Program &
Abstract Book

21st Annual

DATA & DINE

Postdoctoral Research Symposium

April 28, 2023

PennState
College of Medicine

Program

09:15 – 09:45 am

Room C3621

Coffee

Please join us for coffee before we begin our program.

09:45 – 10:00 am

Room C2860

Opening Remarks

Leslie Parent, MD
Vice Dean, Research and Graduate Studies
Professor, Department of Public Health Sciences, and Microbiology and Immunology, PSU

10:00 – 11:00 am

Room C2860

Keynote I

"Researcher to Regulator: Lessons learned on my path to FDA"

Andrew R. Kelleher, PhD
Clinical Reviewer
Office of New Drugs
U.S. Food and Drug Administration

11:15 – 12:15 pm

Room C3621

Poster Session

Discover the research conducted by our postdoctoral community.

12:15 – 1:00 pm

Room C3621

Lunch

Please join us for lunch and refreshments.

1:15 – 2:15 pm

Room C2860

Oral Presentation Session

Outstanding Postdoctoral Scholar Award Winner 2022

Siddharth Sunilkumar, PhD, *Department of Cellular and Molecular Physiology*

Bond and Bradley Postdoc Travel Award winners

1. **Stephanie Schell, PhD,** *Department of Dermatology*
2. **Lu Qin, PhD,** *Heart & Vascular Institute*
3. **Marina Chulkina, PhD,** *Department of Medicine*

2:15 – 3:00 pm

Room C2860

Graduate Career Services Overview & Postdoc Career Options

Jessica Kirkwood, MS
Director of Graduate Career Services

Introducing the Core Facilities

Maria Bewley, PhD
Associate Professor of Biochemistry and Molecular Biology
Interim Director of Institutional Core Facilities
Pennsylvania State University, College of Medicine

03:00 – 3:45 pm **Keynote II**

Room C2860

"Life with Small Molecules"

Arun Sharma, PhD
Professor of Pharmacology
Director, Organic Synthesis Shared Resource
Penn State University, College of Medicine

3:45 – 4:15 pm **Award Presentation & Closing Remarks**

Room C2860

A message from **Dr. Judith Bond, PhD**
Evan Pugh Professor Emeritus, Penn State University
Adjunct Professor, Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill

Gail Thomas, PhD
Director, Office of Postdoctoral Affairs
Professor, Medicine, Division of Cardiology, Clinical and Translational Science Institute and Heart and Vascular Institute, PSU

Showcasing Postdoctoral Research

The Penn State College of Medicine Postdoctoral Society wants to thank each of you for attending this important event! We are grateful for the support of our mentors, colleagues and lab mates and are thrilled to have the opportunity to showcase our work. This is the twenty-first year of Data and Dine, which has become a wonderful annual tradition at the College of Medicine.

Our postdoctoral community is spread across many departments in the College of Medicine and includes many international researchers. While traditionally viewed as a stepping stone on the path to becoming a tenured professor, postdoctoral research is an opportunity to receive additional training for many different professions. We serve as researchers and mentors within our laboratories, and our skills and expertise are critical for our mentors' projects.

"Data and Dine" is an annual Postdoctoral Research Symposium designed to be a semi-social scientific event to celebrate the exciting research accomplishments of the postdocs on the Penn State College of Medicine campus. Data and Dine was designed for Postdoctoral Scholars and Fellows as an opportunity to share their research with the entire College of Medicine community and to network with fellow postdoctoral researchers and faculty members.

After several years of virtual events, we are excited to host this in-person exhibition of our campus's postdoctoral research. We have numerous posters and three oral presentations being presented at the event today, showcasing the ongoing research by the postdoctoral community. Additionally, we are thrilled to celebrate the excellence of our postdoctoral researchers and their mentors by announcing the winners of several awards. We encourage you to take advantage of this event and learn more about the research accomplishments of our postdoctoral scholars and fellows. Take time to view your colleagues' abstracts and posters as you never know where you may find your next collaboration!

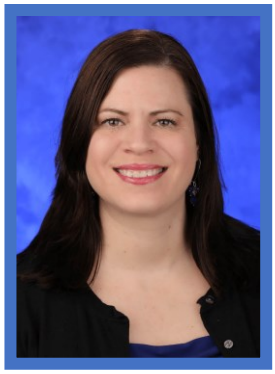
This event is made possible by the active participation among postdocs throughout the campus. The Penn State College of Medicine Postdoctoral Society and the Office of Postdoctoral Affairs would like to thank you all for joining us to make this event a success.

Best regards,
Data and Dine Planning Committee

Data And Dine Planning Committee

Gail D. Thomas, PhD
Director, Office of Postdoctoral Affairs

Jaci Wildner
Administrative Support Coordinator



Jessica Kirkwood, MS
Director of Career Services

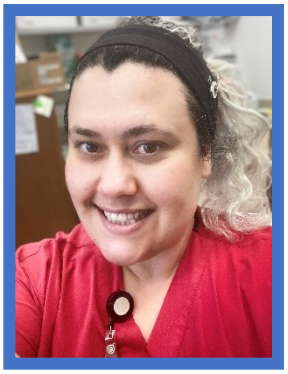
Rinki Kumar, PhD
Postdoctoral Scholar, Microbiology and Immunology

Samantha Spencer, PhD
Postdoctoral Scholar, Microbiology and Immunology

Navaneetha Krishnan Bharathan, PhD
Postdoctoral Scholar, Dermatology

Suchitra Mohanty, PhD
Postdoctoral Scholar, Microbiology and Immunology

Anna Fakhardo, PhD
Postdoctoral Scholar, Pediatrics



Seyma Demirsoy, PhD
Postdoctoral Scholar, Neurosurgery

Acknowledgements

The Data and Dine Postdoctoral Research Symposium is organized by the Office of Postdoctoral Affairs and the Penn State College of Medicine Postdoctoral Society. Our deepest gratitude to **Drs. Judith S. Bond and S. Gaylen Bradley** for the annual **Bond & Bradley Awards for Postdoctoral Trainees**.

We would like to thank **Dr. Leslie Parent** for her opening remarks. We are immensely grateful to our Keynote Speakers **Drs. Andrew Kelleher** and **Arun Sharma** for taking their time to share their expertise and experiences with us. We also appreciate **Jessica Kirkwood** and **Dr. Maria Bewley** for speaking about the resources Penn State Hershey provides from Graduate Career Services and our research cores, respectively.

We are incredibly thankful for the guidance and support from the Director of the Office of Postdoctoral Affairs **Dr. Gail Thomas** and Administrative Support Coordinator **Jaci Wildner**. From the Penn State College of Medicine Postdoctoral Society, we appreciate the dedication of **Drs. Rinki Kumar** (President), **Navaneetha Krishnan Bharathan** (abstract book and introductory video), **Samantha Spencer** (abstract book, poster organization), **Suchitra Mohanty** (Outstanding Poster Award Chair), **Anna Fakhardo** (Outstanding Postdoctoral Scholar Award Chair), and **Seyma Demirsoy** (Outstanding Mentor Award Chair), without whom this event would not have been possible.

We also want to express our gratitude to **Drs. Joseph Wang, Hyun Jin Kwun, Daniela Zarnescu, Sophia Allen, Maria Bewley, Vladimir Spiegelman, Kathleen Sturgeon, and Rameeza S. Allie** for volunteering in the Outstanding Postdoctoral Scholar Award Committee. We would like to thank **Drs. Amrendra Kumar, Brian A. Hain, Kamalesh Verma, Li Yunzhan, and Tiaosi Xing** for serving on the Outstanding Mentor Award Committee. We also extend our thanks to **Drs. Amanda Nelson, Edward Harhaj, Hyun Jin Kwun, Shilpi Paul, Yuan-Wan Sun, Zissis Chroneos, Zia Rahman, Sathi Babu Chodisetti, Todd Schell, Chris Norbury, Rong Jin, Valerie Brown, Iryna Pinchuk, Arati Sharma, Andrew Kowalczyk, Sara Stahley, and S. Rameeza Allie** for serving as judges for the Outstanding Poster Award.

Lastly, we want to thank all of you because your participation is the key to making this symposium a success!

This annual event is organized **for** postdocs **by** postdocs. If you would like to serve on the Postdoctoral Society Executive Council or help to plan the National Postdoc Appreciation Week and the 22nd Annual Data and Dine, we have open positions! Please contact us at COMpostdocs@pennstatehealth.psu.edu to learn more.

More information about the Penn State College of Medicine Postdoctoral Society can be found at https://sites.psu.edu/postdocs/.

Bond & Bradley Awards For Postdoctoral Trainees

The Penn State College of Medicine Postdoctoral Society has established **Bond & Bradley Awards for Postdoctoral Trainees**, some of which will be presented to outstanding postdoctoral fellows or scholars at the annual Data and Dine event. The awards presented today include the Outstanding Postdoctoral Scholar Award, given to a postdoctoral scholar or fellow who has shown excellence in their postdoctoral research, and the Outstanding Poster Awards, presented to several exceptional postdoctoral poster presentations at today's event. Today's oral presentations will be delivered by winners of the Bond & Bradley Travel Award, a quarterly award which funds presentations of postdoctoral research at conferences. These awards are made possible by a generous donation from **Drs. Judith S. Bond and S. Gaylen Bradley** to the Penn State College of Medicine Postdoctoral Society. The endowment inaugurated in 2012 through this donation has provided, in perpetuity, the financial support for these awards.

The Penn State College of Medicine Postdoctoral Society sincerely acknowledges the kind support from

Drs. Judith S. Bond and S. Gaylen Bradley

Keynote Presentation I

Andrew R. Kelleher, PhD

Clinical Reviewer, Office of New Drugs
U.S. Food and Drug Administration

Dr. Andrew Kelleher completed his dissertation research in the Jefferson-Kimball Laboratory (Physiology) where he investigated molecular mechanisms responsible for the regulation of skeletal muscle protein synthesis. During his PhD, he developed an interest in product development, completed the TechCelerator@Hershey program, and worked with PSU to patent (provisional) a medical device. This experience earned him a Presidential Management Fellowship (PMF) in the U.S. Federal Government's accelerated leadership program for recent graduates. During his PMF, he worked in executive healthcare management, strategic planning, and program management in the Veterans Health Administration.

