Advancing Hispanics/Chicanos & Native Americans in Science

SACNAS Mid-Atlantic Regional Meeting

"Uniting Diverse Communities Through STEM"

Monday June 10th, 2019

University of Pennsylvania

Biomedical Research Building, 1st Floor Lobby

421 Curie Blvd.

Philadelphia, PA 19104

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Welcome Letter

Dear attendee,

On behalf of the SACNAS Chapter at the University of Pennsylvania, we welcome you to the Mid-Atlantic SACNAS Regional Meeting!

Today's meeting attracts trainees and faculty from across Philadelphia and the Mid-Atlantic region of the United States. The meeting consists of two keynote speakers from Penn, Dr. Shelley Berger and Dr. Ben Garcia. Interspersed between the speakers are a career panel, a professional development session on science communication lead by Dr. Dina Garcia and Dr. Jayatri Das, and a networking lunch for the trainees to interact with various faculty. Additionally, trainees will also have the opportunity to present posters on their research. This meeting is an excellent opportunity for students to present their work, network with scientists and peers across institutions, and learn about groundbreaking research being conducted in related fields.

The UPenn SACNAS Chapter was established in 2016 by enthusiastic graduate students hoping to promote diversity in STEM at the University of Pennsylvania and surrounding regions. Since its establishment, the Chapter has been very active in providing support and opportunities for growth to the Penn community, including monthly SACNAS Science Cafés, outreach opportunities, and scientific and professional development workshops. This year, our Chapter is excited to expand its reach by hosting a SACNAS Regional Meeting, where we hope to learn from our peers and foster a diverse scientific environment.

We encourage you to become a member of SACNAS. Your support makes events like this possible. We hope you enjoy today's meeting, and consider joining us for future UPenn SACNAS Chapter events!

Yours sincerely,

UPenn SACNAS Chapter Regional Meeting Planning Committee

#SACNASMidAtlantic19 #SACNASchapters

Sponsors

We would like to thank all of our sponsors for their generous contribution to this event. Their support was key to making this meeting possible.

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Meeting Schedule

THE 2019 MID-ATLANTIC SACNAS REGIONAL MEETING

Monday, June 10, 2019 • Biomedical Research Building Auditorium/Lobby

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8:30am Breakfast, Registration, and Poster Set-up

9:30am Welcoming Remarks

Nicole Hernandez & Vanessa Fleites, *Penn SACNAS Chapter Co-Presidents*

Drs. Arnaldo Diaz and Raquel Castellanos, *Office of Research & Diversity Training, Penn SACNAS Chapter Advisors*

9:45am Native American Blessing

Tina Fragoso, *Lenni-Lenapi Tribe, Associate Director, Equity and Access, Office of Undergraduate Admissions, University of Pennsylvania*

10:00am Keynote Lecture

Dr. Shelley Berger, *Daniel S. Och University Professor, Genetics, Cell and Molecular Biology Department, Perelman School of Medicine, University of Pennsylvania; Director, Penn Epigenetics Institute*

10:40am Career Panel - Beyond a PhD

With Scientists from: Academia, Industry, Teaching, Medical Writing, and Agency

12:00pm Networking Lunch

1:00pm Student Poster Session

2:45pm Science Communication Workshop

Dr. Dina Garcia, *2017 AAAS Mass Media Fellow, Assistant Professor, Department of Health Behavior and Policy, Virginia Commonwealth University*

Dr. Jayatri Das, *Chief Bioscientist, The Franklin Institute, Philadelphia*

4:15pm Keynote Speaker

Dr. Benjamin Garcia, *Presidential Professor of Biochemistry and Biophysics, Perelman School of Medicine, University of Pennsylvania*

4:45pm Poster Awards Announcement

4:55pm Closing Remarks

5:00pm Reception

Keynote Speakers Bios

Shelley L. Berger, Ph.D.

Shelley Berger, Ph.D., is the Daniel S. Och University Professor at University of Pennsylvania, and joined the Penn faculty in 2009. She is a member of the Departments of Cell & Developmental Biology, Genetics, and Biology. She serves as founding and current director of the Epigenetics Institute in the Penn Perelman School of Medicine. Dr. Berger earned her PhD from University of Michigan and was a post-doctoral fellow at Massachusetts Institute of Technology. She previously held the Hilary Koprowski Professorship at the Wistar Institute in Philadelphia. Dr. Berger's research focuses on epigenetic regulation of gene expression in cellular aging and senescence, in cancer, in learning and memory, and underlying organismal level behavior in ant societies. Dr. Berger is an elected member of the American Academy of Arts and Sciences, the National Academy of Medicine, and the National Academy of Sciences. She recently founded a company based on her research on brain epigenetics of learning and memory aimed at treatments for PTSD and addiction memory.

Ben Garcia, Ph.D.

Dr. Garcia received his Ph.D. in quantitative mass spectrometry based proteomics in 2005 at the University of Virginia under Donald Hunt, and then was an NIH Postdoctoral Fellow at the University of Illinois with Neil Kelleher from 2005-2008. From there Ben was appointed as an Assistant Professor in the Molecular Biology Department at Princeton University from 2008-2012, until his recruitment as the Presidential Associate Professor of Biochemistry and Biophysics at the University of Pennsylvania Perelman School of Medicine in 2012. He was promoted to full Professor in 2016, and named the John McCrea Dickson M.D. Presidential Professor in 2018. His research interests include using quantitative proteomics to characterize highly modified proteins, especially those involved in epigenetic mechanisms. He has published over 260 publications. Dr. Garcia has been recognized with many honors and awards for his research including an NIH Director's New Innovator award, the Presidential Early Career Award for Scientists and Engineers (PECASE), the Ken Standing Award, the American Chemical Society Findeis award and in 2018 the prestigious American Society for Mass Spectrometry Biemann Medal.

Career Development Speaker Bios

Dina Garcia, Ph.D.

Dina Tamar García is a Xicana scientist born in Guadalajara, Jalisco, México and raised in Milwaukee, Wisconsin. She currently serves as a tenure-track assistant professor in the Department of Health Behavior and Policy at Virginia Commonwealth University's School of Medicine. Her research, which aims to uncover the underlying causes and mechanisms of oral health inequities with the long term goal of developing interventions targeting different causal pathways, has been funded by the National Institute of Dental and Craniofacial Research (NIDCR) and the Delta Dental of Iowa Foundation. Her passion to make research findings accessible to the public led her to become a 2017 American Association for the Advancement of Science Mass Media Fellow. As a science writer, she covers public health topics for CNN Español, which has distribution to more than 40 million households in Latin America and more than 6 million households in the United States and Puerto Rico.

Jayatri Das, Ph.D.

Jayatri Das, Ph.D. is Director of Science Content and Chief Bioscientist at The Franklin Institute and an invited Fellow of the Center for Neuroscience & Society at the University of Pennsylvania. She has led development of two of the Institute's permanent exhibitions—Your Brain, a national award-winning exhibition about the neuroscience and psychology of the human brain, and SportsZone—and directs various programming initiatives to advance informal science education about areas of emerging science and their societal impact. She also serves as an advisor to the National Informal STEM Education (NISE) Network.

Arnaldo Díaz Vázquez, Ph.D.

Arnaldo Díaz Vázquez, Ph.D., is the Assistant Dean for Research Training Programs, Director of Recruitment and Retention of Diversity Scholars, Director of the Office of Research Training Programs, and Adjunct Assistant Professor in the Department of Systems Pharmacology and Translational Therapeutics. Among several functions as Assistant Dean, Dr. Díaz Vázquez works collaboratively with University leadership, Associate Deans and Directors, and program faculty to develop and implement targeted outreach, recruitment, and retention strategies aimed at increasing the number of students from underrepresented (UR) backgrounds pursuing PhDs in biomedical graduate programs. Dr. Díaz Vázquez works with and provides academic and professional career development for trainees from underrepresented backgrounds across the spectrum of undergraduate, post-baccalaureate, graduate, and postdoctoral programs in the biomedical sciences. He directs the Summer Undergraduate Internship Program (SUIP) and the Post-Baccalaureate Research Education Program (PennPREP). Dr. Díaz Vázquez is also the Co-Director of the Penn - Postdoctoral Opportunities in Research and Teaching (PennPORT) IRACDA Program and oversees diversity programming between Penn and partner teaching institutions (Lincoln University; Rutgers University, Camden; Delaware County Community College). He also serves as the Penn liaison for The Leadership Alliance, an academic consortium developing UR students into leaders, and represents Penn Medicine in developing research training partnerships across the University for recruitment, retention, and support of scholars with diverse backgrounds. These opportunities enable him to interact with highly qualified undergraduate and graduate students interested in pursuing studies in the biomedical sciences, as well as with colleagues from other institutions working toward the same goal nationwide.

