophyll-*a*, phaeophytin, temperature, pH, pressure, dissolved oxygen, conductivity and flow rate were measured, as well as macroinvertebrate community composition were quantified at each site in duplicate. Preliminary results suggest that GI type did not influence the diversity of benthic macroinvertebrates, although differences were determined among streams. Interestingly, phaeophytin was significantly different among the GI categories. Chironomids, baetids and hydropsychids were mostly found in all the sites assessed. However, known sensitive bioindicators taxa such as Ephemeroptera, Plecoptera and Trichoptera (EPT) did not differ among sites and ranged from 17% to 51% of the composition; showing that most of these sites are degraded, despite the presence and proximity of GI. Future samplings will be conducted until 2021 to determine how benthic macroinvertebrates can be used as bioindicators of GI sites effectiveness in the Detroit-Metro area.

9. Genomic and transcriptomic characterization of RNA methyltransferases in breast cancer

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RNA methylation is catalyzed by RNA methyltransferases (RNMTs) which regulate the structure, stability, translation, and function of every major class of human RNA. To date, 58 RNMTs have been identified. Previous studies revealed that mutation and dysregulation of several RNMTs is associated with cancer. However, the genomic and transcriptomic alterations of RNMTs as well as their functional roles in cancer initiation and progression remain poorly characterized. Genomic alterations of each RNMT in an array of human cancers were assessed, with an enriched focus on breast cancer. Furthermore, associations between recurrent alterations and gene expression levels, clinicopathological features, and disease-free survival were also examined. Comprehensive genomic and transcriptomic analyses of 58 RNMTs in more than 10,000 primary tumors using TCGA and METABRIC datasets revealed a subset of RNMTs, including TRMT12, NSUN2, and FTSJ3, which have high frequencies of genomic amplification in breast cancer. We found that different subtypes of breast cancer have different patterns of copy number and expression of each RNMT. We also found that FTSJ3 was associated with higher grade and advanced stage of breast cancer. A genome-wide loss-of-function shRNA screen in a large panel of tumor lines revealed that FTSJ3 was also required for the survival of some tumor cell lines. Furthermore, FTSJ3 depletion caused apoptosis and suppressed breast cancer cell survival with minimal effect on normal-like breast cancer cell survival. Our findings provide a framework for further study of the functional consequences of RNMT alterations in human cancer and for developing therapies that target RNMTs in future.

11. Degron capability of the hydrophobic C-terminus of the polyglutamine disease protein, ataxin-3

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Ataxin-3 is a deubiquitinase and polyglutamine disease protein whose cellular properties and functions are not entirely understood. Mutations in ataxin-3 lead to the age-related, neurodegenerative disease Spinocerebellar Ataxia Type 3 (SCA3), an incurable, dominantly inherited disorder that is a member of the polyglutamine family of diseases. The isoforms that result from splicing of *ATXN3* are differently toxic *in vivo*, as a result of faster proteasomal degradation of one isoform compared to the other. The isoforms vary only at the C-termini, suggesting that the hydrophobic C-terminus of the more rapidly degraded form of ataxin-3 (here referred to as isoform 2) functions as a degron signal—that is, a peptide sequence that expedites the degradation of its host protein. Here, we sought to explore this idea. We present evidence that: 1) the C-terminus of ataxin-3 isoform 2 signals the degradation of the SCA3 protein in a proteasome-dependent manner; 2) that this effect from the C-terminus of isoform 2 does not require the ubiquitination of ataxin-3; and 3) that the isolated C-terminus of isoform 2 also enhances the degradation of an unrelated protein. Our data indicate that the C-terminus of ataxin-3 isoform 2 is a degron, increasing overall understanding of the cellular properties and management of the SCA3 protein in the mammalian cell environment.

13. Determining the effect of *Tau* and mitochondrial function in response to traumatic brain injury

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Traumatic brain injury (TBI), defined as damage to the brain resulting from an external mechanical force, can lead to impairment of cognitive and physical function. TBI is an emerging health epidemic with ~2.5 million incidents severe enough to cause hospitalization or death. This study utilizes *Drosophila melanogaster*, a highly tractable genetic model organism for studying human diseases, to investigate TBI outcome. Flies subjected to rapid acceleration and impact exhibit TBI related symptoms consistent with other mammalian and human studies. The primary effect of TBI is axonal damage, which when coupled with brain injury triggers a cascade of events increasing phosphorylation of *Tau* (a microtubule associated protein) and mitochondrial dysfunction. Uninterrupted transport of mitochondria, which harbor the machinery to generate ATP, relies on the ability of phosphorylated *Tau* to stabilize microtubules. However, aberrant *Tau* phosphorylation causes depolymerization of microtubules, *Tau* filament formation, disruption of mitochondrial dynamics and increases cell death. This study hypothesizes that changes in *Tau* activity and mitochondrial function have an impact in response to TBI. We make use of EGFP fused *Tau* insertion (*Tau*-EGFP) and *Tau* knock-out (*Tau*-KO) fly lines to assess the impact of TBI on *Tau* activity. In addition, fly line with selective expression in motor neurons of a fusion of GFP with a mitochondrial import signal (Mito-GFP) is employed to assess mitochondrial impairment post-injury. We have observed increased Tau activity, increased mitochondrial activity and locomotion impairments post-TBI. Our results establish that changes in *Tau* activity and mitochondrial function play an important role in the outcome of TBI. We further propose to study if TBI mediated mitochondrial dysfunction regulates *Tau* expression and vice-versa.

15. Role of phosphatidylinositol 4-kinase IIIα in prostate cancer cells

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The CXCR4-CXCL12 chemokine signaling axis plays a key role in migration and bone metastasis in prostate cancer (PC). The lipid-raft associated CXCR4 regulators were identified through Single Isotope Labelling of Amino-acids in Cell-culture (SILAC) analysis in PC3 cell lines with stable CXCR4 over-expressed and knocked-down. CXCR4 was shown to interact with phosphatidylinositol 4-kinase III alpha (PI4KIIIα or PI4KA) and SAC1 lipid phosphatase. PI4KA is an evolutionarily conserved mammalian kinase that converts PI to PI4P; and SAC1 dephosphorylates PI4P to PI. CXCR4 is shown to interact with PI4KA through its adaptor proteins EFR3B and TTC7B, recruiting it to the plasma-membrane for PI4P generation. We demonstrate this interaction in PC3 cells, and stimulation with CXCL12 further enhances the recruitment of adaptor proteins to CXCR4. This is also shown through co-localization using immunofluorescence. EFR3B interaction is also observed with multiple chemokine receptors. PI4KA knockdown leads to inhibition of PC cell invasion in response to their respective chemokine ligands. Furthermore, PC tumor microarray data show increased PI4K expression in metastatic PC tissue vs localized or normal adjacent tissue. These data suggest a novel interaction between PI4KA and CXCR4, promoting tumor cell invasion and metastasis. Hence pharmacological targeting of PI4KA and/or its adaptor proteins may prove therapeutically beneficial and enhance survival in PC patients.

17. Elucidating the structure-function relationships in the interactions of the androgen receptor, ELK1, and the platform antagonist, KCI807, in prostate cancer

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Prostate cancer (PC) is generally dependent on the androgen signaling axis for growth. Advanced PC is managed by androgen deprivation therapy (ADT). However, ADT has many side effects, and tumors frequently progress by restoring AR signaling, leading to castration resistant prostate cancer (CRPC). A more strategic therapy approach would disrupt AR signaling that is critical for PC growth but not for essential physiological roles of AR in normal tissues. We have previously identified ELK1 as an AR tethering protein essential for activation of a critical set of androgen/AR growth genes in various PC models, including those resistant to castration and enzalutamide. We also established that the AR A/B domain binds ELK1 by co-opting its two ERK docking sites. A lead candidate drug molecule (KCI807) that blocks AR's association with ELK1 and inhibits PC/CRPC tumor growth was discovered; KCI807 has a limited target gene set enriched for functions in cell cycle progression and mitosis.
To further drug development efforts, we must identify and characterize the ELK1 docking site recognition sites in the AR A/B domain. We applied a mammalian two-hybrid assay to map the A/B domain using overlapping deletion constructs. Our findings indicate two putative recognition sites for ELK1 in the AR A/B domain and exclude a role for the amino-terminal half of the A/B domain. Further studies of the mapped motifs will reveal more about the biology of the AR-ELK1 interaction and aid in the design of next generation antagonists to selectively target ELK1-dependent signaling by AR in PC/CRPC tumors.

19. Manganese-enhanced MRI (MeMRI) reveals greater neural activity in the rostral ventrolateral medulla (RVLM) over time in sedentary and physically active rats

*Moved to poster\ session II

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Cardiovascular disease (CVD) continues to be the leading cause of death in the United States. CVD is associated with increased sympathetic nerve activity (SNA). Previously, our laboratory observed greater SNA in sedentary rats compared to physically active controls after direct activation of the rostral ventrolateral medulla (RVLM) –the primary regulator of SNA. The purpose of this study was to examine changes in RVLM neuronal activity over time in sedentary versus active animals using manganese-enhanced MRI (MeMRI), a noninvasive imaging method used in longitudinal studies. We hypothesized that MeMRI signal intensity, an estimate of RVLM activity, would increase over time and be greater in sedentary animals. T1-weighted MRI images were evaluated at baseline and 24 hours after i.p. injection of $MnCl_2$ (66mg/kg) in four-week old, male Sprague Dawley rats. Animals were randomly selected into active (n=11) or sedentary (n=10) conditions and placed in cages with or without running wheels, respectively. We obtained baseline and post-$MnCl_2$-injection scans at week 11 and 12. Following sedentary or active conditions, the absolute change in MeMRI signal at week 12 (343.4 ± 38.8 and 280.9 ± 45.7 i.u., respectively) was greater than week 0 (229.4 ± 28.2 and 241.82 ± 28.2 i.u, respectively, $p<0.05$), suggesting an increase in RVLM activity over time. However, RVLM activity was not different between active or sedentary animals at week 12 ($p=0.27$). Although these results do not support our hypothesis, this study reveals new insight into increasing RVLM activity over time and the related risk of developing CVD in humans.