After Dr. Kelleher's PMF, he converted to a full-time position in the FDA's Office of New Drugs where he served as a regulatory project manager. He developed expertise in pharmaceutical regulatory affairs and learned how to manage the review of drug and biologic applications for clinical trials and marketing. Merging this experience with his scientific research training, he transitioned to a clinical reviewer position. In his current position, he reviews study reports, safety reports, proposals for clinical trials, and meeting requests containing questions from industry. This requires integration of knowledge of biological processes, clinical safety, study design, regulatory policy, and skills in written and oral communication.

Keynote Presentation II

Arun Sharma, PhD

Professor of Pharmacology
Director, Organic Synthesis Shared Resource
Penn State University, College of Medicine

Dr. Arun Sharma completed his doctoral work in organic synthesis at North-Eastern Hill University in Shillong, India in the Chemistry Department. From there, he worked as a postdoctoral researcher first in Spain under Dr. Palomo on the synthesis of β-amino acids using asymmetric Mannich reaction and asymmetric Darzens reaction. During a second postdoc in France under Dr. Guillaumet, he researched the synthesis, biological evaluation, and structure-activity relationships of inhibitors of arylalkylamine N-acetyltranferase.

Dr. Sharma joined the Penn State College of Medicine in 2004. His lab focuses on the design and development of novel small drug-like molecules as potential cancer therapeutic and preventive agents, and testing them in various *in vitro* and *in vivo* cancer models. This effort has resulted in the development of some potent anti-cancer agents and understanding of their efficacy, toxicity, pharmacokinetics, and mechanisms of action.

Oral Presentations

OUTSTANDING POSTDOCTORAL SCHOLAR AWARD WINNER 2022

Siddharth Sunilkumar, PhD
Postdoctoral Scholar, Department of Cellular and Molecular Physiology

Title: "REDD1: A Key Mediator of Inflammation in Diabetic Nephropathy"

BOND AND BRADLEY POSTDOC TRAVEL AWARD WINNERS

Stephanie Schell, PhD
Postdoctoral Scholar, Department of Dermatology

Title: "Keratinocytes and immune cells in the epidermis are key drivers of inflammation in hidradenitis suppurativa providing a rationale for novel topical therapies"

Lu Qin, PhD
Assistant Professor, Heart & Vascular Institute

Title: "Exaggerated P2X Signaling Pathway in Muscle Afferent Following Hindlimb Muscle Ischemia-Reperfusion"

Marina Chulkina, PhD
Postdoctoral Scholar, Department of Medicine

Title: "MAPKAPK2 signaling: target for Crohn's disease-associated fibrosis"

Poster Presentations

Brijesh Singh Chauhan, PhD
Advisor: Daniela Zarnescu, PhD
Department: Cellular and Molecular Physiology

Poster #1

Identify TDP-43 dependent, muscle-specific alterations in new protein synthesis, *in vivo*

Brijesh Singh Chauhan, Samantha Macklin, and Daniela C Zarnescu*

*Department of Cellular and Molecular Physiology, College of Medicine, Penn State Milton S. Hershey Medical Center, PA 17033

TDP-43 can act as a negative and positive regulator of translation, in a target-specific manner and within specific subcellular compartments. In axons, loss of TDP-43 was shown to cause abnormal transport and translation of mRNAs encoding ribosomal proteins, while puromycin incorporation experiments show that cytoplasmic TDP-43 overexpression inhibits translation more globally. Using ribosomal tagging we have recently shown that TDP-43 alters the association of mRNAs with ribosomes causing alterations in the translation itself, cellular energetics, and synaptic function among other pathways. These findings underscore TDP-43's involvement in translation, however its targets, and their impact on the homeostasis of neuromuscular synapses remain a poorly understood aspect of TDP-43 biology and its relationship to neurodegeneration in ALS/FTD. Here we explored the muscle side of the neuromuscular junction (NMJ) where the local translation is known to occur. Here, we examined TDP-43's impact on new protein synthesis using Non-Canonical Amino-acid tagging (NCAT) *in vivo*, in the context of Drosophila models of TDP-43 proteinopathy. NCAT allows for the cell-type specific analysis of newly synthesized proteomes by combining targeted expression of a mutated methionyl-tRNA synthetase referred to herein as MetRS* with NCAT incorporation and click chemistry. Our experiments show that TDP-43 overexpression (OE) in muscles reduces new protein synthesis, with mutant TDP-43 showing a more pronounced effect compared to wild-type TDP-43 OE. We also report several muscle proteins altered by TDP-43 at the level of translation, including FMRP, a known translational regulator.

Marina Chulkina, PhD
Advisor: Iryna V. Pinchuk, PhD
Department: Medicine

Poster #2

MAPKAPK2 signaling: target for Crohn's disease-associated fibrosis

Chulkina M.[1], McAninch S.1, Rohmer C.[1], Koltun W.[2], Yochum G.[3], Beswick E.J.[4], Pinchuk I.V.[1]

[1]The Pennsylvania State University College of Medicine, Department of Medicine, Hershey, PA
[2]The Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, PA
[3]The Pennsylvania State University College of Medicine, Department of Biochemistry and Molecular Biology, Hershey, PA
[4]University of Utah School of Medicine, Salt Lake City, UT

Background: Crohn's disease (CD) is a multifactorial disease involving an abnormal immune response to gut microbiota in genetically-susceptible individuals, resulting in chronic inflammation. Fibrosis is the major complication of CD. No targeted therapies are currently available to revert CD-associated fibrosis. We recently reported an increase in MAPKAPK2 (MK2) activity within CD-inflamed intestinal tissues compared to the non-inflamed and healthy controls. An increase in MK2 activity in CD intestinal mucosa was greatly associated with mesenchymal stromal cells, known as myo-/fibroblasts (MFs). Mesenchymal cells are the major effectors in profibrotic processes in CD. MK2 is known to regulate the expression of a-SMA, a marker of activated fibroblasts, and the number of a-SMA+ cells is increased in CD-related fibrosis. We hypothesize that the MK2 pathway is critical to the pro-fibrotic responses of MFs in CD and is a potential therapeutic target for CD-related fibrosis.
Results: We observed increased activation of MK2 *in situ* in fibrotic mucosal colonic tissue of CD patients in comparison to non-inflamed CD tissue. An increase in MK2 activity in response to TGF-β1 (as a central pro-fibrotic mediator) was observed *in vitro* in primary human CD-MF by Western blot. Inhibition of MK2 activity in CD-MFs with the MK2-specific inhibitor PF-3644022 (1 μM) showed significantly reduced basal and TGF-β1-induced levels of the profibrotic genes including COL1A2, ACTA2, TNC, FN1. We also observed inhibition of TGF-β1-induced MF differentiation by evaluation of a-SMA expression in CD-MF by IF-microscopy. Using of MK2 inhibitor in a therapeutic modality in chronic IL-10 KO murine models of CD significantly reduces MF-linked pro-fibrotic responses *in vivo*, which was measured by the expression of pro-fibrotic genes, collagen deposition, and collagen thickness. Deletion of MK2 within MFs prior to induction of chronic DSS colitis significantly reduced clinical signs of the disease, decreased fibrosis complication, and downregulated expression of key CD-relevant pro-fibrotic genes Col1α2, TNC, Fn1 Il-6 in colonic tissue in mice.
Conclusion: Our data suggest that MK2 is a key signaling pathway responsible for the pro-fibrotic activation of CD-MFs. Targeting this MK2 pathway within MFs could be a desirable strategy for improving the efficacy of current therapeutic approaches for CD-associated fibrosis.

This work was supported by NIDDK R01DK103150 and DoD Medical Research multi-PI initiative #PR210832.

Josh Dorsi, PhD
Advisor: Krish Sathian, MBBS, PhD
Department: Neurology

Poster #3

Sound Symbolism in Words and Nonwords

Josh Dorsi[1], Simon Lacey[1], Lynne Nygaard[2], Krish Sathian[1]

[1]The Pennsylvania State University College of Medicine, Department of Neurology, Hershey, PA, USA
[2]Emory University, Department of Psychology, Atlanta, GA, USA

Sound symbolism refers to the association between the sound of a word and its meaning (Lockwood & Dingemanse, 2015). For instance, real words such as "balloon" and "spike" are considered to sound round and pointy, respectively, as well as referring to round or pointy objects (Sučević et al. 2015). The phenomenon is often studied using correspondences between speech sounds and cross-sensory or semantic features. For example, the pseudoword "bouba" is ascribed to round shapes while "kiki" is ascribed to pointed shapes (Ramachandran & Hubbard, 2001). The role of sound symbolism in real language is not well studied (Sidhu et al., 2021), and is the subject of this investigation. Participants rated the sounds of real words and pseudowords using a "very round" to "very pointy" scale. These words and pseudowords were recorded for this experiment but were chosen based on prior studies (McCormick et al., 2015; Sidhu et al., 2021). We first confirmed that our pseudowords were sound-symbolic. We found a significant, high correlation between our ratings of the pseudowords and the ratings previously reported for the same pseudowords (spoken by a different talker). Our second analysis extends these findings to the meanings of the real words. We tested if our ratings of each word's sounds corresponded to what each word means. Prior ratings of printed versions of these words indexed the relative roundedness/pointedness of the objects each word referred to. Here we found a high positive correlation between our ratings of the sound structure of each word and ratings of the shape properties of the word's referent, providing key support for the existence of sound symbolism in real language.

This work was supported by departmental funds.

Shunsuke Eguchi, PhD
Advisor: Michael Pfeiffer, MD
Department: Cardiology, Heart and Vascular Institute

Poster #4

New vs Tried and True: Is RVGLS Better than Conventional Echocardiographic Measurements to Assess Mortality Risk in Submassive Pulmonary Embolism?