Dr. Díaz Vázquez received a B.S. in Chemistry from the University of Puerto Rico-Río Piedras and was recruited to the Chemistry-Biology Interface Training Program at Texas A&M University in 2002. Dr. Díaz Vázquez received his Ph.D. in 2008 in the lab of Dr. Paul Cremer in the Department of Chemistry. During his Ph.D. studies, Dr. Díaz Vázquez was awarded the Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship (Parent F31) award. Following his Ph.D., Dr. Díaz Vázquez pursued postdoctoral training in Cancer Pharmacology at the University of Pennsylvania.

Francheska Colon-Gonzalez, Ph.D.

Francheska Colon-Gonzalez is a Senior Scientist in the Translational Pharmacology Clinical Operations group at Merck. During her 7 years in this role she has contributed to early development of drugs in several therapeutic areas including infectious disease, neuroscience, inflammation and diabetes. Before this role, Francheska completed a Clinical Pharmacology Fellowship at Thomas Jefferson University where she served as sub-investigator for phase 1 trials conducted at their Clinical Research Unit and also conducted research studying the potential link between obesity and colon cancer. Francheska holds a PhD in Pharmacology from the University of Pennsylvania and a bachelor's degree in chemistry from the University of Puerto Rico.

Sergio Nanita, Ph.D.

Sergio Nanita is currently a Principal Investigator at the Advanced Analysis department of DuPont Nutrition & Biosciences. As a mass spectrometrist, Sergio focuses on developing state-of-the-art analytical methods and providing structure elucidation expertise for the discovery and development of new DuPont products. Since 2006, Sergio has held various scientific roles across different departments of the company, providing analytical chemistry expertise to advance R&D programs at DuPont Crop Protection, DuPont Electronics & Imaging, DuPont Transportation & Advanced Polymers, and DuPont Nutrition & Biosciences. Sergio has been a volunteer at the American Chemical Society (ACS) for many years. Most recently, he served on the Committee on Ethics from 2012 to 2015, and he is currently a member of the ACS International Activities Committee and the ACS Committee on Corporation Associates. Sergio earned a B.S. in chemistry from the University of Puerto Rico in 2001 and a Ph.D. in analytical chemistry from Purdue University in 2005. He was recognized as one of the top 40 analytical chemists under 40 worldwide in the 2014 and 2018 Power Lists published by The Analytical Scientist magazine. Sergio has authored 30 publications and given 60 presentations/panel discussions, including 4 keynote lectures.

Deborah Stull, Ph.D.

Dr Deborah Stull is an Associate Director in the Post Baccalaureate Pre-Health Program in the College of Science of Technology at Temple University and faculty member (practice track) in the Department of Biology. She holds a degree in biology from Cornell University (BA, 1993) and a graduate degree in neurobiology from Yale University (PhD, 1998) and did her post-doctoral training at Harvard University. Before returning to Temple in 2016, Dr Stull worked in the field of medical communications/education as a medical writer and a medical writing manager. In these roles, she worked as part of a team to manage publications for global pharmaceutical companies, which included working as a strategic partner to develop publication plans and scientific platforms as well as liaising with key opinion leaders to facilitate the development of primary and secondary articles in peer-reviewed journals and abstracts, posters, and slides for presentation at national and international conferences and symposia. She was also a member of the teaching faculty at Temple University, where she taught courses in neuroscience and scientific writing and won the Dean’s Distinguished Teaching Award and the Lindback Award for Distinguished Teaching.

Teresa Ramírez, Ph.D.

Dr. Ramírez is currently the Diversity and Inclusion Policy and Outreach Specialist at the Office of Public Affairs at Federation of American Societies for Experimental Biology (FASEB). Dr. Ramírez a scientific influencer, mentor, first-generation and community role model that inspires many to obtain their dreams and goals regardless of any challenges that may arise. She has no limits and mentors many students from coast to coast. She actively participates in the Latino community as an advocate for Latinos in Science, Technology, Engineering and Mathematics (STEM). She is the first from her family to have graduated from college and to have obtained a doctorate degree in Molecular Pharmacology and Physiology from Brown University. She has been a long member of the Society for the Advancement of Hispanic/Chicano and Native Americans in Science (SACNAS), whose mission is to foster the success of Chicanos/Hispanics and Native Americans, in attaining advanced degrees, careers, and positions in leadership in STEM. Dr. Ramírez is passionate about sharing her love for science and firmly believes in the importance of mentorship and how it can create a positive impact in the lives of others as it did on hers.

Shivon Robinson, Ph.D.

Dr. Robinson attended Williams College, where she majored in Psychology and Biology. She then pursued her doctoral degree at the University of Pennsylvania, in the laboratory of Dr. Irwin Lucki at the University of Pennsylvania. After earning hed Ph.D., Dr. Robinson applied and was accepted into the Penn Postdoctoral Opportunities in Research Teaching (PORT) program, which combines a traditional postdoctoral research experience with mentored teaching experience. During this time, she conducted her postdoctoral work in the laboratory of Dr. Julie Blendy and also taught courses at Delaware County Community College and Rutgers University-Camden. This summer, she will be returning to Williams College as a tenure-track Assistant Professor.

Student Poster Abstracts

1. Izmarie Poventud-Fuentes

An endothelialized microfluidic platform to evaluate how bleeding stops after a puncture injury

Izmarie Poventud-Fuentes, Keon Woo Kwon, Maurizio Tomaiuolo, Timothy J. Stalker, Lawrence F. Brass, Dongeun Huh
University of Pennsylvania

Studies in mice have shown that hemostatic plugs that stop blood loss after a vessel injury have a heterogeneous structure. A gradient of agonists generated at the injury site results in differences in the extent of platelet activation and distribution of fibrin. To bridge the findings of studies in mice with hemostasis in humans, we developed a microfluidic platform that incorporates essential components of hemostasis and allow us to address specific questions about the contribution of these components to hemostasis. This blood-vessel-on-a-chip consists of three compartments: (1) “blood” channel where human blood is perfused over a confluent endothelial cells (ECs) monolayer, a (2) “vessel wall” made of a type I collagen 3D hydrogel that contains tissue factor (TF) as a procoagulant, and an (3) “extravascular” channel to create a pressure drop for blood leakage after a piercing injury a needle. Citrated human blood was recalcified and perfused at venous shear rate. Platelet accumulation and fibrin formation were monitored with real time fluorescence imaging. We found that after the ECs monolayer is injured and blood is perfused, a platelet rich plug seals the perforating injury within 10 minutes. Platelets selectively aggregate at the injury site and a subpopulation of platelets get activated. Greater fibrin formation and platelet activation is seen when TF is present in the hydrogel. Our system mimics key aspects of the hemostatic response seen in mice, including a platelet rich plug that stops blood loss and a heterogenous, but organized hemostatic plug structure.

2. Barbara Romero Dueñas

Subversion of Host Endocytic Trafficking

Barbara Romero Dueñas
University of Delaware

Legionella pneumophila is an opportunistic Gram-negative bacterium that causes Legionnaires’ disease, a type of pneumonia with increased severity for individuals with a weakened immune system. L. pneumophila is phagocytosed by alveolar macrophages and remains enclosed in a membrane-derived vacuole throughout infection. Its ability to survive and replicate in this compartment is due to the type IV secretion system that facilitates the translocation of over 300 effector proteins into the host cytosol. Many of these proteins function to subvert vesicular trafficking to hijack vesicles from the endoplasmic reticulum-to-Golgi trafficking pathway to camouflage the Legionella-containing vacuole (LCV). The L. pneumophila effector protein AnkX catalyzes a novel post-translational modification of Rab1 and Rab35 through covalent addition of a phosphocholine moiety to a serine residue on the target protein. Here, we broaden the understanding of AnkX function by presenting evidence that it disrupts endocytic trafficking. We determined AnkX’s subcellular localization to the plasma membrane and tubular membrane compartments by using superresolution microscopy and immunogold transmission electron microscopy. We observed that mcherry-AnkX colocalizes with Rab35, a Rab GTPase in charge to regulating the recycling of cargo back to the plasma membrane via the fast recycling pathway. Furthermore, we demonstrate that the phosphocholination activity of AnkX is critical for both disruption of endocytic recycling and for inhibiting fusion of the Legionella-containing vacuole with lysosomes. Finally, using the DQ Red BSA assay, we quantified the extent to which AnkX disrupts endocytic trafficking. Future studies will focus on understanding how AnkX disrupts endocytic trafficking and how it assists in lysosome evasion.

