15th Annual GDBBS DSAC Student Research Symposium

Tuesday, January 23rd, 2018

Cox Ballroom

DSAC

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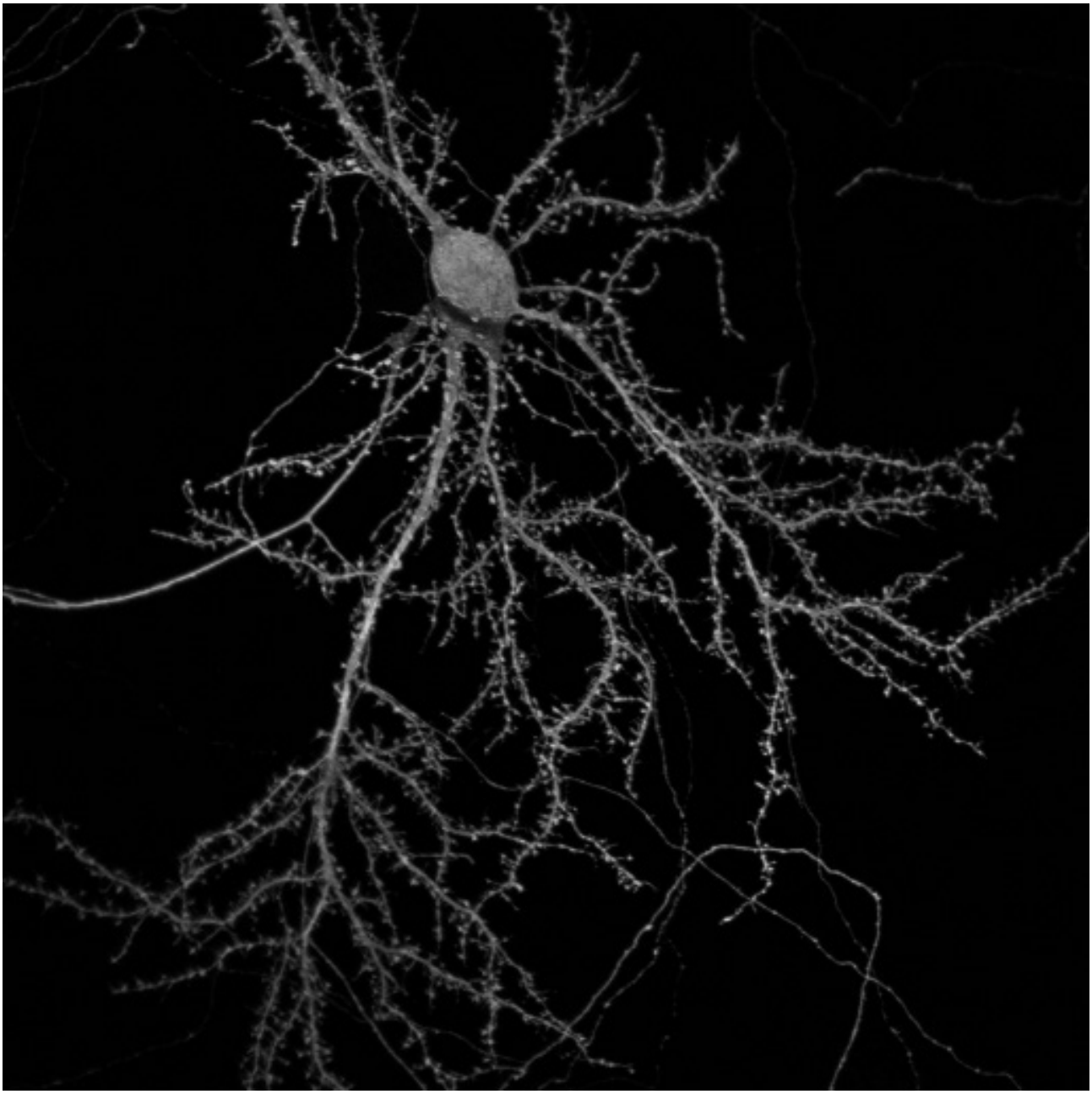
ICI Image Contest Winners

1st Place, ICI Image Contest



Kyle Gerber, MSP

3D projection of z-stacks taken on a confocal scope of the F-actin cytoskeleton of a dissociated hippocampal mouse neuron in culture visualized using transiently transfected LifeAct-Ruby.

The 15th Annual GDBBS DSAC Student Research Symposium
Tuesday, January 23rd, 2018
Cox Ballroom

8:00-8:30AM – Breakfast

Session 1: Methods & Computational Biology 8:30-9:30AM

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BIOLOGICAL APPLICATIONS OF CRYO-ELECTRON MICROSCOPY

8:45 – Varun Saravana (NS)
THE ROLE OF DOPAMINE IN SENSORIMOTOR ADAPTATION

9:00 – Riley Perszyk (MSP)
METHYL GROUPS INTERCONVERT A SERIES OF NMDA RECEPTOR ALLOSTERIC MODULATORS FROM POSITIVE TO NEGATIVE MODULATION THAT SHARE A BINDING SITE

9:15 – Nitya Sharma (GMB)
IDENTIFICATION OF TRANSCRIPTION FACTOR RELATIONSHIPS ASSOCIATED WITH ANDROGEN DEPRIVATION THERAPY RESPONSE AND METASTATIC PROGRESSION IN PROSTATE CANCER