21. Vision and motor deficits due to loss of Vps11 function in a zebrafish model of genetic leukoencephalopathy

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Purpose: Genetic Leukoencephalopathies (gLEs) are white matter disorders affecting the central nervous system, causing progressive abnormalities in the visual and motor systems. A mutation in *VPS11* has been identified as a causative allele of gLE in Ashkenazi Jewish individuals, with a high carrier rate of 1:250. VPS11 forms membrane tethering complexes with three additional VPS proteins to control crucial cellular processes in the endolysosomal and autophagy pathways. Here, we are characterizing two zebrafish *vps11* mutants as potential models for gLE.

Methods: Behavioral responses to visual and acoustic cues was performed at 5 and 7 days post-fertilization using the DanioVision tracking system. In addition, optokinetic response (OKR) analysis was performed at 5 dpf to test visual acuity.

Result: Behavioral analysis showed that *vps11* mutant fish could visualize changes in light and dark backgrounds, but OKR analysis indicated the animals were functionally blind and not able to make out an image. In regard to motor movement, no difference in response to alternating light-dark backgrounds was observed between the mutant and wild-type larvae at 5 dpf, but a significant reduction in movement and velocity of the mutants at 7 dpf. Mutants also showed significant reduction in movement to non-visual, acoustic stimuli. Together, these results suggest that loss of Vps11 function has a progressive adverse effect on visual sensory and motor systems in zebrafish larvae.

Conclusions: Our findings support the use of zebrafish to further characterize the vision and motor defects associated with loss of Vps11 function.

23. The interaction of MNRR1 and CHCHD10 with cytochrome *c* oxidase

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Mitochondrial oxidative phosphorylation generates most of the cellular energy required for life. Cytochrome c oxidase (COX), or complex IV, is the terminal enzyme of the electron transport chain. The enzyme complex irreversibly transfers an electron from cytochrome c to oxygen, which is the proposed rate limiting step of the electron transport chain. Therefore, the regulation of COX function is critical for energetic homeostasis. Our lab has found that two members of the CX9C protein family copurify with COX isolated from bovine tissue. We have previously shown that these proteins, mitochondrial nuclear retrograde regulator 1 (MNRR1, also known as CHCHD2) and CHCHD10, regulate mitochondrial function. Furthermore, MNRR1 requires phosphorylation by Abl2 kinase to interact with COX efficiently. Our current hypothesis is that MNRR1 binds directly to COX, while CHCHD10 binds indirectly through interaction with MNRR1. This interaction allows for the phosphorylation of MNRR1 by Abl2 kinase. We are currently studying the mechanism of interaction of these proteins with COX using various techniques including dynamic light scattering spectrophotometry, nanothermometry, binding kinetics, and mass spectroscopy.

25. FOXQ1 stimulates WNT-signaling through transcriptional activation of WNT5B to promote the epithelial to mesenchymal transition

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Aberrant induction of the epithelial to mesenchymal transition (EMT) is an acknowledged mechanism of acquired metastatic competence and drug resistance in many epithelial cancer types. FOXQ1 has been shown to be specifically upregulated in the triple negative subtype of breast cancer (TNBC) where is it associated with worse clinical prognosis. However, the role of FOXQ1 within the EMT transcriptional network has not been extensively characterized. In this study, we employed chromatin immunoprecipitation and RNA sequencing in a human mammary luminal epithelial cell line with ectopic FOXQ1 (HMLE/FOXQ1), as a model of breast EMT. We identified FOXQ1 localization within the promoter regions of prominent EMT-TFs, including TWIST1, ZEB1, FOXC2 and SIX2. Further, FOXQ1 direct gene targets are enriched in signaling pathways previously associated with EMT, including the WNT-signaling pathway. Within the WNT pathway, the WNT5B signaling ligand was a direct target for transcriptional activation by FOXQ1. Disruption of WNT5B expression attenuated EMT-associated stem-like traits. Further, FOXQ1 and WNT5B expression are correlated across all TCGA patient breast samples and differentially upregulated in ER- breast cancer. Additionally, both FOXQ1 and WNT5B expression were associated with worse recurrence-free survival. Our data supports that WNT5B is a critical FOXQ1 target for mediating EMT features and suggests that disrupting the FOXQ1-WNT5B axis could be a potential strategy to target the EMT cell population in TNBC patients.

27. Human cytomegalovirus induced cytoplasmic reorganization in a three-dimensional cell-based model

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Human cytomegalovirus (HCMV) induces a drastic reorganization of the Endocytic Recycling Compartment (ERC) to form the cytoplasmic virion assembly compartment (cVAC), the site of virion maturation and egress. The cVAC is a large structure that occupies much of the cytoplasm in HCMV-infected cells. It consists of a bounding ring composed of tubular structures derived from the Golgi and *trans*-Golgi, with the interior of the ring containing numerous vesicles that are positive for early endosome antigen 1; a microtubule organizing center is at the center of the complex. At this point, observations of ERC reorganization and cVAC biogenesis have only been visualized in traditional two-dimensional monolayers of adherent fibroblasts, which are not representative of living tissues. To further our understanding of this reorganization and cVAC formation, we aim to develop a three-dimensional cell-based model to provide more insight to how HCMV influences changes in organelle shape and structure. We are developing a three-dimensional cell-spheroid model based on a liquid overlay spheroid cell culture system that demonstrates the formation of a fibroblast micro-tumor in a non-adherent vessel. Cells are able to maintain their normal morphology, and cell to cell interactions have an added z-dimension. Combining three-dimensional cell culture, histological processing, immunofluorescent microscopy, and three-dimensional computational reconstructions, this system will provide insight to how HCMV influences cytoplasmic morphology in a three-dimensional environment that more closely mimics the structure of human tissues.

29. Anti-oxidant treatment in fructose-induced salt-sensitive hypertension reverses vascular dysfunction and improves arterial pressure

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High fructose diet increases renal reactive oxygen species (ROS) production which enhance renal sodium reabsorption and renin secretion. Concurrent high sodium consumption induces hypertension before frank metabolic syndrome occurs. Prolonged hypertension causes vascular dysfunction by reducing compliance, leading to end-organ damage. Daily treatment with Tempol®, a ROS scavenger, prevented increases in mean arterial pressure (MAP) associated with a fructose and high sodium (FHS) diet. We hypothesized that daily administration of Tempol® with a FHS diet will improve aortic and renal resistive index. Male Sprague-Dawley rats were fed either 20% glucose or 20% fructose in drinking water with normal (0.4%) sodium chow for one week followed by 3.5 weeks of normal or high (4.0%) sodium chow. Half the rats in each group were supplemented with Tempol®, 15 mg/400 g daily in drinking water. Hemodynamics were monitored by telemetry and ultrasonography was performed under isoflurane anesthesia. Final MAP did not differ among groups. However, the change from baseline in FHS groups was significantly elevated compared with controls (6.64 vs. -0.5 mmHg, respectively; $p<0.005$); Tempol® administration prevented the increase in MAP. Despite increased MAP, plasma renin activity in FHS groups was not suppressed. Ultrasonography revealed increased aortic pulse wave velocity and renal resistive index in FHS groups but did not achieve significance. Tempol® reversed this aortic dysfunction but had no effect on renal hemodynamics. These results indicate that ROS play a critical role in developing systemic vascular dysfunction in FHS hypertension; however, additional mechanisms may govern renal hemodynamics in this pathologic state.

31. Lysine 39 acetylation of cytochrome *c* in ischemic skeletal muscle and its functional effects related to ischemia/reperfusion injury

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Cytochrome *c* is an essential protein located in the mitochondrial intermembrane space. It is an electron carrier in the proposed rate-limiting step of respiration and has other life-sustaining functions such as ROS scavenging. On the other hand, Cytcochrome *c* release from the mitochondria is the committing step for apoptosis. Cytochrome *c* can also peroxidize cardiolipin, facilitating its own release from the mitochondria, thus activating apoptosis. This makes Cytochrome *c* a key regulator of cellular life and death decisions. Our group previously identified phosphorylation sites that regulate Cytochrome *c* under normal conditions. Interestingly, we identified a novel, specific acetylation of Lysine residue 39 in ischemic porcine tibialis anterior muscle. We generated a recombinant acetylmimetic mutant of Cytochrome *c* (K39Q) for *in vitro* functional assays. Acetylmimetic Cytochrome c demonstrated an increase in Cytochrome *c* Oxidase activity, rate of oxidation, and heme degradation. It also demonstrated a reduction in superoxide scavenging ability, Caspase-3 activation, and cardiolipin peroxidase activity, suggesting an increase in ROS and apoptosis. Identifying the functional role of posttranslational modifications during ischemia will increase our understanding of muscle ischemia-reperfusion injury and provide a target for medical therapies to limit tissue damage. This is especially relevant for knee replacement surgery, which requires a tourniquet that leaves a leg ischemic for 90 minutes. Our results indicate that acetylation may be a modification contributing to reperfusion injury.

