Graduate Research Forum 2021

Abstract Booklet

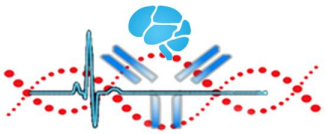
Council of Biomedical Graduate Students

March 25th to March 26th 2021

Presented by
UToledo College of Medicine and Life Sciences
and
UToledo College of Pharmacy and Pharmaceutical Sciences

COLLEGE OF MEDICINE AND LIFE SCIENCES
THE UNIVERSITY OF TOLEDO
Biomedical Science Program

BIOMEDICAL SCIENCE GRADUATE PROGRAM



THE UNIVERSITY OF
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COLLEGE OF PHARMACY AND PHARMACEUTICAL SCIENCES
THE UNIVERSITY OF TOLEDO

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Dean's Message

Dr. Christopher J. Cooper, M.D.

The Health Science Campus Graduate Research Forum is a student-led forum organized by the Council of Biomedical Graduate Students since 1979. This forum has been instrumental in creating a collaborative atmosphere that allows students to share their research with their peers, while improving their own presentation skills.

Beginning in their second year, all students in the Biomedical Science Program are expected to participate either with oral talks or poster presentations of their research projects. The oral and poster presentations are judged by faculty and postdoctoral fellows, with 1st, 2nd, and 3rd place cash awards subsequently presented in each of the two presentation categories.

In addition, every year, the Council of Biomedical Graduate Students collaboratively chooses and invites distinguished scientific keynote speakers to share their stories and inspire our students. This year, the students admirably adapted to the current situation and turned the forum completely virtual. These student-led decisions are also wonderful examples of how the Council of Biomedical Graduate Students reinforces leadership qualities to our trainees.

Dr. Christopher J. Cooper, M.D.
Dean
College of Medicine and Life Sciences
University of Toledo

Welcome

Sayani Bhattacharjee

The Council of Biomedical Graduate Students (CBGS) has been organizing the Graduate Research Forum (GRF) in collaboration with the College of Pharmacy over the last four decades. However, due to the COVID-19 pandemic, we had to cancel this forum in 2020. Since things have still not returned back to the way they were before, CBGS has decided to adapt to the current circumstances and host this research forum virtually.

GRF is a great platform for students and faculty to learn about the research being done in other tracks and form collaborations. Therefore, we are happy to see such remarkable participation from students and faculty, despite the forum being virtual. We are very thankful to the Biomedical Science program faculty and post-doctoral fellows for their overwhelming support in organizing this forum. We have 71 students registered for the 2021 GRF, with 45 of them presenting. The forum being virtual will allow students, fellows and faculty to attend more sessions from their lab/office. We hope everyone will utilize this opportunity and interact with all our presenters.

We are excited to have a keynote speech by Dr. Lynn Matrisian, who is the Chief Science Officer at the Pancreatic Cancer Action Network (PanCAN). Listening to her speech about biomedical research from different perspectives will be a great learning opportunity for our graduate students. I am thankful to her for cordially accepting our invitation and patiently supporting us while we figured out the several intricacies of this virtual format.

Planning a research forum in itself is a difficult task. The council had to rethink the whole format to host this forum virtually. I am thankful for having such a brilliant team of graduate students without whom organizing this forum would have been impossible. Finally, I would like to thank

Drs. Kandace Williams and David Giovannucci for guiding the council and providing us with their invaluable advice. I hope all attendees enjoy the forum and that our first virtual Graduate Research forum becomes a big success.

Sayani Bhattacharjee
President
Council of Biomedical Graduate Students
University of Toledo

About CBGS

The University of Toledo Council of Biomedical Graduate Students consists of officers and representatives from the College of Medicine and Life Sciences and the College of Pharmacy and Pharmaceutical Sciences at the University of Toledo. This includes the Biomedical Science Graduate Program and related graduate programs in Pharmacy, and from the Center of Excellence in Biomarker Research & Individualized Medicine (BRIM) at the Health Science Campus.

The overarching goals of the council include:

- Facilitate discussion and collaboration among the graduate student body
- Represent the interests of BMSP and other graduate programs before UT Faculty, the Graduate Students Association and University Administration
- Organize social and professional events to enrich the graduate student life experience

We meet regularly, at least once per month, to discuss any current issues that need to be addressed and to plan and organize upcoming events. The meetings are open to all graduate students to encourage discussion of ideas and concerns pertaining to graduate student life. However, only elected members of the Council may vote during the meetings.

Annual events organized by the CBGS include

- Graduate Student Picnic A summer social event for new and current students
- Career Forum Held in autumn to help guide students for career decisions
- Graduate Research Forum Held during the spring semester to allow students to showcase their research and get helpful advice from faculty and fellow students

Visit us at http://www.utoledo.edu/med/grad/biomedical/cbgs/

Keynote Speaker

Dr. Lynn Matrisian, PhD

Dr. Lynn Matrisian is a Molecular Biologist who is currently serving as the Chief Science Officer of the at the Pancreatic Cancer Action Network (PanCAN). She has dedicated her life to fighting the world's toughest cancer. She oversees PanCAN's overarching Scientific goals, including the Grants Programs and Programs focused on improving personalized and precision medicine approaches.

Dr. Matrisian graduated from Bloomsburg University In 1975 in Medical technology and received her PhD in Molecular Biology from the University of Arizona. She completed her Post-Doctoral Research at Uniersity of Arizona and at INSERM and CNRS in France. She has been teaching at Vanderbilt University over the past 30 years and performing research in the domain of translational cancer research and matrix metalloproteinases.

Dr. Matrisian has been an integral part of several National Cancer Institute (NCI) initiatives, including the Pancreatic Cancer Working Group, the Clinical Trials and Translational Research Advisory (CTAC) Committee and CTAC Translational Research Strategy Subcommittee. She served as one of the co-chairs of NCI's Translational Cancer Research Working Group and as Special Assistant to the NCI director leading the implementation team.

Dr. Matrisian has been recognized for her contributions and excellence in research. She has received the Paget-Ewing Award from the International Metastasis Society, the NIH Merit Award and is a Fellow of the American Association for Cancer Research Academy for major contributions that have propelled significant innovation and progress against cancer.

Keynote Speech

Dr. Lynn Matrisian, PhD
Chief Science Officer
Pancreatic Cancer Action Network
PanCAN

Blind Men and Elephants: Biomedical Research from Many Perspectives

3 PM – 4 PM

Click Here to Join

Program

Date	Session	Time	Notes
March 25th, 2021	Poster Session 1 Poster Session 2 Poster Session 3 Poster Session 4 Poster Session 5 Poster Session 6	10 AM – 12 PM	All Poster Sessions will happen simultaneously
	Oral Session 1	1 PM - 2 PM	
	Oral Session 2	2 PM - 3 PM	
	Oral Session 3	3 PM - 4 PM	
March 26th, 2021	Poster Session	10 AM – 11 AM	
	Oral Session	11 AM – 12 PM	
	Lunch	12:30 PM – 1:30 PM	Only for registered Students
	Keynote Speech	3 PM to 4 PM	

Virtual Conference Links

Oral Presentations

- Oral Session 1: click here to join
- Oral Session 2: click here to join
- Oral Session 3: click here to join

Poster Presentations

- Oral Session 1 click here to join
- Oral Session 2 click here to join
- Oral Session 3 click here to join
- Oral Session 4 click here to join
- Oral Session 5 click here to join
- Oral Session 6 click here to join

Keynote Speech

- Lunch with the Speaker click here to join
- Keynote Speech click here to join

Group Assignments

Oral Presentations

Group 1	Ishan Manandhar
	Joshua Breidenbach
	Irum Syed
	Ahmed Abokor
	Chrysan Mohammed
Group 2	Sachin Aryal
	Melissa Curtis
	Veani Fernando
	Jonnelle Edwards
	Joshua Letson
Group 3	Justin Creeden
	Nilanjana Saferin
	Caoqinglong Huang
	Kathryn Becker
	Yetunde Makinwa

Poster Presentations

Group 1	Deepti Gurung
	Iluja Gautam
	Fathima Dhilhani Mohammed Faleel
	Abdul-Rizaq Hamoud
Group 2	Sukanya Chakravarty
	John Dillon
	Juthika Mandal
	Khaled Alganem
	Mohammad Ali
Group 3	Smrithi Sugumaran Menon
	Xue Mei
	Saloni Malla
	Nicole Bell
	Rawan Alnafisah
Group 4	Sara Moore
	Yashna Walia
	Apurva Lad
	Shruti Ghai
	Ali Imami
Group 5	Emily Waigi
	Safalta Khadka
	Syed Hasan
	Shreyasi Ganguly
	Mitchell Harberson
Group 6	Hunter Eby
	Nicholas Henkel
	Rachel Golonka
	Daniyah Almarghalani
	Kaitlyn Zigulis

Guidelines

Virtual Oral Presentation Guidelines

- PowerPoint will be used for the oral presentations. There is no restriction for the number of slides per presentation. Please make sure all text, figures and diagrams on the slides are clear and legible.
- Each presenter will be given an assigned "Group" for which each group will be given a specific WebEx link for their oral presentation. When it is your turn for presenting, the moderator will allow you access to *Share Screen*.
- Each oral talk will be given a maximum of 15 minutes including time for questions. Presenters are advised to limit their presentations to 10 minutes (max 12 minutes) to allow time for questions.
- Judging Criteria: Judging will be based on knowledge of the subject, organization and clarity of the talk, conclusions supported by data, ability to finish the talk in allotted time, ability to answer questions, and overall presentation.

Virtual Poster Presentation Guidelines

- To design a virtual poster, please find attached a template whose slide size is 36 inches high by 48 inches wide [these are the same dimensions that would have been used to make a live poster (size - 3 feet high and 4 feet wide)]. If the attached template is not compatible with your computer, you can customize the slide size on your own device. To do so, go to the *Design* tab in PowerPoint and then on the right side you will see the option for *Slide Size*. Once this option is clicked, then you will see the availability for *Custom Slide Size*. After choosing this icon, you will be able to change the width and height to 48 inches and 36 inches respectively (input as 48 in and 36 in). After pressing *Okay* an option screen will pop-up to ask for either the *Maximize* or *Ensure Fit*. Choose the *Ensure Fit* Option. If you have any questions on designing the virtual poster, please do not hesitate to contact CBGS.

- Please make sure all text, figures and diagrams are clear and legible. As a reference: Title font size (if Arial style) can be between 72-88 pt (depends on the length of the title), Section title (e.g., Methods) font size between 58-60 pt, Abstract font size between 30-32 pt, Introduction/Conclusion font size between 30-36 pt. NOTE: These font sizes are NOT FIXED and can be adjusted according to the amount of research you are presenting. In line with this, the attached template is NOT FIXED as you can modify according to the number of figures that you are presenting. However, please keep within the dimensions of 3 feet high by 4 feet wide.

- If you wish to show data in the form of videos, a PowerPoint presentation can be used for that specific piece of data.

- Once you have completed your poster, please save it as a PDF file. These PDF files will be put on Slack so that everyone will have the opportunity to view your poster.

- Each presenter will be given an assigned "Group" for which each group will be given a specific WebEx link for their poster presentation. When it is your turn for presenting, the moderator will allow you access to *Share Screen*.

- Each poster presentation will be given a maximum of 15 minutes, including time for questions. Presenters are advised to limit their explanation of posters to 10 minutes (max 12 minutes) to allow time for questions. NOTE: For you and the audience to properly see the entire poster while presenting, please follow these quick-step instructions: (i) open the PDF file for your poster, (ii) go to the *View* tab on the top left, (iii) under *View*, choose the option *Full Screen Mode* (not Read Mode). You can use your cursor to zoom in to each section of your poster.