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10:15 – Amber Caldara (CB)
A DEFECT IN DESMOGLEIN 1 LIPID RAFT ASSOCIATION CAUSES SEVERE DERMATITIS, MULTIPLE ALLERGIES, AND METABOLIC WASTING (SAM) SYNDROME AND REVEALS A NOVEL PATHOMECHANISM FOR HUMAN DISEASE

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10:45 – Suzanne Mays (MSP)
DISCOVERY OF IMPROVED AGONISTS OF THE ANTI-DIABETIC NUCLEAR RECEPTOR, LRH-1

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11:30 – Joseph McMillan (PBEE)
LINKING TRANSMISSION POTENTIAL OF MULTIPLE VECTORS TO OBSERVED PATTERNS OF PATHOGEN TRANSMISSION

11:45 – Maria White (IMP)
HETEROLOGOUS PACKAGING SIGNALS ON HA LIMIT INFLUENZA A VIRUS REASSORTMENT

12:00 – Jessica Trost (MMG)
IDENTIFICATION OF INFLUENZA HA STEM REGION RESIDUES THAT TRIGGER MEMBRANE FUSION ACTIVITY AND ALTER HA STABILITY

12:15 – Jessica Shartouny (IMP)
HARNESSING AN INNATE FROG DEFENSE PEPTIDE AS AN ANTI-INFLUENZA AGENT

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1:00-1:45 – Odd-Numbered Poster Presentations
1:45-2:30 – Even-Numbered Poster Presentations

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4:30 – Katie Ponder (CB)
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Reception and Awards 5:30-7:00PM

Oral Presentation Abstracts

2nd Place, ICI Image Contest
Rebecca Dillard, MMG
Bacteriophages infecting a bacterial cell by cryo-electron tomography

Session 1:
Methods & Computational Biology
8:30AM

Rebecca Dillard, MMG **8:30AM**

BIOLOGICAL APPLICATIONS OF CRYO-ELECTRON MICROSCOPY

Rebecca S. Dillard[1,*], Cheri M. Hampton[1,*], Joshua D. Strauss[1,*], Zunlong Ke[1,2,*], and Elizabeth R. Wright[1,3].

[1]Division of Pediatric Infectious Diseases, Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA 30322, [2]School of Biology, Georgia Institute of Technology, Atlanta, GA 30332, [3]Robert P. Apkarian Integrated Electron Microscopy Core, Emory University, Atlanta, GA 30322,

[*]These authors contributed equally to this work.

Recent developments in sample preparation, imaging, and data processing have led to a dramatic expansion of cryo-electron microscopy (cryo-EM) in structural biology. In cryo-EM, the sample is rapidly frozen, vitrifying the specimen in a close-to-native state, followed by imaging in the electron microscope and image processing to reveal structural features. We have applied advancements at several steps of the workflow, such as the use of new substrates and methods for sample preparation, phase plates and direct electron detectors for cryo-EM imaging, and cryo-correlative light and electron microscopy (cryo-CLEM) to improve imaging and provide more information about biological specimens. Specific examples include the use of affinity grids to improve HIV-1 particle concentration and distribution, phase plate imaging of ϕCbK bacteriophage lysed *Caulobacter crescentus* and reovirus T1L to improve contrast, direct electron detector imaging of coliphage BA14 to reduce beam-induced motion, and cryo-CLEM of transfected mammalian cells to localize virus-like particles. These improvements have led to tremendous growth in the field of cryo-EM by providing structures to higher resolutions and answers to increasingly complex biological questions.

Varun Saravana, NS **8:45AM**

THE ROLE OF DOPAMINE IN SENSORIMOTOR ADAPTATION

Varun Saravanan[1,2], Lukas A Hoffmann[1,2], Amanda L Jacob[2] and Samuel J Sober[2]

[1]Neuroscience Graduate Program, GDBBS, Laney Graduate School, Emory University [2]Dept. of Biology, Emory University

Sensorimotor learning is ubiquitous in complex motor behaviors. However, the neural mechanisms driving behavioral plasticity are not well understood. Dopamine has been implicated in reinforcement learning, i.e., learning driven by rewarding or aversive external cues. However, the role of dopamine in sensorimotor adaptation, wherein an organism learns through evaluation of its sensory feedback rather than from external reward or punishment, has not been well characterized. We have developed learning paradigms to study these two types of sensorimotor learning in Bengalese finches (*Lonchura striata* var. *domestica*). Male Bengalese finches spontaneously produce songs containing complex sequences of vocal gestures (syllables). We have previously shown that depleting dopamine in a song-specific basal ganglia nucleus (Area X) impairs reinforcement learning in songbirds. Here, we tested the role of dopamine in sensorimotor adaptation. We used the same dopamine depletion paradigm mentioned above in conjunction with a learning paradigm in which the pitch (fundamental frequency) of a bird's auditory feedback is manipulated in real time through custom-built headphones, a manipulation that robustly drives sensorimotor adaptation. Our results suggest two hypotheses for the role of dopamine that we will distinguish using mathematical modeling.