33. Cross-talk between intraflagellar transport and intramanchette transport, two cargo transport systems essential for mammalian sperm flagella formation

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Sperm flagella formation is a complex process that requires cargo transport systems to deliver structural proteins for sperm flagella assembly. Two cargo transport systems, the intramanchette transport (IMT) and Intraflagellar transport (IFT), have been shown to be essential for spermatogenesis and sperm flagella formation. IMT exists only in elongating spermatids, whereas IFT is responsible for the delivery of cargo proteins in the developing cilia/flagella. Our laboratory discovered that mouse meiosis expressed gene 1 (MEIG1), an essential protein for sperm flagella formation, is present in the cell bodies of spermatocytes and round spermatids, but it is translocated to the manchette. An IFT-B complex component, IFT20, is present in the Golgi bodies of spermatocytes; it is also present in the manchette of the elongating spermatids. Given that both IFT20 and MEIG1 are present in the manchette, and both are essential for normal spermatogenesis, we hypothesized that the two proteins are in the same complex. This is supported by the fact that both proteins were co-precipitated from the testis extracts using specific IFT20 antibody. In the sucrose gradient assay, the two proteins were present in similar fractions. MEIG1 distribution was not altered in the conditional *Ift*20 mutant mice; however, IFT20 protein drifted toward lighter fractions in the Meig1 mutant mice. In the IFT20-deficient mice, MEIG1 was still present in the manchette of the elongating spermatids; conversely, IFT20 was no longer present in the manchette of the elongating spermatids of MEIG1-deficient mice. Our data suggests a cross-talk between IMT and IFT.

35. Environmentally relevant PFAS exposures in a zebrafish model: Health effects and genomic assessment

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Per- and polyfluoroalkyl substances (PFAS) are mainly used as industrial or commercial surfactants and are present in many common household products, including nonstick cookware, popcorn bags, and cosmetics. PFAS consist of over 5,000 chemicals, all of which have a similar fully-fluorinated carbon chain. The carbon-fluorine bonds render these chemicals extremely resistant to degradation, leading to their persistence and bioaccumulation in the environment and organisms, including aquatic life and mammals. Due to this persistence, more research is needed on PFAS toxicity. Current research links PFAS endocrinerelated issues, among other health concerns. Despite phasing out production in the United States, two of the most environmentally common PFAS compounds, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), are found in the ug/L range in blood samples from the general population. These compounds also persist in waterbodies. In fact, our lab detected PFOA and PFOS in the Lake Huron-to-Erie corridor at maximum levels of 4ng/L and 3ng/L, respectively. The EPA lifetime health advisory for PFOA and PFOS in drinking water is 70 parts per trillion (70ng/L). Thus, in this study, we exposed embryonic zebrafish to environmentally and socially relevant levels of 0ng/L, 7 ng/L, 70 ng/L and 700 ng/L PFOS and PFOA, from 4 hours post-fertilization (hpf) to 120 hpf. We measure morphological endpoints and assess their response to light and dark as an indicator of neurological health. Finally, we examine disrupted gene expression in endocrine-related pathways in exposed larvae.

37. Timing is everything: HCMV cVAC biogenesis depends on pUL103 expression late in infection

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Human cytomegalovirus (HCMV) is an enveloped, single segment, double-stranded DNA virus. HCMV infection causes disease in immunocompromised (HIV patients, transplant recipients) and immunonaive (fetuses, neonates) populations. Current treatments are effective but are either limited in use or can lead to organ damage and/or antiviral resistance, and no vaccines are available. Additional antiviral targets are needed. HCMV pUL103 is a potential antiviral target. pUL103 is a conserved herpesvirus protein present in the tegument, a layer of proteins and mRNA between the envelope and capsid of HCMV virus particles (virions). pUL103 helps HCMV reorganize cellular secretory machinery (Golgi, endosomes) during formation of the cytoplasmic virion assembly compartment (cVAC) that facilitates efficient virion production. pUL103 is also important for cell-to-cell spread and virion maturation. The structure and mechanisms functions of pUL103 are unknown. For more focused mechanistic studies of pUL103's activities during cVAC biogenesis, we sought to identify the temporal window when the protein must be present for cVAC biogenesis to occur. We used an FKBP-based system that enables regulation of pUL103 stability in the presence or absence of the stabilizing ligand Shield-1. We found that newly synthesized pUL103 is needed for cVAC formation. We found that late in infection, pUL103 needs to be present for >24 hours for development of normal cVAC morphology. We are working to define the relationship between pUL103-driven cVAC biogenesis and extracellular virus output and the stages of cVAC development, including identification of its interacting partners during the course of cVAC biogenesis.

39. Variation in the thermostability of the Norovirus protease constructs

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The discovery and development of antiviral agents capable of providing clinical benefit for the treatment of Norovirus infections have been the focus of considerable research efforts. However, no antiviral chemotherapeutic agents for this indication are yet available. Norovirus encodes a 3C- like protease (NV 3CLpro) that is responsible for the cleavage of the viral polyprotein into mature viral proteins. The NV 3CLpro is conserved and represents an attractive target for the design of antivirals. RS-3150 and RS-2905 our lead antiviral compounds have been shown to have nanomolar inhibition of the Norovirus protease, but are often associated with a lack of selectivity, as well as off-target effects. Further studies are needed to enhance and optimize the potential of our lead compounds, but also to determine at which concentration a maximum stabilizing effect of our lead compounds can be obtained. We ran several assays using the Analysis by Differential Scanning Fluorimetry (or Thermal Shift Assay) technique and noticed some good findings. Higher compound concentration doesn't help the viral protease to stabilize. The lower the compound concentration the higher is the melting temperature. Higher is the melting temperature (Tm) tighter is the Norovirus protease bounded to our two lead compounds.

41. Role of serine-47 phosphorylation of cytochrome *c* in brain ischemia/reperfusion injruy

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Most strokes are ischemic, where blood flow to the brain is prevented by occlusion of a blood vessel. Reperfusion strategies are used to rescue the ischemic tissue, but immediate reperfusion can paradoxically induce further damage leading to 'reperfusion injury'. Reactive Oxygen Species (ROS) production during reperfusion remains one of the major factors causing reperfusion injury. Hence regulation of cellular respiration is important to attenuate reperfusion injury, since the mitochondrial Electron Transport Chain (ETC) is the major source of ROS production. Cytochrome *c* (Cyt*c*) is a protein that acts as an electron carrier in the ETC and plays a significant role in cell death. Our recent data indicate that Cyt*c* purified from mammalian brain is phosphorylated on serine-47 (S47). Importantly, this phosphorylation is lost under ischemia, as seen in stroke. Our model predicts that ischemia-triggered dephosphorylation of Cyt*c* leads to increased tissue damage during reperfusion through the following mechanism: ischemia → Cyt*c* dephosphorylation → maximal ETC activity during reperfusion → pathologically high mitochondrial membrane potential → ROS burst → release of Cyt*c* from the mitochondria → apoptosis. The role of the S47 phosphorylation of Cyt*c* was characterized *in vitro* using a recombinant phosphomimetic Cyt*c* mutant (S47E) and controls (WT, S47A). To further test our model, cell lines stably expressing the same Cyt*c* variants were generated to characterize the role in respiration, apoptosis, ROS production and membrane potential. Our data suggests that S47 phosphorylation of Cyt*c* is a protective modification that decreases cell death and ROS production, preventing reperfusion injury.

43. Construction and characterization of single chain antibodies against glucose-regulated protein 94

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Monoclonal antibody (mAb) drugs have shown promising applications for the treatment of cancer and autoimmune diseases. Recombinant single-chain variable fragment (ScFv) antibody constructs provide advantage alternatives for full length immunoglobulin molecules. Glucose-regulated protein 94 (GRP94) is a heat shock protein 90 (HSP90)-like protein in the lumen of the endoplasmic reticulum (ER), serving as chaperones for secreted and membrane proteins. GRP94 has been implicated with a function in inflammatory processes by acting as an endogenous ligand of toll-like receptors (TLRs). Our present research project aims to develop ScFv antibodies that can neutralize GRP94 for use as an anti-inflammatory reagent. Our strategy is to clone the VH and VL regions of IgG genes of hybridoma cell lines that produce anti-GRP94 mAbs using RT-PCR, sequence them and construct the cDNAs into ScFv expression vectors. A secretion signal segment, an inter-VH/VL GGGGS linker segment and an affinity purification tag will be incorporated to produce ScFv antibodies in E. coli culture. ELISA titration and Western blotting will be performed to characterize the recombinant antibodies for affinity and specificity to GRP94. These experimental studies will lay a foundation for further research on the understanding of GRP94â€™s role in inflammation and the use of anti-GRP94 ScFv to treat inflammatory diseases such as rheumatoid arthritis.

45. PAK4-NAMPT dual inhibition as a novel strategy for therapy resistant pancreatic neuroendocrine tumors

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Pancreatic neuroendocrine tumors (PNET) remain an unmet clinical need. In this study, we show that targeting both nicotinamide phosphoribosyltransferase (NAMPT) and p21-activated kinase 4 (PAK4) could become a synthetic lethal strategy for PNET. The expression of PAK4 and NAMPT was found to be higher in PNET tissue compared to normal cells. PAK4-NAMPT dual RNAi suppressed proliferation of PNET cell lines. Treatment with KPT-9274 [currently in a Phase I trial or analogs, PF3758309 (the PAK4 selective inhibitor) or FK866 (the NAMPT inhibitor)] suppressed the growth of PNET cell lines and synergized with the mTOR inhibitors everolimus and INK-128. Molecular analysis of the combination treatment showed down-regulation of known everolimus resistance drivers. KPT-9274 suppressed NAD pool and ATP levels in PNET cell lines. Metabolomic profiling showed a statistically significant alteration in cellular energetic pathways. KPT-9274 given orally at 150 mg/kg 5days/week for 4 weeks dramatically reduced PNET sub-cutaneous tumor growth. Residual tumor analysis demonstrated target engagement in vivo and recapitulated in vitro results. Our investigations demonstrate that PAK4 and NAMPT are two viable therapeutic targets in the difficult to treat PNET that warrant further clinical investigation.