- Judging Criteria: The judging will be based on knowledge of the subject, explanation of background and significance, organization of poster, clarity of presentation, conclusions supported by data, ability to finish presentation in allotted time, ability to answer questions, and overall presentation.

Part II

Oral Presentations

Group 1

Supervised Machine Learning for Microbiome-Based Classification of Inflammatory Bowel Diseases

Oral-1

Ishan Manandhar

Ishan Manandhar, Ahmad Alimadadi, Sachin Aryal, Patricia B. Munroe, Bina Joe, Xi Cheng

Inflammatory bowel diseases (IBD) are characterized by chronic inflammation of the gastrointestinal tract. Despite various clinical approaches being available for diagnosing IBD, such as blood tests and colonoscopy, misdiagnosis of IBD occurs frequently, thus there is a clinical need to improve diagnosis of this condition. Since significant alterations in gut microbial compositions are reported in IBD patients, we hypothesized that gut microbiome data can be used to develop an artificial intelligence-based strategy for diagnostic screening of IBD. To test our hypothesis, fecal 16S metagenomics data of 729 IBD patients and 700 non-IBD controls collected from the American Gut Project were analyzed using five supervised machine learning (ML) models: random forest (RF), decision tree, elastic net, support vector machine and neural networks. Fifty differentially abundant bacterial taxa were identified (LEfSe: LDA > 3) between the IBD and non-IBD groups. ML classifications, trained with these 50 taxonomic features, achieved a testing AUC (area under the receiver operating characteristics curve) of 0.80 using the RF model. Next, we tested if operational taxonomic units (OTUs), instead of bacterial taxa, could be used as ML features for diagnostic classification of IBD. Top 500 high-variance OTUs were trained with the five ML models described above, and an improved AUC of 0.82 was achieved by RF. Further, we tested the capability of the RF model to distinguish between Crohn's disease (CD) and ulcerative colitis (UC) using 331 CD and 141 UC samples. A total of 117 differentially abundant bacterial taxa (LEfSe: LDA > 3) were identified and the RF model trained with these bacterial features achieved a testing AUC of 0.91. Furthermore, the RF model trained with the top 500 high-variance OTUs achieved a slight improvement of AUC to 0.92. In summary, we demonstrated robust supervised ML modeling for diagnostic screening of IBD and its subtypes.

Aerosolized Harmful Algal Bloom Toxins Induce Type 1 In ammation of the Airways

Oral-1

Joshua Breidenbach

Joshua D. Breidenbach, Thomas M. Blomquist, Andrew L. Kleinhenz, Apurva Lad, Robin C. Su, James C. Willey, Je rey R. Hammersley, Amira Gohara, Ronald M. Wooten, Erin Crawford, Nikolai Modyanov, Deepak Malhotra, Steven T. Haller, David J. Kennedy

Harmful algal blooms are on the rise globally and pose serious health concerns due to the release of cyanotoxins, which are harmful to both humans and the environment. Microcystin-LR (MC-LR) is one of the most frequently produced cyanotoxins and has recently been detected in aerosols generated by the normal motions of a ected bodies of water. However, the human health e ects of MC-LR aerosols on pulmonary health remain largely unknown. We and others have previously observed that aerosol MC-LR exposure has a pro-in ammatory in uence on the airways, however this in ammation has yet to be thoroughly characterized. Therefore, the objective of this study was to determine the extent of the pro-in ammatory e ects of MC-LR on the airways to elucidate the implications of exposure in healthy and at-risk human populations. To address these knowledge gaps, an in vitro 3D primary human airway model was utilized. Additionally, mouse inhalation exposures in which C57BL/6J mice (prone to Type 1 in ammation) and BALB/c mice (prone to Type 2 in ammation) were compared. Gene and protein abundance in both human and mouse models found increases in cytokines associated with granulocytic in ammation (CXCL1, GM-CSF, CCL3, CCL2), thus suggesting a general in ammatory response. Importantly, this response was observed in the C57BL/6J but not the BALB/c mice, suggesting a speci city for Th1 and Th17 driven Type 1 in ammation. Speci cally, male C57BL/6J mouse lungs exposed to MC-LR produced signi cant ($p<0.05$) fold increases in cytokines by protein abundance compared to vehicle control [IL-17a (6.0 0.71), IL-12 (2.3 0.09), CCL3 (8.6 0.58), and CXCL1 (5.4 0.39)], while male BALB/c mice produced no signi cant increase. The results of this study warrant further investigation into the potential impact of MC-LR aerosol exposure in at-risk human populations with pre-existing Type 1 in ammatory pulmonary conditions.

Identi cation of Factor H-binding proteins expressed by Burkholderia pseudomallei

Oral-1

Irum Syed

Irum A. Syed, Laura S. Nejedlik, Caroline L. Lambert, Michael E. Woodman, Minal Mulye, Viviana P. Ferreira, Jason F. Huntley, and Ronald M. Wooten

Background

Melioidosis is caused by the encapsulated Gram-negative organism Burkholderia pseudomallei (Bp). Due to its low LD50, high infectivity, and antibiotic resistance, Bp is classi ed as a Tier 1 select agent and there is great interest in characterizing virulence factors that may be targets for novel therapeutic agents. Our lab has previously shown that Bp resistance to uptake and clearance by macrophages and neutrophils is overcome following su cient bacterial opsonization.

Hypothesis

We hypothesize that Bp serum resistance is mediated by the expression of outer membrane proteins that bind complement negative regulator Factor H to prevent optimal complement activation on the bacterial surface and evade critical host immune mechanisms. Identi cation of the proteins responsible for Factor H binding may uncover novel therapeutic targets to prevent and/or treat melioidosis. Methods and Results: Factor H binding by Bp was demonstrated using the direct Factor H-binding assay and the bound Factor H was con rmed to be functionally active via cofactor assay. Candidate Bp Factor H-binding proteins were identi ed by both in silico analysis of the Bp proteome and far-western analysis of Bp outer membrane proteins following 2D SDS-PAGE with subsequent mass spectrometry. Evaluation of candidate Factor H-binding proteins is described.

Conclusions

Intact, live Bp can bind Factor H in a functionally active form in vitro. Expression of Bp outer membrane protein OmpA confers the ability to bind Factor H. Bp OmpA is highly conserved across numerous important Burkholderia pathogens and may serve as a comprehensive therapeutic target.

Moving Forward

Mutation of the predicted Factor H-binding residues of OmpA within the Bp chromosome is underway. Ahead of mutant construction, OmpA function on live bacteria will be

blocked using polyclonal anti-OmpA serum, and antiserum-blocked Bp will be assessed for Factor H-binding, serum sensitivity, and complement deposition.

Elevated serum bile acid levels alter erythrocyte composition in C57BL/6 mice irrespective of sex

Oral-1

Ahmed A. Abokor

Ahmed A. Abokor, Piu Saha, Rachel M. Golonka, Beng San Yeoh, Matam Vijay-Kumar

Bile acids (BA) are amphipathic molecules with detergent-like properties whose canonical function is to emulsify lipids and fat-soluble vitamins from our diet. Recently, new insights delineate an assortment of physiological roles for BA in various organ systems. Systemically elevated quantities of BA (alias cholemia) is commonly associated as a concomitant outcome of liver disease, however, rarely measured in healthy individuals due to being an asymptomatic feature. When screening our mice colony, we observed a subset of mice had signi cantly elevated BA quantities in their sera (>40μM/L) and were appropriately classi ed either low or high serum total BA accordingly (L-TBA and H-TBA respectively). Complete blood count analysis of H-TBA mice displayed a signi cant reduction of hematocrit and hemoglobin levels, suggestive of hemolytic anemia. Correspondingly, analysis for mature and immature erythrocytes (alias reticulocytes) via ow cytometry revealed an increased percentage of immature peripheral CD71+ Ter119+ erythrocytes in H-TBA mice, further implying the presence of anemia. In contrast, we observed erythrocytes from H-TBA mice were signi cantly resistant to osmotic-induced hemolysis. Additionally, erythrocytes incubated in the presence of either H-TBA serum or exogenous BA (e.g., cholate, deoxycholate) also displayed protection against hemolysis. Further, erythrocyte membrane physiology di ered between the groups with H-TBA mice exhibiting reduced Na+/K+ATPase activity, membrane phospholipid contents, and glycoprotein quantities. Overall, these ndings highlight a novel, non-canonical role of BA in the vascular system. Future studies may uncover how these striking e ects of BA impact blood-related diseases such as malaria and other disease models.

Paraoxonase 3 is Renoprotective in a Dahl Salt-Sensitive Rat Model of Chronic Kidney Disease

Oral-1

Chrysan Mohammed

Chrysan J. Mohammed, Fatimah K. Khalaf, Prabhatchandra Dube, Dhanushya Battepatti, Andrew L. Kleinhenz, Amira Gohara, Steven T. Haller, David J. Kennedy

Introduction

Paraoxonase 3 (Pon3), is one of the three isoforms comprising the paraoxonase gene family. Unlike Pon1 and Pon2, there is a paucity of knowledge regarding Pon3. Pon3 is synthesized in the liver and can circulate bound to high-density lipoproteins. There is signi cant expression in the kidney also. Decreased Pon activity is associated with adverse clinical outcomes in the setting of chronic kidney disease (CKD). We tested the hypothesis that absence of Pon3 is mechanistically linked to progression of renal injury in a Dahl salt-sensitive model of hypertensive renal disease.

Methods/Results

Experiments were performed on wild type Dahl salt-sensitive (SS) rats and Pon3 knock-out (SS-Pon3-KO) rats. To initiate salt-sensitive hypertensive renal disease, 10 weeks old SS-wild type and SS-Pon3-KO rats were maintained on high salt diet (8% NaCl) for 8 weeks. After 8 weeks, rat kidneys were sectioned for histopathology. During the course of the study, mortality was observed in 23.8% (5 out of 21) of the SS-Pon3-KO males (mean length of time until death = 39 days) while no mortality was observed in male SS-wild type on high salt. Upon histological examination, kidneys from SS-Pon3-KO rats demonstrated signi cant ($p<0.0001$) increase in renal injury as noted by increased protein cast formation and tubular atrophy (both $p<0.0001$) compared to SS-wild type. Kidneys from SS-Pon3-KO also showed increased vascular hypertrophy and glomerular sclerosis compared to SS-wild type despite similar degrees of hypertension. SS-Pon3-KO rats had signi cantly more renal brosis ($p<0.0078$) and increased renal in ammation ($p<0.0001$) as demonstrated by increased interstitial immune cell accumulation compared to kidneys from SS-wild type on high salt. We noted that SS-Pon3-KO had signi cantly decreased ($p<0.05$) glomerular ltration rate compared to SS-wild type rats.

Conclusion

These ndings suggest a potential new role for Pon3 in regulating renal in ammation and brosis in the setting of hypertensive renal disease.