3. Jaimarie Sostre

Hepatic insulin signaling coordinates the adaptive response to cold

Jaimarie Sostre-Colón, Matthew Gavin, William Quinn III, Paul M. Titchenell
University of Pennsylvania

The ability to maintain body temperature in cold environments is essential for mammalian survival. The brown adipose tissue (BAT) plays an important role in the defense of body temperature through non-shivering thermogenesis. Upon cold exposure, the BAT uses glucose and fatty acids to convert chemical energy to heat through mitochondrial uncoupling protein 1 (UCP1). Activation of the thermogenic gene program and ample availability of substrates to fuel ensuing thermogenic response are necessary for proper BAT function. The liver has been shown to play a role in providing substrates to fuel non-shivering thermogenesis and to orchestrate systemic carbohydrate and lipid metabolism. The liver coordinates metabolism through insulin-dependent activation of the serine/threonine kinase Akt.

4. Matias Escobar

JAK-STAT Signaling Modulates the Survival of Cancer Cells in Dormancy

Matias Escobar-Aguirre, Takashi Nakamura, Francesco Marino, Tien-Chi Pan, Dhruv Pant, Lewis Chodosh
Cancer Biology Department, Perelman School of Medicine, University of Pennsylvania

Breast cancer is the leading cause of cancer mortality in women, mainly due to incurable metastatic recurrence arising after initial treatment. Recurrent tumors arise from a presumptive pool of residual tumor cells (RTCs) that persist in a dormant state after treatment. The mechanisms enabling dormant tumor cell survival and recurrence are poorly understood. Hence, identifying the pathways underlying tumor dormancy and recurrence is critical to reduce breast cancer mortality. Our laboratory has developed genetically modified mouse models for human breast cancer that recapitulate key steps during breast cancer progression. Transgenic mice that conditionally express the HER2/neu oncogene (MTB/TAN mice), develop mammary tumors upon oncogene induction, and conversely, tumors regress following oncogene down-regulation. However, a small number of RTCs survive oncogene inhibition and persist in a dormant state, and ultimately seed spontaneous recurrent tumors. To explore potential pathways that may be required for RTCs survival during dormancy, our lab generated gene expression data sets from MTB/TAN derived tumor cells in dormancy. Moreover, we developed an in vitro (IVD) assay that faithfully recapitulates cell cycle progression and gene expression patterns observed during in vivo dormancy. Our observations suggest that JAK-STAT signaling is activated during dormancy; we hypothesize that JAK-STAT signaling inhibition impairs the survival of dormant cells. We aim to define the impact of JAK-STAT inhibition in residual disease and tumor recurrence, and to elucidate the mechanism of JAK-STAT activation in dormant cells. Altogether, these studies have the potential to uncover new treatments for breast cancer patients by targeting the susceptibilities of dormant tumor cells.

5. Mariel Mendoza

TRIM28 as a candidate mutant p53 interacting partner in cancer cells

Mariel Mendoza, Katherine Alexander, Enrique Lin Shiao, Charly Ryan Good, Benjamin A. Garcia, Shelley L. Berger
University of Pennsylvania

p53 is a transcription factor that is mutated in over 50% of cancers. Missense mutations in the DNA binding domain of p53 can result in a gain-of-function (GOF) phenotype, leading to increased cell proliferation and tumor formation. Our lab previously showed that prevalent mutant p53 (mtp53) forms modify chromatin through their interaction with ETS2 and activation of non-canonical transcriptional targets (MOZ, MLL1, and MLL2). Aside from ETS2, other mtp53 partners that have been identified, including Sp1, NF-Y, and PML. However, whether specific proteins are critical for the stability and the GOF effect of mtp53 remains to be seen. To this end, we developed a quantitative mass spectrometry-based strategy, combined with molecular and genomic approaches, to identify and validate novel mtp53 binding partners from cancer cell

lines with varying GOF p53 mutations. Our preliminary data identified the transcriptional corepressor TRIM28 as a candidate mtp53 interacting partner, as it was identified in all 4 GOF cell lines tested (VU1365, HUPT3, MDA468, and PANC1). Knockdown of TRIM28 in MDA468 cells caused a decrease in cell viability. TRIM28 has been shown to interact with MDM2 to promote wild type p53 ubiquitylation and degradation; however, its role in regulating mtp53 has not been determined. Ultimately, our studies will identify and validate further novel proteins critical for the GOF activity of mtp53. Characterizing these novel interacting partners of mtp53 will shed light into the molecular mechanisms underlying cancer and thus will provide new therapeutic targets to destabilize mutant p53 interactions in cancer cells.

6. Kahealani Uehara

Regulation of Phosphatidylcholine Synthesis by mTORC1

Kahealani Uehara, Matthew Gavin, Paul Titchenell
University of Pennsylvania

Non-alcoholic fatty liver disease (NAFLD) is now recognized as the leading cause of liver transplants affecting 25% of the world population. NAFLD can progress to a more severe form of liver disease, non-alcoholic steatohepatitis (NASH). Currently, there are no FDA approved treatment for NAFLD and NASH. In the liver, insulin regulates hepatic lipid homeostasis by increasing de novo lipogenesis, suppressing breakdown of fatty acids and promoting TAG esterification. VLDL-TAG production and its subsequent secretion from the liver is controlled by the biosynthesis of phosphatidylcholine (PC), the main phospholipid coating lipoproteins. Defects in PC synthesis lead to decreased VLDL-TAG secretion and ultimately, hepatic steatosis. Our lab recently demonstrated that downstream of PI3K/Akt signaling, mammalian target of rapamycin complex 1 (mTORC1) controls VLDL-TAG secretion through regulating CCTα, the rate-limiting enzyme in PC synthesis. Therefore, the goals of this study are (1) to elucidate the relationship between mTORC1 and CCTα protein, and their subsequent control of hepatic PC synthesis, and (2) to determine whether this mechanism can be exploited to treat NASH. I hypothesize that mTORC1 directly phosphorylates and stabilizes CCTα to control PC synthesis and that in vivo activation of mTORC1 will be sufficient to prevent NASH. Here, we identify Ser315 as a phosphorylation residue regulating CCTα activity and protein levels, and as a potential substrate of mTORC1. Additionally, we demonstrate that activation of mTORC1 prevents steatosis, inflammation, fibrosis, and liver damage in an inducible NASH mouse model.

7. Andrea Acevedo

Development of novel inhibitor in the MAPK pathway

Andrea Acevedo, Mike Grasso, Ronen Marmorstein
University of Pennsylvania

In melanoma and other cancers, the mitogen-activated protein kinases (MAPK) pathway is a key oncogenic signaling system that often stimulates uncontrolled cell growth. Unfortunately, current medical treatments targeting key kinase proteins in this pathway (BRAF or MEK) produce drug resistance which motivates the search for alternatives in cancer therapy. Here we develop novel small molecule kinase inhibitors that simultaneously target both BRAF and MEK, an unexplored strategy so far to understand MAPK signaling, which can likely lead of new melanoma therapies.

8. Julian Stoute

A journey of an RNA dimethyladenosine methyltransferase finds its substrate(s)

Julian Stoute, Hui Shen, Kathy Liu
Department of Biochemistry and Molecular Biophysics, University of Pennsylvania

Chemical modifications of RNA play an important role in their processing, structure, and biological functions. Research into RNA modifications has mainly been focused on tRNA and rRNA while non-coding RNAs and mRNA are poorly characterized for the most part. Our research has found that the writer enzyme dimethyl adenosine methyltransferase 1 (DIMT1), a writer protein established to create the N-6,6-methyladenosine (m6,6A) modification in rRNA, is additionally capable of modifying mRNAs. This new function of DIMT1 has led to new exciting discoveries in the biological function of

DIMT1 and the roles it plays in translation and glioblastoma. In addition, we have obtained the structure of DIMT1 through x-ray crystallography which has provided insights into both the RNA and SAM binding sites. Our findings suggest an oncogenic role of DIMT1 through the promotion of mRNA translation.