47. HDAC6 regulates Chk1 stability in response to radiation-induced DNA damage

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Histone Deacetylase 6 is a class IIb HDAC, a deacetylase of α-tubulin that regulates cell migration and motility. Over the last decade, HDAC6 has been characterized as an oncogenic protein in a variety of tumor types. We have since found that HDAC6 is upregulated across all three subtypes of non-small cell lung cancer (NSCLC), and that HDAC6 depletion can sensitize NSCLC cell lines to DNA damage. Our initial radiotherapy trials confirmed that HDAC6 knockdown can sensitize cells via PARP-1 cleavage, γ-H2AX foci persistence, and trypan blue exclusion. Interestingly, these trials also revealed that total Chk1 protein levels failed to resolve in HDAC6-knockdown cells. Chk1 is a Ser/Thr kinase activated by ATR in response to a variety of DNA aberrations, including the resected ends of a DNA double-strand break. Active Chk1 prevents the cell from progressing through S and G2 phase, and resolution of Chk1 is essential for cell cycle progression. Further analysis revealed that the stable Chk1 is active in HDAC6 knockdown cells, in stark contrast to our control cells where both total and active Chk1 resolve shortly after γ-H2AX foci become undetectable. Examination of overexpressed and purified Chk1 and HDAC6 confirmed that these two proteins interact, that Chk1 specifically interacts with the DAC1 domain of HDAC6, and that HDAC6 can ubiquitinate Chk1 in vitro. We propose that HDAC6 regulates Chk1 protein levels via ubiquitination, and that elimination of HDAC6 prevents cells from escaping S/G2 and subsequently disables the cells' ability to resolve radiation-induced DNA damage, promoting cell death.

49. Attenuated response to hydromorphone during buprenorphine stabilization associated with injection opioid use and quicker opioid lapse during buprenorphine dose tapering

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Background: Several factors are associated with increased likelihood of opioid relapse: longer duration of use, more frequent use, and injection drug use (IDU); however, we do not know the precise mechanism by which these factors lead to relapse. This study examined whether response to high-dose hydromorphone (HYD) during buprenorphine (BUP) maintenance is modulated heroin-use characteristics (e.g. IDU). We also explored whether response to HYD predicted lapse during BUP dose-tapering.
Methods: Substance-use data were collected from non-treatment seeking opioid-using volunteers (N=55) who were stabilized on 8-mg/day BUP maintenance then (during inpatient stay) received double-blinded intramuscular HYD 24mg and rated its subjective effects. Participants were discharged and a subset (N=36) underwent a double-blind BUP dose-taper over 3 weeks.
Results: IDU history was associated with higher peak craving (t=2.46, *p*=.017), and lower HYD-induced peak effects for total agonist symptoms (t=2.78, *p*=.008), VAS good effect (t=2.24, *p*=.029), and VAS high (t=2.82, *p*=.007). Response to HYD was in turn associated with days to lapse. Individuals reporting less HYD-induced VAS liking, good effect, and high lapsed quicker during the BUP dose taper. A regression model found that HYD liking positively predicted days to lapse ($F(1,32)=14.8$, $p=.001$, $r^2=30.1\%$).
Conclusion: Characteristics of heroin use (e.g. IDU) may decrease sensitivity to BUP (higher craving) and HYD (less liking) resulting in greater sensitivity to BUP dose tapering (quicker opioid lapse). Subjective response to high-dose HYD challenge during moderate-dose BUP maintenance is strongly associated with days to opioid lapse, suggesting that cross-tolerance plays an important role in BUP efficacy.

51. Global phosphorylation profiles of primary human skeletal muscle cells

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Type 2 diabetes is a type of metabolic disease characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both. Insulin resistance is a main characteristic feature of type 2 diabetes. Skeletal muscle insulin resistance in particular is considered to be the primary indicator of this disease as it is evident decades before β-cell failure and overt T2D. Skeletal muscle cells are the major site of insulin-stimulated glucose uptake (>70%) in the postprandial state in humans. Protein phosphorylation regulates many key cell signaling events, including insulin signaling. Abnormal protein phosphorylation has been implicated in the development of skeletal muscle insulin resistance and T2D. In the present study, human skeletal muscle biopsies were obtained from lean insulin sensitive and obese insulin resistance participants. The resulting peptides from the two groups were analyzed by UPLC-ESI-MS/MS using an Orbitrap Fusion Lumos. We have identified >14,000 phosphorylation sites in 4,800 proteins, which is one of the largest catalogs of experimentally determined phosphorylation sites in primary human skeletal muscle cells. Among all phosphorylation sites identified, >9,000 were specifically localized and these localized phosphorylation sites are assigned to >3,800 proteins. We identified phosphorylation sites in 200 kinases and kinase subunits and 29 phosphatases subunits of protein phosphatase 2A.

53. PP2A inhibition overcomes TRAIL resistance in triple negative breast cancer

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Triple-negative breast cancer (TNBC) is an aggressive disease that does not respond to widely used targeted/endocrine therapies because of the absence of progesterone, estrogen and HER2 receptors. Previous studies indicated that the majority of TNBC cells are highly sensitive to TRAIL-induced apoptosis, but the development of TRAIL resistance limits its efficacy. In this study, we evaluated the effects of protein phosphatase 2A (PP2A) inhibition on TRAIL-induced cell death in TRAIL-resistant TNBC cells. We generated two TRAIL-resistant cell lines from TRAIL-sensitive parental cells (MDA-MB-231 and SUM159). We found that both TRAIL resistant cell lines are sensitive to the PP2A inhibitor LB-100 as compared to their corresponding TRAIL-sensitive counterparts. Similar results are confirmed in a panel of TNBC cell lines that are intrinsically resistant to TRAIL. Mechanistically, we found that TRAIL-resistant TNBC cells express higher basal levels of AMP-activated protein kinase (AMPK) than TRAIL-sensitive cell lines. We also observed that acute treatment with LB-100 increases PD-L1 expression in TNBC. Collectively, these data suggest that the inhibition of PP2A activity could be a novel therapeutic strategy for overcoming TRAIL resistance in TNBC.

55. Integrating cortico-cortical evoked potentials and diffusion imaging for whole-brain dynamic tractography

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An objective of neuroscience is to describe the structural-functional networks which support cognition. Cortico-cortical evoked potentials (CCEPs) can identify functional networks in the human brain; following electrical stimulation of cortical electrodes, evoked responses at distant cortical areas indicate connectivity. However, CCEPs do not provide information about the structures which conduct the signal. We used diffusion-weighted imaging (DWI)-based tractography to estimate inter-electrode "wire" properties. According to V=IR, resistance directly influences voltage and current. Therefore, we modeled resistance as streamline length divided by mean fractional anisotropy (FA; len/FA) and hypothesized that it is CCEP amplitude and latency, while conduction velocity is proportional to FA. Seventeen neurosurgical patients underwent DWI scans and CCEPs during extraoperative recordings using subdural grids. CCEPs were elicited by trains of 1 Hz, 5 mA stimuli; peak and latency were defined as the maximum negative voltage within 10-50 ms post-stimulus. Electrodes were co-registered to DWI for tractography. All electrodes were pooled in three regressions. Len/FA predicted log (amplitude) and latency [R^2=0.78, β=-0.033, p=3.49e-10; R^2=0.59, β=0.44, p=2.81e-9]; FA predicted sqrt(velocity) [R^2=0.20, β=3.68, p<1e-10]. Age, sex, hemisphere, antiepileptic drugs, and epileptic zone were not correlated with CCEPs (p's>0.05). As resistance decreases, CCEP amplitude and velocity increase exponentially, while latency decreases. We utilized these relationships for dynamic tractography atlas visualizations at the individual and group level. We demonstrated that the white-matter network can predict CCEPs, though the nonlinear relationship between CCEPs and resistance suggests the influence of further unobserved factors. The dynamic tractography atlases provide a deeper look at the structural-functional networks supporting human cognition.

POSTER SESSION II

2. Drug design studies of Zika virus protease inhibitors

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Zika Virus protease catalyzes the processing of the viral polyprotein. This is an essential step in the replicative cycle making it an attractive target for drug design. Currently, the lead compound in the lab is RS-3203 (cn-716), which has been shown to have nanomolar inhibition of the ZIKV protease but has very poor cell permeability. Our objective was to identify novel inhibitors from the MCULE database that have high cell permeability. Using Schroedingers Phase and HTVS tools, we screened the 9 million purchasable compounds from MCULE and identified 10 potential inhibitors of the ZIKV protease with greater predictive values for cell permeability.

4. Different sensory neurons modulate specific steps of oogenesis in response to different food types

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The sensory system integrates multiple environmental cues to regulate animal physiology. Likewise, sensory neurons in the worm Caenorhabditis elegans modulate various physiological processes, including reproductive patterns in response to different bacterial diets, which serve as an important environmental cue for the animal. Previously, we have shown that worms grown on E. coli CS180 produce fewer progeny compared to worms grown on E. coli OP50. However, worms on CS180 have a faster rate of reproduction. Now we show that the low progeny number on CS180 is due to an early onset of oogenesis, which is primarily modulated by a pair of taste neurons known as ASJ. We also demonstrate that this sensory influence on oogenesis requires the signaling of an insulin-like peptide INS-6 from the ASJ taste neuron. E. coli CS180 also promotes faster reproduction rates by accelerating oocyte maturation rates. In contrast to onset, oocyte maturation rate is largely under the influence of the olfactory neuron AWA pair. Moreover, the AWA effect on oocyte maturation appears to be independent of INS-6. Together our data indicate that specific sensory neurons detect certain bacterial food-derived cues to modulate distinct steps in oogenesis onset versus oocyte maturation via two different signaling pathways.