Group 2

Gut Microbiome Based Machine Learning for Diagnostic Screening of Cardiovascular Disease

Oral-2

Sachin Aryal

Sachin Aryal, Ahmad Alimadadi, Ishan Manandhar, Bina Joe, Xi Cheng

Cardiovascular disease (CVD), as the leading cause of death worldwide, has many di erent types of morbid conditions, such as hypertension, heart failure, and atherosclerosis, which could develop simultaneously or lead to each other. An array of di erent clinical assays and imaging approaches is required for a comprehensive evaluation of cardiovascular health. Therefore, a systematic screening of any existing cardiovascular dysfunction could save diagnostic time and initiate early therapeutic interventions. Gut microbiota dysbiosis has been reported in patients with certain types of CVD, such as hypertension. Therefore, we hypothesized that gut microbiome data could be trained with supervised machine learning (ML) models for initial systematic CVD diagnosis. To test our hypothesis, we analyzed 16S rRNA sequencing data from stool samples collected through the American Gut Project. The stool 16S metagenomics data of 478 CVD and 473 non-CVD subjects were analyzed using ve supervised ML algorithms: random forest (RF), support vector machine, decision tree, elastic net, and neural networks (NN). Interestingly, we identi ed 39 di erential bacterial taxa between the CVD and non-CVD groups, but initial ML classi cations, using these taxonomic features, could only achieve an AUC (0.0: perfect antidiscrimination; 0.5: random guessing; 1.0: perfect discrimination) of 0.58 (RF and NN). Alternatively, the top 500 high-variance features of operational taxonomic units (OTUs) were used for training ML models and an improved AUC of 0.65 (RF) was achieved. The top 25 highly contributing OTU features (HCOFs) were further selected from those high-variance OTU features for re-training the ML models, and interestingly, an improved AUC of 0.70 was achieved using the RF model. Overall, our study identi ed dysregulated gut microbiota in the CVD patients and further developed a gut microbiome-based ML approach for the rst time for a promising systematic diagnostic screening of CVD.

The e ects of developmental pyrethroid pesticide exposure in mouse brain using integrative multiomics

Oral-2

Melissa Curtis

Melissa Curtis, Ali S. Imami, Khaled Alganem, Justin F. Creeden, Rammohan Shukla, James Burkett

Autism Spectrum Disorder is a cluster of incurable neurodevelopmental disorders with a prevalence of 1 in 54 people. Despite its very high incidence and rise in prevalence each year, less that 10% of autism cases arise from an identi able cause. This is in part because the causes are poorly understood, and thought to be both genetic and environmental. The recent CHARGE study (among others) has suggested that developmental exposure to pyrethroid pesticides, a common pesticide widely used due to its supposed safety, can lead to an increase in autism risk. To further evaluate the developmental e ects of pyrethroid pesticide exposure, experiments were performed using two independent cohorts of mouse dams which were fed pyrethroid pesticide (or vehicle) during pregnancy and lactation. The o spring were raised to adulthood and euthanized for tissue collection. Split-sample study transcriptomics, kinomics, and metabolomics analyses will be performed on the brain tissue collected. Multiomics integration, and other bioinformatic analyses, will be performed using the generated datasets to gain a more comprehensive understanding of the multi-modal biophenotype induced from the exposure. Results for each of the analyses and the multiomics integration will be discussed in the context of contribution of developmental pesticide exposure to autism risk.

Arginine Metabolism In Tumor-Associated Macrophages: A Target to Induce Immunogenic Shift in Breast Cancer

Oral-2

Veani Fernando

Veani R. Fernando, Xunzhen Zheng, Vandana Sharma, Saori Furuta

Conventional therapies targeting breast cancer often become futile due to the development of resistance. Thus, immunotherapy has emerged as an alternative strategy. However, this approach has yielded only moderate responses in most subtypes of breast cancer. This is largely due to the immunosuppressive nature of tumor microenvironment (TME) harboring a large number of tumor associated macrophages (TAMs) that exhibit the immunosuppressive M2-type rather than immunogenic M1-type. Therefore, reprogramming M2 TAMs towards M1 TAMs would induce an immunogenic shift in breast TME and improve the e cacy of immunotherapy. Since distinct phenotypes of M1 vs. M2 TAMs are attributed to their di erential arginine metabolism, modulating arginine metabolism has been proposed as a strategy to reprogram TAMs. M1 TAMs metabolize arginine to produce nitric oxide (NO) which helps exert anti-tumor activities. In contrast M2 TAMs metabolize arginine to produce polyamines which exert pro-tumor activities. Such di erence in arginine metabolism between M1 and M2 TAMs is owing to di erential availability of tetrahydrobiopterin (BH4), the essential co-factor of NO synthase (NOS). We thus hypothesized that supplementing sepiapterin, the endogenous precursor of BH4, in M2 TAMs would re-direct their arginine metabolism towards NO synthesis and reprogram them to M1 TAMs. Sepiapterin has been successfully utilized in treating di erent metabolic disorders in clinics. Thus, it is expected to produce little systemic toxicity. Our in vitro experiments, show that sepiapterin treatment of M2 TAMs elevated NO production, while downregulating polyamine production. Importantly, this caused a shift of their phenotype from M2-type to M1-type. Consistently, sepiapterin-treatment of ex vivo-cultured mammary tumors e ectively reprogramed M2 TAMs to M1 TAMs, resulting in a signi cant decrease of tumor mass. These results strongly suggest that sepiapterin could induce an immunogenic shift in breast TME and be potentially utilized as an immunotherapeutic drug in clinics.

Pro-Resolving Lipid Mediators Reduce Acetylcholine-Induced Contractions in Hypertensive Resistance Arteries

Oral-2

Jonnelle Edwards

Jonnelle M. Edwards, Emily Waigi, Cameron G. McCarthy, Bina Joe, Camilla F. Wenceslau

It is well known that low-grade chronic in ammation induces vascular dysfunction and contributes to hypertension. On the other hand, the resolution of in ammation is an active phenomenon to switch o the in ammatory processes after harmful stimuli removal and facilitate the return to homeostasis. Increasing the levels of pro-resolving mediators to promote the resolution of in ammation is emerging as a novel therapeutic approach. Arachidonic acid, docosahexaenoic acid, and eicosapentaenoic acid produce pro-resolving lipid mediators lipoxin A4 (LXA4), resolvin D1 (RvD1), and resolvin E1 (RvE1), respectively, through the 5-lipoxygenase enzymatic pathway. However, it is unknown if pro-resolving lipid mediators can ameliorate dysfunction in arteries from hypertensive animals. Therefore, we hypothesized that pro-resolving lipid mediators decrease acetylcholine-induced contractions in arteries from hypertensive rats (SHR). As expected, low concentrations (100 nM) of acetylcholine-induced relaxation in arteries from both normotensive (WKY) and hypertensive rats, however high concentrations (1 µM) of acetylcholine-induced contraction in arteries from SHR, but not in WKY [Maximum response (Emax): WKY: 94.5 3.3 vs. SHR-control: 44.9 12.5* %, t-test *vs. WKY, p=0.01). Treatment with the pro-resolving lipid mediators did not change acetylcholine-induced relaxation in arteries from WKY (Vehicle: 94.5 3.3 vs. RvD1: 95.8 0.8; RvE1: 90.1 7.1; LXA4: 93.5 3.9 %, p>0.05). However, incubation with RvE1 abolished acetylcholine-induced contraction in arteries from SHR and promoted relaxation (Vehicle: 44.9 12.5 vs. RvE1: 94.1 3.5%, t-test *vs. vehicle, p<0.05). While acetylcholine-induced contraction abolishment from incubation with RvD1 and LXA4 in arteries from SHR did not reach signi cance due to the small sample size, we did observe a tendency towards improvement. Overall, our work suggests that the RvD1, RvE1, or LXA4 may be used as a new therapeutic tool to speci cally improve vascular function in hypertension.

The Role of Nitric Oxide in TGF -Mediated Activation of Mammary Fibroblasts

Oral-2

Joshua Letson

Joshua Letson, Saori Furuta

Each year, thousands of women across the world will be diagnosed with some form of breast cancer, making it the most common cancer diagnosis in women. While preventative techniques and treatments have helped to reduce the mortality rate, the incidence rate has risen rapidly over the last several decades. Researchers are then tasked with nding new ways of combating this very common disease. A major risk factor for breast cancer is the density of the breast tissue. Women with dense breast tissue are unfortunately at a higher risk of contracting this disease. This has led many scientists to look at ways of reducing the density of the breast tissue. One seemingly unanticipated way to alter the density may be through a small signaling molecule known as nitric oxide (NO). Most notably, NO is used by our bodies for vasodilation of blood vessels and for neuronal signaling, but we are nding that it may help to also reduce the density of breast tissue. We have shown that NO levels decrease in breast cancer cell lines and this results in an increase in tissue density. A decrease in NO may then lead to downstream brous protein production. A major protein involved in the production of brous proteins that results in sti ness is transforming growth factor (TGF). TGF overactivation can result in increased brous production by broblasts. We showed that restoring the NO level can help to minimize TGF activation and result in decreased production of brous proteins by broblasts. Restoration of the basal NO level in pre-cancerous patients or women who are susceptible to this disease may help to reduce incidence and mortality rates.

Group 3

Kinase Fingerprinting in Pancreatic Cancer

Oral-3

Justin F. Creeden

Justin F. Creeden

Background: In many human pathologies, organ brosis may cause functional impairment and negative clinical outcomes.

Signi cance of Problem: In addition to overt clinical symptoms, biophysical brotic barriers may also obstruct drug delivery.

Hypothesis: Targeting protein tyrosine kinases involved in organ brosis may provide two-fold clinical bene t. First, small molecule protein tyrosine kinase inhibitors may modulate pathophysiologic signaling pathways to improve brotic diseases. Second, these inhibitors may diminish biophysical brotic barriers to enhance the delivery of other therapeutic agents.

Experimental Design: We used patient-derived pancreatic ductal adenocarcinoma cell lines and wild-type control tissue. We combined kinome array technology with bioinformatic upstream kinase identi cation pipelines to identify protein tyrosine kinases di erentially active in brotic contexts.

Result: We identify kinases previously reported as being di erentially active in pancreatic ductal adenocarcinoma. Our data also identify kinases previously unreported or understudied in pancreatic ductal adenocarcinoma and its accompanying brotic processes also known as pancreatic cancer desmoplasia.

Conclusion: Our data identi es new protein tyrosine kinases which may mediate pancreatic cancer desmoplasia.

The role of Rho/ROCK signal pathway in cellular reprogramming and cytoskeleton regulation in Glioblastoma.

Oral-3

Nilanjana Saferin

Nilanjana Saferin, Qin Yang

Glioblastoma Multiforme (GBM) is one of the most aggressive form of brain tumors. Current treatment strategies include chemo- and radiation therapy in combination, however prognosis remains poor. Oncogenic transformation of glial cells is often associated with altered expression of genes that are components of signal transduction pathways, usually related to diverse cellular functions like cell adhesion, cell division, growth, proliferation, cell death, and response to its environment. A critical factor in cancer progression is cell migration in response to environmental stimuli such as growth factors. Upon binding to cell surface receptors, these chemo attractants stimulate intracellular signaling pathways that regulate reorganization of the actin cytoskeleton. Studies have shown the importance of actin dynamics and actin binding proteins involved in several types of highly metastatic cancer. One of the major e ectors in actin cytoskeleton reorganization is Rho associated protein kinase or ROCK. Inhibitors of ROCK (ROCKi) have been shown to have signi cant inhibitory e ects in cancer progression.

Cellular reprogramming has gained signi cant momentum in the past few years. Cancer cell reprogramming into normal-like cells has a high potential in the development of treatment strategies. Previous studies in our lab have established a novel strategy of reprogramming GBM cells into neural-like cells by using ROCKi. In this study we are trying to investigate the e ect of ROCK signaling on GBM reprogramming and on actin dynamics, and its role in tumor cell microtube formation and neuron axonogenesis. Regulation of F-actin by the ROCK pathway may be di erent in both neuron axonogenesis and microtube formation, depending on di erent reprogramming stages and which downstream factors of the ROCK pathways involved. Therefore, understanding the underlying mechanism and the role of individual players in the ROCK signaling pathway can potentially develop into a treatment strategy for GBM and other cancers.