9. Leon Morales

Utrophin Vector Protected by Central Tolerance as Potential Cure for Muscular Dystrophy

Leon Morales, Yafeng Song, Alock Malik, Mihail Petrov, Margaret E. Choi, Marilyn A. Mitchell, Tejvir S. Khurana, Joe N. Kornegay, Hansell H. Stedman
University of Pennsylvania

The essential protein product of the Duchenne muscular dystrophy gene is dystrophin, a rod-like 427 kD protein that protects striated myocytes from contraction-induced injury by linking the cortical cytoskeleton to the extracellular matrix. Most patients with DMD have multi-exon frame-shifting deletions, while many with the milder allelic disease Becker MD have frame-preserving mutations that change the length of dystrophin's 150 nm rod domain. Utrophin, a dystrophin paralog, retains many of the structural and protein binding elements of dystrophin. Importantly, normal thymic expression in DMD patients should protect utrophin by central immunologic tolerance. Leveraging a deep analysis of dystrophin's molecular evolution with a focus on the stability of the rod domain, we designed a codon-optimized, synthetic transgene encoding a 25 nm miniaturized utrophin (μUtrophin), deliverable by AAV vectors. Here we show that μUtrophin is a highly functional, non-immunogenic substitute for dystrophin, preventing the most deleterious histological and physiological aspects of muscular dystrophy in small and large animal models. Following systemic administration of an AAV-μUtrophin to neonatal dystrophin-deficient mdx mice, all histological and biochemical markers of myonecrosis and regeneration are completely suppressed throughout growth to adult weight. In the dystrophin-deficient Golden Retriever model, μUtrophin non-toxically prevented myonecrosis even in the most powerful muscles. In a stringent test of immunogenicity, focal expression of μUtrophin in the deletional-null German Shorthaired Pointer model produced no evidence of cell-mediated immunity, in sharp contrast to the robust T cell response against similarly constructed μDystrophin. These findings support a model in which utrophin-derived therapies can be used to treat clinical dystrophin deficiency, with a favorable immunologic profile and preserved function in the face of extreme miniaturization.

10. Mariana Argenaziano

High Resolution Genome-wide Promoter-focused Connectome Implicates Microglia Causal Genes for Alzheimer's Disease

Mariana Argenziano, Elisabetta Manduchi, Sheridan Littleton, Michelle E. Leonard, Chun Su, Sumei Lu, Kenyaita M. Hodge, James A Pippin, Gerard D. Schellenberg, Matthew E. Johnson, Andrew D. Wells, Struan F.A. Grant, Alessandra Chesi
Children's Hospital of Philadelphia, University of Pennsylvania

Background: Microglia plays a central role in the pathogenesis of Alzheimer's Disease (AD). Genome-wide association studies (GWAS) have identified multiple genomic variants associated with inflammation and microglial immune response. However, GWAS signals associated with a trait are not necessarily the precise localization of culprit effector genes. High-resolution chromatin conformation capture-based techniques offer a valuable tool to understand GWAS signals that reside in non-coding regions. Method: We used a high-resolution Capture-C characterize the physical genome-wide interactions of all human promoters in HMC3 cells. A custom Agilent library was designed to target both ends of DpnII restriction fragments that overlap promoters of both protein-coding and noncoding transcripts. In parallel, we generated ATAC-seq open chromatin maps to filter for informative proxy single nucleotide polymorphisms (SNPs) for each of 38 AD common independent sentinel SNPs reported to date. Result: ATAC-seq yielded 43 candidate SNPs in open chromatin for 14 of these loci. By further constraining on our promoter connectome data, at both one and four DpnII fragment resolution (median distance between interacting regions 24kb and 122kb; median region size = 265bp and 1,441bp), we observed contacts to "open" promoters for 12 putative target genes, relevant to four of the original GWAS loci. These included RTFDC1 at the 'CASS4' locus and MADD and PACSIN3 at the 'CELF1' locus. Conclusion: We observed

informative contacts between proxy SNPs and putative effector genes for ~11% of AD GWAS loci in the human microglia-specific context. Further efforts in other relevant cell types should shed light on additional signals.

11. Kimberly Milla

Developmental differences in prefrontal cortex activity during performance of the Tower of Hanoi puzzle - a fNIRS study

Kimberly Milla[1,2], Elham Bakhshipour[1,2], Amanda Plumb[4], Barry Bodt[3], Reza Koiler[1,2], Nancy Getchell[1,2]
[1]Biomechanics and Movement Sciences Interdisciplinary Program, University of Delaware; [2]Developmental Motor Control Laboratory, Department of Kinesiology and Applied Physiology, University of Delaware; [3]Biostatistics Core, College of Health Sciences, University of Delaware; [4]School of Health and Life Sciences, Federation University Australia, Ballarat, VIC, AUS

Our group has characterized hemodynamic activity in the prefrontal cortex (PFC) during the Tower of Hanoi (ToH) task in adults, however to our knowledge this has not been investigated in children. We examined PFC activity in typically developing (TD) children using functional Near-Infrared spectroscopy (fNIRS) as they solved ToH puzzles. Two conditions were presented to participants; the first condition utilized a traditional 3D model requiring manual manipulation. The second condition used a 2D computerized model that presented equivalent executive function demands yet with diminished motor requirements. We aimed to further understand the PFC role in these two ToH conditions in children. Seventeen TD children (5F/12M, $\bar{x}$ = 10.8 ± 2.0 y.o) solved puzzles in 2 blocks of 3, 1-minute epochs. Participants had a mean MABC-2 percentile of 55.9. Data were analyzed using a mixed effects ANOVA with participants nested within blocks, and within factors of 2D vs 3D. In accordance to adult data, results showed a significant interaction between blocks and conditions, p = 0.0023, meaning that participants that began the protocol with 3D had significantly lower ΔHbO in their second block. Contrary to findings in adults, ΔHbO between conditions and blocks was not significantly different. In conclusion, this study supports evidence where learning and performance benefited the most by introducing the most complex condition first, followed by the simpler condition. This knowledge about developmental differences in PFC activity will guide future research to discern the areas of impairment on the perception-cognition-action continuum in developmental disabilities, such as DCD.

12. Solymar Rolón-Martínez

Amygdala-TRN projections amplify tone-evoked activity in auditory thalamus and cortex.

Solymar Rolón-Martínez, Mark Aizenberg, Maria N. Geffen
University of Pennsylvania

Associating emotional responses with sensory cues can lead the nervous system to alter behavior to future representations of these cues. Here, we identify a novel pathway between the baso-lateral amygdala (BLA), an emotional learning center in the brain, and the thalamic reticular nucleus (TRN), and demonstrate that activation of this pathway amplifies sound-evoked activity in the central auditory pathway. We stimulated BLA using channelrhodopsin (ChR2) while recording neuronal activity in the auditory cortex (AC) in response to a presentation of random tone sequences in awake, head-fixed mice. Optogenetic activation of the BLA suppressed spontaneous activity (paired t-test, p=0.0007), while amplifying tone-evoked response amplitude in AC (paired t-test, p=8.5e-5, n= 8). Inspection of fluorescence following Retrobead injections in TRN revealed direct projections from BLA to TRN. We next directly activated projections from the BLA to TRN by positioning the optic cannula over TRN. We found that there was a significant suppression of spontaneous activity (paired t-test, p=0.003, n= 7), and a significant increase in tone-evoked responses in AC (paired t-test, p=3.9e-8) and in the auditory thalamus (Medial Geniculate Body, MGB) (paired t-test, p=3.4e-7, n = 5). These results are consistent with the hypothesis that the changes in AC responses with BLA activation are a result of projections from BLA to TRN via MGB. We demonstrate a possible novel circuit mechanism for amplification of sensory representation of behaviorally relevant signals and provide a potential target for treatment of neuropsychological disorders, in which emotional control of sensory processing is disrupted.

13. Claudia Lopez-Lloreda

Role of the unfolded protein response in mediating levels of amyloid precursor protein secretases in HIV-induced neurotoxicity

Claudia Lopez-Lloreda , Cagla Akay-Espinoza, Kelly L. Jordan-Sciutto
Department of Pathology, School of Dental Medicine, University of Pennsylvania

Aging is increasingly appreciated as a contributor to HIV-associated neurocognitive disorders (HAND). Accumulation of plaques composed of amyloid-beta (Aβ) is observed in aging-related neurodegenerative disorders. Aβ is produced by the cleavage of amyloid precursor protein (APP) by BACE1, which is precluded by cleavage of APP by ADAM10. Aβ accumulation and increased BACE1 levels were observed in HAND models, and excitotoxic injury was shown to decrease ADAM10 levels, suggesting increased amyloidogenic and decreased non-amyloidogenic processes as potential contributors to HIV-mediated neurotoxicity. In models of AD, BACE1 upregulation was shown to be mediated by the unfolded protein response kinase PERK. We hypothesized that APP processing is dysregulated by changes in BACE1 and ADAM10 and that this is mediated by the PERK pathway in HIV-induced neurotoxicity. Primary rat neurons were treated with HIV-infected monocyte-derived macrophages supernatants (HIV/MDMs), NMDA, or a PERK activator (PA) with or without 1-h PERK inhibitor pre-treatment. ADAM10 levels were lower in cultures treated with HIV/MDMs, NMDA, and PA, compared with untreated cultures. HIV/MDM- and NMDA-mediated decreases were further exacerbated by PA treatment. NMDA and PA led to an increase in BACE1 levels in treated cultures compared to untreated cultures. Similarly, BACE1 levels were increased in cultures treated with both NMDA and PA compared with individual treatments. Importantly, HIV/MDM- and NMDA-mediated toxicity was attenuated by PERK inhibition and exacerbated by PERK activation. These results suggest a reduction in the non-amyloidogenic APP processing might be contributing to HIV-related neurotoxicity, which could be exacerbated by activation of the PERK pathway.