Shunsuke Eguchi [1], Yoshiyuki Orihara [1], Michael Pfeiffer [1], Brandon Peterson [1], Mohammed Ruzieh [2], Zhaohui Gao [1], John Boehmer [1], John Gorcsan III [1], Ryan Wilson [1]

[1] Heart and Vascular Institute, Pennsylvania State University College of Medicine, PA
[2] Division of Cardiovascular Medicine, University of Florida College of Medicine, FL

Background: Venous thromboembolism including pulmonary embolism (PE) represents the third leading cause of vascular disease worldwide. Right ventricular (RV) systolic dysfunction has been identified as a prognostic marker for adverse clinical events in patients with acute PE. Strain echocardiography is an evolving imaging modality which measures myocardial deformation and can be used as an objective index of RV function. This study compared RV global longitudinal strain (RVGLS) to conventional echocardiographic parameters for predicting mortality in patients with submassive PE.

Methods: Retrospective cohort study of patients with submassive PE between 2010 and 2018. RVGLS was applied retroactively using TomTec® software. The primary outcome was all-cause mortality at 30 days. Receiver operating characteristic (ROC) analysis was performed for RVGLS and conventional echocardiographic parameters; tricuspid annular plane systolic excursion (TAPSE), pulsed Doppler S' wave (TDI S'), RV diameter (RVD) and systolic pulmonary artery pressure (SPAP). In addition, Kaplan-Meier curves were used for evaluation.

Results: 253 patients were analyzed. RVGLS was performed in 232 (91.7%). Mortality at 30 days was 12.5%. RVGLS had a significantly higher area-under the curve (AUC) of 0.884 compared to TAPSE, TDI S', RVD and SPAP ($p < 0.001$). Utilizing an absolute RVGLS value of 17.5%, ROC curve for 30-day mortality had 92.9% sensitivity and 72.1% specificity. Kaplan-Meier curves showed that patients with absolute RVGLS less than 17.5 % had higher risk of 30-day mortality compared to the other patients (HR 19.7, $p < 0.001$). Multivariable analysis revealed only RVGLS independently associated with 30-day mortality ($p < 0.001$).

Conclusion: RVGLS predicted short-term mortality in submassive PE more accurately than conventional echocardiographic parameters. Since RVGLS must be useful in risk stratifying patients with submassive PE at highest risk of mortality, it holds promise for incorporation into treatment pathways. Further study is needed to validate these findings and determine the role of RVGLS in submassive PE.

Upendarrao Golla, PhD
Advisor: Arati Sharma, PhD and David Claxton, MD
Department: Medicine, Division of Hematology and Oncology

Poster #5

Ex Vivo Culturing of Primary AML Cells Facilitates the Study of Developmental Therapeutics

Upendarrao Golla[1], Satyam Patel[2], Arati Sharma[2], David Claxton[1]

[1]The Pennsylvania State University College of Medicine, Department of Medicine, Hershey, PA, USA
[2]The Pennsylvania State University College of Medicine, Department of Pharmacology, Hershey, PA, USA

Studies with acute myeloid leukemia (AML) cell lines have limited potential as they tend to acquire mutations, thus, do not represent typical leukemias found in patients. Ex vivo culturing of primary human AML patient cells is therefore of interest; however, the long-term culture of these cells has been limited by rapid differentiation and loss of clonogenicity. Thus, we aimed to evaluate culture conditions using a cytokine cocktail, allowing long-term expansion and phenotypic maintenance of primary AML cells in vitro. Different culture conditions were constituted by combination of cytokines (SCF, FLT-3L, TPO, IL-6, IL-3, GCSF, GM-CSF) and small molecules (SR1, UM729) in serum-free StemSpan SFEM media. The ability of different growth mediums to support the expansion and clonogenicity of 6 primary AML cells (collected from blood/bone marrow) over two weeks was assessed. Additionally, cell surface markers (hCD34, hCD45, hCD123, hCD117) were measured by flow cytometry during the culture period. All tested cultured conditions exhibited successful cell proliferation (4-6-fold expansion) and survival of primary AML cells over two weeks of culture. In addition, the growth media successfully supported 3.5-fold CD34+ stem cell expansion. Growth mediums with early-acting cytokines (SCF, FLT-3L, TPO, and IL-6) and small molecules resulted in phenotypic maintenance of cell surface markers (CD34, CD123) and secondary clonogenicity of primary AML cells over the culture period. The addition of late-acting cytokines (IL-3, GCSF, and GM-CSF) showed a higher growth rate but negatively affected the cell surface markers and clonogenicity. Secondary colony counts (day-9 culture) showed a significant positive correlation with CD34 expression levels. Thus, CD34 levels could serve as a potential surrogate marker for the clonogenicity of primary AML cells. Furthermore, two primary AML cells post-culture (Day 4, Day 8) showed successful engraftment in xenograft mice. On an application note, the optimal condition from our results was used to study the effects of C6 ceramide nanoliposomes (CNL) in AML patient cells. Interestingly, the AML patient cells treated for two weeks with IC15 and IC30 doses of CNL led to cell cycle arrest, reduced CD34 expression and clonogenicity relative to control cells. The CNL findings from primary cells are different from that of cell lines cultured under the same conditions. Thus, our optimal growth conditions may facilitate researchers to understand AML biology and study various therapeutics under development using primary AML cells.

This work was supported by Kenneth F. Noel Memorial Fund (DC), The Penn State Cancer Institute (PSCI), and NIH/NCI P01CA171983 (subaward to DC).

Brian A. Hain, PhD
Advisor: David L. Waning, PhD
Department: Cellular and Molecular Physiology

Poster #6

Loss of regulated in development and DNA damage (REDD1) affects bone morphology in adult mice

Brian A. Hain[1,2] and David L. Waning[1,2,3]

[1]Penn State University College of Medicine, Department of Cellular and Molecular Physiology, Hershey, PA, USA
[2]Penn State Cancer Institute (PSCI) Hershey, PA, USA
[3]The Penn State Center for Orthopaedic Research and Translational Science (CORTS), Hersey, PA, USA

Bone growth, bone remodeling, and recovery after injury to bone are critical clinical concerns. Regulated in development and DNA damage (REDD1) is a mediator of cellular stress responses and has been extensively studied in muscle and other tissues. REDD1 inhibits the Akt-mTORC1 signaling pathway during periods of imbalanced physiological homeostasis, but its role in bone is largely unknown. Our data shows that REDD1 plays an important role in normal bone morphology. The objective of this study is to characterize REDD1's role in bone in the adult skeleton and to investigate how REDD1 impacts ovariectomy-induced bone loss. We used 12-week-old female global REDD1 knockout (R1KO) and wild-type (WT) mice to measure changes in trabecular and cortical bone by microCT. Compared to WT mice, R1KO mice had higher trabecular number (Tb.N), lower trabecular thickness (Tb.Th), and lower trabecular separation (Tb.Sp) while maintaining overall trabecular bone volume (BV/TV) in the distal femur and proximal tibia. Cortical thickness (Ct.Th) was also lower in R1KO mice at the femoral midshaft. We found that bones from R1KO mice had higher numbers of both osteoclasts and osteoblasts compared to WT mice at the distal femur. These data show that loss of REDD1 has a profound effect on bone. Because R1KO mice had altered bone morphology, we isolated primary osteoblasts from the calvaria of 2-week-old R1KO mice and WT mice, differentiated cells into mature osteoblasts, and measured calcification by alizarin red staining and measured alkaline phosphatase (ALP). We found that cells from R1KO mice were positive for alizarin red and ALP earlier than calvaria cells from WT mice. Since REDD1 is a key stress response element and important regulator of osteogenesis, we tested the bone response in a pathophysiological model of bone loss. We used bilateral ovariectomy (OVX) or sham surgery in WT and R1KO mice. Mice were euthanized 14 days after surgery, and trabecular bone parameters were measured in the distal femur using microCT. In OVX mice, R1KO animals exhibited higher BV/TV, Tb.N and Tb.Th, and lower Tb.Sp compared to WT OVX mice. These data suggest that REDD1 is important for normal bone morphology and in response to bone loss in mice. Future studies will use osteoblast-specific REDD1 knockout to investigate the roll of REDD1 in osteoblasts and in osteoblast-osteoclast crosstalk and using the potential for treatments for bone loss.

Takuto Hamaoka, PhD
Advisor name: Jian Cui, PhD
Department: Heart and Vascular Institute

Poster #7

The effect of cyclooxygenase inhibition on peripheral venous distension reflex in healthy humans

Takuto Hamaoka[1)], Urs A. Leuenberger[1)], Anthony Kronfli[1)], Zhaohui Gao, Cheryl Blaha[1)], Jonathan Carter Luck[1)], Paul Dalton[1)], Lawrence I. Sinoway[1)], and Jian Cui[1)].

1) Penn State Heart and Vascular Institute, Pennsylvania State University College of Medicine, Hershey, PA 17033

Background: Venous distension in limbs evokes a pressor reflex (venous distension reflex, VDR). Group Ⅲ and Ⅳ nerves, innervating peripheral veins, are suggested as the afferent arm of the VDR. Prostaglandins stimulate/sensitize group Ⅲ/Ⅳ nerves. The purpose of this study was to evaluate the effect of cyclooxygenase (COX) blockade on muscle sympathetic nerve activity (MSNA) and blood pressure (BP) responses to venous distension.
Hypothesis: We hypothesized that inhibition of prostaglandin synthesis by local COX blockade would attenuate the MSNA and BP responses to peripheral venous distension.
Methods: Nineteen healthy volunteers (age, 27 ± 5 years) participated in the study with a randomized, double-blind, placebo-controlled, and crossover study design with two separate visits. To induce venous distension, a volume of solution (saline alone or 9 mg ketorolac tromethamine in saline) was infused into the vein in the antecubital fossa of an arterially occluded forearm. During the procedure, beat-by-beat heart rate (HR), BP, and MSNA were recorded simultaneously. The vein size at the site with the catheter for the infusion was measured with ultrasound. This study is associated with a registered clinical trial (NCT03513770).
Results: In both visits, the venous distension procedure significantly increased the vein size, and the increase in vein size was not different between the visits ($P > 0.05$). A significant decrease ($P < 0.001$) in TXB2 level (an index for prostaglandin synthesis) by the procedure was observed only in the ketorolac visit. In both visits, the venous distension procedure significantly increased BP, HR, and MSNA (all, $P < 0.05$). The increase in mean arterial pressure (MAP) and MSNA in the ketorolac visit was significantly lower than in the control visit (ΔMAP, 7.0 ± 6.2 vs. 13.8 ± 7.7 mmHg; ΔMSNA, 6.0 ± 7.1 vs. 14.8 ± 7.7 bursts/minute; both, $P < 0.05$).
Conclusion: The presented data show that COX blockade attenuates the responses in MSNA and BP to peripheral venous distension. The results suggest that COX products play a key role in evoking afferent activation responsible for the VDR.