Observing Collateral Sensitivity in Pancreatic Cancer Cells Resistant to Gemcitabine

Oral-3

Caoqinglong (Jackson) Huang
Caoqinglong (Jackson) Huang

Pancreatic cancer is one of the deadliest diseases worldwide. The application of chemotherapies, e.g., gemcitabine, has extended the lifespan of pancreatic patients, and yet it encounters the problem of tumors developing resistance to the treatment. To overcome resistance, several small molecule inhibitors targeting proteins along the metabolic pathway of chemotherapeutic agents have been developed and joined the treatment regimen to enhance chemotherapeutic e cacy while constraining toxic side e ects of escalating dosage of chemotherapies. Ideally, these inhibitors would outcompete or synergize with chemotherapies, and ultimately restrain tumor growth. Inspired by this methodology, we attempted and observed collateral sensitivity in a gemcitabine-resistant cell model from a small molecule inhibitor candidate, LQZ-7F-1, targeting survivin, a protein essential to cell cycle progression and apoptosis. We also discover that among the survivin inhibitors we have tested, this particular candidate has shown better growth inhibitory e ect on the resistant cell model than the parental one as a single agent, suggesting that it may be developed as a tool to study collateral sensitivity. We are working to validate its activity and to elucidate its mechanism of action in collateral sensitivity.

A ROCK/mDia Signaling Axis Regulates Cytoskeletal Structure in Glioblastoma Tumor Microtubes

Oral-3

Kathryn Becker

Kathryn N. Becker, Krista Pettee, Amanda Sugrue, Kevin Reinard, Jason Schroeder, Kathryn M. Eisenmann

Invasive motility limits treatment e cacy and is a signi cant contributor to poor outcomes in glioblastoma (GBM). GBM tumor microtubes are actin- and microtubule-enriched membrane tubes that facilitate invasive motility and underlie many components of GBM pathophysiology. Rho-GTPases mediate GBM invasion through localized activation of cytoskeletal e ector proteins, such as mammalian Diaphanous-related formins (mDia) and Rho-associated protein kinase (ROCK). GBM invasion depends on a delicate balance between mDia-mediated extension of leading-edge structures (ie: tumor microtubes) and ROCK-mediated contraction of trailing cell bodies. In this study, we assessed the roles of ROCK and mDia in tumor microtube-associated GBM invasion using a 3D patient-derived neurosphere model of GBM invasion. Neurospheres were embedded in 3D matrices and treated with the small molecule inhibitor of ROCK (Y-27632) and the small molecule agonist of mDia (IMM-02). Treatment with Y-27632 alone reduced the total distance of cell body migration and increased tumor microtube length. Tumor microtubes extending from Y-27632 treated neurospheres displayed an atypical undulant morphology, further suggesting that ROCK inhibition modi es primary invasion programs. Treatment with IMM-02 alone profoundly reduced total area of neurosphere invasion, distance of cell body migration, and length of tumor microtubes. Combination treatment e ects (Y-27632 + IMM-02) were time dependent. At 96 hours, combination treatment reduced total area invaded and length of tumor microtubes in comparison to Y-27632 alone, but no signi cant di erence was observed in comparison to IMM-02 alone. Western blot analysis of free- oating patient-derived 3D neurospheres and semi-adherent 2.5D monolayer cultures demonstrated that agonism of mDia formins with IMM-02 results in the progressive loss of mDia1 and mDia2 protein expression. Therefore, endogenous mDia regulatory mechanisms triggered in response to continuous agonist-mediated mDia activation may inhibit mDia function more e ectively than direct antagonism strategies in GBM. Conclusively, both IMM-02 and Y-27632 treatment disrupt the tumor microtube mechanism of GBM neurosphere invasion.

The Role of ATR in Glucose Metabolism Dysregulation in Carcinogenesis

Oral-3

Yetunde Makinwa

Yetunde Makinwa

Deregulated glucose metabolism is a key hallmark seen in cancer cells and so starving cancer cells to death has been an important cancer research focus for many years. Ataxia telangiectasia and Rad3-related protein (ATR) is a well-researched serine/threonine-protein kinase of the PI3K family. It plays an important role in regulating DNA damage repair in the nucleus and cytoplasmic ATR functions as a key anti-apoptotic protein at the mitochondria following UV damage. We have discovered that actively dividing cells in a glucose-starved medium have lower amounts of ATR over time. However, the opposite happens once terminally di erentiated, ATR becomes overexpressed in a glucose-starved environment. We believe ATR may be involved in the many biochemical changes that occur in glucose metabolism in cancer cells. This provides an interesting regulatory pathway that can be exploited, to develop more e ective cancer therapies in the future.

Part III

Poster Presentations

Group 1

Targeting dynamics of 14-3-3- for the treatment of Pancreatic Cancer

Poster-1

Deepti Gurung

Deepti Gurung, Jacob Danielson, JingYuan Liu

Pancreatic cancer is the third-most-common cause of cancer-related deaths in the US. The 5-year relative survival of pancreatic cancer patients after diagnosis is only 10%. Drug development for pancreatic cancer has greatly advanced over the past decade. However, chemoresistance exacerbates challenges in improving the e cacy of the current treatment regimens. 14-3-3- is a small, homodimeric, regulatory protein, mostly expressed in epithelial cells. In pancreatic cancer cells, it promotes metastasis, and increases cell cycle arrest upon DNA damage due to anticancer drugs and radiation i.e. chemoresistance development. Also, overexpression of is correlated with a poor survival rate in pancreatic cancer patients. It belongs to 14-3-3-protein family with other six isoforms (, , , , , and) which are involved in diverse cellular pathways such as regulation of signal transduction, apoptosis, adhesion, cellular proliferation, di erentiation, and survival. The discovery and development of -isoform-selective inhibitors are indispensable because existing 14-3-3 inhibitors exhibit high toxicity as they are non-speci c to form. A -isoform speci c inhibitor presents a good target to improve cancer treatment outcomes. The fact that primary and secondary sequences, as well as ligand binding sites, are highly conserved among 14-3-3-isoforms, exert challenges to develop isoform speci c inhibitors for the form. We found potential di erences in their dynamic properties among 14-3-3-isoforms when unbound by a ligand using Molecular Dynamics Simulation and validated by Biological Small-angle X-ray scattering methods. Unbound 14-3-3- displayed unique, wide-open conformation and more signi cant exibility, in comparison to other unbound isoforms. Further e orts to identify -isoform speci c inhibitors by utilizing its unique dynamic properties are being made. Meanwhile, we also identi ed that folate may bind to 14-3-3-via virtual screening. Experimental validation and determination of the binding mode of folate with 14-3-3- are under the way.

E ect of platelets on immune responses against Klebsiella pneumoniae

Poster-1

Iluja Gautam

Iluja Gautam, Chadwick Huss, Zachary Storad, Leah M. Wuescher, Randall G. Worth

Klebsiella pneumoniae is a gram negative bacterium recognized as the most common cause for hospital acquired cases of pneumonia in USA. It is responsible for 3% to 8% of all nosocomial bacterial infections including septicemia, endocarditis and urinary tract infections. Even with adequate treatments, the mortality rates of these infections can range from 30 to 50%. Previous research suggests that mice with low platelet counts have lower rates of survival and higher bacterial burdens during K. pneumoniae derived sepsis. However, it is not known if platelets can directly kill K. pneumoniae and aid host defense against the pathogen. The purpose of the current study was to understand the e ect of platelets on survival and growth of K. pneumoniae. Whole blood samples from human and mice were incubated with K. pneumoniae in presence and absence of the potent platelet agonist thrombin. Thrombin reduced CFU by 43.9% in mouse blood and 57.8% in human blood compared to unstimulated blood. Moreover, blood from platelet-depleted mice did not show a signi cant decrease of CFUs compared to blood from wild-type mice (2.1% vs. 59.9% respectively). Interestingly, puri ed platelets are not able to reduce CFU independent of MOI or thrombin stimulation. Ongoing studies aim to investigate the mechanisms by which platelets can indirectly enhance the killing of K. pneumoniae in whole blood. Elucidating the role of platelets in these infections can ultimately lead to the identi cation of novel therapeutic targets and improve patient outcomes.

A Novel Endogenous Regulatory Mechanism of 20-HETE in CKD

Poster-1

Fathima Dhilhani Mohammed Faleel

Dhilhani Faleel, Fatimah K. Khalaf, Shungang Zhang, Prabhatchandra Dube, Deepak Malhotra, Steven T. Haller, David J. Kennedy

The Na/K-ATPase (NKA) is a key regulatory enzyme in the kidney that is capable of mediating both physiological and pathophysiological signal transduction. Our group and others have demonstrated both clinical and experimental evidence that continuous activation of NKA-Src signaling by its endogenous ligand, cardiotonic steroids (CTS), leads to persistent renal in ammation and brosis and contributes to the development of chronic kidney disease (CKD). In addition, the arachidonic acid metabolite 20-Hydroxyeicosatetraenoic acid (20-HETE) is thought to play a major role in low-grade in ammation associated with CKD. Furthermore, 20-HETE inhibits NKA pumping activity in renal tubules. On this background, we sought to elucidate the molecular mechanism by which 20-HETE causes renal injury, and hypothesized that 20-HETE interacts with the NKA and activates the NKA/Src/ERK signaling complex to cause renal in ammation and brosis. First, our experimental hypertensive CKD rat model showed a signi cant elevation of renal cortex 20-HETE levels as well as a marked increase in proin ammatory cytokines, including IL-6 and TGF- . Moreover, expression of the pro brotic marker collagen-1 and oxidative stress marker 8-Oxo-2'-deoxyguanosine were signi cantly increased in the hypertensive CKD rats compared to control rats. These e ects were signi cantly attenuated after the treatment with pNaKtide, a speci c NKA-Src signaling complex inhibitor. In-vitro addition of 20-HETE to a renal proximal tubule cell line (LLC-PK1) showed a signi cant increase in pSrc and pErk levels which was reduced in LLC-PK1 cells where NKA was reduced (PY-17). 20-HETE activation of pSrc and pErk in LLC-PK1cells was also reduced by speci c inhibition of the NKA-Src signaling complex with pNaktide. Furthermore, Molecular Docking analysis (Autodock) demonstrated that 20-HETE had favorable docking scores that were similar to well-known NKA ligands such as ouabain, marinobufagenin, and telocinobufagin (simulated binding free energy -5.5). Collectively, these ndings suggest that 20-HETE may directly interact with the NKA and is capable of activating the NKA-Src signaling complex, thus stimulating renal in ammation and brosis in CKD.

A bionformatics characterization of cancer subtype clusters

Poster-1

Abdul-Rizaq Hamoud

Abdul-rizaq Hamoud, Justin F. Creeden, Robert E. McCullumsmith, Rammohan Shukla

The cancer eld is often searching for relevant molecular-mechanisms that contribute to the pathophysiology of various cancer-subtypes. The development of publicly-available databases has presented a unique opportunity to investigate these mechanisms. We used DisGeNET, a database that has curated >24,000 gene-disease associations from a wide-array of diseases. We used DisGeNET to cluster >750 disease pro les into three distinct clusters. One such cluster included only-cancer subtypes which suggests commonly shared molecular-mechanisms. This cluster was used for bioinformatics analysis of shared-pathways, and drug-targets. We expect these ndings to expand our understanding of the commonalities of cancer subtypes and potential treatments.