14. Natalia Quijano Cardé

Investigating the Efficacy of GluK1-containing Kainate Receptor Inhibition to Treat Alcohol Addiction

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Alcohol use disorder (AUD) is a serious neuropsychiatric condition affecting millions of people worldwide. The heterogeneity of the disease underscores the need to expand the number of pharmacotherapeutics to treat AUD patients. Topiramate (TPM) is an antiepileptic drug that has been shown to modulate ethanol drinking patterns in humans. TPM has many pharmacological targets and affects many cellular processes and, therefore the molecular target for its effects on AUD is not clear. Among several mechanisms, TPM acts as a non-selective antagonist of kainate receptors containing the GluK1 subunit (GluK1*KARs), which is encoded by *GRIK1* in humans. Interestingly, pharmacogenetic studies have shown that a single nucleotide polymorphism (SNP, rs2832407) in *GRIK1* exerts an influence on the predisposition to develop alcohol dependence and modulates the efficacy of topiramate treatment to reduce drinking. Thus, our study examined the ability of LY466195-mediated selective inhibition of GluK1*KAR to modulate responses to alcohol in a mouse model of alcohol dependence. Our results indicate that selective GluK1*KAR inhibition reduces ethanol intake and preference in mice undergoing short-term (24-h) and protracted (1 week) withdrawal in a dose-dependent manner. In mice undergoing short-term withdrawal, 20 mg/kg LY466195 treatment was sufficient to attenuate the manifestation of physical signs of withdrawal. Interestingly, we observed that chronic ethanol exposure in the intermittent two-bottle choice drinking paradigm affects the rewarding properties of ethanol as measured in the conditioned place preference (CPP) paradigm and with *in vivo* accumbal microdialysis. While mice chronically treated with ethanol in the I2BC failed to acquire/display ethanol CPP (1.5 g/kg ethanol), an acute administration of LY466195 (20 mg/kg) was sufficient to rescue the response observed in alcohol-naïve mice. We also found that LY466195 injection normalized dopamine responses to acute ethanol injection in mice undergoing short-term withdrawal from the I2BC. In summary, our data suggest that GluK1*KARs play an

important role in modulating the reinforcing properties of ethanol that maintain addiction. Overall, our findings support the hypothesis that GluK1*KARs represent an attractive pharmacological target for the treatment of AUD.

15. Wisberty Gordián Vélez

Engineered Dopaminergic Axonal Tracts within a Tubular Hydrogel Encasement

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Parkinson's disease (PD) is a disorder characterized by tremors, slowness of movement, and rigidity. Symptoms emerge from the degeneration of dopaminergic (DA) neurons in the substantia nigra, resulting in reduced dopamine input to the striatum. Current treatments, such as L-DOPA therapy and deep brain stimulation (DBS), focus on mitigating symptoms without addressing the cause. Our approach consists on fabricating micro-tissue engineered neural networks (TENNs) for implantation from the cortical surface to the striatum and using them as axon-based "living DBS", restoring the lost dopamine in a controllable manner upon optical stimulation. These micro-TENNs were created by isolating embryonic rat DA neurons, aggregating them, and transducing them to express light-responsive ion channels and seeding an aggregate within the lumen of a micro-column made of agarose or photo-crosslinked methacrylated hyaluronic acid hydrogel. With long-term culture, these neurons extended axons along the extracellular matrix-filled lumen, similar to the cytoarchitecture of the nigrostriatal pathway and reaching ~9 mm by 30 days. For validation in vitro, confocal microscopy demonstrated integration between DA axons and striatal aggregates, and ChR2-transduced micro-TENNs exhibited optically-evoked dopamine release. Proof-of-concept studies showed that after 1 week in vivo micro-TENN neurons can survive, maintain their structure, and integrate with host tissue. In future studies, we will functionalize our hydrogel with pro-survival signaling cues for improved in vivo performance and transition to the use of human stem cell-derived neurons as the cell source. Ultimately, we seek to assess the capacity of micro-TENNs to restore striatal dopamine and improve motor control in PD rats following optical stimulation.

16. Erika Davidoff

Self-Assembling Hydrogel Coatings for Improving Brain Implant Biocompatibility

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Common treatments for epilepsy, tremor, Parkinson's disease, and other neurological disorders involve implanting electrodes into specific brain nuclei. However, these treatments' effectiveness is hampered by the brain's inflammatory foreign body response to the implant. Hydrogel coatings for implanted electrodes may attenuate these factors as gels' elastic moduli more closely resemble brain tissue. The coatings are also able to absorb energy to cushion the tissue. Covalently linked hydrogels such as poly(ethylene glycol) diacrylate (PEGDA) are strong candidates due to availability and biocompatibility; however high strains can permanently sever their covalent bonds. In addition to these coatings, we are investigating non-covalently linked gel systems such as guest-host networks held together by hydrophilic/hydrophobic interactions, and we have been developing a custom in vitro bioreactor that accurately and reliably simulate the 2 Hz, 30μm increments that have been found to represent micromotion in the brain to compare the effectiveness of each type of soft hydrogel coating. We have also begun quantitatively characterizing strain fields around uncoated and PEGDA-coated probes using particle image velocimetry. Our inexpensive bioreactor proves a robust tool for quantitatively comparing hydrogel coatings for brain probes in vitro, reducing the need for more extensive in vivo testing. We are presently synthesizing non-covalently linked gel networks including guest-host interaction-based gels, polymer-nanoparticle gels, and peptide beta sheet networks, and will be analyzing their efficacy at reducing foreign body response using this bioreactor with the fluorescent bead agarose and 3D cell culture tissue mimics.

17. Yoliem S. Miranda Alarcon

A Thermoreversible and Photoactive Collagen-Based Scaffold for Tissue Engineering Applications

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Rutgers University

In addition to its innate bioactivity, structural anisotropy, and superior biocompatibility, collagen is a major biomaterial of interest for tissue engineering because of the versatility imparted by its chemical composition. Collagen has been used as a building block to develop scaffolds, but its weak mechanical properties serve as a major impediment. To this end, we have synthesized collagen methacrylamide (CMA) by adding methacrylate groups to lysine residues on type-I collagen, which renders the collagen photoactive; CMA can be rapidly crosslinked through exposure to UV light in the presence of a photoinitiatior. Functionalization with methacrylamide groups also imparted a second, serendipitous property that makes CMA a unique material for 3D printing scaffolds. Like collagen, CMA can self-assemble into fibrillar hydrogels at physiological pH and temperature, but unlike collagen, CMA reversibly disassembles into a liquid macromer suspension when temperature is lowered to 4oC. Photocrosslinking after self-assembly eliminates thermoreversibility. Combined, these two properties enable a number of exciting applications, such a 3D printing and cell encapsulation. We have tested the potential for cell encapsulation of CMA using mesenchymal stem cells (MSCs) due to the cell's potential to differentiate into a variety of cells. We are leveraging from the innate mechanosensitivity of stem cells to develop a matrix with tunable stiffness to differentiate cells. In this work, we assess the optimization of the conditions for UV-crosslinking including UV exposure time and photoinitiator concentration. Preliminary data indicates good cell viability of MSCs encapsulated in CMA hydrogels.

18. Khadija Wilson

Understanding epigenome and proteome remodeling caused by novel germline histone H3.3 mutations during neurodevelopment

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Histone H3.3 (H3.3) is a histone variant that plays a role in cellular inheritance as ablation of H3.3 expression leads to loss of active gene states and dysfunction of heterochromatin telomeric structures. H3F3A and H3F3B, the two genes known to encode H3.3, are ubiquitously expressed in all human cells with higher expression in the ovaries, testes, uterus and brain. Somatic mutations in the H3F3A genes have been reported as oncogenic drivers of pediatric glioblastomas. More recently, here at the Center for Applied Genomics at the Children's Hospital of Philadelphia novel germline mutations in both H3F3 genes have been discovered in a small cohort of patients who suffer from a common pattern of neurodevelopmental disorders, seizures and craniofacial abnormalities. Here we hypothesize that mutant H3.3 (mH3.3) change the regulatory capacity of mH3.3 containing chromatin and therefore modulate gene expression and ultimately the cellular proteome. To this end, we developed stable murine astrocyte cell lines expressing either wild type H3.3 or mH3.3 (G90R, T45I) to study by quantitative mass spectrometry the histone post translational modification changes to the mH3.3 containing nucleosomes and subsequent proteome alterations. Our preliminary data has identified downregulation of chromatin remodeler proteins, as well as upregulation of mitochondrial proteins following reprogramming of the reprogrammed mH3.3 encrusted epigenome. Ultimately, our studies aim to identify and validate potential epigenetic and proteome-wide factors involved in these novel neurodevelopmental disorders. Understanding the basic mechanisms of how these new histone mutations function in neurodevelopment may allow re-classification of epigenome reprogramming in neurological contexts.