Riley Perszyk, MSP **9:00AM**

METHYL GROUPS INTERCONVERT A SERIES OF NMDA RECEPTOR ALLOSTERIC MODULATORS FROM POSITIVE TO NEGATIVE MODULATION THAT SHARE A BINDING SITE

***Riley E. Perszyk*[1]**, Brooke M. Katzman[2], Hirofumi Kusumoto[1], Steven Kell[2], Yesim Altas Tahirovic[2], Rhonda L. Moore[2], David Menaldino[2], Pieter Burger[2], Dennis C. Liotta[2] and Stephen F. Traynelis[1].

[1]Department of Pharmacology, Emory University [2]Department of Chemistry, Emory University

N-methyl-D-aspartate receptors (NMDARs) are ionotropic glutamate receptors that have important roles in the CNS and have been implicated in multiple neurological disorders. Previous NMDAR targeted compounds are poorly tolerated, leading to efforts to identify compounds with reduced side effects. We describe here how modest changes to the structure of a series of negative allosteric NMDAR modulators with submaximal inhibition at saturating concentrations were capable of interconverting negative to positive modulation. Further analysis revealed shared properties of both types of modulators, including the ability to enhance agonist potency. Moreover, both positive and negative modulators display a use-dependence that requires glutamate and glycine to be bound to the receptor before modulators can act with high potency. Data suggests that positive and negative modulators share structural determinants of action. Analysis of the enantiomers of two compounds in the series suggests both components of the racemic mixture bind to the same site on the receptor but with different effects on receptor function. The combination of the properties of this series suggests that certain compounds may be uniquely capable of selectively augmenting extrasynaptic NMDARs. Thus, this compound may be a useful tool to probe the contribution of extrasynaptic NMDARs to normal and pathological circuit function.

Nitya Sharma, GMB **9:15AM**

IDENTIFICATION OF TRANSCRIPTION FACTOR RELATIONSHIPS ASSOCIATED WITH ANDROGEN DEPRIVATION THERAPY RESPONSE AND METASTATIC PROGRESSION IN PROSTATE CANCER

Nitya V. Sharma[1], Kathryn L. Pellegrini, PhD[2], Veronique Ouellet, PhD[3], Felipe O. Giuste[4], Selvi Ramalingam[5], Kenneth Watanabe, PhD[5], Eloise Adam-Granger[3,] Lucresse Fossouo[3], Sungyong You, PhD[8], Michael R. Freeman, PhD[8], Paula Vertino, PhD[9,10], Karen Conneely, PhD[10,11], Adeboye O. Osunkoya, MD[3,5,10], Dominique Trudel, MD,PhD[3,6,], Anne-Marie Mes-Masson, PhD[3,7], John A. Petros, MD[2,10,12], Fred Saad, MD[3,13,14], and Carlos S. Moreno, PhD[5,10].

[1]Genetics and Molecular Biology PhD Program, Emory University, [2]Department of Urology, Emory University School of Medicine, [3]Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM)/Institut du cancer de Montréal and Université de Montréal, Montreal, QC, Canada, [4]MSTP/MD PhD, Emory University, [5]Pathology and Laboratory Medicine, Emory University School of Medicine, [6]Department of Pathology and Cellular Biology, Université de Montréal, Montreal, QC. Canada, [7]Department of Medicine, Université de Montréal, Montreal, QC. Canada, [8]Division of Cancer Biology and Therapeutics, Departments of Surgery & Biomedical Sciences, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, [9]Department of Radiation Oncology, Emory University School of Medicine, [10]Winship Cancer Institute of Emory University, [11]Department of Human Genetics, Emory University, [12] Atlanta VA Medical Center, [13]Department of Surgery, Université de Montréal, Montreal, QC, Canada, [14]Université de Montréal Endowed Chair in Prostate Cancer, Montreal, QC, Canada

Patients with recurrent, aggressive prostate cancer typically undergo androgen deprivation therapy (ADT), but the benefits are often short-lived, and responses are variable. To investigate differential responses to ADT, we performed whole transcriptome analysis of 20 patient-matched Pre-ADT biopsies and Post-ADT prostatectomy specimens, and identified two subgroups of patients with either a strong or weak transcriptional response to ADT. We found that all patients lost transcriptional signatures indicative of the AR-dependent subtype (PCS2). The strong responders maintained the more aggressive subtype (PCS1) signal, while the weak responders lost expression of these genes and more resembled an AR-suppressed, basal, (PCS3) subtype. Computational analyses identified transcription factor coordinated groups (TFCGs) enriched in the strong responders network. Leveraging a large public dataset of over 800 metastatic and primary samples, we identified 20 TFCGs in common between strong responders and metastatic lesions, including GLI3/GLI2, SOX4/FOXA2/GATA4, ERF/ETV5/ETV3/ELF4, and a TFCG containing JUN, JUNB, JUND, FOS, FOSB, and FOSL1. We found that many TFCGs in the metastatic network were subsets of larger TFCGs in the strong responders network, revealing potentially critical transcription factor associations. Using this unbiased approach, we have identified transcriptional regulators associated with differential ADT responses and metastatic disease progression.