Group 2

A novel viral restriction factor against Coronaviruses

Poster-2

Sukanya Chakravarty

Sukanya Chakravarty, Sonam Popli, Gayatri Subramanian, Ritu Chakravarti, Saurabh Chattopadhyay

COVID-19 (Corona virus disease-2019) pandemic caused signi cant damage, including numerous human fatality, worldwide for over a year now. COVID-19 is caused by the Severe Acute Respiratory Syndrome-coronavirus 2 (SARS-CoV2) a positive-sense single stranded RNA virus belonging to the beta-coronavirus family. The cellular interferon (IFN) system is the rst line of defense against a wide range of virus infections. Viral entry is sensed by various cellular sensors, also known as pattern recognition receptors (PRRs), which bind to the viral nucleic acids, that serve as pathogen associated molecular patterns (PAMPs) and activate the downstream signaling pathway. The activation of innate signaling leads to the induction of type-I IFN, which is secreted and acts in an autocrine as well as paracrine manner to trigger IFN-stimulated genes (ISGs). The ISG-encoded protein products function as viral restriction factors by speci cally inhibiting stages of viral replication. In recent studies, our lab has identi ed a subset of viral restriction factors against respiratory viruses. Here, we tested these subset of ISGs against the coronavirus infection, and our results indicate that we have a novel restriction factor against coronavirus. The ISG-de cient cells showed increased coronavirus infection at various times post-infection. As a part of the antiviral mechanism, we investigated the cellular responses to virus infection in ISG-expressing or non-expressing cells. The ISG-de cient cells showed the impaired synthesis of antiviral genes and increased activation of cellular metabolic pathways in virus-infected cells. Overall, we have uncovered a new viral restriction mechanism that can be applied to restrict the COVID-19-causing virus infection.

The role of matrix metalloproteinases in the pathology of radiation-induced oral mucositis

Poster-2

John Dillon

John Dillon, Jessica Saul-McBeth, Jacqueline Kratch, Ishmael Parsai, Heather Conti

Oral Mucositis (OM) is a deleterious side e ect of radiotherapy targeting the head and neck. The severe ulcers that form can result in increased hospitalizations and cessation of cancer treatment. E ective therapies without side e ects are lacking for OM. In order to develop more successful treatments, a better understanding of the pathophysiology of OM is necessary. Following damage, matrix metalloproteinases (MMPs) are essential for tissue remodeling and leukocyte tra cking. However, if expressed in excess, MMPs can cause disproportionate in ammation and impede healing. Because the roles of MMPs during OM are not completely understood, we assessed expression of MMPs during peak damage. RNA-seq was performed comparing sham to irradiated mice and a total 1892 genes were di erentially expressed, with 407 genes signi cantly upregulated and 271 genes signi cantly downregulated in the irradiated tongue tissue. Of note, MMP10, 1a/b,8,13,12, and 27 showed a 2 Log2 fold change and P-value 0.05. Expression of these genes was veri ed by qPCR. In all, radiation induces transcription of MMPs that may contribute to the pathology of OM. Future studies will investigate the kinetics of MMP gene expression to gain a better understanding of each during the course of OM in order to inform drug development.

Concerted diurnal rhythms of gut microbiota with salt-sensitive hypertension and renal injury

Poster-2

Juthika Mandal

Juthika Mandal, Saroj Chakraborty, Xi Cheng, Sarah Galla, Anay Hindupur, Piu Saha, Beng San Yeoh, Blair Mell, Ji-Youn Yeo, Matam Vijay Kumar, Tao Yang, Bina Joe

Aberrant diurnal rhythms of blood pressure (BP) are well known to be associated with hypertension, however whether rhythmicity of microbiotal composition is associated with BP remains unknown. We hypothesized that BP and gut microbiotal composition follow synchronous rhythms and contribute to the progression of hypertension. To test this hypothesis in the context of salt-sensitivity, we examined groups of Dahl Salt-Sensitive (S) rats for their diurnal rhythms of gut microbiota and BP. Major shifts in diurnal patterns of speci c groups of microbiota were observed between the dark(active) and light(rest) phases, which signi cantly correlated with the diurnal rhythmicity of BP. Diurnal rhythms of Firmicutes, Bacteroidetes and Actinobacteria were independently associated with BP and colonic expression of Bmal1. Discrete genera were observed to correlate independently or interactively with one or more of the following 3 factors- 1) BP rhythm, 2) dietary salt, 3) amplitude of BP. Metagenomic functional analysis revealed diurnal rhythmicity of microbiotal pathways. During the active phase of the host, microbiota upregulated biosynthetic processes whereas during the resting phase of the host, microbiota upregulated degradation pathways of metabolites. These diurnal changes in microbiota, their functional pathways and BP response was prominently associated with a concerted rhythmicity of renal Lipocalin 2 and Endothelin1. Collectively, these data demonstrated the existence of synchronous diurnal rhythms of BP and renal in ammation with diurnal reshaping of gut microbiota in salt-sensitive hypertension. Such a concerted rhythmicity with peaks observed at the mid-active phase suggests that targeting this timepoint to reshape microbiota and/or intervene with medication could bene t hypertensives.

Multi-omics integration of active kinome and transcriptional signatures in pancreatic cancer

Poster-2

Khaled Alganem

Khaled Alganem, Justin F. Creeden, Xiaolu Zhang, Ali S. Imami, Jaroslaw (Jarek) Meller, Robert E. McCullumsmith

Understanding of complex biological systems and diseases requires an investigative look at di erent molecular domains. Researchers are now able to get access to transcriptomics, genomics, and proteomics data to investigate the underlying systemic biology of cellular processes and disease signatures. There is a big e ort of leveraging these omics datasets for multi-omics integration analyses. However, we observed a lack of e ort of integrating broad-based protein kinase activity, also called the active kinome, with gene expression datasets. Such integration is critical to move the eld forward since gene expression data are limited in their ability to re ect the functional state of a biological system; that is, changes in post-translational modi cation, such as phosphorylation, can have a profound e ect on cellular functions without any change in expression levels of the signaling molecules in the pathway. Given the importance of the active kinome in signal transduction and its role in many cellular and disease processes, we developed a pipeline to integrate active kinome and gene expression signatures using a network-based algorithm. The prize-collecting Steiner forest (PCSF) algorithm is used to generate and identify biological subnetworks that characterize disease signatures and highlight potential novel drug targets. We used our software to model patient-derived pancreatic ductal adenocarcinoma cell lines network by integrating active kinome and gene expression signatures. The results highlighted known pancreatic cancer (PC) targets like the growth factor receptor-bound protein 2 (GRB2), Jun Proto-Oncogene (JUN), and-catenin (CTNNB1), and potential novel targets like Peroxisome Proliferator Activated Receptor Delta (PPARD) and REST corepressor 1 (RCOR1). Our approach demonstrated its ability of highlighting known PC targets but also resulted in potential new leads that can be further investigated.

Potential Mechanism for Impaired Cognitive Dysfunction After Intracerebral Hemorrhage

Poster-2

Mohammad Ali

Mohammad Ali, Daniyah A. Almarghalani

Intracerebral hemorrhage (ICH) is a type of stroke that involves bleeding within the brain parenchyma. It is caused by rupture of small arteries and leak of blood due to hypertensive changes or other vascular abnormalities. ICH is a common type of hemorrhagic stroke and accounts for about 10% of all strokes. The fatality rate of ICH is high with it being about 40% at one month and 54% at one year. Risk factors of ICH include hypertension, smoking, excessive alcohol consumption, hypocholesterolemia, and drug use.

Co lin inhibitor compound (SZ3) was successfully developed recently in our lab for the treatment of ICH targeting secondary brain injury. In this study, we aimed to investigate a potential mechanism that is responsible for impaired cognitive dysfunction. This was done in a bacterial collagenase model of ICH followed by the treatment with SZ3 compound compared to a vehicle group.

Six to eight-week-old mice were divided into three di erent groups: a control group, a vehicle group, and a SZ3 treatment group. ICH was induced by the injection of collagenase directly into the brain stratum which led to disruption of the blood brain barrier. Behavioral parameters for the assessment of functional and cognitive de cits were performed using rotarod, grip strength, T-maze, wire hang, inverted screen, open led and neurologic de cit scores in all three groups after ICH. For protein expression assessments, mice will be euthanized and then the brains will be dissected for hematoma volume measurement, western blotting and immunostaining. A signi cant cognitive impairment was noted between the control group and vehicle group compared to the SZ3 treatment group. SZ3 treatment led to an enhanced neurobehavioral performance and parameters compared to the control and the vehicle group.

Group 3

Functional evaluation of neutrophil-derived properdin in a novel functional assay.

Poster-3

Smrithi Sugumaran Menon

Smrithi S. Menon, Neeti S. Galwankar, Sara R. Moore, Sadik A. Khuder, Viviana P. Ferreira

The alternative pathway (AP) of complement is an essential immune e ector mechanism, contributing to systemic and/or local in ammation. Properdin, the only positive regulator of the AP, is required for stabilization of AP enzymatic convertases. Properdin also binds to certain surfaces, in vitro, activating complement by recruiting de novo C3bBb convertases. Properdin is present in serum as dimers, trimers and tetramers in a 1:2:1 ratio, with tetramers the most active, followed by trimers and dimers. Activated neutrophils are an important source of serum properdin and release it from secondary granules into local cellular microenvironments. However, the distribution of neutrophil-secreted properdin oligomers (which would correlate with properdin function), and whether this distribution modulates local in ammatory processes, are unknown. We generated a novel ELISA-based assay that measures properdin function that correlates with the presence of higher-order properdin oligomers. Using this assay, properdin from PMA-activated neutrophil supernatants had signi cantly lower activity than serum properdin ($p<0.0001$), and varied between healthy donors. To understand whether serum is required for enhancing properdin function (i.e. by allowing properdin oligomerization), neutrophil supernatants were pre-incubated with properdin-depleted serum, followed by measurement of properdin function by ELISA. No increase in neutrophil-derived properdin function was observed. Currently, additional characterization of this phenomena is underway, including assessing whether function of neutrophil-derived properdin is also lower than serum properdin when it is secreted from neutrophils stimulated with activators other than PMA. By delineating the distribution of neutrophil-derived properdin, our study will contribute to the understanding of molecular mechanisms of AP regulation in in ammatory microenvironments.