Funding source: This study was supported by National Institutes of Health Grants R01 HL144781 (to J.C. and L.I.S).

Amrendra Kumar, PhD
Advisor: Nelli Mnatsakanyan PhD
Department: Cellular and Molecular physiology

Poster #8

Structural Insights into the Inactivation Mechanism of Mitochondrial Megachannel

Amrendra Kumar[1], Daniel Morris[1], Yangyu Wu[2], Nelli Mnatsakanyan[1]

[1]The Pennsylvania State University College of Medicine, PA, USA
[2]Yale University School of Medicine, New Haven, CT, USA

Calcium-induced mitochondrial swelling, subsequent uncoupling of respiration, and cell death occur in mammals under hypoxic conditions of ischemia-reperfusion injury of the heart and brain. These changes are due to the activation of the mitochondrial megachannel also known as the mitochondrial permeability transition pore (mPTP). Remarkably, embryos of *Artemia franciscana,* brine shrimp tolerate anoxic conditions for years, and are suggested to lack the anoxia-stimulated calcium-regulated mPTP. Recently, mammalian ATP synthase was shown to undergo calcium-induced conformational changes to form an uncoupling channel of mPTP. This study aimed to investigate the structure and function of *Artemia franciscana* ATP synthase and its contribution to inactive and calcium-insensitive mPTP. We used mitochondrial swelling and calcium retention capacity (CRC) assays, electron microscopy (EM) imaging of mitochondria, electrophysiology studies, and cryo-EM of purified ATP synthase to investigate the mystery of inactive mPTP in *Artemia*. CRC and swelling assays of mitochondria isolated from *Artemia* confirmed the absence of calcium-induced mPTP reported previously in this organism. While mammalian ATP synthase purified from pig heart mitochondria forms calcium-activated, ATP-inhibited channels in our electrophysiology recordings, ATP synthase purified from *Artemia* larvae showed Ca^{2+} insensitive brief openings after prolonged latencies. The cryo-EM structure of *Artemia* ATP synthase revealed the strikingly different structure of the membrane-embedded subunits of the F_O subcomplex, elucidating the inactivation mechanism of Ca^{2+}-insensitive mitochondrial megachannel in this organism. Comparative structural and electrophysiological analysis of mammalian and *Artemia* ATP synthases will reveal the structural basis of ATP synthase leak channel formation and its role in mPTP.

This work was supported by National Institute of Aging Grants K01AG054734 and RF1AG072484 (to NM), by Penn State College of Medicine Startup Funds

Rinki Kumar, PhD
Advisor: Chris Norbury
Department: Microbiology and Immunology

Poster #9

Type III interferon enhances cytomegalovirus infection *in vitro* and *in vivo*

Rinki Kumar[1], Irene Reider[1], Nick Buchkovich[1] and Chris Norbury[1].

[1]Department of Microbiology and Immunology, Penn State College of Medicine, Hershey, Pennsylvania.

There are three types of interferons, type I (T1, a, b, e, k, w), type II (T2, g) and type III (T3, l 1-4). While type I and II are known to inhibit HCMV infection, it has been shown that transplant recipients harboring SNPs in IFN l3 have significantly lower HCMV loads. This indicates the potential of a previously unidentified proviral role for T3 interferons during CMV infection. To test this, we treated fibroblasts with T1-IFN (50ng/ml IFN- b) or type T2-IFN (100ng/ml IFN- g) and observed HCMV spread was inhibited as expected. Intriguingly, virus spread was enhanced in the presence of T3-IFN (IFN- l, 50ng/ml), in cells that expressed the IFNlR, but not in cells that did not. Thus, T1- and T3-IFNs have directly opposing effects on HCMV replication *in vitro*, although both of these IFNs share common signaling pathways that include STAT1, STAT2 and IRF9. Inhibitors of the proximal signaling events from each receptor indicated that blockade of common, but not T3-IFN unique, signaling pathways, blocked the T3-IFN enhancement of HCMV spread. Therefore, the proviral effect of T3-IFNs likely occurs via unique gene signatures induced downstream of the immediate signaling pathways.

We tested this effect *in vivo*, by infecting wildtype (WT) mice with MCMV and measuring induction of IFNl transcripts in various organs. IFN l was induced in spleen (d3), lung (d5) and kidney (d5), but not in salivary gland or liver. When we compared replication of MCMV in WT mice to IFNlR$^{-/-}$ mice we observed a significant decrease in viral DNA in the lung (d4) and spleen (d5), but not kidney, of IFNlR$^{-/-}$ mice, confirming the proviral role of IFN l *in vivo*. Interestingly, this has no correlation to tissue-specific expression of IFNlR, because a higher expression of IFNl R was seen in salivary gland and lung than in spleen, kidney, or liver. In addition to a proviral role of IFNl acting directly upon infected cells, T3-IFNs can also act upon immune cell populations that control MCMV replication *in vivo*. We did not observe any IFNlR-modulated response of gd T cells, ab T cells (CD4$^+$ and CD8$^+$), NK T cells, NK cells or B cells. However, a marked increase in the dendritic cell response, including cDC2, monocyte-derived DC, and plasmacytoid DC was seen in the spleen but not the kidney of IFNlR$^{-/-}$ mice. This is consistent with a T3-IFN-mediated modulation of the early immune response that controls MCMV replication *in vivo*, thereby accounting for the differential replication we observed in spleen vs kidney. Therefore, IFN displays both a direct proviral effect on virus replication *in vitro* and *in vivo*, and an indirect effect upon viral replication and spread *in vivo* by negatively impacting the anti-MCMV DC response. Taken together, these results identify a potential novel role for T3-IFN in CMV infection, particularly in epithelial and placental tissues where T3-IFNs are the primary IFNs produced upon viral infection.

G. Vinodh Kumar
Advisor: Krish Sathian, MBBS, PhD
Department: Neurology

Poster #10

Acoustic parameters underlying sound-symbolic mapping of auditory pseudowords to different domains of meaning: a machine learning approach

G. Vinodh Kumar[1], Ana Maria Hoffmann[4], Kaitlyn L. Matthews[4], Simon Lacey[1,3], Lynne C. Nygaard[4] & K. Sathian[1,2,3]
[1]Penn State College of Medicine and [2]Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA; [3]Penn State College of Liberal Arts, University Park, PA, USA; [4]Emory University, Atlanta, GA, USA

Sound symbolism refers to non-arbitrary mapping between the sound of a word and its meaning, e.g., auditory pseudowords like "bouba"/"kiki" are perceived as sounding rounded/pointed, respectively. Previously (Lacey et al., 2020, Cog Sci, 44:e12883), we showed that ratings of 537 pseudowords on a rounded-to-pointed scale were significantly correlated with three acoustic parameters measuring spectro-temporal properties (spectral tilt (ST), temporal fast Fourier transform (FFT), speech envelope (SE)) and nine voice parameters measuring voice characteristics (harmonics-to-noise ratio (HNR), pulse number, fraction of unvoiced frames (FUF), mean autocorrelation, shimmer, jitter, mean pitch, pitch standard deviation and voice duration). Here, we used a machine learning approach to investigate which combinations of these parameters best predicted ratings of the same set of pseudowords on scales representing categorical opposites for seven meaning domains: shape (rounded/pointed), size (small/big), brightness (bright/dark), weight (light/heavy), texture (hard/soft), arousal (calming/exciting) and valence (good/bad). Pairwise dissimilarities between all pairs of pseudowords were computed for each parameter: for spectro-temporal parameters, we rescaled the pairwise dissimilarity values, computed from corresponding Pearson correlations (1-rp), to lie between 0 and 1; for voice parameters, we rescaled their values to 0 – 1, and computed pairwise absolute differences. Subsequently, we evaluated all 4094 possible parameter combinations using a k-nearest-neighbors algorithm ($k = \sqrt{537} \approx 23$). For each combination, we iteratively computed the Euclidean distance in n-parameter space between each pseudoword and the remaining 536 to find its 23 nearest neighbors. The algorithm predicted a rating for each pseudoword based on the modal perceptual rating of its neighbors. Subsequently, we used the Spearman correlation between predicted and perceptual ratings to quantify the algorithm's performance and identify the best performing model. Finally, we employed multiple regression analysis to quantify the influence of each acoustic parameter that comprised the best performing model. Our results indicate that sound-symbolic mappings across meaning domains rely on different patterns of multiple parameters and that each acoustic parameter contributes differently depending on the meaning domain. This approach could be applied to real words to measure the degree of sound-symbolic mapping in natural languages unconfounded by semantic bias.

This work was supported by departmental funds.

Gregory S. Lambert, PhD
Advisor: Leslie J. Parent, MD
Department: Medicine

Poster #11

RSV Gag genomic RNA selection may be facilitated by host transcriptional condensates

Gregory S. Lambert[1], Breanna Rice[1], Rebecca Kaddis Maldonado[1], Malgorzata Sudol[1], and Leslie J. Parent[1,2]

Departments of [1]Medicine and [2]Microbiology & Immunology, Penn State College of Medicine, Hershey, PA 17033

Although many effective antiretroviral agents exist, none targeting the steps in retroviral assembly have been approved for clinical use. As such, further characterization of the mechanisms governing retroviral assembly has great therapeutic potential. Retroviral Gag proteins perform the critical function of selecting and packaging two copies of unspliced viral RNA (USvRNA) as the genome for each nascent virion. In contrast to previous assertions that Gag performs this function in the cytoplasm or at the plasma membrane, our lab has demonstrated that Rous sarcoma virus (RSV) Gag traffics to the nucleus and colocalizes with USvRNA at transcriptional burst sites. Furthermore, decreasing nuclear localization of retroviral Gag results in diminished genome packaging, suggesting this nuclear pool of Gag plays an important role in genomic RNA (gRNA) selection. Indeed, we have observed viral ribonucleoprotein complexes (vRNPs) translocating from the nucleus to the cytoplasm, presumably as part of their trafficking pathway en route to forming nascent virions.