19. Elelbin Ortiz

The role of synaptotagmin 7 (syt7) isoforms in establishing the acoustic startle threshold

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Behavioral thresholds are the point at which stimuli are sufficient to elicit a response from an organism. Proper establishment of baseline behavioral thresholds during development is critical for proper responses to the environment, including for threat detection. The acoustic startle response is a highly conserved behavior that demonstrates acute regulation of its threshold by sensory experience, as well as a species specific, baseline threshold. Dysregulation of the startle threshold is a hallmark of a variety of neurodevelopmental disorders, but despite its clinical and biological significance, the molecular and genetic mechanisms underlying establishment of the startle threshold are unknown. Zebrafish are an excellent model organism for understanding how the acoustic startle threshold is established due to the conserved behavior and underlying circuits of the acoustic startle response among vertebrates. Through a forward genetic screen, the Granato lab identified five zebrafish mutant lines that exhibit a lowered baseline acoustic startle threshold (Marsden et al, 2018). Through linkage analysis using RNA sequencing, we identified a single base pair change in a single isoform of synaptotagmin 7a (syt7a) as the potential causative mutation in the escapist mutant line. syt7a encodes for a calcium binding protein important for vesicle release and recycling at synaptic terminals. Using gene editing, I am generating an independent mutation in syt7a to confirm its role in establishing the startle threshold. I am also generating transgenic lines that express syt7a in different startle circuit cell types to identify where syt7a is sufficient to establish the startle threshold. Overall, this project will provide understanding of the role of a synaptic protein in establishing an acoustic behavioral threshold.

20. Christopher Salazar

A Novel Rab GTPase Restricts Dendritic Branching

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Dendrite development depends on numerous extracellular and intracellular cues to ensure proper structure and function. However, the regulatory mechanisms of dendrite development remain incompletely understood. To better understand dendrite development, we are utilizing the PVD somatosensory neuron with its highly stereotyped 'menorah'-like dendrites. The Menorin genetic pathway consists of several factors that function from different tissues to promote PVD dendrite development. While progress has been made in understanding factors that promote formation of dendritic branches, much less is known about factors that restrict branching. During a genetic screen, we have identified a locus that encodes for a putative, uncharacterized Rab GTPase, which we name rab-X. Time course analyses determined that the number of branching points was significantly increased in adult animals. This suggests rab-X suppresses dendritic branching into adulthood. A transcriptional reporter shows expression to be in the epidermis from early embryonic through adult stages and transgenic expression of a rab-X cDNA in the epidermis is sufficient to rescue the mutant phenotype. Genetic analyses show that the Menorin pathway is largely epistatic to rab-X, indicating it may function in the same genetic pathway. In addition, we found that a rescuing N-terminal translational RAB-X fusion displays intracellular, perinuclear localization. We will present our progress to (1) determine whether mutations in rab-X affect localization of components of the Menorin pathway, to (2) determine the subcellular localization of rab-X, and to (3) determine if GTPase activity of rab-X is necessary for restricting dendritic growth.

21. Juan J Mesa

Characterization of a Streptomyces coelicolor rhomboid knockout mutant

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Rhomboids are intramembrane proteases present in all forms of life and widely distributed in bacteria. Rhomboids are loosely associated with cell signaling yet their function in prokaryotic physiology is mostly unknown. Streptomyces are gram positive bacteria commonly found in soil that have a complex developmental cycle that includes spore germination, production of secondary metabolites and formation of aerial mycelia. The signaling network that regulates the Streptomyces life cycle is not fully characterized yet. Our hypothesis is that rhomboids play a role in the signaling mechanisms of Streptomyces. Using bioinformatics tools we identified SCO3855 in Streptomyces coelicolor, the model organism for Streptomyces. SCO3855 codes for a putative rhomboid protease present in all Streptomyces strains analyzed. This gene complemented a well characterized bacterial rhomboid mutant (AarA from Providencia stuartii) demonstrating that SCO3855 is an active rhomboid protease. Using CRISPR technology a SCO3855 knock out (KO) was constructed. The corresponding complementation strain was also created. Here we report the characterization of the SCO3855 rhomboid KO mutant. We analyzed three strains, the wild type, the KO and the corresponding complementation strain. Blind analysis was performed in triplicates and assessed for statistical significance. We used microscopy to compare spore morphology and production of actinorhodin was assayed spectrophotometrically. Our results show that the KO mutant has an altered developmental cycle as shown by shorter spores and impaired actinorhodin production. The complemented strain partially recovers the wild type phenotypes. In summary, SCO3855 plays a role in the life cycle of S. coelicolor supporting our hypothesis.

22. Clarissa Guzman-Roman

The role of enhancer-promoter loops and H3K4me2 in transcriptional memory

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Rapid activation of gene expression programs is required for organisms to respond to environmental signals. A major effector of rapid gene activation is transcriptional memory (TM), an evolutionarily conserved mechanism that allows cells to have a quicker or more robust transcriptional response to a previously experienced environmental signal. Our lab has discovered that ecdysone-inducible genes, key developmental genes in Drosophila, exhibit TM. A factor required for TM is the nuclear pore protein Nup98. Nup98 binding at genes that exhibit TM has been found to promote dimethylation of histone H3 lysine K4 (H3K4me2), an active chromatin mark also associated with TM in yeast and human cells. However, the role of H3K4me and the writers of this chromatin mark in TM of ecdysone-inducible genes is not known. Our lab has also shown that Nup98 mediates enhancer-promoter (E-P) loop formation and physically interacts with architectural proteins at ecdysone-inducible genes during ecdysone induction, which is maintained in the memory state. These observations led us to hypothesize that Nup98-mediated enhancer-promoter loops and H3K4 methylation contribute to TM of hormone-responsive genes. In order to define the role of H3K4me2, we measure the difference in expression of ecdysone-inducible genes during TM in Drosophila cells depleted for H3K4 methyltransferases (Trx, Trr). We observed that loss of Trx or Trr lead to loss of TM. ChIP-qPCR experiments also showed that H3K4me2 is enriched and maintained at the promoters of ecdysones-inducible genes after ecdysone-induction. Together, our results support a model, in which H3K4me2 and enhancer-promoter loops contribute to TM.

23. Jennifer Aleman

Nuclear pore protein Megator attenuates dosage compensation of the male X chromosome

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The nuclear pore complex (NPC) is well known for its role in nuclear-cytoplasmic transport. A role for the NPC in gene expression has been an emergent topic in recent years as certain nucleoporins have been found in the nuclear interior, binding to chromatin. Megator, (Mtor) makes up the nuclear basket of the NPC and appears to form an intranuclear matrix-like structure that binds along chromatin in Drosophila polytenized salivary gland nuclei. Since Mtor has been implicated in both RNA biogenesis and dosage compensation, I examined the effect of Mtor on localization of a non-coding RNA that is part of the dosage compensation complex, roX1. Using RNA FISH in Drosophila salivary gland nuclei, I detected an increase in nuclear soluble roX1 in Mtor-depleted conditions. The increased presence of roX1 was due to increased levels of transcription of roX1 in male nuclei. In addition to roX1, a number of other X-linked genes exhibited a male-specific increase in expression via qPCR assays upon depletion of Mtor. To confirm the male-specific upregulation of X-linked genes, we performed RNA-Seq in male and female salivary glands in both control and Mtor knockdown conditions. Our results confirmed our initial finding – the most notable change in gene expression observed upon Mtor depletion was an upregulation of X-linked genes in males. These results suggest that Mtor normally functions to restrict dosage compensated gene expression. Overall this work uncovers a novel gene regulatory role for a nuclear-scaffold forming nucleoporin in the context of the epigenetic phenomenon of dosage compensation.