Increased Host Energy Metabolism in the Proximal Colon-Microbiota Interface Elevates Blood Pressure

Poster-3

Xue Mei

Xue Mei, Blair Mell, Saroj Chakraborty, Xi Cheng, Ji-Youn Yeo, Rachel M. Golonka, Piu Saha, Yuan Tian, Andrew D. Patterson, Matam Vijay-Kumar, Tao Yang, Bina Joe

Hypertensive subjects present with alterations in gut microbiota and short chain fatty acids (SCFAs). SCFAs are the major metabolic products of bacterial fermentation in the intestine. While acetate and propionate are energy sources for peripheral tissues, butyrate is the primary energy source for the host colonic epithelium via -oxidation or glycolysis. Since butyrate is known to elevate blood pressure (BP), we hypothesized that the mechanism of gut microbial butyrate-mediated elevation in BP is linked with an increased energy metabolism in the proximal colon. To test this hypothesis, 7 weeks old concomitantly raised male germ-free Sprague Dawley rats (GF, n=5-6) were compared with GF acquiring microbiota acutely for 10 days (germ-free conventionalized rats, GFC, n=6) for (1) BP, (2) cecal butyrate by proton nuclear magnetic resonance (1-H NMR), (3) microbial pro ling by 16S RNA sequencing and (4) proximal colonic transcriptomic signatures for energy metabolism by real time RT-qPCR. GFC rats acquired microbiota successfully and represented an energy-repleted state with a marked increase of the colonic energy substrate, butyrate. Interestingly, GFC rats had a signi cant increase in systolic and diastolic BP compared to GF rats ($p<0.05$). This increase in BP was associated with a signi cant upregulation of 11 genes tested by RT-qPCR ($p<0.05$) for energy metabolism pathways (-oxidation and glycolysis) in the colon of the GFC rats compared to GF rats. These genes are: Ppar, Ffar2, Acss1, Acadl, Cpt2, Hk2, Pfkp, Pgam1, Gpd2, Sirt3 and Crat. Our data reported here is the rst to provide evidence for a direct relationship between host energy metabolism at the proximal gut-microbiota interface and BP regulation. Further, our studies suggest that butyrate, which is a predominant colonic energy metabolite, contributes to the mechanism governing this relationship between energy metabolism in the proximal colon with BP regulation.

Novel Chyrsin-De-allyl PAC-1 hybrid analogue as an potential anticancer agent against TNBC

Poster-3

Saloni Malla

Saloni Malla, Hariteja Ramapuram, Buthina A. Al-Oudat, Amit K. Tiwari

Triple negative breat cancer (TNBC), known for its aggresive nature and heterogeneity, is characterized by the absence of estrogen receptor, progesterone receptor and human epidermal growth factor. Compared to non-TNBC, TNBC has higher rate of relapse, poorer prognosis, higher metastasis risk, accounting for one-forth of all breast cancer deaths. Recently, through molecular hybridization of Chrysin and de-allyl Pac-1, both of which have been reported to induce caspase-dependent apoptosis in several cancers, we designed and synthesized new chrysin-De-allyl-Pac-1 hybrid analogues. These analogues tethered with several aromatic heterocyclic cores were screened against TNBC cell lines such as MDA-MB-231 and BT-20 for their in-vitro anti-proliferative e cacy. For mechanistic studies, compound 4g that exhibited the most potent activity (IC50 value of 9.40 1.45 M in MDA-MB-231 and 10.43 0.20 M in BT-20 cells) and a great safety pro le against normal breast cancer cells, HMEC cells (IC50 value >100 M), was selected. The results demonstrated that compound 4g signi cantly arrested cell cycle at the G-2 phase and resulted in mitochondrial dysfunction as indicated by signi cant loss of mitochondrial membrane potential. Permeabilization of mitochondrial outer membrane by pore formation occurs through activation of pro-apoptotic protein BAK, followed by release of cytochrome C into the cytosol, which inturn activate initiator caspases like caspase-9 and executioner caspases like caspase-7, ultimately leading to apoptotic cell death. Accordingly, MDA-MB-231 cells treated with 4g resulted in upregulation of pro-apoptotic protein, BAK, enhanced the expression of cytochrome C and promoted the cleavage of caspase-9 and caspase-7, suggesting that 4g-induced cell death is due to activation of the intrinsic apoptotic pathway. Therefore, our ndings suggest that 4g may be an e ective lead for the future pre-clinical development of potential anticancer agents against TNBC

Vasoactive Intestinal Peptide Expressing Interneuron (VIPIN) Development in the Infralimbic-Medial Prefrontal Cortex (IL-mPFC)

Poster-3

Nicole Bell

Nicole Bell, Ipe Ninan

Anxiety disorders are the most prevalent of the adolescent onset mental disorders and seen to e ect females at higher rates than males. This statistic, alongside recent ndings of development-dependent neurobiological changes from preadolescence to adulthood, has emboldened attention towards the possible development-dependent mechanisms in increased incidence of anxiety disorders in adolescents. This is particularly important as the increased anxiety disorders during adolescence coincides with a diminished threat extinction, an inhibitory learning necessary to regulate anxiety behaviors, and an altered function in the ventromedial prefrontal cortex. Since synaptic inhibition mediated by local GABAergic neurons plays an important role in sculpting cortical circuitry, synaptic plasticity and the generation of cortical rhythms, it is important to understand how GABAergic neurons in the infralimbic medial prefrontal cortex (IL-mPFC), a brain region analogous to the human ventromedial prefrontal cortex, develops during pre-adolescence to adulthood and whether it is possible to identify adolescence-speci c events in the IL-mPFC that are pertinent to anxiety-related behaviors. GABAergic interneurons are diverse with parvalbumin interneurons (PVINs) and somatostatin interneurons (SSTINs) being the most abundant, and function to inhibit the excitatory pyramidal neurons (PyNs). Acting to inhibit the PVINs, SSTINs and PyNs are the vasoactive intestinal peptide interneurons (VIPINs) by direct GABAergic transmission. This study focuses on the development of VIPIN-mediated GABAergic synaptic transmission to PVINs, SSTINs, and PyNs in preadolescent, adolescent and adult mice. We utilize optogenetic techniques to stimulate VIPINs while using whole cell patch clamping to measure GABAergic currents in PVINs, SSTINs and PyNs to observe age-dependent di erences in inhibitory post synaptic current (IPSC) amplitudes. These studies are expected to shed light on how VIPINs contribute to the prolonged rearrangement in the mPFC during pre-adolescence to adulthood and its potential e ect on the developmental regulation of threat memory and hence, anxiety-related behaviors.

Integration of Proteomics and Bioinformatics toward Antipsychotics Induced Pathways in Schizophrenia

Poster-3

Rawan Alna sah

Rawan S. Alna sah, James Reigle, Adam J. Funk, Jaroslaw (Jarek) Meller, Robert E. McCullumsmith, Rammohan Shukla

Schizophrenia (SCZ) is a severe and disabling psychiatric disorder with a complex and multifactorial etiology. Typical and Atypical antipsychotics use mainly to treat SCZ positive symptoms and mange negative and cognitive de cit however, these agents produce di erent e ects on brain structure. In postmortem schizophrenia studies, antipsychotic treatment is considered as potential confounding factor, and alterations found in postmortem brain are maybe best thought of occurring as a result of long-term treatment with antipsychotic. The overarching goal of this exploratory study is to investigate SCZ proteome from the dorsolateral prefrontal cortex (DLPFC) that has primary functions in working memory and decision making, highlighting dysregulated pathways that may be altered by antipsychotics. Nano liquid chromatography coupled electrospray tandem mass spectrometry allowed to identify 478 di erentially expressed proteins ($p<0.05$) in the DLPFC in SCZ. The most a ected proteins included synaptic proteins, metabolic or mitochondrial-associated proteins. To understand the most signi cantly enriched pathways associated with our protein dataset, we applied novel bioinformatic tools to identify top pathways associated with SCZ as well as pathways altered by antipsychotics. Our analysis shows enriched pathways of synaptic, cytoskeleton, bioenergetic, and protein kinase signaling pathways. These results are the rst to simultaneously investigate comprehensive changes of protein expression at the SCZ proteome. This study provides further characterization of pathways altered in SCZ proteome as well as pathways altered by antipsychotics. We demonstrate that proteomic and bioinformatic approaches provide a complementary basis to investigate speci c candidate proteins which were previously unknown or overlooked.

Group 4

Oligomer distribution of properdin is altered in disease

Poster-4

Sara R. Moore

Sara R. Moore, Sean A. Ehinger, Smrithi S. Menon, Janet S. Lee, William Bain, Gowthami M. Arepally, Brahm H. Segal, Viviana P. Ferreira

The classical, lectin, and alternative pathways of the complement system are essential for overall immunity and in ammation. Properdin, a positive regulator of complement, is critical for optimal alternative pathway function. Properdin is a 50 kDa protein that circulates in blood as dimers, trimers, and tetramers of head-to-tail associated identical monomers, in a 1:2:1 ratio, with tetramers being more active than the other oligomers. Human properdin levels and properdin knockdown/inhibition animal models demonstrate both protective and deleterious properdin roles in disease. However, the ratio of properdin oligomers in disease, which may have direct functional consequences independent of the concentration, remain unknown. To address this gap, we developed a novel assay that detects di erences in properdin function due to changes in properdin oligomer distribution in the sample. Our objective herein was to characterize properdin concentration and function from patient biospecimens with respiratory failure, ovarian cancer, and coagulopathies. Properdin concentration, as determined by a sandwich ELISA, was lower in ovarian cancer, heparin-induced thrombocytopenia, and respiratory failure compared to controls, and higher in venous thrombosis compared to controls. Properdin function was then assessed by using the ELISA-based functional assay, where the samples are assessed at equivalent concentrations and thus the readout correlates with the presence of more tetramers versus other, less active, oligomers. The results indicate properdin function was increased in patients with respiratory failure compared to healthy controls. This data indicates, for the rst time, properdin oligomer distribution is altered towards higher-order forms in respiratory failure, leading to enhanced properdin function. Future work includes completing preliminary results of properdin function in cancer and coagulopathies in order to achieve adequate power, visualizing the speci c oligomer distribution in the samples using FPLC, and expanding our studies to include arthritis, and polycystic ovary syndrome. Our ndings will signi cantly help understand how excessive complement activation mediates disease.

Dysregulation of Nitric Oxide Production Leads to Upregulation of Erbb2 Expression During Breast Cancer

Poster-4

Yashna Walia

Yashna Walia, Gang Ren, Xunzhen Zheng, Saori Furuta

Breast cancer is a disease in which breast cells come to divide uncontrollably, forming a mass which if left untreated could invade distant tissues and organs. Among women in the US, breast cancer has the highest percentage of cancer related death, only preceded by lung cancer. Facing the catastrophic statistics, there remains an urgent need to improve our understanding of breast cancer etiology. Our project primarily focuses on Erythroblastic Oncogene B (ERBB2/HER2), an oncogenic protein that accounts for over 25% of breast cancer cases and is associated with poor clinical outcome. We found that downmodulating nitric oxide (NO) production in healthy animals upregulates HER2 expression in mammary epithelial cells (MECs). In contrast, restoration of the physiological NO levels in breast cancer cells by supplementing sepiapterin, the endogenous precursor of NO synthase (NOS) cofactor BH4, suppresses HER2 expression and cellular proliferation. As the mechanistic bases of NO-mediated HER2 regulation, we are currently seeking to determine the role of S-nitrosylation, NO-mediated covalent modi cation of the protein. Our study demonstrates that reduction of NO contributes to breast tumorigenesis by deregulating HER2 expression and suggests that the restoration of physiological NO level by supplementing sepiapterin may serve as a potential robust therapeutic strategy for breast cancer.