6. The role of SIN3 in metabolism sensing and gene expression

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SIN3 is a scaffold protein involved in gene expression regulation. SIN3 binds to many proteins through its PAH. SIN3 regulates genes through the activity of HDAC, a histone deacetylase, and LID, a histone demethylase. Furthermore, SIN3 has been shown to regulate metabolic pathway, including one carbon metabolism. I am interested in how SIN3 can sense metabolic flux in the cell. We have identified SIN3 interactors by immune-precipitating SIN3 from cells in glycolytic block, followed by LC-MS/MS. Additionally, we have identified key metabolic genes that are directly regulated by SIN3, further strengthening our hypothesis that SIN3 is a metabolic sensor that affects metabolism by direct gene regulation of key metabolic enzymes.

8. Examining the decay rate of a hybrid light-matter state with ultrafast transient absorption.

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Molecules form bonds by exchanging electrons between different atoms to form molecular orbitals. Analogously to the molecular orbital picture an electron undergoing a molecular electron transition can interact with a photon of a cavity mode to form a hybrid light-mater state containing an upper and lower polariton. In this presentation a cavity polariton was formed by coupling the Soret transition of Zinc (II) tetraphenyl porphyrin (Zn-TPP) to a cavity mode. Upon coupling the molecular and cavity modes the rate at which the hybridized state decays can be monitored with a transient absorption measurement. Transient absorption is a pump-probe measurement. A pump pulse of 400 nm is used to stimulate the Soret region of the sample. After stimulation of the Soret band white light generated by a CaF crystal is used to probe the excited state. A photodiode with a 430 nm bandpass filter is used to detect the resulting signal. It is hypothesized that the excited state absorption will decay more slowly in the hybridized material as opposed to a free space Zn-TPP molecule. Moreover, it is hypothesized that the rate of decay can be tuned by changing the coupling strength between the molecular and cavity modes. The significance of this study is that if the decay rate in the kinetic trace of the transient absorption is due to strong light-matter coupling then this hybridization can be used to influence the photo reactivity of molecules.

10. Sculpting an imperfect flower: The study of KNUCKLES in primordia regulation

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The evolution of sex determination in plants is a central problem in plant evolutionary biology. Currently, there have been limited studies in which the sex determination genes are identified yet we do not know most of the alternative downstream pathways that lead to developmental differences in plants that exhibit sexual dimorphism. Addressing this gap in knowledge is important as it will give insight into the genetic regulation of developmental processes in unisexual flowers and in angiosperm flowers in general. The investigation into the link between the differential expression patters of genetic pathways and the differential expression in floral development involves the differential expression of AG, WUS, and the proposed transcription repressor gene KNUCKLES (KNU) as they relate to the differential formation of floral organ primordia in male and female *Spinacia oleracea* flowers. Our central hypothesis is that the AG-KNU-WUS pathway regulates the differential morphogenesis of organ primordia between male and female flowers leading to sexual dimorphism in spinach. To test this hypothesis, molecular genetics tools are utilized to quantify KNUCKLES temporal and spatial expression patterns, along with functional testing. Preliminary studies have begun that include characterizing KNU-like gene expression and the phenotypes of KNU-like knockdowns in *S. oleracea*. Preliminary results show strong phenotypes in the vegetative tissue that are related to the regulation of organ primordia and meristem maintenance.

12. The role of g-Protocadherin isoform diversity in retinal direction selective circuit formation

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The *Pcdhg* gene cluster encodes the γ-Protocadherins (g-Pcdhs), 22 cell adhesion molecule isoforms capable of generating thousands of distinct cell-cell recognition complexes through multimer formation and homophilic interaction. The g-Pcdhs regulate complex processes during neural development, including cell survival in many types of retinal neurons and self-avoidance in starburst amacrine cells (SACs). It is hypothesized that g-Pcdh isoform diversity provides each neuron with a unique "barcode", allowing neurites to recognize and avoid "self" while forming synapses with "non-self" neurites. To study how much isoform diversity is required for this self/non-self discrimination, a CRISPR/Cas9 approach was used to generate a series of mutant mouse lines with reduced g-Pcdh isoform diversity. We will analyze strains with between 1 and 16 intact isoforms. We are using Brainbow fluorescent labelling and dendrite tracing to analyze the morphologies of SACs in these lines, hypothesizing that decreased diversity will result in decreased reciprocal contacts between SACs, as neurites will treat each other as "self". We are taking two approaches to test the functional significance of these morphological changes. SACs provide inhibitory input to ON/OFF direction selective ganglion cells (ooDSGCs) to promote direction selectivity. We are using patch clamp electrophysiology to test if reduced g-Pcdh isoform diversity disturbs ooDSGC directional tuning. To measure behavioral outputs, we are analyzing the Optomotor response (OMR) and looming response, which test the ability to detect motion through the ON and OFF pathways respectively. We present preliminary data concerning the above work.

14. Investigating microstructural changes in Parkinson disease patients using diffusion magnetic resonance imaging

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Background: Parkisnon disease (PD) is a neurodegenerative disease characterized neuropathologically by deposition of protein aggregates in neuronal cell bodies and dendrites, called lewy bodies. In addition to motor impairments, patients also suffer from cognitive decline which is thought to be due to lewy body spread in cerebral cortex. To better understand the cortical microstructural changes mediating cognitive impairment in PD, we aim to analyze cortical integrity using diffusion MRI.
Methods: 10 PD and 5 age-matched healthy controls (HC) were recruited. Overall cognitive status, depression scale, hallucination scale and executive memory testing (Symbol digit modality test) were done. Diffusion MRI was done using the following b-values: 0, 711, 2000 and 2855 s/mm2. Anatomical T1 image was also acquired. Freesurfer was used to segment regions of interest and measures of cortical integrity were extracted from regions. Non-parametric t-test was used to compare measures of cortical integrity.
Results: There was no significant changes in cortical thickness between groups. There was a significant reduction in intracellular volume fraction in PD group, more pronounced in right hemisphere. There was a significant increase in orientation dispersion index in PD group. Areas with altered cortical integrity included frontal lobe, entorhinal cortex, anterior cingulate and lateral occipital lobe. These areas are known to be associated with higher cognitive function and mediate cognitive decline.
Conclusion: NODDI might be sensitive for cortical integrity changes associated with PD pathology.

16. Functional analysis of candidate SNPs in ATM and BRCA2

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Genetic testing for cancer predisposition via gene panels has been widely successful in predicting hereditary cancer risk. For many cancers much of the genetic risk remains unknown, including over half in hereditary ovarian cancer. Much of this missing heritability may be accounted for in rare and private mutations in affected families. There is a need for a method to rapidly curate candidate SNPs from high risk populations and determine precise functional significance for each. Previously, our lab has employed bioinformatics analysis to curate a list of candidate SNPs from a cohort of patients with likely hereditary cancer syndromes, but no known genetic cause. From these, SNPs of interest were chosen with higher probability of deleterious effects for further study, low minor allele frequency (< .05), and presence in key genes related to DNA repair and cell cycle control. Here, a series of six rare (MAF < .02) SNPs in ATM and one controversial SNP in BRCA2 overrepresented in our cohort are selected for significant functional studies. Our lab has been able to construct plasmid models of all seven SNPs and perform colony survival assays on a number of model cell lines assessing for sensitivity to DNA damage for these SNPs. Preliminary results show that the SNP BRCA2 K3326X, which produces a 92 amino acid truncation, is likely pathogenic when combined with a second damaging allele in Rad51D.

18. The RING-type E3 ubiquitin ligase of ICP0 is regulated by multiple factors to achieve the specific PML-I ubiquitination during HSV-1 infection

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Infected cell protein 0 (ICP0), an immediate early protein of Herpes Simplex Virus 1 (HSV-1), serves as an E3 ubiquitin ligase, marking multiple cellular proteins for proteasomal degradation. Among ICP's targets, PML is one of the main organizers of discrete nuclear sub-domains called ND10. As an immediate cellular response after infection, ND10s converge to viral DNA, to silence the viral genes. After ICP0 synthesis, it degrades PML immediately to disintegrate ND10 structures, abolishing viral gene repression. Previously, we reported ICP0 recognizes PML isoforms differentially. Degradation of PML-II, IV and VI relies on the function of a SUMO-interacting motif (SIM) located in amino acids 362-364 of ICP0. However, PML-I degradation is orchestrated by a bipartite-domain located in amino acids 1-83 and 245-474. Here, we delineate the regulatory mechanism of ICP0 E3 targeting PML-I. We report that: (i) The localization of PML-I in ND10 is an essential prerequisite for its degradation by ICP0; (ii) SIM362-364 is required to target SUMOylated PML-I for ubiquitination and degradation while residues 1-83 recognize the exon 9 of PML-I. ICP0 lacking both regions neither interacts with nor ubiquitinates PML-I; (iii) ICP0 N-terminus shares some sequence homology to the C-terminus of PML-I, implying a possible evolutionary mimicry of ICP0 to PML-I; (iv)Both arms of ICP0 bipartite-domain place similar heterogenous ubiquitin chains on PML-I. Our data indicates that besides the SUMO-interaction used for degradation of most PML isoforms, HSV-1 has developed a SUMO-independent strategy to ensure PML-I degradation, suggesting a possible unique restrictive function of PML-I in HSV-1 infection.