Session 2:

Human Disease & Disorders

9:45AM

Kameryn Butler, GMB **9:45AM**

IDENTIFICATION AND EVALUATION OF NOVEL EPILEPSY-ASSOCIATED VARIANTS

Kameryn M. Butler[1], Olivia Moody[2], Cristina da Silva[3], John J. Alexander[1,3], Andrew Jenkins[2], Andrew Escayg[1]

[1]Department of Human Genetics, Emory University, Atlanta, GA 30322, [2]Departments of Anesthesiology and Pharmacology, Emory University, Atlanta, GA 30322, [3]EGL Genetics, Tucker, GA 30084

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures caused by neuronal synchrony and hyperexcitability. The Emory Genetics Laboratory (EGL) offers a targeted sequencing panel comprising 110 known epilepsy genes, referred to as the 'epilepsy and seizure disorder' (ESD) panel, that detects a positive finding in 25% of referred epilepsy patients. The ESD panel is derived from a larger sequencing library of approximately 5000 evidence-based disease genes, making this a valuable resource for identifying putative disease-causing variants in patients with negative or inconclusive results from the ESD panel. To date, I have identified candidate variants in genes associated with epilepsy, autism spectrum disorder, intellectual disability, and other neurodevelopmental disorders, as well as, in genes not currently associated with disease. A novel *GABRA2* missense variant was identified to be *de novo* in an individual with epileptic encephalopathy and cerebral palsy. Functional studies of the single point mutation in the TM2 segment of the alpha-2 subunit revealed a constitutively open ion channel that was unresponsive to GABA, but with overall decreased protein expression. In conclusion, we are utilizing this rich source of available sequence data to better understand the molecular mechanisms underlying epilepsy through the identification of novel genetic variants.

Jaquelyn Zoine, CB **10:00AM**

EX VIVO EXPANDED, PATIENT DERIVED γδ T CELLS PROVIDE A THERAPEUTIC BENEFIT WHEN COMBINED WITH LOW DOSE CHEMOTHERAPY

Jaquelyn T. Zoine[1,2] , Kathryn S. Sutton[2] , Alexandria Jefferson[2] , Kelly C. Goldsmith[2] , Christopher B. Doering[2] , H. Trent Spencer[2]

[1]Graduate Program in Cancer Biology, Emory University, Atlanta, GA, [2]Department of Pediatrics, Emory University, Atlanta, GA

γδ T cells are an attractive candidate for anticancer immunotherapy because of their intrinsic antitumor properties, specifically their role in antibody-dependent cellular cytotoxicity (ADCC) and recognition of stress antigen. We have developed a method for expanding, storing, and genetically engineering γδ T cells, and we have focused on the use of these cells to treat neuroblastoma. γδ T cells from peripheral blood mononuclear cells can be expanded to >70% of the culture. In vitro we show ex vivo expanded γδ T cells are cytotoxic against several neuroblastoma cell lines, and stress antigens recognized by γδ T cells are upregulated for ~6 hours after a 1 hour exposure to temozolomide (TMZ), which is an anti-neuroblastoma chemotherapy agent. Further, combining γδ T cells expressing CD16 (which enables ADCC) with dinutuximab induces 30% increased neuroblastoma cell death compared to γδ T cells alone. To test the in vivo effectiveness of γδ T cells, NSG mice growing an IMR5 neuroblastoma tumor were administered the expanded cells. Tumor regression was achieved using a combination of γδ T cells, dinutuximab and TMZ. We hypothesize this combination can advance treatment of neuroblastoma because lower doses of chemotherapy are effective, which overcomes the major toxicity of current regimens.

Amber Caldara, CB **10:15AM**

A DEFECT IN DESMOGLEIN 1 LIPID RAFT ASSOCIATION CAUSES SEVERE DERMATITIS, MULTIPLE ALLERGIES, AND METABOLIC WASTING (SAM) SYNDROME AND REVEALS A NOVEL PATHOMECHANISM FOR HUMAN DISEASE

Josh Lewis[1*], ***Amber L. Caldara***[1,3*]**,** Nicole L Strong[1], Sara N Staley[1,2], Ilya Levental[4], James K Wahl III[4], Alexa L Mattheyses[1], Takashi Sasaki[6], Kazuhiko Nakabayashi[7], Kenichiro Hata, Yoichi Matsubara, Akemi Ishida-Yamamoto, Masayuki Amagai, Akiharu Kubo and Andrew P Kowalczyk

*Authors contributed equally to this work

[1]Department of Cell Biology, Emory University School of Medicine, Atlanta, Georgia, USA. [2] Graduate program in Biochemistry, Cell and Developmental Biology, Emory University School of Medicine, Atlanta, Georgia, USA, [3]Graduate Program in Cancer Biology, Emory University School of Medicine, Atlanta, Georgia, USA, [4]Department of Integrative Biology and Pharmacology, University of Texas Health Science Center at Houston, Texas, USA [5]Department of Oral Biology, College of Dentistry, University of Nebraska Medical Center, Lincoln, Nebraska, USA, [7]National Research Institute for Child Health and Development, Tokyo, Japan [8] Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan [10]Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia, USA

Desmogleins are the core component of the desmosome, cell-cell adhesion structures that are critical for epidermal integrity. Previous reports illustrate that desmogleins traffic to lipid rafts and that the integrity of lipid rafts is critical for desmosome formation. Here, we describe a mutation within the transmembrane domain (TMD) of desmoglein 1 (DSG1) which causes Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome. Modeling of this mutation predicts a shortening of the TMD and a lower probability of raft association. Furthermore, biochemical and imaging approaches revealed that the DSG1 mutant is defective in targeting to lipid rafts. DSG1 levels in patient epidermis were reduced, and DSG1 was mislocalized and aberrantly clustered at cell-cell borders in patient skin. Expression of the mutant DSG1 in a cell culture model revealed that the mutant protein has partially impaired trafficking to the cell surface, and once there is deficient in desmosome incorporation. These results demonstrate that lipid raft association is essential for normal desmoglein function. To our knowledge this is the first report in which a defect in lipid raft targeting causes a human disease, and suggest that loss of lipid raft association may be an under-appreciated pathomechanism in human disease.