Antioxidant Therapy Restores Hepatic Phase I & Phase II Metabolic Enzymes Altered by Exposure to Microcystin-LR in a Murine Model of Diet-induced Non-alcoholic Fatty Liver Disease

Poster-4

Apurva Lad

Apurva Lad, Jonathan Hunyadi, Joshua D. Breidenbach, Jacob Connolly, Fatimah K. Khalaf, Prabhatchandra Dube, Shungang Zhang, Andrew L. Kleinhenz, David Baliu-Rodriguez, Dragan Isailovic, Terry Hinds, Deepak Malhotra, Steven T. Haller, David J. Kennedy

Non-alcoholic Fatty Liver Disease (NAFLD) causes signi cant alterations to the metabolism of therapeutic drugs. We have previously demonstrated that chronic exposure to low doses of microcystin-LR (MC-LR), an environmental liver toxin, induces signi cant hepatotoxicity in the form of hepatic micro-vesicular lipid accumulation and oxidative stress in mice with NAFLD in addition to impaired hepatic metabolism and excretion of MC-LR compared to MC-LR exposed healthy mice. In the current study we tested the hypothesis that augmentation of hepatic drug metabolism pathways with targeted anti-oxidant therapies would improve MC-LR metabolism and reduce hepatic injury in NAFLD mice exposed to MC-LR. Antioxidants included augmentation of the glutathione detoxi cation pathway with N-acetylcysteine (NAC) and interruption of speci c Src kinase-mediated oxidant signaling pathways with a novel peptide (pNaKtide). Histologic analysis revealed signi cant increase in hepatic in ammation with MC-LR exposure which was attenuated in both antioxidant treatment groups ($p<0.05$ vs MC-LR for both). 8-OHDG levels in urine and protein carbonylation in liver, both markers of oxidative stress, were signi cantly downregulated upon antioxidant treatment after MC-LR exposure. Analysis of key drug transporters as well as Phase I & II enzymes using quantitative PCR (qPCR) revealed that exposure to MC-LR signi cantly upregulated expression of the drug transporter Abcb1a by 248% vs Vehicle. Cyp3a11, a Phase I enzyme belonging to the Cytochrome P450 family, was signi cantly upregulated by 125% in the MC-LR exposed group vs Vehicle. Phase II enzymes, Pkm (Pyruvate kinase, muscle) was upregulated by 163% whereas Pklr (Pyruvate kinase, liver, and red blood cell) was signi cantly downregulated by 142% and Gad1 (Glutamic acid decarboxylase) was downregulated by 117%. Antioxidant therapy with both pNaKtide and NAC signi cantly attenuated these changes ($p<0.05$ vs MC-LR) and restored microcystin detoxi cation. These results suggest that NAFLD signi cantly alters the metabolism of MC-LR and this can be reversed with targeted antioxidant treatment.

Role of Extracellular Vesicles-miRNA in Glioblastoma Multiforme

Poster-4

Shruti Ghai

Shruti Ghai, Qin Yang

Glioblastoma Multiforme (GBM) remains the deadliest form of tumor with median survival rate of less than 2 years and poor prognosis. Cell heterogeneity, complexity and ability to invade contributes to its aggressiveness. Extracellular vesicles (EV) play a key role in maintaining the homeostasis of the tumor microenvironment favorable of tumor growth, progression and invasion in GBM cells. EVs have gained importance by performing bidirectional communication between normal stromal cells and GBM cells, modulating the tumor microenvironment. miRNAs are small non-coding RNAs that carryout post transcriptional gene regulation resulting in either tumor suppression or oncogenic function. According to the recent studies, oncogenic EV miRNAs which are packaged EV along with other nucleic acids and protein molecules are known for their function in encouraging invasion, angiogenesis, metastasis, chemoresistance and providing escape from immune surveillance. Hence understanding the oncogenic signaling of these miRNAs in regulating the above-mentioned tumor hallmarks can help us develop therapeutic strategies against the most formidable GBM progression. Reprogramming GBM cells to induced neurons in our lab has opened a huge door to exploit the e ects of these miRNA in GBM cells in comparison of induced neurons. By systematically screening the miRNA library using single cell RNA-seq, six candidate miRNAs involved in GBM-EV functions were selected. RT-PCR were conducted to validate the results. We want to understand the consequences these miRNAs on GBM angiogenesis and invasion by using CRISPR mediated knockouts. Furthermore, performing proteomics, bioinformatics and functional studies we will examine functional activity of the miRNAs on their target proteins using knockdown models. Thus, examining EV-miRNA in GBM can help us combat its progression while opening doors for personalized therapies.

Uncovering Kinase Network Perturbations in Schizophrenia: A Bayesian Approach

Poster-4

Ali Sajid Imami

Ali S. Imami, Rammohan Shukla, Robert E. McCullumsmith

Kinases are an integral part of the cellular signaling circuitry. In recent years, we have uncovered a wealth of evidence linking individual kinases to particular conditions and have identi ed how inhibition of certain kinases can lead to therapeutic bene ts. The majority of this research has focused on recombinant kinases in-vitro. However, kinases do not act alone in-vivo; They act as a network with complex interdependencies and multiple pathways from one kinase in the network to the other. The availability of microarray based methods like the Pamgene PamChip (r) has allowed for activity pro ling of multiple kinases simultaneously. This data is valuable for understanding how a system of kinases interacts in the presence of other kinases.

In this study, we propose a method to deconvolve and construct a kinase interaction network from the PamChip(r) Assay output using Bayesian Network Modelling. We then apply this method to the assay data on case vs control data from Post mortem brain samples from Laser Microdissection (LMD) Samples from Schizophrenia Paitents and paired controls.

The ability to deconvolve and construct such networks from the PamChip Assays allows us to not just visualize the network in particular conditions, but also allows us to compare them across conditions and see how a network changes in response to disease. The same technique can then be applied to drug treated cells to identify potential treatments that reverse a diseased network to its reference state.

Group 5

Soluble Protein Oligomers induce Endoplasmic Reticulum Stress in Acute Conditions in Mesenteric Resistance Arteries from Male and Female Mice.

Poster-5

Emily Waigi

Emily W. Waigi, Nicole R. Bearss, Jonnelle M. Edwards, Thaddaeus R. Castaneda, Cameron G. McCarthy and Camilla F. Wenceslau

Toxic soluble protein oligomers (SPOs) are a well established pathogenic mechanism of alzheimer's disease. They are also found in the peripheral vascular system, and their accumulation leads to vascular dysfunction and cell death. However, the precise mechanism linking increased circulating levels of SPOs and vascular dysfunction remains unknown. We therefore hypothesized that SPOs are recognized by the vasculature leading to endoplasmic reticulum (ER) stress which further induces the release of SPOs and vascular injury.

In acute conditions in male and female mice arteries, ER stress induction with SPOs (0.1mM) induced endothelium-depdndent exacerbated vasodilation compared to vehicle [Male: EC50: Vehicle -6.6 0.1 (n=7) vs. SPOs: -7.0 0.1 (n=4), p=0.03; Female: EC50: Vehicle -6.7 0.1 (n=6) vs. SPOs: -7.3 0.06 (n=5), p=0.001]. This was similar for arteries treated with ER stress inducer tunicamycin (5mg/ml, positive control), thus SPOs and ER stress induce endothelium-depndent exacerbated vasodilation independent of sex. ER stress inhibitor 4-Phenylbutyric acid (2mM) restored the exacerbated vasodilation induced by SPOs suggesting that SPOs trigger ER stress in acute conditions independent of sex. Interestingly, SPO inhibitor K01-162 (10mM) did not restore the exacerbated vasodilation induced by tunicamycin in male mice arteries, but this response was restored in female mice arteries, suggesting that ER stress induction in arteries from females also leads to the release of SPOs, escalating a feed-forward mechanism of further SPO release. Phenylephrine-induced vascular contraction did not change in the presence of tunicamycin or SPOs independent of sex.

Collectively, these results demonstrate that SPO's exacerbate endothelium-dependent vasodilation acutely and may contribute to vascular damage.

Social Determinants of Health: Interacting within an Interprofessional, Online, Asynchronous Workshop

Poster-5

Safalta Khadka

Michael J. Peeters, Safalta Khadka, Shipra Singh, Heather Sloane, Monica Holiday-Goodman, Temeaka E. Gray

Background: Social Determinants of Health (SDoH) knowledge is vital for all healthcare professionals to promote health and prevent diseases; although, various professions discuss SDoH from di erent perspectives. Quality interprofessional education (IPE) involves students from 2 or more professions interacting to learn with, about, and from each other. We conducted a one-week SDoH workshop focused on quality IPE among four health-professions (social work, public health, nursing, and pharmacy). Methods: Workshop learning objectives were to observe and identify neighborhood-level SDoH factors, and then examine their impact and application to clinical cases. Before the workshop, students were intentionally divided into interprofessional teams of 6 students (1-2 social work, 0-1 public health, 2 nursing, 2 pharmacy). Next, each team was assigned a neighborhood block in the city. Over 1-week, workshop activities included: completing a pre-workshop quiz, watching a SDoH primer video, posting a video self-introduction to their team, responding to two teammate's self-videos, completing a windshield survey (driving around the assigned block and making SDoH-related observations of the neighborhood), responding to the impact of observed SDoH on two clinical cases, post reply videos to two teammates' responses, re ectively-writing about their workshop experience, and completing a post-workshop quiz. Results: 264 students participated (33 public health, 61 social work, 74 nursing, 96 pharmacy). Students demonstrated a signi cant SDoH knowledge increase from pre to post workshop (pre-quiz =14 (SD=2.3), post-quiz =16 (SD=2.1); $p<0.001$; Cohen's-d=0.8, large e ect-size). Qualitative analysis of evaluations showed that many students enjoyed interacting with their interprofessional teammates; though, some student felt that synchronous face-to-face would have been better than this asynchronous distance-learning version. Furthermore, all workshop faculty agreed that signi cant IPE interaction took place among students from participating professions. Conclusion: Students from multiple professions learned SDoH-content and interacted (quality IPE= learning with, from, and about each other) in this asynchronous online SDoH workshop.

Aged Female Rats Divergent for Exercise Capacity Di er in Cognitive Ability

Poster-5

Syed Hasan

Syed Abdul-Moiz Hasan, Marwin Li, Ana Maria Gregio Hardy, Lauren G. Koch

Previously, we have demonstrated that rats selectively bred for low (LCR) and high (HCR) exercise capacity divide the mean for lifespan (LCR =24 Months and HCR 32-34 Months). We have also shown that male LCR rats segregate with risk factors which are strongly associated with Alzheimer's disease and dementia. The Alzheimer's Association also reports higher prevalence in females, and that exercise promotes a healthy metabolism and brain. In this study, we tested cognitive ability in aged LCR and HCR female rats.

HCR (n=14) and LCR (n=13) rats (24 months) were studied. Exercise capacity using a speed-ramped treadmill running test and total distance run (m) was calculated. HCR rats ran signi cantly longer distances on average (509.55 ± 45.11m) than LCR rats (82.50 ± 7.50m, p= 2.56e-07), demonstrating signi cant di erences in exercise capacities are being maintained throughout old ages in our model. We implemented the use of a Y-maze to analyze spatial memory as a parameter of cognitive dysfunction using EthovisionXT video tracking system. Interaction with a previously unexplored space was determined by a) time spent in the novel arm, to determine relative time being spent in unexplored territory, and b) a discrimination ratio calculated by: 100 x (novel arm entries)/ [total entries] was used to determine the rate of entering/re-entering unexplored territory. Our results show HCR rats spent signi cantly more time proportionally than LCR rats in the novel arm (40% vs 19%, $p<0.05$), but did not di er in the number of entries. This implies that HCR rats are more spatially aware of a new unexplored territory, since they are entering the same amount of times, but spending more time exploring the new territory. We conclude that female LCR and HCR rats divide for cognitive function with aging and may be useful models for the study of Alzheimer's disease and related dementias.