Our investigation into how RSV Gag localizes to transcriptional burst sites has been aided by utilizing proteomic analysis to identify host factors that interact with RSV Gag. Among those identified were members of the host transcription machinery, including members of the Mediator complex. Interestingly, many of the identified proteins are known to participate in the formation of transcriptional biomolecular condensates (BMCs)—membraneless organelles which compartmentalize transcription machinery via a complex set of specific and nonspecific interactions—to increase binding selectivity and efficiency. Based on the observation that RSV Gag forms distinct nuclear foci resembling BMCs in cells, we examined whether Gag forms BMCs using *in vitro* assays and advanced imaging techniques. With this knowledge in hand, this work seeks to identify interactions between RSV Gag and host transcription machinery that are important for the participation of Gag in transcriptional condensates. This work addresses gaps in our knowledge concerning the molecular mechanisms underlying the role of nuclear Gag in gRNA packaging and aims to identify host cell factors that may play a role in localization of Gag to transcription sites. Overall, this work will utilize biochemical, biophysical, and advanced imaging techniques to test the novel hypothesis that retroviral Gag proteins leverage transcriptional condensates to facilitate genomic RNA selection.

This work was supported by NIH R01 CA76534 (LJP).

Alex Y. Lin, PhD
Advisor: Keith C. Cheng, MD PhD
Department: Experimental Pathology

Poster #12

Role of maternal mRNA degradation in whole body cellular phenotypes caused by DNA polymerase α deficiency

Alex Y. Lin[1,2], Georgia Thomas[1,2], Casey Smallwood, Khai Chung Ang[1,2], Damian van Rossum[1,2], Victor Canfield[1,2], and Keith C. Cheng[1,2]

[1]The Jake Gittlen Laboratories for Cancer Research, Penn State College of Medicine, Hershey, PA, USA;
[2]Division of Experimental Pathology, Department of Pathology, Penn State College of Medicine, Hershey, PA, USA
[3]Emergency Veterinarians, Veterinary Emergency Group, Hoboken, NJ, USA

Pleiotropy caused by single-gene mutations is common and poorly understood. A zebrafish null mutant of DNA polymerase α subunit B, huli hutu (hht), evolves a complex pleiotropy across multiple organ systems over 5-7 days, including nuclear fragmentation in the eye and brain and nuclear atypia (a cellular feature common in human cancers and pre-cancers), in gastrointestinal organs. This complex pleiotropic pattern of hht phenotypes is associated with DNA damage and explained by cell duplication-dependent dilution of wild-type maternal pola2 in homozygous mutant embryos, whose pola2 mRNA becomes undetectable by 24 hours post-fertilization (hpf). Inhibition of DNA synthesis by aphidicolin or hydroxyurea in wild-type embryos from 24 hpf phenocopied the pleiotropic pattern of hht. These results are consistent with a model in which cell duplication-dependent dilution of pola2 results in nuclear fragmentation and cell death in rapidly-replicating cells, and cellular features become distorted in larger cells that are able to survive due to fewer replicative cycles.

This work has been supported by NIH 5R01 AR052535 and the Jake Gittlen Cancer Research Foundation.

Steffy B Manjila, PhD
Advisor: Yongsoo Kim, PhD
Department: Neural and Behavioral Sciences

Poster #13

Characterization of the Oxytocin receptor (OxtR) enriched dorsal endopiriform cortex (EPd): a novel area for shifting gears from surveillance to attention

Steffy B Manjila[1], Seoyoung Son[1], Yuan-Ting Wu[1], Hannah Kline[1], Rebecca Betty[1], Kirsteen N Browning[1] and Yongsoo Kim[1]

1The Pennsylvania State University College of Medicine, Department of Neural and Behavioral Sciences, Hershey, PA, USA

Oxytocin (Oxt) is an essential neuropeptide that regulates diverse physiological functions via central projections in the brain. Oxt producing neurons reside mainly in the hypothalamus, and its actions are mediated by a single receptor, the Oxt receptor (OxtR) that is expressed in distinct brain regions and in peripheral tissues. Oxt neurons send long range projections to multiple areas within the brain that often express OxtRs. Our quantitative analysis of Oxt long range projections in correlation with OxtR expression identified a unique area, the dorsal Endopiriform nucleus (EPd) that has the highest Oxtr density with very sparse Oxt projections in the mouse brain. EPd is a small group of neurons medial to the piriform cortex and ventral to the claustrum, mainly implicated in temporal lobe epileptogenesis. However, the anatomical connectivity and functional relevance of this OxtR dense region is unclear. Here, we have investigated the whole brain input-output mapping of the OxtR neurons in the EPd (OxtR-Epd) using serial two photon tomography and light sheet imaging techniques. OxtR-EPd broadly project to four functional circuits that regulate olfaction, internal state, emotion (limbic) and memory. Whole brain retrograde monosynaptic mapping revealed strong inputs from similar functional circuits with a larger fraction of inputs from olfactory areas and the basal forebrain area. Further, we performed an in-vivo miniscope recording and found tonic neuronal activity in the OxtR-EPd during a non-attentive state. Surprisingly, activity of OxtR-EPd is selectively attenuated upon novel cues (social and non-social). Anatomical characterization of EPd also reveals complex inputs that could attenuate the activity when surveillance mode gets shifted to attention. In summary, our results suggest that the OxtR-EPd serves as an integration hub for olfactory related information and plays a key role in shifting gears from general surveillance to novelty-based attention.

This work was supported by NIH grant (R01MH116176) (YK).

Suchitra Mohanty, PhD
Advisor: Edward Harhaj, PhD
Department: Microbiology and Immunology

Poster #14

KDR/VEGFR2 interacts with HTLV-1 Tax to prevent its autophagic degradation and is required for the survival of Tax+ HTLV-1-transformed cells

Suchitra Mohanty[1], Alfonso Lavorgna [2], Sujit Suklabaidya [1], Nyater Ngouth[3], Steve Jacobson[3], Edward W. Harhaj[1, 2*]

[1]Penn State University College of Medicine, Department of Microbiology and Immunology, Hershey, PA, USA
[2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD, USA
[3]Viral Immunology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20814, USA

The human T-cell leukemia virus type 1 (HTLV-1) is an enveloped retrovirus, and the causative agent of adult T-cell leukemia/lymphoma (ATLL), and inflammatory diseases including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). The HTLV-1 transactivating protein, Tax regulates viral gene expression and acts as a potent oncogene that interacts with and modulates a plethora of host cellular proteins and triggers the aberrant activation of signaling pathways such as NF-κB to drive clonal proliferation and survival of infected T cells. However, the regulation of Tax expression and protein stability by host cellular proteins is largely unknown. Hence, the identification of host proteins that control Tax expression and stability could potentially yield targets to develop novel therapeutic approaches for ATLL. We have conducted a kinome-wide shRNA screen to identify host factors crucial for the survival of an HTLV-1-transformed T cell line, MT-2. The top hit in the screen was the tyrosine kinase receptor KDR/VEGFR2, which we have validated by using shRNAs or small molecule inhibitors through western blots and flow cytometry assay. We examined the interaction between Tax and KDR by co-immunoprecipitation and proximity ligation assay in HTLV-1-transformed T cell lines. Inhibition of KDR with shRNAs or small molecule inhibitors induced caspase-dependent apoptotic cell death selectively in Tax+ HTLV-1-transformed T cells. Furthermore, inhibition of KDR elicited autophagic degradation of Tax and diminished the chronic activation of NF-κB. We found that Tax upregulated KDR expression and formed a complex with KDR in HTLV-1-transformed T cells. We also revealed tyrosine phosphorylation of Tax by KDR and validated through *in vitro* kinase assay. Collectively, our results have demonstrated a critical role of KDR/VEGFR2 in protecting Tax from degradation by autophagy. This knowledge could be exploited as a potential strategy to target Tax in Tax+ ATLL and HAM/TSP patients.

This work was supported by Penn State Cancer Institute and NIH R21 AI166335.

Yoshiyuki Orihara, PhD
Advisor: Michael Pfeiffer, MD
Department: Cardiology, Heart and Vascular Institute

Poster #15

Taking a New Look: Novel Echocardiographic Measurements to Quantify the Risk of Death in Patients with Submassive Pulmonary Embolism

Yoshiyuki Orihara (1), Shunsuke Eguchi (1), Michael Pfeiffer (1), Brandon Peterson (1), Mohammed Ruzieh (2), Zhaohui Gao (1), John Boehmer (1), John Gorcsan III (1), Ryan Wilson (1)

(1) Pennsylvania State University, College of Medicine, Heart and Vascular Institute
(2) University of Florida, College of Medicine, Division of Cardiovascular Medicine

Background: Submassive pulmonary embolisms (PE) are common and carry significant mortality. Previous studies have demonstrated right heart dysfunction is a prognostic marker for adverse events and mortality. Recently, strain images, a novel method of right sided chamber quantification, have been developed to evaluate cardiac function more accurately. Moreover, strain imaging is reported to predict the mortality in various cardiac diseases. However, its usefulness in the evaluation of submassive PEs remains undetermined.
Method: Retrospective cohort study of patients with submassive PE between 2010 and 2018. The "strain" parameter as a novel method to trace endocardium approximates muscle deformation. Right ventricular global longitudinal strain (RVGLS), right ventricular free wall strain (RVFWS), and right atrial strain (RAS) were analyzed using TomTec® application. Primary outcome evaluated all-cause mortality at 30 days. Receiver operating characteristic (ROC) was performed for evaluation.
Result: 232 patients were analyzed. There was 13% mortality at 30 days. RVGLS showed a bimodal distribution between non-survivors and survivors. And non-survivors had a much lower RVGLS value (Mean value, 13.3 % in non-survivors and 19.5 % in survivors). Distributions for RVFWS and RAS were similar to RVGLS (Mean value for RVFWS and RAS, 15.1 % and 20.7 % in non-survivors and 21.7 % and 30.8 % in survivors, respectively). ROC curves demonstrated optimal absolute cutoff values of 17.5% for RVGLS [sensitivity (SE) 1.000, specificity (SP) 0.733, AUC 0.935]; 17.1 % for RVFWS [SE 0.724, SP 0.856, AUC 0.858]; and 27.1 % for RAS [SE 0.963, SP 0.685, AUC 0.879]. Significant differences were observed between AUC for RVGLS and RVFWS ($p < 0.001$), and AUC for RVGLS and RAS ($p = 0.03$).
Conclusion: Right sided strain analysis has prognostic value for identifying patients with submassive PE at increased mortality risk. RVGLS outperforms other right sided chamber strain measurements. Further study is needed to determine the role of RVGLS in patients with submassive PE.