24. Antonia Bass

Elucidating the mechanisms underlying noncanonical inflammasome responses to *Legionella pneumophila*

Antonia Bass and Sunny Shin
University of Pennsylvania

Host recognition of intracellular bacterial pathogens results in the formation of a multiprotein complex termed the inflammasome, which leads to the recruitment and activation of inflammatory caspases, which promote IL-1 family cytokine secretion and pyroptosis, an inflammatory form of cell death. In mice, interferon-gamma (IFN-γ) is a potent inducer of the noncanonical inflammasome, which is triggered in response to bacterial lipopolysaccharide (LPS). IFN-γ functions in mice include promoting rupture of pathogen-containing vacuoles and bacteriolysis of cytosolic bacteria in order to release LPS and other pathogen-derived products into the cytosol, resulting in host recognition and inflammasome activation. Whether and how IFN-γ promotes noncanonical inflammasome activation in human macrophages is poorly understood. In this study, we use Legionella pneumophila, an intracellular gram-negative bacteria, to study the innate immune response in human macrophages. We hypothesize that in human macrophages, IFN-γ plays a similar role as in mouse macrophages to promote membrane rupture of the Legionella-containing vacuole and activate the noncanonical inflammasome. We evaluated the inflammasome response of Legionella-infected unprimed or IFN-γ-primed primary human macrophages, as well as conducted RNAi-mediated knockdown of human IFN-γ-induced proteins to determine their role in inflammasome activation. We also used confocal microscopy to determine whether IFN-γ promotes the presence of ruptured Legionella. Together, our results indicate that IFN-γ is a key factor in human inflammasome activation during Legionella infection. This study elucidates aspects of human innate immune response to gram-negative bacterial pathogens and may provide insight into developing therapeutics to prevent gram-negative sepsis.

25. Natasha Lopes Fischer

Coxiella burnetii uses its Type IV Secretion System to suppress host cytokine upregulation and secretion

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Host immune cells use multiple strategies to detect and protect against bacterial infections. One common defense pathway is the activation of Pattern Recognition Receptors (PRRs) by bacterial ligands. Once triggered, PRRs activate the NF-κB and MAPK signaling pathways to upregulate cytokine expression and secretion from the host cell, alerting the body to the infection. Some pathogens have evolved strategies to evade this defense mechanism to remain undetected by the host. The bacterium *Coxiella burnetii* is thought to evade multiple host immune pathways. *Coxiella* primarily infects alveolar macrophages and causes the emerging disease Q fever. This pathogen uses a specialized type IV secretion system (T4SS) to inject bacterial effector proteins into the host cytoplasm. These effectors modulate host cellular processes and allow bacterial replication. Despite causing major changes to the host cell, *Coxiella* does not induce a strong cytokine response. I hypothesize that *Coxiella* suppresses this host response using bacterial effectors. To test this hypothesis, I infected a human monocytic cell line with wildtype bacteria or bacteria lacking a functional T4SS, and performed qPCR, ELISA and immunoblot assays to determine differences in the immune response to these bacteria. My preliminary results suggest that *Coxiella* uses its T4SS to inhibit the NF-κB pathway, suppressing cytokine upregulation and secretion. In the future, I will conduct a screen of *Coxiella* effectors to identify those that may be suppressing host signaling pathways. Results from this study will provide insights into pathogen evasion strategies and may provide targets for improved therapeutics for Q fever.

26. Guadalupe Ceja

Leptomeningeal B Cell Aggregates Associate with Subpial Pathology in a Natural Model of Multiple Sclerosis

Ms, Megan McGeehan[1], Mr. Miles Miller[1], Dr. Priscila Farias, DVM[1], Dr. Charles Bradley, DVM[1], Dr. Melissa Sanchez, DVM[1], Dr. Edward Stopa, MD[2], Dr. Charles Vite, DVM, PhD[1], Prof. Amit Bar-Or, MD[1,3] and Dr. Jorge I Alvarez, PhD[1]
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Background: Multiple sclerosis (MS) is an idiopathic demyelinating disease in which meningeal immune cell infiltrates correlate with accelerated clinical disease progression. Interactions of distinct immune cell subsets and resident stromal/endothelial cells at sites of such chronic inflammation are therefore of considerable interest. The study of MS meningeal immunity has been limited due to constrained access to MS specimens, the long clinical course of the disease and the confounding factors of experimental models. Unlike models such as experimental autoimmune encephalomyelitis, naturally occurring models offer a unique opportunity to understand MS pathogenesis and provide a more compelling framework for translational research. Objectives: We propose granulomatous meningoencephalomyelitis (GME), an idiopathic demyelinating disease of young dogs with a female bias, as a natural model to study neuropathological mechanisms of MS, particularly within the leptomeningeal compartment. Methods: We determined the pathological changes occurring in GME brains (n=45) by MRI imaging and histo/immunofluorescent analysis. Results: We predominantly found perivascular mononuclear cell infiltration in the cortex and white matter associated with moderate demyelination. The leptomeningeal space, which represents an important niche supporting immunological activity, displayed areas of focal and disseminated gadolinium enhancement that correlated with heavy lymphocytic infiltration. These leptomeningeal infiltrates had collections of proliferating (Ki67+) B cells, germinal center B cells, plasma cells and follicular dendritic cells contained in a specialized network of collagen fibers resembling conduit networks and associated with the expression of the lymphorganogenic chemokines CXCL13 and CCL21. T cells localized in the periphery of these B cell clusters were characterized by low frequencies of T regulatory cells. Although perivascular parenchymal infiltrates contained clusters of B cells, they lack the cellular and extracellular matrix signatures found in the meningeal compartment. Finally, the presence of leptomeningeal B cell clusters correlate with increased subpial demyelination,

neuronal degeneration and axonal pathology. Conclusion: Thus, our findings indicate that the leptomeningeal microenvironment sustains the development of organized immune cell aggregates during chronic neuroinflammation and suggest GME as a novel naturally ocurring model to study leptomeningeal B cell driven inflammation and neuropathology.

27. Leticia Kuri-Cervantes

LONGITUDINAL DYNAMICS OF FOLLICULAR CD4+ T CELLS IN ACUTE SIV INFECTION

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Tfh cells play a critical role in germinal center (GC) formation and B cell maturation. GC-Tfh in lymph nodes (LN) are sites for preferential SIV infection and replication. Changes in Tfh cells in early acute SIV infection may be a major determinant in the development of effective antibody-mediated control of SIV infection. Eighteen rhesus macaques were infected with SIVmac251 and underwent staggered necropsy during acute and chronic infection. Tfh cells from LN and spleen were immunophenotyped. We further examined LNs to quantify and localize viral RNA (vRNA) using immunohistochemistry, and performed gene expression and pathway enrichment analyses on sorted Tfh cells from LNs. The frequency of Tfh cells decreased after 10 days post-infection (d.p.i.) and partially rebounded after 20 d.p.i across tissues. Phenotypic profiles in Tfh from the spleen clustered separately from LN after 10 d.p.i. Although plasma viremia (pVL) peaked 10 d.p.i., vRNA in LNs was detectable as early as 5 d.p.i. within follicles and the T cell zone. Tissue vRNA was increased until 90 d.p.i. but was not preferentially found within follicles. Transcriptional profiling of Tfh-related genes showed profound modulation of cytokine production and inflammatory pathways. Functions were partially recovered after 20 d.p.i. irrespective of the increasing vRNA in tissues. tSNE analyses showed independent clustering pre- and post-infection, suggesting a partial recovery in responsiveness in later stages of infection. SIV infection has a profound effect in Tfh frequencies, phenotypic and genetic profiles across tissues since acute infection, that may directly impact the early induction of SIV-specific antibody production.

28. Blanca Rodriguez

Bacterial Membrane Vesicle-associated Nucleic Acids Induce Interferon-ß Expression in Murine Macrophages

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Duke University

Bacterial nucleic acids are important pathogen associated molecular patterns sensed by innate immune cells during infection. However, it is currently unclear how bacterial RNA is secreted and whether specific types of RNAs are selected for secretion during infection of host cells. Pathogenic bacteria secrete nanosized, spherical, proteolipidic structures termed membrane vesicles (MV), which contain a concentrated payload of biologically active macromolecules. MVs are important mediators of pathogen-host interactions and are often internalized via receptor-mediated endocytosis, leading to the intracellular delivery of immunomodulatory macromolecules. We sought to evaluate whether MVs produced by the human pathogen, Staphylococcus aureus, contain biologically active RNA. Here we report that S. aureus release MV-associated RNA that are protected from nuclease degradation. MV-associated RNA was transferred to cultured murine macrophages and induced significant Interferon-ß mRNA expression largely through endosomal Toll-like receptor (TLR) signaling. Upon exposure to nuclease-treated MVs, TLR3-/- and TLR7-/- macrophages produced very little IFN-ß mRNA. TLR3 recognizes double-stranded RNA (dsRNA), which points to the possibility that S. aureus MVs are packaged with immunostimulatory dsRNA molecules. TLR7 has previously been found to recognize S. aureus tRNA and single-stranded RNA. This suggests that endosomal RNA receptors are activated in cultured mouse macrophages upon MV exposure, likely due to immunostimulatory properties of MV-associated RNA. Our findings show for the first time an MV-mediated mechanistic pathway by which S. aureus-derived immunomodulatory RNAs are delivered to host cells. Elucidating the specific mechanisms by which MV-associated RNAs are trafficked intracellularly and recognized by endosomal TLRs will be examined in future experiments.