Targeting the thioesterase activity of FASN using modi ed proton pump inhibitor lansoprazole in breast cancer

Poster-5

Shreyasi Ganguly

Shreyasi Ganguly, Jian-Ting Zhang

Cancer cells have altered metabolism to sustain malignant phenotype. Increased de novo synthesis of fatty acids catalyzed by Fatty Acid Synthase (FASN) has been observed in many cancers. FASN condenses acetyl CoA and malonyl CoA to produce palmitate using ATP and NADPH. However, non-lipogenic normal cells do not express FASN, making FASN an ideal anti-cancer drug target. FASN has also been reported to regulate DNA repair activity via the NHEJ pathway by increasing PARP1 expression. Recently, Proton Pump Inhibitors (PPIs) have been shown to also inhibit FASN by binding to the thioesterase (TE) domain of FASN. It has also been observed that some PPI metabolites also are also active in inhibiting FASN. In this study, I hypothesize that further modi cation of PPIs may make PPIs better FASN inhibitors. To test this hypothesis, I will work with a medicinal chemist to synthesize new analogs of one PPI, lansoprazole, by modifying the benzene ring based on knowledge of the structure-activity relationship of lansoprazole metabolites. These newly synthesized compounds will be tested for their activities in inhibiting FASN activity, binding to the thioesterase domain of FASN, inhibiting cancer cell survival, and FASN-mediated DNA repair activities.

Oxytocin Neural Inhibition Weakens Bremelanotide-enhanced Sexual Function

Poster-5

Mitchell Harberson

Mitchell T. Harberson, Jennifer W. Hill

Oxytocin is a key hormone in male sexual function. When administered to the lateral ventricle of the brain in mice, oxytocin induces penile erection that is blocked by oxytocin receptor antagonists. Additionally, circulating oxytocin levels stimulate epididymal contractions during ejaculation and correlate with the intensity of orgasm. From our published data, expression of melanocortin 4 receptors (MC4Rs) only on oxytocin neurons in mice was enough to recover from the sexual de cits seen in a global MC4R knock out. However, it is not known if MC4Rs directly depolarize or increase the frequency of action potential ring in oxytocin neurons. We hypothesize that oxytocin neural inhibition will block the improved sexual function seen during administration of the MC4R agonist, bremelanotide. We have generated mice with cre-dependent expression of the inhibitory designer receptor, hM4Di, and cre expression under the control of the oxytocin promoter. When these mice are administered intraperitoneal clozapine-N-oxide (CNO), oxytocin neurons will undergo prolonged (hours) inhibition. Experimental animals and wild-type controls will be given four di erent drug regiments (Saline/saline, CNO/saline, saline/bremelanotide, CNO/bremelanotide) prior to recorded overnight sexual studies. Footage of sexual studies will undergo comprehensive mating analysis that illustrates the sexual desire and erectile and ejaculatory capabilities of these male mice. Additionally, we sacri ced the mice under one of the four drug regiments and excised the brain. Brain sections were immunostained for the protein c-fos as an indicator of neuronal activation. Additionally, serum samples were collected to detect circulating oxytocin levels. Overall, we expect CNO injection will lead to impaired ejaculation under saline and bremelanotide administration. Furthermore, we expect impaired ejaculation to correlate lower circulating oxytocin levels.

Group 6

Enhancing pathway analysis using Natural Language Processing and Text-Mining

Poster-6

Hunter Eby

Hunter M. Eby, Ali S. Imami, Robert E. McCullumsmith, Rammohan Shukla

Pathway analysis is an important tool used in biomedical research and aids our understanding of gene expression data gathered from omic approaches. The method involves nding statistical enrichment of user provided gene list in gene-set associated with a well-de ned biological pathway. Currently, the method faces three major hurdles. First, redundancy within the gene sets; second, nding the bigger picture amongst the overwhelming amount of data, and third, lack of methods to harmonize ontologies from di erent sources for instance, reactome, KEGG, Gene Ontology, and other similar repositories of gene sets. To overcome these hurdles, we developed a text-mining based approach which builds upon Bidirectional Encoder Representation Transformers (BERT), a natural language processing platform and relies on de nition of a given ontology/pathway to create a database of embedding (a learned representation of the de nition). De nitions from user provided list of GO-term is matched with the embedding data base and a theme representing the list is generated using a weighing factor term frequency inverse document frequency(tf_idf), to lter most important words. Our approach expanded upon other methods relying on the semantic similarity and outperforms other available tools including the industry standard parent-child analysis on several benchmarks involving time to perform the analysis, reproducibility and coverage of results. An R package named pathwayHUNTER is under development.

Perturbations of nutrient sensing in the pathogenesis of Alzheimer's Disease

Poster-6

Nicholas Henkel

Nicholas Henkel, Xiaojun Wu, Khaled Alganem, Abdul-rizaq Hamoud, Stephen Curtis, Robert E. McCullumsmith

Adenosine-monophosphate activated kinase (AMPK) is a master regulator of energy and nutrient sensing in cells. Under conditions of energy deprivation, AMPK serves to shut down cellular pathways that consume energy substrates like ATP while revving up pathways that produce ATP. AMPK is implicated in the pathogenesis of neurodegenerative disorders, like Alzheimer's dementia (AD), suggesting that perturbations of nutrient sensing and energy regulation are disrupted in this disorder. To date, there have been no studies which have functionally characterized AMPK in post-mortem, human brain. AMPK is a heterotrimer composed of alpha, beta, and gamma subunits. AMPK is regulated by phosphorylation of the alpha subunit and is also under allosteric regulation by binding of AMP to the gamma subunit. LKB1 is the primary upstream kinase that phosphorylates the alpha subunit, activating the heterotrimer. Interestingly, this phosphorylation site can be glycosylated to control the enzyme's activity by O-linked N-acetylglucosamine (GlcNAc) transferase (OGT). Herein, we report widespread dysregulation of the LKB1-AMPK axis in the dorsolateral prefrontal cortex (DLPFC) of post-mortem AD brain. The transcript level of the regulatory subunit, gamma-1, is decreased in AD while the beta-subunit transcripts are increased. With a dysregulation in the transcript levels, there is also a decrease in the overall AMPK activity in AD. Both protein and transcript levels for LKB1 and OGT are increased. However, this corresponds to a decrease in global glycosylation in the DLPFC by OGT.

Natural, early onset cholestasis sustains bone growth in aged mice

Poster-6

Rachel Golonka

Rachel M. Golonka, Piotr Czernik, Piu Saha, Ahmed A. Abokor, Beng San Yeoh, Beata Lecka-Czernik, Matam Vijay-Kumar

Hepatic Osteodystrophy is a metabolic bone disease (i.e., osteoporosis, osteopenia) that can occur in individuals with chronic liver disease. This extrahepatic complication is frequent for patients with cholestasis because bile flow obstruction causes the spillover of bilirubin and bile acids into systemic circulation. Notably, we have found that a subset of wild-type (WT) littermates in our mouse colony exhibit early onset anicteric cholestasis (WT-AC) as categorized by these parameters at the time of weaning: lower body weight, significantly elevated serum total bile acids, diminished cholesterol, and absence of hyperbilirubinemia. In this study, we investigated how the natural cholestasis found in WT-AC mice impacts liver and bone health after aging to 8 months. Compared to the growth retardation observed at weaning, aged WT-AC mice had normal body weight most likely attributed to their hyperphagia. As expected, WT-AC mice showed indicators of mild liver cirrhosis at the gross, histological, and mRNA levels. Unexpectedly, micro-CT scanning and histological staining of the tibia revealed an improved bone morphology in WT-AC mice. Changes in bone mass and structure included an increase of bone volume and connectivity density, but a decrease in thickness and spacing in the trabecular compartment. Comparatively, cortical bone was thicker and denser (albeit not significant) but displayed less bone marrow area in WT-AC mice. Interestingly, putative genes that negatively regulate osteoclast differentiation (e.g., Rankl, Opg) were highly expressed in WT-AC mice. Additionally, osteoblast genes (e.g., Runx2, Osx, Wnt10b) responsible for bone mass accumulation were found to be significantly upregulated in WT-AC mice. This corresponded with an increase of serum insulin-like growth factor 1, an anabolic agent that promotes osteoblast differentiation. Overall, this study delineates a novel finding that natural cholestasis sustains bone growth even after aged mice reach peak bone mass.

The critical role of cofilin signaling in hemorrhagic brain injury induced-microglial activation and neuroinflammation in mice

Poster-6

Daniyah Almarghalani

Daniyah A. Almarghalani, Zahoor A. Shah

Intracerebral hemorrhage (ICH) is the second most frequent cause of stroke after ischemic stroke. It accounts for 15% of all strokes and has the highest mortality rates. About 50% of patients die within the first month of attack, and those who survive suffer from long-term disabilities and neurological deficits. Only 20% of patients who survive ICH achieve functional independence after 6 months. The understanding of the molecular mechanisms underlying ICH is not studied well, in particular, the secondary brain injury-induced neuroinflammation or microglial activation. In this study, we investigated the role of cofilin in microglial activation and inflammation following ICH. Our preliminary studies in human ICH autopsy brain sections indicated that intracellular cofilin is localized within microglia and is associated with microglia morphological changes and activation of surrounding microglia. We subjected different cohorts of mice to intra-striatal collagenase injection-induced ICH and sacrificed at different time-points to analyze cofilin signaling up to 21 days. Using Western blotting and quantitative real-time PCR, we observed cofilin levels in the ipsilateral striatum starting from day 3 to day 21. Using immunohistochemistry analysis, activated microglia were observed to be increased after ICH from day 1, especially around the hematoma. Activated microglia were associated with morphological changes from highly ramified into an amoeboid shape mainly around the hematoma. In conclusion, we believe that cofilin over-expression plays an essential role in the activation of microglia and subsequently leads to neuroinflammation following ICH. Developing cofilin antagonism might provide novel alternatives for ICH therapy.

Expression of FcgRIIA across species

Poster-6

Kaitlyn Zigulis

Kaitlyn Zigulis, Randall G. Worth

FcgRIIA, (CD32a), a low affinity receptor for the Fc region of immunoglobulin G (IgG) is expressed on the surface of several immune cells and uniquely expressed on platelets. Known as the only Fc receptor to be expressed on platelets, and previously thought to be limited in expression to humans, it has recently been brought to the forefront for its role in heparin induced thrombocytopenia and in systemic thrombosis as a result of anti-CD40L therapy. More recent studies of FcgRIIA have shown that it is not unique to humans and therefore, studying which organisms express FcgRIIA could be important for designing effective preclinical trials. To have the best potential research, it was necessary to identify which organisms, other than humans, express FcgRIIA on immune cells and platelets. Using a consensus sequence of human FcgRIIA, the sequence was analyzed using NCBI protein blast to gain a data set of "hits" in other organisms with defined similarity or identity to FcgRIIA. Similar sequences were then aligned using ClustalX2 to locate areas of strong similarity or where single nucleotide polymorphisms were present. These alignments, visually showing the percent identity, allowed for further comparisons and creation of phylogenetic trees using MEGA. Moreover, heatmap analysis of similarity showed which organisms expressed the highest levels of similarity in defined areas of the protein compared to humans. Using these approaches, we discovered that many organisms contain similarity in the conserved immunoglobulin superfamily domains in the extracellular portion of FcgRIIA although typically the similarity was in adhesion receptors and not Fc receptors. However, only two organisms, Chimpanzees and Orangutans, shared 100% similarity in the cytoplasmic domain including the critical ITAM signaling domain. We've previously defined the importance of the ITAM sequence of FcgRIIA for efficiency of phagocytosis and phagolysosome fusion. In summary, we've identified the organisms with the most similarity to humans with respect to FcgRIIA are Chimpanzees and Orangutans. Having identified the organisms most closely related to humans with respect to FcgRIIA, in future studies that involve anti-platelet biologics, a more effective model can be used for preclinical trials.

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