20. Investigating the role of unconventional translation and mRNA toxicity in Spinocerebellar Ataxia Type 3

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Spinocerebellar Ataxia Type 3 (SCA3), the most common, dominantly inherited ataxia in the world, is an age-related neurodegenerative disease caused by an anomalous expansion in the CAG triplet nucleotide repeat of the gene ATXN3 that encodes the deubiquitinase, ataxin-3 with an expanded polyglutamine (polyQ) region. While it is indisputable that most of the toxicity in SCA3 derives from mutated ataxin-3, the full scope of SCA3 pathogenesis is unclear. Our exploration into SCA3 steps back from the causative protein, ataxin-3, and probes the potential involvement of its mRNA. mRNA may play a toxic role in polyQ-induced degeneration beyond encoding for ataxin-3. One primary notion for mRNA-induced toxicity in CAG expansion disorders is the possibility of repeat-associated non-AUG (RAN)-initiated translation. RAN translation allows for translational initiation and elongation through a nucleotide repeat strand in the absence of an AUG initiation codon and in multiple reading frames, resulting in the production of multiple homo-polymeric repeat-containing proteins. Here, we present evidence from mammalian cell- and Drosophila-based models of SCA3 that utilize novel ATXN3 transgenes to examine the role of mRNA toxicity and RAN translation in SCA3. We observe RAN translation from ATXN3 constructs in mammalian cells, as well as increased toxicity from transgenes that allow for RAN translation in flies compared to counterparts that prevent RAN translation. Our ongoing work delves into tissue-specific and molecular mechanisms that underlie the possibility of RAN translation and mRNA toxicity in SCA3.

22. The PI3K and HDAC dual inhibitor CUDC-907 and venetoclax cooperatively target metabolic processes utilized by leukemia initiating cells in acute myeloid leukemia

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Acute myeloid leukemia (AML) continues to be a challenging disease to cure and urgently needs new more effective therapies. Although remission is possible, relapse is very common. This is caused by leukemia initiating cells (LICs). Our previous studies utilizing the selective Bcl-2 inhibitor, Venetoclax, have shown that its antileukemic activity is enhanced by the dual inhibitor of PI3K and HDACs, CUDC-907 (Fimepinostat). CUDC-907 induces apoptosis in AML cell lines and primary patient samples via upregulation of Bim, downregulation of Mcl-1 and c-Myc, and inactivation of ERK and PI3K. Based on the important roles c-Myc, and the ERK and PI3K pathways play in cellular metabolism, we hypothesized that Venetoclax and CUDC-907 cooperate in inducing metabolic reprogramming, leading to suppression of oxidative phosphorylation (OXPHOS) and eradication of LICs, which depend on OXPHOS for survival. Consistent with our hypothesis, combined treatment of AML cell lines with CUDC-907 and Venetoclax resulted in significant alterations in the levels of metabolites involved in the TCA cycle and pyrimidine metabolism, among other pathways. This was accompanied by cooperative inhibition of OXPHOS by the two agents. Additional studies are underway to determine the effects on leukemia initiating cells in patient-derived xenograft models. The results from this study will form a solid foundation for clinical evaluation of this promising combination therapy for the treatment of AML.

24. Real life contextualization of exposure therapy using augmented reality: A clinical trial for arachnophobia

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The most effective treatment for phobias and PTSD is exposure therapy—clinician-guided patient exposure to feared objects/situations until fear is extinguished. Exposure therapy is effective, yet few people receive this intervention due to absence of feared objects in clinical settings. Augmented reality (AR) overcomes this treatment barrier. Using AR, patients see their real-world surroundings with the addition of augmented products. This allows for exposure to feared objects in real-life contexts, which is critical as contextualization is key to safety learning. Using a patent-pending method, we initiated a clinical trial of AR exposure therapy (ARET) for the treatment of spider phobia in a sample of n=24. 13 participants were randomized to one-session treatment at maximum duration of 1hr. 11 were randomized to waitlist. The behavioral approach task was selected as our primary outcome to measure the individual's ability to directly interact with a live tarantula. Self-report measures of spider phobia included the Spider Phobia and Fear of Spiders Questionnaires (SPQ and FSQ). All measures were collected at baseline, one-week, and one-month follow-up. There was a significant main effect of group on participants' behavioral approach distance ($F(1,17)=33.891$, $p<.001$, $\eta_p^2=.666$), and a significant group x time interaction ($F(2,16)=16.543$, $p<.001$, $\eta_p^2=.674$). There was a significant main effect of group on participants' FSQ ($F(1,17)=48.892$, $p<.001$, $\eta_p^2=.742$) and SPQ ($F(1,17)=28.499$, $p<.001$, $\eta_p^2=.626$). Finally, there was a significant group x time interaction (FSQ: $F(IV\ 2,16)=24.477$, $p<.001$, $\eta_p^2=.754$ and SPQ: $F(2,16)=7.420$, $p=.005$, $\eta_p^2=.481$). The treatment group's distance to live tarantula decreased to zero in all participants, while the control group's did not. Our findings demonstrate efficacy of ARET for spider phobia and are expanding this method to other phobias and PTSD.

26. Characterization of ZupT a zinc transporter found in *E. coli*

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Zinc and iron have been shown to be important in oxidative stress resistance and maintaining normal cellular functions. ZupT is a metal transporter found in *E. coli* which has been shown to transport a wide variety of substrates including zinc and iron and belongs to the ZIP family of zinc transporters. It shares close homology with human ZIP proteins, particularly within the transmembrane domains. Biochemical studies of ZupT show that it contains a metal binding site specific for zinc, but capable of binding iron, cadmium, manganese, lead, and copper. A secondary site was found to bind a second iron ion. In vivo assays indicate that this protein may be involved in resistance to hydrogen peroxide induced stress. Future studies will determine if the secondary iron binding site plays a regulatory role and which metals transported may impact the phenotype of hydrogen peroxide resistance. Human ZIP transporters can be modeled biochemically with ZupT to determine their metal selectivity. These proteins play important roles in ischemia/reperfusion injury, various cancers including prostate cancer, and neurodegenerative disorders. Their individual contribution to pathogenesis is often associated with the metal transported, which is not necessarily zinc its primary substrate. Studies with ZupT offer the first metal binding studies with the entirety of a ZIP protein and are crucial to the overall understanding of transport and function.

28. Fundamental insight into the structure and broadband emission of two-dimensional hybrid organic-inorganic perovskites

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Two-dimensional hybrid organic-inorganic perovskites (2D HOIP) are promising single source materials in future applications for more efficient white light sources. Macroscopically the observed broadband emission in these materials is important in the potential applications in new white light sources. We hypothesize that charged defects drive the broadband emission. We will determine the kinds of charged defects and their effects on the structure and the broadband emission. First, we must fundamentally understand the pristine crystal structure. We will employ first-principles computational methods based on the density functional theory by first modeling the pristine crystal structures. The 2D HOIPs we study are butyl-ammonium lead iodide, hexyl-ammonium lead iodide and benzyl-ammonium lead iodide. We calculate the band structure and the vibrational frequencies of these materials with the implementation of Quantum Espresso. Experimentally, we observe a broadband emission peak between about 600 nm and 1000 nm in the photoluminescence spectra of these materials. In addition, we observed frequency changes in the Raman spectra as a function of cooling. The vibrational frequency calculations allow us to vibrationally assign the Raman shifts we observe experimentally. The comparison of our observed experimental data with the calculations provide a better fundamental understanding of the microscopic pristine structure of our materials. The microscopic pristine crystal structure is the first step in our study as we aim to determine the effects of charged defects in our materials.

30. Age-related differences in the myelin microstructure in subregions of the human corpus callosum across a healthy lifespan sample

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The corpus callosum (CC), consisting of over 300 million myelinated fibers, is the largest white matter tract in the human brain and serves as a super-highway of connections joining homologous cortical regions across hemispheres. Post-mortem studies of subcortical white matter suggest a prolonged period of myelination extending into middle age, followed by demyelination in the elderly. Multi-echo (ME-T2) imaging, an advanced magnetic resonance imaging (MRI) technique, can efficiently characterize myelin microstructure. This is achieved by modeling the multi-exponential spin-spin T2 relaxation of water trapped between myelin sheaths, yielding the measurement of myelin water fraction (MWF), a direct proxy for myelin content. We investigated age-related differences in myelin content in the CC, divided into 5 subregions of interest (ROIs), in 398 healthy individuals (236 females, 7-85 years). Voxel-wise multi-T2 component analysis was conducted for each ROI. MWF is expressed as a fraction of the total water signal. Independent of CC subregion, MWF demonstrated an inverted quadratic relationship with age [$F(14,1962) = 172.4$, $p = 0.000$]. Post-hoc analyses revealed a significant quadratic relationship with age in all sub-regions. The most anterior region, CC1, demonstrated the highest magnitude of age effect [$F(2,393) = 99.77$, $p = 0.000$], whereas the lowest magnitude effect was in CC2 [$F(2,393) = 133.5$, $p < 0.000$], located just posterior to CC1. Results support the existence of an inverted U shaped trajectory of myelin content across the lifespan, peaking around the middle age. Future longitudinal studies utilizing MWF in the CC are required for confirmation of these results.