Kondaiah Palsa, PhD
Advisor: Prof. James R. Connor, PhD
Department: Neurosurgery

Poster #16

Role of blood-brain barrier endothelial cells released extracellular vesicles in brain iron transport

Kondaiah Palsa[1], Stephanie L. Baringer [1], Vladimir S. Spiegelman[2], Ian A. Simpson[3], James. R. Connor[1]

[1]Department of Neurosurgery, Penn State College of Medicine, Hershey, Pennsylvania
[2]Department of Pediatrics, Penn State College of Medicine, Hershey, Pennsylvania
[3]Department of Neural and Behavioral Sciences, Penn State College of Medicine, Hershey, Pennsylvania

Iron is essential for normal brain development and function. We previously demonstrated that in addition to transferrin, ferritin heavy chain (FTH1) also transports iron to the brain via endothelial cells. The mechanism of Tf and FTH1bound iron release from blood-brain barrier endothelial cells (BBBECs) to the brain parenchyma remains unclear. Herein we investigated the role of extracellular vesicles (EVs) in mediating the transfer of FTH1 or Tf across the BBBECs. The study used ECs and astrocytes derived from human induced pluripotent stem cells (hiPSC) and ECs are grown in bicameral chambers. When cells were exposed to 55Fe -Tf or 55Fe-FTH1, the 55Fe activity in the basal chamber EV fraction was significantly higher than in the supernatant fraction. GW4869, a potent inhibitor of EVs inhibited the EVs release from the ECs to the basal side, as well as Tf, FTH1, and iron transport compared to the control. Furthermore, the release of endogenous Tf, FTH1, and EVs number is regulated by the iron concentration of the endothelial cells. The release of EVs containing iron was independent of hepcidin regulation indicating this mechanism by-passes a major iron regulatory pathway. We further demonstrated that EVs containing FTH1, Tf, and iron are taken up by human astrocytes, thereby identifying a new pathway for these cells to obtain iron. These results indicate that iron transport across the BBB is mediated via the EVs pathway and is modified by the iron status of the ECs providing evidence for novel alternate mechanisms of iron transport into the brain that is hepcidin independent. The ability of GW4869 to, reduce iron transport into the basal side suggests that blocking exosomes maybe be a therapeutic strategy for the treatment of patients suffering from diseases associated with excess brain iron.

This work was supported by the National Institute of Neurological Disorders and Stroke - R01NS113912.

Thiruvelselvan Ponnusamy, PhD
Advisor: Shanmughapriya Santhanam, PhD
Department: Heart and Vascular Institute

Poster #17

Mitochondrial Magnesium regulates mitochondrial permeability transition and Alzheimer's disease pathogenesis

Thiruvelselvan Ponnusamy[1], Amrendra Kumar[2], Natarajaseenivasan Kalimuthusamy[3], Nelli Mnatsakanyan[2], Shanmughapriya Santhanam[1]

[1]Heart and Vascular Institute, Department of Medicine, Department of Cellular and Molecular Physiology, Pennsylvania State University, College of Medicine, Hershey, PA, USA
[2]Department of Cellular and Molecular Physiology, Pennsylvania State University, College of Medicine, Hershey, PA, USA
[3]Neural Sciences, Lewis Katz School of Medicine at Temple University, Philadelphia, USA

Magnesium (Mg^{2+}) is an abundant intracellular divalent cation and an essential co-factor. Like calcium, Mg^{2+} is also compartmentalized to mitochondria. Mrs2 is the only known molecular machinery associated with mitochondrial Mg^{2+} (mMg^{2+}) influx. We show Mrs2 to form a voltage-gated Mg^{2+} selective channel with multiple sub-conductance states in planar lipid bilayer recordings. Apart from its canonical function of activating enzymes within the TCA cycle and ETC, our previous work showed mMg^{2+} to bind the N-terminal mitochondrial Ca^{2+} Uniporter (MCU) regulating acidic patch (MRAP) and reduces MCU-mediated mitochondrial Ca^{2+} (mCa^{2+}) uptake. Because mMg^{2+} regulates mCa^{2+} uptake and mCa^{2+} overload is associated with AD progression, we anticipate a loss of mMg^{2+} homeostasis in Alzheimer's disease (AD) to overload mCa^{2+} and predispose the neurons to mitochondrial permeability transition pore (mPTP)-mediated cell death. As expected, our results showed mMg^{2+} uptake to be significantly reduced in AD cells. Intriguingly, the decrease in mMg^{2+} was not due to a decrease in mRNA or protein levels; instead, Mrs2 was post-translationally modified by oxidation resulting in a loss of function. Also we show the loss of mMg^{2+} to be associated with increased mCa^{2+} overload, bioenergetics crisis, and mPTP-mediated cell death. To define whether impaired mMg^{2+} influx causally contributes to mCa^{2+} overload and mPTP-mediated cell death, we expressed a cysteine null ($Mrs2^{\Delta CF}$) mutant in AD cells. We observed that cysteine nullification rendered Mrs2 insensitive to oxidation and oxidative inhibition and protected AD cells from mCa^{2+} overload-mediated cell death. Our work defined oxidative stress to inactivate Mrs2, dysregulate mMg^{2+} homeostasis, positively regulate MCU-mediated mCa^{2+} overload, mPTP-mediated cell death, and AD progression. Though the role of mPTP in aging and neurodegenerative diseases is known, our study will show how altered mMg^{2+} regulates mCa^{2+} overload-mediated mPTP opening and AD progression.

Asia Poudel, PhD
Advisor: Guy Townsend, PhD
Department: Biochemistry and Molecular Biology

Poster #18

Elucidating differential hyaluronan utilization determinants among human gut bacteria

Asia Poudel, Jennifer L. Modesto, and Guy E. Townsend

Department of Biochemistry & Molecular Biology, Penn State College of Medicine, Hershey, PA, 17033

The mammalian gut microbiota utilizes various dietary, host, and microbial glycans to successfully colonize the intestine. One abundant class of microbial-accessible glycans called glycosaminoglycans (GAGs) are linear polymers of repeating disaccharide units that serve as an important nutrient source to intestinal bacterial populations including the Bacteroides, a dominant collection of species prevalent across human populations worldwide. Bacteroides species employ specialized polysaccharide utilization loci (PULs) to utilize distinct GAG classes that include chondroitin sulfate (CS), hyaluronic acid (HA), dermatin sulfate (DS), and heparin. A single PUL found in many Bacteroides species confers access to heparin, while a distinct PUL confers access to CS, HA, and DS in others. Interestingly, the CS/HA/DS utilization PUL always confers access to CS and DS but HA is utilized in species-specific manner. Here, we employed a recently developed transcriptional reporter to identify genes that facilitate HA utilization in Bacteroides thetaiotaomicron (Bt). We demonstrate that loss of four CS/HA/DS-specific lyases eliminates CS detection and utilization but retains the ability to detect and utilize HA. Using classical forward genetics, we identify two genes necessary for HA utilization in the absence of these periplasmic lysases and hypothesize that heterologous expression of either will confer access to HA in Bacteroides species that normally only utilize CS.

Asif Raza, PhD
Advisor: Arun Sharma, PhD
Department: Pharmacology

Poster #19

Pre-clinical chemopreventive efficacy of a novel hybrid p-XSC-aspirin compound in a NNK-induced lung cancer model

Asif Raza[1], Daniel Plano[2], Amandeep Singh[1], Cesar Aliaga[1], Shantu Amin[1], Arun K. Sharma[1]

[1]Penn State University College of Medicine, Department of Pharmacology, Hershey, PA
[2]Universidad de Navarra, Spain

1,4-Phenylenebis(methylene)selenocyanate (p-XSC) was on the National Cancer Institute´s (NCI) list of chemopreventive agents but was eventually discarded due to systemic toxicity issues. This toxicity could partially be due to the release of poisonous hydrogen cyanide generated after p-XSC metabolizes to form active bis-selenol (p-XSeH). To address this concern, we recently designed and developed p-XS-Asp, with the rationale that it would cleave *in vivo* to release the active p-XSeH and aspirin instead of undesired HCN, thus making the compound less toxic and possibly more potent than p-XSC. p-XS-Asp inhibited NNK-induced lung tumorigenesis in A/J mice more effectively than p-XSC and was also more tolerable. At doses of 15 ppm and 7.5 ppm Se, p-XS-Asp showed a significantly marked decrease in the percentage of lung cancer incidence *in vivo* with only 50% and 87% of tumor incidence, as compared to p-XSC (79% and 100%), respectively. NNK-control showed a 100% tumor incidence. Likewise, the tumor multiplicity for p-XS-Asp group was 0.87 and 1.93 tumors/mouse as compared to the NNK-control (11.53) and p-XSC (1.66 and 4.10 tumors/mouse, respectively) at the two doses tested. Notably, blood chemistry and tissue analyses did not show systemic toxicity for the p-XS-Asp fed group. Although these results were highly encouraging, this model does not reveal at what stage of carcinogenesis p-XS-Asp acts. Therefore, in the current study, we evaluated the stage-specificity of p-XS-Asp in NNK-induced lung carcinogenesis in A/J mice models.