Carlie Hoffman, NS **10:30AM**

SV2C AS A MEDIATOR OF DOPAMINE VESICLE FUNCTION

Carlie Hoffman[1]**,** Kristen A. Stout[2], Amy R. Dunn[3], Gary W. Miller[1]

[1]Emory University, Environmental Health Department, Atlanta, GA, USA, [2]Northwestern University, Feinberg School of Medicine, Department of Physiology, Chicago, IL, USA, [3]The Jackson Laboratory, Bar Harbor, ME, USA

One mechanism thought to contribute to the dopamine neurodegeneration seen in Parkinson's disease (PD) is disruption of vesicular function. The synaptic vesicle glycoprotein 2 (SV2) is known to help maintain proper vesicular function, and the SV2C variant has been associated with the dopamine system and PD. SV2C expression is enriched in dopaminergic brain regions, SV2C expression is disrupted in PD brain, and variations in the human SV2C gene are correlated with responsiveness to levodopa and the protective effect of nicotine on PD risk. To examine the role of SV2C on dopamine vesicle function, we produced two model systems: mice with a genetic deletion of SV2C (SV2C-KO) modeled loss of SV2C expression, while transfection of SV2C into vesicular monoamine transporter 2 (VMAT2)-expressing cells modeled SV2C overexpression. We demonstrate that SV2C-KO animals have decreased dopamine release in the striatum, nucleus accumbens, and ventral pallidum. Furthermore, purified vesicles from SV2C-KO animals have a reduced ability to retain stored dopamine. By treating cells with a fluorescent analog of dopamine and imaging them via live-cell total internal reflection fluorescence (TIRF) microscopy, we show that transfection of SV2C results in increased vesicular uptake of dopamine. These results identify SV2C as a regulator of dopamine vesicle function.

Suzanne Mays, MSP **10:45AM**

DISCOVERY OF IMPROVED AGONISTS OF THE ANTI-DIABETIC NUCLEAR RECEPTOR, LRH-1

Suzanne G. Mays[1] Autumn R. Flynn, C. Denise Okafor, Jeffrey Cornelison, Richard J. Whitby, Michael Dugan, John W. Calvert, Nathan Jui, and Eric A. Ortlund

Departments of [1]Biochemistry, [2]Chemistry, and [3]Surgery, Emory University, Atlanta, GA. [4] University of Southampton, Southampton, UK.

Liver receptor homolog 1 (NR5A2, LRH-1) is an orphan nuclear hormone receptor that regulates diverse biological processes, including lipid and glucose metabolism, proliferation, and the resolution of endoplasmic reticulum stress. Preclinical studies have demonstrated a great therapeutic potential of targeting LRH-1 for treatment of diabetes and cardiovascular disease; however, development of LRH-1 modulators has been challenging. In a recent study, systematic modifications to one of the few known chemical scaffolds capable of activating LRH-1 failed to improve efficacy substantially. Here, we use x-ray crystallography, molecular dynamics simulations, and cellular activation assays to explore conformational changes and receptor-ligand interactions associated with LRH-1 activation by a set of related agonists. Unexpectedly, two closely related agonists exhibit completely different binding modes and mechanisms of activation. We identify a receptor contact that acts an anchor point to stabilize the ligand core, enabling more predictable targeting of desired parts of the pocket. This was used as a basis for rational design of the most potent and selective agonists reported to date.

Session 3:

Immunity & Pathogen Transmission

11:15AM

Taryn McLaughlin, IMP **11:15AM**

CD4+ T CELL LINEAGE COMMITMENT IN *MYCOBACTERIUM TUBERCULOSIS* AND *SCHISTOSOMA MANSONI* CO-INFECTED INDIVIDUALS

Taryn McLaughlin[1] Jeremiah Khayumbi[2], Joshua Ongalo[2], Benson Muchiri[2], Joan Tonui[2], Felix Hayara Odhiambo[2], Cheryl L. Day[1, 3]

[1]Emory Vaccine Center, Emory University, Atlanta, GA;
[2]Center for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya;
[3]Department of Microbiology & Immunology, Emory University School of Medicine, Atlanta, GA

Effective Th1 T cell responses are necessary to control *Mycobacterium tuberculosis* (Mtb) infections. Helminths stimulate Th2 immune responses, which antagonize Th1 cells. As such, we sought to investigate whether co-infection with the helminth, *Schistosoma mansoni*, is associated with Mtb infection. In a cohort of adults in Kenya, the prevalence of *S. mansoni* infection is 20% overall, but this proportion is higher amongst Mtb-infected individuals than Mtb-uninfected healthy controls (HC). While *S. mansoni* infection is more associated with active tuberculosis disease (TB) than latent Mtb infection (LTBI), parasite burden is higher in individuals with LTBI than TB. To determine the influence of *S. mansoni* on T cell immunity, we evaluated the frequency, lineage, and functionality of T cell responses in PBMCs from adults in Kenyan. Individuals were split by Mtb and *S. mansoni* infection status: HC, LTBI and TB, +/- *S. mansoni* infection. Within HC, infection with *S. mansoni* is associated with lower frequencies of cytokine-producing T cells. However, in LTBI and TB, *S. mansoni* co-infection is associated with higher frequencies of cytokine-producing T cells, which produce both Th1 and Th2 cytokines. These data suggest that lineage specific T cell responses are altered during co-infection with Mtb and *S. mansoni.*