29. Eleanor Rivera

Quality of Life and Perceived Needs Among Older Adults Receiving Long-term Services and Supports

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Long term services and supports (LTSS) are vital for older adults with physical and cognitive disabilities. LTSS can be provided in settings such as nursing homes, assisted living, or via community-based services. The aim of this study is to describe the perceived needs for older adults new to LTSS, examine whether those needs are met in the first three months of LTSS, and determine the relationship with quality of life (QoL). This secondary analysis included data from 470 older adults new to LTSS (average age: 81, 71% female, 51% white, 35% black, 20% Hispanic.) The main outcome of QoL was measured using a single item ("How would you rate your overall quality of life at the present time?"). Perceived needs included supportive equipment devices, transportation, physical therapy, and social activities. Analyses at baseline and three months included t-tests, ANOVAs and simple regression modeling. LTSS recipient reported needs at baseline were: 29% supportive equipment, 31% transportation, 20% physical therapy, and 25% social activities. Those who reported needs at baseline had a lower QoL than those who reported no needs (for all). At three months reported needs decreased by an average of 6% (range: 3%-10%). QoL ratings were associated with changes in physical therapy and social activities needs at three months. The implications of these results related to LTSS recipients' QoL in the first three months of services, with emphasis on physical therapy and social activities needs, is an opportunity to be more person-centered in delivery of care.

30. Claudia Tatiana Galindo-Martinez

The importance of the chlorophyte Ostreobium in the coral-dinoflagellate symbiosis

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The scleractinian coral symbiosis with dinoflagellates confers corals the capacity to build reefs in oligotrophic environments. The optical properties of the coral skeleton allow the coral to be one of the most efficient light collectors in nature. However, the solar irradiance and the coral high light absorption efficiency make corals vulnerable during stressful conditions. A natural response in photosynthetic organisms exposed to stressful highlight conditions is a reduction in the optical cross-section. However, in corals, any reduction in the optical cross-section produces a large increase in the light availability due to the multiple light scattering by the coral skeleton. Consequently, when corals have a considerable reduction in the optical cross section, they reach the limits of tolerance for the coral-dinoflagellate symbiosis by beginning a positive feedback loop that only ends in the breakdown of the coral-dinoflagellate symbiosis (i.e. coral bleaching). The excessive light stress makes the remaining dinoflagellates recovery impossible within the coral tissue. This rise the question about how the corals can recover after a bleaching event. In this research, I will explore how endolithic algae Ostreobium sp. within the coral skeleton helps the coral to recover from bleaching. The reduction in the dinoflagellate population within the coral tissue during a bleaching event increases the light availability within the coral skeleton and allows the chlorophyte Ostreobium to bloom near the coral skeleton surface. As a result, the Ostreobium population within the coral skeleton reduces the multiple light scattering effect allowing the repopulation of the coral tissue by the dinoflagellates.

31. Keerthana Gnanapradeepan

The African-specific S47 variant of the p53 tumor suppressor gene alters cell metabolism

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The TP53 gene, often referred to as the guardian of the genome, is the most frequently mutated gene in human cancer. This gene encodes the tumor suppressor p53, a master regulator of various processes such as programmed cell death, growth arrest and senescence. However, there is increasing evidence that highlights the role of p53 in tumor suppression with regards to maintaining metabolic homeostasis. Our lab has identified a polymorphic variant of p53 that encodes a serine residue instead of a proline at amino acid 47 (hereafter S47). This variant is most prevalent in African and African-American individuals, and mice and humans carrying this variant have increased cancer risk and impaired response to therapy. Using both mouse models and human cells, we have found that S47 cells have significantly altered metabolism compared to the WT counterpart. Specifically, S47 mice have increased weight and increased lean content compared to WT mice. These mice also show increased fitness in treadmill studies. Analyses of cell metabolism in S47 murine and human cells indicate that S47 cells show increased glycolysis and glycolytic flux, along with increased oxygen consumption rate on a Seahorse analyzer. The combined data support the premise that the S47 variant confers increased cancer risk but also increased metabolic fitness; the latter may explain the high rate of this variant in certain regions of Africa. By clearly elucidating the roles of WT p53 and the S47 variant in the context of metabolism, we hope to uncover new therapeutic avenues and ultimately enable more personalized medicine approaches for individuals who carry this variant.

32. Viridiana Avila

A small talk involved in photosymbiosis: miRNAs regulating gene expression in the upside down jellyfish during metamorphosis and heat stress

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miRNAs are eukaryotic small RNAs responsible for the regulation of a significant part of the transcriptome. They act by binding in a complementary fashion to an untranslated sequence on their target genes. miRNAs have been implicated in the evolution of novel phenotypic traits. It has been suggested that they have played important roles in animal body plan evolution and speciation. Furthermore several studies on cross-species miRNAs trafficking suggest that these molecules may regulate ecological interactions (e.g. host-pathogen) between species. We hypothesize that miRNA regulation can be involved in the establishment of photosymbiosis in C. xamachana. By focusing on this fascinating phenomenon we hope to shed light on the role these small RNAs as regulators of key biological processes involved in symbiosis. Through small RNA and mRNA sequencing we identified several miRNAs and their gene target repertoires in C. xamachana expressed during the onset of metamorphosis/symbiosis stages and symbiosis breakdown (by thermal stress) in fully developed/symbiotic ephyras. Our preliminary results suggest a complex miRNA regulatory network involved in the early onset and disruption of symbiosis.

33. Kopo Oromeng

High-frequency Data Reveals Spatio-temporal Controls of Solute Cycling in a Semi-Arid Environment, Okavango Delta, Botswana

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The Okavango Delta in semi-arid northwestern Botswana is one of the largest wetland in sub-Saharan Africa. The Delta receives water from an annual flood pulse from the Angolan subtropics and local rains. Processes that transfer solutes from the watershed to the Okavango River, the timing of solute delivery, as well as the fate of solutes in the Okavango Delta are not well understood. We used data loggers to record water level, temperature, electrical conductivity, and air temperature data-set at a 1 hour resolution from November 2010-2011.Loggers were deployed at the inlet (Mohembo) and the main outlet (Maun) of the Delta. Our objectives were to document the temporal variations of discharge and solutes and to assess the factors that control solute input into the Delta. Spatio-temporal variation in discharge showed that river inflow to the Delta peaked at 392 m^3/s in February and twice between March-April at 678.7 m³/s, before receding in October while discharge at the outlet of the Delta peaked at 19.2 m^3/s in August, then receded in November. The average TDS concentration of inflow to the Delta was 69.9 mg/L and 15.7 mg/L in the Delta outflow. We recorded anomalously high solute concentrations at the inlet during the receding limb of the hydrograph in September-November and much lower concentrations between March and September. Anomalously high solute concentrations during the receding limb were from saline groundwater influx in the upper watershed, while the high solute concentrations during the arrival of the flood pulse are derived from dissolution of salts on the floodplains and adjacent wetlands. River outflow from the Delta had higher solute concentrations and much less temporal variability compared to river inflow. These results indicate that the high temporal solute flux in the Okavango River is controlled by groundwater influx at low discharge and rains and the flood pulse front at increasing discharge.

34. Nathaniel H Spilka

The Effects of Ovarian Hormones on Substance Use: Preliminary Daily Diary Data

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Men have historically higher rates of substance use and substance use disorder (SUD) compared to women. However, women who use substances experience more negative health-related consequences. One factor that is thought to contribute to these sex differences is the influence of fluctuations of ovarian hormones, estrogen and progesterone, throughout the menstrual cycle (MC). Specifically, research suggests that these hormones modulate dopamine release in response to substance use, which could influence substance use behavior and subjective response (i.e. satisfaction or enjoyment). Participants completed online surveys every day over the course of the 3 MCs. The surveys assessed daily substance use and subjective response to substance use among nicotine-dependent women. In addition, participants provided blood up to 5 different times to evaluate blood hormone levels. A repeated measures ANOVA showed that self-reported substance use and subjective experience of use did not significantly differ during the MC ($p>0.05$). These preliminary results may be subject to change since data recording is still ongoing.