32. Investigating the interaction between the hydrophilic N-terminal domain and the transmembrane domain of ZntA from *E. coli*

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ZntA from *Escherichia coli* is a member of the P1B-ATPase family and confers resistance specifically to toxic levels of Pb(II), Zn(II), and Cd(II). The N-terminal domain of ZntA is ~120 residues long and contains one copy of the metal-binding motif GXXCXXC. A CPC motif, as well as a conserved Asp714 in the eighth transmembrane, are essential for the binding of a second metal ion in the transmembrane domain. ΔN-ZntA, a truncated version of the transporter lacking the N-terminal domain, is still able to confer resistance to toxic levels of Pb(II), Zn(II), and Cd(II), but at a lower catalytic rate. The hydrophilic N-terminal domain is thought to dock with the transmembrane domain and pass on metal ions, thereby increasing catalytic activity. We hypothesize that this docking occurs in the form of electrostatic interactions between an amphipathic helix containing three positively charged residues in the transmembrane domain and a region of negative charge in the N-terminal domain. To investigate this interaction, we first used protein structure homology modeling software to predict the full structure of ZntA. This allowed us to identify possible electrostatic interactions between the two domains. Next, we constructed a triple mutant of ZntA, in which all three positively charged residues were mutated to an alanine. We are currently investigating the resistance of the triple mutant to Pb(II), Zn(II), and Cd(II) by assessing its time course of growth. The next step is to investigate the catalytic activity of the triple mutant compared to wildtype ZntA.

34. Characterization and targeting of TMPRSS13 in breast and colorectal cancer

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Breast cancer (BCa) and colorectal cancer (CRC) remain significant public health burdens in the United States and globally, despite advances in screening techniques and treatments. The discovery of novel, targetable biomarkers is therefore important to improve outcomes in these cancers. Cancer progression is often accompanied by increased expression of pericellular proteases capable of degrading the extracellular matrix and cleaving pro-oncogenic signaling molecules. TMPRSS13, a member of the type II transmembrane serine protease (TTSP) family, has emerged as a potential biomarker and therapeutic target in BCa and CRC. Little is currently known about the biochemical and pro-oncogenic properties of TMPRSS13. We have found that TMPRSS13 is post-translationally modified by phosphorylation and N-linked glycosylation, both of which may play a role in TMPRSS13â€™s catalytic activity, localization, and oncogenic properties. Using site-directed mutagenesis of predicted N-linked glycosylation sites, we demonstrate a significant decrease in the catalytic activity of TMPRSS13 with abrogation of glycosylation of two sites in its serine protease domain. This impairment of catalytic activity causes 1) reduction of TMPRSS13 auto-activation and 2) reduction of the ability of TMPRSS13 to activate its protein substrate, prostasin. The intracellular domain of TMPRSS13 contains multiple predicted phosphorylation motifs for the ERK1 and ERK2 MAP kinases. Using gene silencing and pharmacological kinase inhibitors, we are currently assessing the role of ERK1/ERK2 for TMPRSS13 function. Together, these studies will provide insight into the biochemical, cellular, and pro-oncogenic properties of TMPRSS13 and determine whether TMPRSS13 targeting may provide an avenue for developing improved BCa and CRC intervention drugs.

36. Single-cell neurotoxicogenomics of lead exposure in *Drosophila*

Jenna Isherwood[1] and Douglas Ruden[2]
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Lead toxicity is a worldwide health problem due to the vast number of sources of exposure, like paint, gasoline, lead pipes, and solder. Lead exposure most significantly affects the developing nervous systems of children, resulting in cognitive dysfunction and neurobehavioral deficits. Lead neurotoxicity results from oxidative damage and ion mimicry, especially of zinc and calcium, which are integral to, for instance, hippocampal neuronal function and neurotransmitter phenotype determination of developing neurons. This study utilized the *Drosophila melanogaster* model to analyze the effects of lead exposure on brain cell type populations, in order to elucidate that lead neurotoxicity affects the nervous system in a cell type specific manner. Publicly available *Drosophila* brain single-cell RNA-seq data was used in conjunction with lab-generated bulk RNA-seq data of control and lead exposed drosophila heads to generate a novel gene expression matrix of drosophila brain cell types. This matrix was used with the deconvolution method CIBERSORT to estimate cell type proportions in the control and lead exposed samples. The cell type proportions were statistically compared to identify brain cell type population sizes significantly altered by lead exposure. This analysis identified three cell types, cells of the gamma lobe of the mushroom body, the alpha/beta lobe of the mushroom body, and MIP neurons, significantly different as a result of lead exposure. These cell types have been characterized as having roles in sleep regulation, learning and memory, and mating, all of which are phenotypes known to be affected by lead exposure.

38. Structure-based design and evaluation of peptidomimetic inhibitors against the human Norovirus protease

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Norovirus is the leading cause of acute gastroenteritis worldwide and can lead to severe chronic infection in immunocompromised patients. Currently, there are no FDA approved therapeutics or vaccines against Norovirus infection. However, progress has been made in terms of identifying the Norovirus protease as a promising drug target due to its necessity in the production of mature viral proteins. Our study has focused on the development of targeted covalent inhibitors against the human strains of Norovirus protease by employing both computational and enzymatic design and evaluation techniques. Analysis of our recently solved apo and complexed crystal structures of Norovirus GI.1 and GII.4 proteases provided additional insights into the binding pocket and active site composition which led to improved inhibitor efficacy. Potential compounds were designed and analyzed using Schrodinger (2019-1) software allowing for predictive ADME screening, covalent docking of inhibitors to the protein structure, and binding affinity analysis. Following in silico design and evaluation, the lead compounds were synthesized, then enzymatically screened against purified Norovirus protease using a FRET-based assay. To date, our lead compounds exhibit nanomolar activity against the Norovirus GII.4 protease as well as the less infectious GI.1 strain.

40. Cardioprotection with ischemic conditioning: Does maintenance of mitochondrial cristae integrity play a requisite mechanistic role?

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Ischemic conditioning – including the paradigms of conventional ischemic preconditioning (IPC) and remote ischemic conditioning (RIPC) – render cardiomyocytes resistant to lethal ischemia-reperfusion injury. Considerable attention has focused on the role of mitochondria during cardioprotection achieved with IPC and RIPC; however, the contribution of mitochondrial morphosis (in particular, maintenance of cristae architecture) to cardiomyocyte fate remains largely unexplored. Accordingly, our goal was to establish whether conditioning-induced cardioprotection may be due in part to a favorable attenuation in the proteolytic cleavage and subsequent release of optic atrophy-1 (OPA1: the molecular regulator of mitochondrial cristae junction integrity) from mitochondria to cytosol. To test this, HL-1 cardiomyocytes underwent 2 hours of simulated ischemia (SI) + reoxygenation (R). This was preceded by either an IPC stimulus (4 5-min episodes of SI+R); an RIPC stimulus (pretreatment with media collected from IPC treated cells); or a time-matched control period. Primary endpoints were: 1) cell viability quantified by Trypan blue staining at 24 hours post-R; and 2) cytosolic expression of OPA1, assessed by immunoblotting at 30 minutes post-R. As expected, both IPC and RIPC attenuated cardiomyocyte death (** $p<0.01$ vs Control; left panel). However, only IPC provided better maintenance of cristae junction integrity: the robust, >15-fold increase in cytosolic OPA1 expression seen in SI+R control cells, was reduced with IPC (**$p<0.01$ vs Control, right panel), while, in contrast, RIPC had no effect ($p=0.96$ vs Control). These data suggest that favorable attenuation of OPA1 proteolysis and maintenance of cristae integrity may not play a common, requisite role in conditioning-induced cardioprotection.

42. Aldehyde dehydrogenase 2 inhibition potentiates 4-hydroxy-2-nonenal induced decrease in angiogenesis of coronary endothelial cells

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Introduction**:** Coronary endothelial cell (EC) dysfunction including defective angiogenesis is reported in cardiac diseases. 4-hydroxynonenal (4HNE) is a lipid peroxidation product, which is increased in cardiac diseases and implicated in cellular toxicity. Aldehyde dehydrogenase (ALDH) 2 is a mitochondrial enzyme which metabolizes 4HNE and reduce 4HNE-mediated cytotoxicity. Thus, we hypothesize that ALDH2 inhibition potentiates 4HNE-mediated decrease in coronary EC angiogenesis *in vitro*.
Methods: To test our hypothesis, first, we treated the cultured mouse coronary EC (MCEC) lines with 4HNE (25, 50 and 75 μM) for 2 and 4 hours. Next, we pharmacologically inhibited ALDH2 by disulfiram (DSF) before challenging the cells with 4HNE.
Results**:** In this study, we found that 4HNE attenuated tube formation which indicates the decreased angiogenesis. Next, we found that 4HNE has significantly downregulated the mRNA and protein expressions of vascular endothelial growth factor receptor (VEGFR) 2, Sirtuin 1 (SIRT 1), Ets related gene (ERG) and nuclear factor κB (NF-κB) in MCECs compared to control. ALDH 2 inhibition by DSF potentiated 4HNE-induced decrease in angiogenesis by decreasing the expressions of VEGFR2, SIRT 1, ERG, and NF-κB relative to 4HNE alone.
Conclusion**:** Thus, we conclude that ALDH2 acts as a pro-angiogenic signaling molecule by alleviating the anti-angiogenic effects of 4HNE in MCECs.