Joseph McMillan, PBEE **11:30AM**

LINKING TRANSMISSION POTENTIAL OF MULTIPLE VECTORS TO OBSERVED PATTERNS OF PATHOGEN TRANSMISSION

Joseph R. McMillan[1], Rebekah Blakney[2], Daniel Mead[3], William Koval[2], Sarah Coker[3], Lance A. Waller[1,4], Uriel Kitron[1,2], Gonzalo Vazquez-Prokopec[1,2]

[1]Emory University, Program in Population Biology, Ecology and Evolution, Atlanta, Georgia, USA
[2]Emory University, Department of Environmental Sciences
[3]University of Georgia, Southeastern Cooperative Wildlife Disease Study, Athens, Georgia, USA
[4]Emory University, Department of Biostatistics and Bioinformatics, Rollins School of Public Health

Theoretical models suggest that species contributions to pathogen transmission are additive between primary (i.e., most responsible for transmission) and secondary (i.e., possibly involved in background transmission) vectors, yet empirical evidence of such contributions are lacking. We linked transmission potential of multiple vectors to observed patterns of pathogen transmission by: 1) conducting longitudinal field surveillance of West Nile virus (WNv) infections in *Culex* spp. mosquitoes and avian host communities in the southeastern US and 2) informing a temperature-dependent vectorial capacity model with field estimates of *Culex* spp. abundances. Contrary to theoretical predictions, increased presence of competent vector species through time did not significantly increase the prevalence of infections in the WNv enzootic system. Instead, timing of seasonal vector emergence, temperature, and host demographics strongly mediated the likelihood of WNv transmission, providing insights on the relevance of the interaction between vector- and host-dependent traits in explaining contributions to transmission by different species.

Maria White, IMP **11:45PM**

HETEROLOGOUS PACKAGING SIGNALS ON HA LIMIT INFLUENZA A VIRUS REASSORTMENT

Maria C. White[1,2], John Steel[1], and Anice C. Lowen[1]

[1]Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA
[2]Immunology and Molecular Pathogenesis Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA

Influenza A virus (IAV) is an RNA virus with eight genomic segments, and this segmentation allows genetic exchange between IAVs through reassortment. These segments contain packaging signals (PS) which direct the incorporation of segments into assembling virus particles. These PS are segment- and strain-specific and could potentially impact reassortment outcomes between different IAVs. Our study aimed to quantify the importance of HA PS mismatch to IAV reassortment using a human H3N2 virus background and HA PS from either pandemic H1N1, H5N8, or H7N9 viruses. We constructed virus pairs containing identical proteins but differing HA PS and genotyped emergent viruses from co-infected cells. Our results show that HA segments carrying H1, H5, or H7 PS are all significantly disfavored for incorporation into an H3N2 background relative to an HA segment with homologous H3 PS. Of the three heterologous subtypes tested, H7 exhibits the lowest incorporation barrier. These data indicate that differences among PS of heterologous HAs could be an important factor in determining the likelihood that two IAVs of public health interest will undergo reassortment. Furthermore, these data suggest that the H7 HA segment could be more likely to enter a human H3N2 background than other HAs, based on PS compatibility.

Jessica Trost, MMG **12:00PM**

IDENTIFICATION OF INFLUENZA HA STEM REGION RESIDUES THAT TRIGGER MEMBRANE FUSION ACTIVITY AND ALTER HA STABILITY

Jessica Trost[1], Wei Wang[1], Summer E. Galloway[1], Lauren Byrd-Leotis[1], David A. Steinhauer[1]

[1]Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, GA 30322, USA

The influenza hemagglutinin (HA) serves two major functions in the viral life cycle, receptor binding and facilitating membrane fusion of the viral and endosomal membranes to release the viral genome into the host cell. HA fusion requires structural changes to occur in the HA, triggered by acidification of endosomes. Amino acid differences at numerous positions within the HA have been shown to correlate with changes in HA stability and the pH at which fusion occurs. We have evaluated expression and fusion for wild type and mutant HAs using qualitative and quantitative fusion assays, and immunoprecipitation assays. Previously, a mutation at the group-2 conserved HA2 residue 17, located near the fusion peptide, was identified as a potential "trigger" residue, an H17Y mutation stabilized the neutral pH structure. Group-1 HAs contain Tyr at HA2 position 17, and comparative structural analyses suggested the highly conserved His at residue 111 of HA1 may serve a similar role for initiating conformational changes. We have examined several group 1 HAs, showing fusion activity is inhibited at acidic pH for HAs lacking a His at HA2 position 111. Identification of invariant "trigger" residues such as these highlight them as potential targets for antiviral and vaccine approaches.