A/J mice were divided into 7 distinct groups (n=30 per group, half male, half female; except group 1 and 2 where n=10). The mice were fed AIN-93M diet (control) or p-XS-Asp diet until they reached termination endpoint of 26 weeks (adenomas) and 40 weeks (adenocarcinomas). Two weeks after the experiment started, all the groups, except for group 1 and 2, were given a single IP injection of 10 µmol (100 mg/kg) of NNK. Group 3 and 4 were on complete control diet and p-XS-Asp diet, respectively. Group 5 (peri-initiation) was on p-XS-Asp for the first 3 weeks and then on the control diet till the end of the experiment. On the other hand, group 6 (post-initiation) was on control diet for 3 weeks and then changed to the p-XS-Asp diet. In the progression group 7, mice were on control diet for 14 weeks and subsequently changed to p-XS-Asp diet. The Group 4 and Group 5 mice showed a remarkable decrease in the tumor multiplicity (TM) and incidence (TI) as compared to the mice on control diet at both 26- and 40-week time-points. These data demonstrated robust inhibition at the peri-initiation stage is mainly responsible for the activity observed in the complete model. The inhibition of both O6-methylguanine and pyridoxobutyl mutagenic DNA adducts by p-XS-Asp shows the compound acts at initial stages of carcinogenesis. RNA-seq data of the tumor tissues showed numerous signaling pathways to be affected in p-XS-Asp treated mice. The exact mechanism of action is under investigation. In summary, our results show p-XS-Asp may be a candidate for clinical evaluation as a lung cancer preventive agent.

Amandeep Singh, PhD
Advisor: Arun K. Sharma, PhD
Department: Pharmacology

Poster #20

Identification of a Novel IGF2BP1 Inhibitor, AVJ16, as Metastasis-Specific Therapeutic Agent

Amandeep Singh[1], Vikash Singh [3], Nadav Wallis[2], Giancarlo Abis[4], Omer Elimelech[2], Froma Oberman[2], Tyler Wood [3], Mayura Dhamdhere [3], Andres Ramos[4], Joel Yisraeli[2], Vladimir S. Spiegelman [3], Arun K. Sharma[1]

[1]Department of Pharmacology and [3]Department of Pediatrics, Penn State Cancer Institute, The Pennsylvania State University College of Medicine, Hershey, PA, USA
[2]Department of Developmental Biology and Cancer Research, Hebrew University Hadassah Medical School, Jerusalem, Israel
[4]Division of Biosciences, Institute of Structural and Molecular Biology, University College London, Darwin Building, Gower Street, London WC1E 6BT, United Kingdom

IGF2BP1 is a multifunctional RNA-binding protein that regulates the stability, localization and translation of its mRNA targets. High levels of IGF2BP1 expression have been shown to be associated with poor prognosis in patients with a variety of cancer types. Given this correlation between elevated IGF2BP1 expression and poor clinical outcomes, the specific activation of IGF2BP paralogs in a wide variety of cancers, and the effectiveness of preventing metastasis in animal models by reducing IGF2BP1 activity, therapies directed at inhibiting IGF2BP1 function constitute a potentially powerful approach for fighting cancer. To identify an efficient IGF2BP1 inhibitor, a fluorescent polarization (FP)-based high throughput screen of over 100,000 small molecules was performed, and the most promising candidates were further validated leading to the identification of a lead compound, "7773," that selectively inhibited IGF2BP1 RNA binding and a variety of its cellular functions. To further optimize '7773' and create more selective, effective, and safe small-molecule inhibitors of IGF2BP1 we conducted a SAR study based on the lead '7773' structure. Novel 27 compounds were designed and synthesized and evaluated for IGF2BP1 inhibition using our novel cell-based split-luciferase assay, which led to the identification of 6 compounds that performed similar or better than '7773'. Cell-based wound healing assay revealed that one of these selected compounds, AVJ16, was especially (>14 times than "7773") effective in inhibiting cell migration in the H1299 cell line that expresses high levels of endogenous IGF2BP1, but not in LKR-M cells that express very low levels of IGF2BP1. The specificity of AVJ16 was further confirmed in LKR-M cells that ectopically express IGF2BP1 – these cells become sensitive to AVJ16 upon overexpression of IGF2BP1 (but not GFP). To further validate the efficacy and specificity of compound AVJ16, we utilized human colorectal cancer cell lines with high (HCT116) and low/no (RKO) expression of IGF2BP1. HCT116 expressing IGF2BP1 but not RKO showed sensitivity towards AVJ16. MST test was used to confirm the direct binding of AVJ16 to IGF2BP1 and showed a 12-fold improvement in binding compared to the lead compound (KD of 1.4 M vs. 17 M for "7773"). NMR data indicated that AVJ16 binds more strongly than compound 7773 to a highly hydrophobic patch, at the interface between KH3 and KH4 domains, in the KH34 di-domain of the protein Together our data provide strong evidence for AVJ16 to be effective and selective in inhibiting IGF2BP1 function by interfering with its ability to bind target RNAs.

Samantha Spencer, PhD
Aron Lukacher, MD, PhD
Department of Microbiology and Immunology

Poster #21

Polyomavirus induces ependyma-specific and Stat1-dependent expression of chemokines in the central nervous system

Samantha Spencer[1], Sarah Carey[1], Aron Lukacher[1]
[1] Pennsylvania State University College of Medicine, Hershey, PA

Immunity of the central nervous system to pathogens is partly established by critical barrier sites. One barrier within the four ventricles, the blood-cerebrospinal fluid (CSF)-brain barrier, is comprised of the choroid plexus epithelial cells separating the vasculature from the CSF, and the CSF from the brain parenchyma by the ependymal cells lining the ventricles. Intracerebroventricular delivery of mouse polyomavirus (MuPyV) in wild-type mice leads to infection of ependymal cells. In Stat1 null mice viral infection is increased, and ependyma effacement is associated with hydrocephalus. Unknown is whether innate immunity and immune cell recruitment via Stat1 signaling by the ependyma limits MuPyV infection of the parenchyma. Dcdc2α-Cre mice, which show recombination in the ependyma and choroid plexus, were crossed with Stat1 $^{fl/fl}$ mice to yield ependyma-specific Stat1 knockout. MuPyV infection was greater in Dcdc2α-Cre+ x Stat1 $^{fl/fl}$ mice than in wild-type controls at 4 days post infection (dpi), but by 7 dpi the wild-type and Dcdc2α-Cre+ x Stat1 $^{fl/fl}$ mice showed similar levels of infection with more MuPyV near the ventricles. Prior studies using the MuPyV-infected Stat1 null mice showed increased monocyte and T cell recruitment. Several cytokines and chemokines (Ccl2, Cxcl10, Cxcl11, and Cxcl16) were elevated at 7 dpi in Dcdc2α-Cre+ x Stat1 $^{fl/fl}$ mice relative to wild-type mice, while Cxcl13 was reduced at 4 and 7 dpi. Of these, Ccl2, Cxcl10 and Cxcl11 showed greater levels near the ventricles in both wild-type and Dcdc2α-Cre+ x Stat1 $^{fl/fl}$ mice. Therefore, the ependyma is an important barrier for protection of the brain against MuPyV infection, and Stat1 signaling in ependymal cells reduces MuPyV infection and immune cell infiltration.

Sujit Suklabaidya, PhD
Advisor: Edward W. Harhaj, PhD
Department: Microbiology and Immunology

Poster #22

The autophagy receptor TAX1BP1 inhibits activation of the cGAS-STING pathway

Sujit Suklabaidya[1], Suchitra Mohanty[1], Loic Dragin[1], Sarah McCormick[2], Young B. Choi[2], Jesse White[1], Christopher Norbury[1], Edward W. Harhaj[1]

[1]The Pennsylvania State University College of Medicine, Department of Microbiology and Immunology, Hershey, PA, USA
[2]Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Negative regulation of innate immune signaling pathways is vital to avoid excessive inflammation and promote homeostasis. TAX1BP1 is a selective autophagy receptor that regulates innate immunity and has been linked to the clearance of protein aggregates (aggrephagy) and bacterial pathogens (xenophagy). The cGAS-STING pathway is a critical regulator of type I IFN and inflammation upon sensing of DNA; however, it is unknown if TAX1BP1 regulates cGAS and/or STING. In this study we used bone marrow-derived macrophages (BMDMs) from Tax1bp1$^{fl/fl}$ x LysM Cre mice and TAX1BP1-knockout (KO) human monocytic THP-1 cells generated by CRISPR/Cas9 to test the hypothesis that TAX1BP1 inhibits cGAS-STING signaling. Here, we show that TAX1BP1-KO THP-1 cells were resistant to infection with the DNA virus, herpes simplex virus 1 (HSV-1), and exhibited increased production of IFN-β, IL-6, and interferon-stimulated genes (ISGs) upon HSV-1 infection. Stimulation with the cGAS agonist G3-YSD or the STING agonist cGAMP also resulted in increased production of IFN-β, IL-6, and ISGs in TAX1BP1-KO THP-1 and BMDMs. Furthermore, cGAMP-induced STING signaling was enhanced in TAX1BP1-KO cells as shown by increased phosphorylation of STING, TBK1, and IRF-3. STING degradation was also impaired after cGAMP stimulation in TAX1BP1-deficient BMDMs suggesting that TAX1BP1 attenuates cGAS-STING signaling by promoting STING degradation. Both cGAS and STING form aggregates when activated, and TAX1BP1-KO cells accumulated protein aggregates upon HSV-1 infection or cGAMP stimulation. TAX1BP1 interacted with both cGAS and STING basally, and these interactions were enhanced upon stimulation with the STING agonist diABZI. Together, these results suggest that TAX1BP1 inhibits the cGAS-STING pathway, potentially by clearing cGAS and STING aggregates through the autophagy pathway.

This work was supported by R01 grant (RO1AI162815) funded by the National Institutes of Health (NIAID).