44. Structure-based design and evaluation of peptidomimetic inhibitors against the quantifying stimulus-based neuronal activity in rat brain using high-resolution photoacoustic imaging

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Current functional imaging techniques, such as functional magnetic resonance imaging, rely upon activity-induced blood flood changes to neurons. This indirect measurement of neuronal activity inherently limits image resolution and specificity. However, advances in transgenic technology and Photoacoustic (PA) methodology have offered new solutions to these limitations. Therefore, we propose using PA imaging in conjunction with a rat model containing a Fos/LacZ gene reporter system to map activated neurons. Fos is an immediate early gene product used as a marker for neuronal activation. Fusion of Fos with the lacZ gene allows active (Fos+) cells to cleave X-Gal prochromogenic substrate (through the lacZ gene product) to form PA active product. Here, we used various stimuli to activate neurons in Fos/LacZ transgenic rats which were then visualized using PA imaging. We subjected Fos/LacZ rats to three conditions: footshock, cocaine bolus, or control (home cage naïve). Ninety minutes post stimulus presentation, X-Gal was delivered directly into the medial prefrontal cortex (mPFC). Animals' brains were then PA imaged ex vivo. PA intensity within the mPFC of acquired images was quantified using ImageJ software. We presently report quantification of PA images taken from stimulated rat brains stained with X-Gal product generated in vivo within activated neurons with detailed PA signal differences between mPFC subregions following stimulus presentation. We discuss the feasibility of this reporter method for neuronal activity based on our acquired images. With this technique, we propose a method of longitudinally monitoring activated neurons in vivo with high resolution and specificity.

46. An amino-terminal threonine/serine motif is necessary for activity of the Crp/Fnr homolog, MrpC, and for *Myxococcus xanthus* developmental robustness

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40-80% of bacteria reside in biofilms, which are encased in exopolymeric substances making them difficult for antibiotics to penetrate. Biofilms inhabit many places, including medical devices, bodies of immunocompromised patients, and pipes, causing problems in health as well as industry. *Myxococcus xanthus* is a Gram negative, non-pathogenic, soil dwelling bacterium that forms a biofilm upon starvation. Cells either 1) aggregate then sporulate inside mounds of 100,000 cells (15% of population), 2) remain dormant outside of mounds (5% of population), or 3) undergo death (80% of population). MrpC is essential to this process and is a member of the widely utilized bacterial Crp/Fnr transcription factor superfamily. MrpC contains a TTSS motif in its N-terminal extension that was previously proposed to be phosphorylated in order to control its function. Our biochemical and genetic analyses, however, revealed that the TTSS motif was not directly phosphorylated, and that MrpC was phosphorylated instead within its cNMP- and DNA-binding domains, likely under non-standard laboratory conditions. A role of MrpC as a developmental buffer was exposed through substitution analysis of the TTSS motif: a TTSS to AAAA mutant fails to aggregate and sporulate, while mutants bearing triple (TAAA or AAAS) or non-consecutive double (TASA) substitutions display variable inter- and intra-clone phenotypes. Electromobility shift assays and immunoblot data showed that TTSS motif is required for full binding of MrpC to DNA, thus allowing activation of target genes, and also likely serves as an important polar motif needed for interaction of MrpC with other proteins.

48. Common reed management as a model for sustainable, community-led invasive species solutions in urban parks.

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This interdisciplinary study aims to document social perceptions and ecological impacts of the common reed (*Phragmites australis*), an invasive wetland plant prevalent in southeast Michigan public parks. Public parks offer essential services to residents and provide social and ecological value to the community. This project examines stakeholder perceptions of common reed invasions in wetland areas of two Detroit area parks, Belle Isle State Park and Lake St. Clair Metro park. Interviews and surveys were used to dissect participants opinions regarding the necessity and effectiveness of invasive species management in public parks. Additionally, ecological assessments were conducted in highly utilized areas of each park and compared to historic bioassessment and chemical treatment data. This study found that resource constraints have limited the management of invasive species, and that each park relies on partnerships with local volunteer organizations for the distribution of educational materials relating to environmental problems associated with invasive plants. Due to different levels and types of park use, and varying stakeholder perceptions about the common reed, each park requires a unique strategy of community engagement suited to parkgoer perceptions to support management outcomes. With our recommendations, both parks could enjoy improved common reed management in popular recreation areas over time. This project creates an interdisciplinary model that increases the understanding of stakeholder perceptions of the invasive common reed (*Phragmites australis*) in public green spaces. The findings from this study will contribute to better management of ecological resources at public parks and support the larger interdisciplinary conversation about invasive plants.

50. Host genetic background affects response to immune checkpoint inhibitors in a B16 melanoma model using Diversity Outbred mice

Justin Hackett and Heather Gibson
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Historically metastatic melanoma has been associated with poor prognosis. The advent of immune checkpoint inhibitors targeting CTLA-4 and PD-1 have greatly improved patient survival in metastatic melanoma, but a significant proportion of patients fail to respond to therapy. To explore the effect of genetic background on immune checkpoint inhibitor efficacy, we have developed a tumor immunotherapy model using genetically heterogeneous Diversity Outbred (DO) mice and the C57BL/6 syngeneic B16F0 melanoma model. To implement genetic diversity, DO mice were crossed with C57BL/6 to generate (C57BL/6xDO)F1 mice. Untreated (C57BL/6xDO)F1 mice (n=34) reliably develop B16F0 tumors after subcutaneous inoculation, with some variation in tumor onset. In a pilot immunotherapy study, 20 (C57BL/6xDO)F1 mice were treated with anti-PD-1/anti-CTLA4 on days 12, 14, and 16, after tumors were palpable. Tumor tissue was collected on day 19 and mice with reduced tumor growth showed an increase presence of CD8+ cells and IFN-γ expression. To test the role of genetics in response to ICI 142 (C57BL/6xDO)F1 mice were treated with combined anti-PD1/anti-CTLA-4 on days 3, 6, and 10 after B16F0 inoculation. Mice receiving therapy show wide variation in tumor onset up to 65 days (mean 20.86 +/- 11.04, CV 52.94%), with 19 never developing tumor by day 88. Preliminary Genome Wide Association shows suggestive associations on chromosomes 8, 12, and 13 with validation underway. This data suggests that the genetic background significantly influences response to treatment and validates further testing of this model and subsequent Quantitative Trait Locus analysis.

52. The impact of cellular developmental state on therapeutic response in glioblastoma

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Glioblastoma (GBM) is an aggressive tumor treated with ionizing radiation (IR) and temozolomide (TMZ). Here we investigate how the developmental state of glioblastoma cells drives cellular response to treatment. Tissue from untreated primary GBM tumors representing diverse genotype was dissociated and cultured in conditions selective for cancer stem cells (CSCs), which were subsequently differentiated into an astrocytic phenotype by culturing in media supplemented with 2% FBS (serum differentiated cells, SDC). As validation, we utilized a machine learning predictive algorithm to estimate the stem-like features of the CSCs and SDCs. Sensitivities of isogenic CSC and SDC populations to TMZ and IR was determined by non-linear fitting of cell-viability dose-response curves. CSCs and SDCs were then subjected to sub-lethal TMZ, IR (4 Gy), or control treatments, in triplicate. Cells were harvested, genomic DNA was isolated and analyzed by Illumina 450k DNA methylation array. RNA was isolated for sequencing, and differentially expressed genes were determined by NOISeq R package. Our results show that GBM CSCs are more vulnerable to both TMZ and IR treatment than the isogenic SDCs. Epigenomic profiling of CSCs reveals a global increase in CpG promoter methylation in response to treatment while SDCs exhibit a decrease in CpG promoter methylation. Transcriptome analysis reveal the upregulation of proliferation genes in the absence of DNA damage response genes in treated CSC in comparison with controls and differentiated cells. These findings underscore the complexity of treating a highly heterogeneous tumor and challenge a strategy of inducing differentiation to increase GBM sensitivity to treatment.

54. Identifying host-intrinsic resistance mechanisms to therapeutic anti-tumor antibody

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Monoclonal antibody (mAb) therapies have greatly improved outcomes for a variety of cancer subtypes. mAbs that target tumor-associated antigens (TAA) facilitate antibody-dependent cellular cytotoxicity (ADCC) and/or the disruption of oncogenic receptor signaling. Humanized mAb trastuzumab targets the TAA human epidermal growth factor 2 (HER2). Despite its reputation as the gold standard treatment for HER2-overexpressing cancers, response rates remain low (â‰¤30% as a monotherapy, â‰¤50% with chemotherapy). This study utilizes the genetically heterogeneous Diversity Outbred (DO) mouse model, produced by non-sibling cross-breeding of 8 inbred mouse strains, to identify host-intrinsic mechanisms of resistance to TAA-mediated immunotherapy. We find a divergent response to anti-Neu (a HER2 homolog) mAb clone 7.16.4 in (DOxBALB/c)F1 mice (n=21) bearing established Neu oncogene-driven mouse mammary TUBO tumors, with 24% showing complete response (CR), 62% showing partial response (PR), and 14% failing to respond (NR). CR mice were protected from a contralateral tumor rechallenge, suggesting adaptive anti-tumor immunity was promoted by mAb therapy. We further measured peripheral anti-tumor immunity by IFNÎ³ ELISPOT using splenocytes (SC) from these mice, which trended toward elevated anti-TUBO T cells in CR versus PR and NR mice. This trend was also seen in serum total anti-tumor IgG levels post-sacrifice. Host-intrinsic regulators are currently being evaluated via a whole-genome array to reconstruct the mosaic of DO parental strain haplotype blocks for each mouse, with analysis to determine genetic loci associating with therapeutic outcome. Future efforts are aimed towards defining the critical genetic loci and causal gene(s) associated with a durable response to mAb therapy.

Notes

Notes

Thank you to our judges!

Anatomy/Cell Biology
Elizabeth Berger
Maria Bykhovskaia
Dennis Drescher
Tomomi Ichinose
Robert Skoff
Ryan Thummel
Shunbin Xu

Biochemistry/ Otolaryngology
Dennis Drescher

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