Jessica Shartouny, IMP **12:15PM**

HARNESSING AN INNATE FROG DEFENSE PEPTIDE AS AN ANTI-INFLUENZA AGENT

Jessica Shartouny[1], Song Hee Lee[1], David Holthausen[1], Joshy Jacob[1]

[1]Emory Vaccine Center, Emory University

Influenza infections are responsible for much of the annual disease and economic burden worldwide. The first defense against influenza is vaccination, however in pandemics or when the predicted vaccine strains are mismatched, antiviral drugs become the next option. Resistance to conventional antiviral agents can develop in a number of influenza subtypes, necessitating the development of novel anti-viral compounds. One source of new agents is in the innate immune repertoire of antimicrobial peptides (AMPs) produced by most forms of life that are involved in the initial response to bacterial pathogens. We have developed a library of AMPs derived from skin secretions of Indian frogs, from which we previously reported an anti-H1N1 peptide. Another peptide, Yodha, has demonstrated potent neutralization activity against H3N2 influenza viruses in *in vitro* assays. Yodha also neutralizes H1N1 and two flaviviruses, indicating that its mechanism is broadly active. In TEM images, we see that Peptide 47 appears to form nets around viruses, which may inhibit cellular entry. As Peptide 47 is also nontoxic to human red blood cells to a high concentration, it is a good candidate for antiviral therapeutic development.

Session 4:

Epigenetics & Gene Expression

2:45PM

Anna Knight, GMB **2:45PM**

EPIGENETIC AGE ACCELERATION AND MICROBIOME COMPOSITION IN AFRICAN AMERICAN WOMEN

Anna K. Knight[1], Alicia K. Smith[2], Elizabeth J. Corwin[3], Anne L. Dunlop[3]

[1]Genetics and Molecular Biology Program, Emory University, [2]Department of Gynecology and Obstetrics, Emory University, [3]Nell Hodgson Woodruff School of Nursing, Emory University

African American women are more likely to have vaginal microbiomes not dominated by *Lactobacillus* than Caucasian women, potentially increasing their risk for vaginal infections, dysregulation of the hypothalamic-pituitary-adrenal axis, and increased stress response. We hypothesize that vaginal microbiome composition is associated with age acceleration, a DNA methylation-based metric previously associated with poor health outcomes. To test this hypothesis, we leveraged data from pregnant African American women who provided vaginal microbiome samples for V3-V4 16S rRNA sequencing and blood samples for DNA methylation analysis on the Human Methylation450 and EPIC BeadChips. DNA methylation data was used to calculate age acceleration. Linear regression models that controlled for cellular heterogeneity and repeated measures on the same subject were used to evaluate the association between age acceleration and vaginal microbiome composition (Shannon and ChaoI alpha diversity). The Shannon diversity index was positively associated with age acceleration ($p=.03$) such that subjects with less even distribution of taxa had a higher age acceleration. This supports our hypothesis that vaginal microbiome composition is associated with age acceleration, and potentially other negative health outcomes. ChaoI diversity was not associated with age acceleration. Future studies will examine the impact of vaginal microbiome diversity on stress and pregnancy complications.

Camilla Margaroli, IMP **3:00PM**

MIGRATION INTO CF AIRWAY FLUID PROMOTES ADAPTIVE TRANSCRIPTIONAL REPROGRAMMING OF HUMAN NEUTROPHILS *IN VIVO* AND *IN VITRO*

Camilla Margaroli[1], Dalia Arafat-Gulick[2], Haydn Kissick[3], Osric Forrest[1], Swetha Garimalla[2], Greg Gibson[2], Rabindra Tirouvanziam[1]

[1]Center for CF and Airways Disease Research, Emory University School of Medicine, Atlanta, GA, USA
[2]School of Biology, The Georgia Institute of Technology, Atlanta, GA, USA [3]Department of Urology, Emory University School of Medicine, Atlanta, GA, USA

Rationale: While neutrophils are generally considered pre-programmed, we investigated whether the profound changes observed in neutrophils recruited to cystic fibrosis (CF) airways were linked to pathological induction of transcription and reprogramming of these cells. **Results:** *In vitro* transmigrated neutrophils and neutrophils from CF airways increased their RNA content by 7-folds compared to matched blood neutrophils. RNA Seq and microarray results showed that airway neutrophils, both *in vivo* and *in vitro*, increased expression of survival genes and down-regulated pro-apoptotic genes, suggesting that CF airway fluid promotes neutrophil survival through *de novo* transcription. Moreover, immune response genes were enriched for antigen presentation pathways in CF airway neutrophils, while neutrophils transmigrated *in vitro* to a chemoattractant control showed increased cytokine and pro-inflammatory signaling. Interestingly, airway and blood neutrophils did not show any RNA expression for NE and other primary granule proteins, e.g., myeloperoxidase, which are expressed during early neutrophil development in the bone marrow. **Conclusions:** These results suggest that neutrophils can adapt and survive in the CF airway environment via the transcription of new genes. From a basic standpoint, our results challenge the paradigm holding neutrophils as short-lived and transcriptionally silent cells and open avenues for RNA-based CF immunotherapy targeting live airway neutrophils.