Venugopal Vangala, PhD
Advisor: Gavin P Robertson, PhD
Department: Pharmacology

Poster #23

Rapid Phenotypic Drift in Cancer Cell Subpopulation Contributes to Tumor Cell Heterogeneity Facilitating Resistance to Anti-cancer Agents

Venugopal Vangala[1], Saketh S. Dinavahi[1], Nazir A Lone[1], Yu-chi Chen[1,] Krishne Gowda[1], Meenhard Herlyn[3], Joseph Drabick[4], Klaus Helm[2], Jiyue Zhu[5], Rogerio Neves[9], Arthur Berg[6], Arun Sharma[1], Shantu Amin[1], Todd Schell[7], and Gavin P. Robertson[1,2,8,9,10,11,12].

[1]Department of Pharmacology, [2]Department of Dermatology, [4]Department of Medicine, [6]Department of Public Health Sciences, [7]Department of Microbiology and Immunology, [8]Department of Pathology, [9]Department of Surgery, [10]Foreman Foundation for Melanoma Research, [11]The Melanoma Center, [12]The Melanoma Therapeutics Program, The Pennsylvania State University College of Medicine, Hershey, PA 17033;
[3]Molecular & Cellular Oncogenesis Program and Melanoma Research Center, The Wistar Institute, Philadelphia, PA, 19104;
[5]Department of Pharmaceutical Sciences, Washington State University College of Pharmacy and Pharmaceutical Sciences, Spokane, WA 99202;

Drug resistance is a major problem limiting cancer treatment, and this study identifies a new form mediated by rapidly drifting cell subpopulations having distinctive phenotypic states that cooperatively provide the entire tumor population with a proliferative survival advantage. This type of drug resistance occurs rapidly through the interconversion between cell states and preventing it would require targeting the cells' ability to interconvert between these phenotypic states, which might require the development of a new category of anti-cancer agents.
Within solid tumors, cell subpopulations exist having distinct phenotypic states, which cooperate to provide the tumor with a survival advantage. To enable this form of functional cooperation, subpopulations reach distinctive equilibria in the proportion of cells having various phenotypes. The mechanisms and processes leading to the establishment of cooperative equilibrium are poorly understood. Here, the mechanism leading to dynamic phenotypic population drift is unraveled biologically using a model of coexisting $ALDH^{high}$ and $ALDH^{low}$ cell populations present in tumors and cultured cell lines. The $ALDH^{high}$ stem-like cells subpopulation existed in a state of constant flux, changing rapidly in size arising de novo from non-stem-like $ALDH^{low}$ cells to enable optimal proliferative expansion of the tumor. Changes in the size of the $ALDH^{high}$ phenotypic cell state functionally altered aldehyde and ROS levels to achieve a novel form of drug resistance mediated by the subpopulations reaching distinctive equilibria in relation to one another.

This research was funded by the Foreman Foundation for Melanoma Research; the Geltrude Foundation; the Penn State Chocolate Tour Cancer Research Fund; and NIH grant R01DK015658.

Tiaosi Xing, PhD
Advisor: Kirsteen Browning, PhD
Department: Neural and Behavioral Sciences

Poster #24

The Nigro-Vagal Modulation Of The Proximal Colon Is Compromised In A Model Of Environmental Parkinson's Disease

Tiaosi Xing#, Giorgia Nanni#, Cameron R. Burkholder#, Kirsteen N. Browning#, and R. Alberto Travagli*

#Department of Neural and Behavioral Sciences,
Penn State College of Medicine, Hershey, PA and
*Neurobiology Research, Newport, NC

Parkinson's Disease (PD) is a prevalent neurodegenerative disease characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which results in tremor, rigidity and bradykinesia. Up to 80% of the PD patients suffer from constipation about 10 to 20 years before experiencing motor symptoms. We previously reported that a monosynaptic pathway connects SNpc to neurons of the dorsal motor nucleus of the vagus (DMV). This monosynaptic pathway modulates the vagal control of gastric and proximal colon motility, and gastric motility is impaired in an environmental model of parkinsonism, induced by oral administration of subthreshold doses of paraquat (P) and lectin (L) (PMID 30302391). The current study was designed to test the hypothesis that nigro-vagal modulation of the proximal colon is compromised in the oral P+L model of parkinsonism.

Proximal colonic motility and tone were recorded in age-matched male rats via a strain gauge aligned with the colonic circular smooth muscle, approximately 3 cm distal to the ileal-cecal valve. Activation of SNpc neurons via microinjection of the ionotropic glutamate selective agonist, NMDA, increased proximal colonic motility (187±52.6% of baseline, n=13; Paired t test, $p<0.0001$) and tone (323±97.2mg, n=14). In our rat model of environmental parkinsonism, baseline colonic motility (155.2±49.6mg, n=5) showed no change compared to control rats (146.6±67.8mg, n=5; Unpaired t test, p=0.0387), however, the ability of NMDA-induced SNpc activation to increase colonic tone and motility was decreased (tone 303.4±70.8mg, n=5 vs 500.8±207.5mg in control rats, n=5; unpaired t test, p=0.0395; motility 139.8±24.8% of baseline, n=4 vs 222.6±62.9% of baseline of the age matched control rats, n=3; unpaired t test, p=0.0439). Gastro-cecal transit, measured using the ^{13}C lactose ureide-breath test, showed that transit time was increased in parkinsonian rats from 132.7±28 min (n=7) to 218.4±59.4 min (n=11; one-way ANOVA, p=0.0026). Chemogenetic inhibition of the nigro-vagal pathway attenuated the delay in transit in parkinsonian rats to 173.2±16.3 min (n=5; one-way ANOVA, p=0.2886 vs control rats).

These data suggest that intestinal transit is delayed, and the ability of the SNpc to modulate proximal colon motility and tone is attenuated in a model of environmental parkinsonism. Impairment of this nigro-vagal pathway may contribute to the severely reduced colonic transit and prominent constipation observed both in patients and in animal models of Parkinson Disease.

Mi Zhou, MD, PhD
Advisor: Yang Yang, PhD, Richard B. Mailman, PhD
Department: Pharmacology

Poster #25

Functional Selectivity-Related Dopamine D_1 Agonists Regulate Age-Related Working Memory

Mi Zhou[1], Jack X. Cimino[1], Richard B. Mailman[1], Yang Yang[1]

[1]The Pennsylvania State University College of Medicine, Department of Pharmacology, Hershey, PA, USA

D_1 agonists have been shown to enhance working memory (WM) in both animals and humans. The pattern of signal transduction mediated by a drug acting at a single receptor (functional selectivity) offers the possibility of developing novel therapies. Cyclic AMP (cAMP) and G protein-independent β-arrestin-related signaling are critical pathways for D_1 receptors. To investigate how signaling bias between cAMP and β-arrestin influences the rescuing effects of D1 agonists in age-related cognitive declines, two D_1 selective agonists (PF-06256142 (PF) and 2-methyldihydrexidine (2MDHX)) were examined. PF, a full agonist at cAMP, but with no intrinsic activity at β-arrestin recruitment; and 2MDHX, a full agonist at cAMP and a super-agonist at β-arrestin recruitment. Novel Object Temporal Order Recognition (NOR) tasks were conducted in Fisher rats of three age groups (4, 8, and 12 months). Our results have shown that the percentage of the time that rats spend exploring the novel object (i.e., a measurement of WM) in 4, 8, and 12 months rats are 71, 61, and 30%, respectively, indicating that age-related deficits in cognition are seen in these rats as in humans. In addition, compared to the vehicle group, PF caused a significant increase in WM in 12-month rats, whereas 2MDHX did not. In the dose-response study, 1 and 10 nmol/kg doses of PF improved WM, whereas 100 or 1,000 nmol/kg did not, consistent with the U-shape dose-response often seen in both murine and primate species. In addition, optimal doses of both PF and 2MDHX enhanced WM in 8 and 12 months rats, but not in 4 months. Finally, we found that rats whose baseline WM was lower showed improvement after D_1 agonists, whereas those with better WM did not (0.46 vs 0.82, $p=0.0018$), suggesting that D_1 agonists have a better effect on rats that have shown cognitive declines. Overall, our findings suggest a difference in how PF and 2MDHX affect age-related WM that may be related to their marked differences in signaling bias. The current study highlights the crucial influence caused by the functional selectivity of drugs and underscores the importance of detailed physiological mechanisms of D_1 ligands.

This work was supported by Children's Miracle Network Research Grant (2022–2023), the National Institutes of Health (RF1 AG071675), and the Penn State Translational Brain Research Center.

Follow the Penn State CoM Postdoctoral Society on Social Media

Twitter: @PSUCoMPostdoc https://twitter.com/PSUCoMPostdoc

Instagram: psucom_postdoc https://www.instagram.com/psucom_postdoc/

Facebook group:
Hershey Postdocs https://www.facebook.com/groups/439767336548787/about/

WhatsApp group for the Postdocs of College of Medicine: https://chat.whatsapp.com/JSvGNk3nOoP5ZoQXmb0oY2

Our goal is to give the CoM Postdocs as much visibility as possible. If you have news that you want to share (e.g., publications, awards, grants etc.), please feel free to tell us and we will post it!

"Connect" is the quarterly newsletter of the Penn State College of Medicine Postdoctoral Society. It brings to the community a glimpse into the activities, events and achievements of the post-doctoral fellows. From warm welcomes to new fellows to "Connect" them with their colleagues, to notifications about opportunities for professional growth and enrichment in upcoming quarters.

"Connect" is a professional platform that aims to bring you the recognition you deserve and an opportunity to showcase your work. Let us know about your publications, grants, awards that you receive or personal milestones, and we will highlight it in our spotlight section. We are keen to hear from you about your work. Write to us for a chance of an interview and let fellow colleagues learn from your experiences.

We invite everyone to write about what matters to you - arts, science, society, philosophy or life in general, or express yourself though photography or cartoons. We call for interesting science images from your research to be featured on the cover page. So, keep connected and look out for the next issue.

Rinki Kumar, PhD
Editor, *Connect*