Amanda Engstrom, BCDB **3:15PM**

LSD1 INHIBITION CONTRIBUTES TO TAU-MEDIATED NEURODEGENERATION IN ALZHEIMER'S DISEASE

Amanda K. Engstrom[1], Rohitha A. Moudgal[1], Alicia Walker[1], David J Katz[1]

[1]Dept. of Cell Biology, Emory University, Atlanta GA, USA

Alzheimer's disease (AD) is an irreversible brain disorder caused by neuronal cell death. AD is associated with the accumulation of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau (NFTs). However, the molecular mechanism remains unclear. Previously, our lab demonstrated that the histone demethylase, LSD1, is autonomously required for neuronal survival, and is mislocalized to NFTs. These data raise the possibility that NFTs contribute to neuronal cell death by sequestering LSD1 in the cytoplasm and interfering with its continuous requirement to repress inappropriate transcription. Consistent with this, LSD1 is depleted from the nucleus in neurons of P301S Tauopahty mice. Additionally, we show that P301S mice heterozygous for *Lsd1* have reduced survival, exacerbated paralysis, and increased hippocampal neurodegeneration. These data suggest that Tau aggregates function through LSD1 *in vivo* in mice. We find that transcriptional changes in P301S mice largely overlap with *Lsd1* heterozygotes. Furthermore, *Lsd1* heterozygosity exacerbates the expression changes induced by the Tau P301S transgene. These data suggest that loss of LSD1 functions molecularly in the Tau aggregate pathway. Taken together, our results indicate that aggregated Tau may lead to neuronal cell death through the loss of LSD1 function. This novel mechanism provides a promising therapeutic.

Shannon Torres, GMB **3:30PM**

HISTONE VARIANT H2A.Z AND BRAHMA ACT COORDINATELY AND ANTAGONISITCALLY TO REGULATE TRANSCRIPTION AND NUCLEOSOME DYNAMICS IN ARABIDOPSIS

E. Shannon Torres[1,2] and Roger B. Deal[1]

[1]Department of Biology, Emory University, Atlanta, GA 30322 [2]Graduate Program in Genetics and Molecular Biology of the Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA 30322

Key tactics plants use to adapt to changes in their environment include regulating transcription and chromatin organization. The histone H2A variant H2A.Z and the SWI2/SNF2 ATPase BRAHMA have overlapping roles in regulating environmentally responsive genes in *Arabidopsis*, but the extent of this overlap was uncharacterized. Both affect nucleosome positioning and stability in different contexts, but their specific roles in transcriptional regulation and chromatin organization need further characterization. We identified 8 classes of genes where H2A.Z and BRM act cooperatively or antagonistically to contribute directly to transcriptional repression and activation of genes involved in development and response to environmental stimuli. We found that H2A.Z contributes to a range of different nucleosomal changes, BRM stabilizes nucleosomes where it binds and destabilizes and/or repositions flanking nucleosomes, and H2A.Z and BRM both contribute to +1 nucleosome destabilization. Both factors also overlap with the binding sites of light-regulated transcription factors, some which are dependent on H2A.Z and BRM for accessibility. Collectively, we characterized the antagonistic and redundant contributions of H2A.Z and BRM to transcriptional regulation, and begin uncovering their interrelated roles in chromatin organization. However, variability observed in their individual functions implies that both BRM and H2A.Z have more context-specific roles within diverse chromatin environments.

Elizabeth Kline, NS **3:45PM**

SYNERGY BETWEEN COMMON GENETIC VARIANT IN ANTIGEN PRESENTATION CAPACITY AND PYRETHROID EXPOSURE AFFECTS PERIPHERAL IMMUNOPHENOTYPE AND NIGROSTRIATAL PATHWAY VULNERABILITY

EM Kline[1], CP Carr[1], KP MacPherson[1], AF Cintron[1], BC Murray[1], GT Kannarkat[1], WM Caudle[2], and MG Tansey[1]

[1]Department of Physiology. [2] Department of Environmental Health, Rollins School of Public Health. Emory University, Atlanta GA 30322

Epidemiological studies have shown a connection between pesticide exposure and the incidence of Parkinson's disease (PD). Pesticides such as the pyrethroids have a direct effect on the dopaminergic system, altering dopamine transporter function and promoting neuronal apoptosis. Pyrethroids may also have an indirect effect on dopaminergic neuron health via the immune system. Immune dysregulation and prolonged inflammation is heavily implicated in PD pathogenesis for many reasons, including microglial activation, infiltration of lymphocytes into the substantia nigra, shifts in the T cell repertoire, especially in the CD4+ compartment, and risk-associated single nucleotide polymorphisms (SNPs) in immune-related gene loci. *rs3129882* is one such risk SNP, located in *HLA-DRA*. A *GG* genotype at this locus is associated with increased risk of PD, as well as increased baseline and inducible expression of MHC-II, depending on PD status. A history of pyrethroid exposure **in addition to** high-risk *rs3129882* genotype increases odds for PD (Kannarkat et al. 2015). We predict there exists a robust connection between genetic and environmental factors driving shifts in the immune system. We present our findings on pyrethroids as immuno- and neurotoxic chemicals, a critical, environmental "hit" to the system influencing risk for PD.

Session 5:

Cell Signaling & Protein Function

4:15PM

Valentina Gonzalez-Pecchi, CB **4:15PM**

TARGETING MYC THROUGH ITS INTERACTION WITH NSD3S

Valentina Gonzalez-Pecchi[1], Jinglin Xiong[1], Yuhong Du[1,2], Haian Fu[1,2]

[1]Department of Pharmacology, and [2]Emory Chemical Biology Discovery Center, Emory University, Atlanta, USA.

MYC is an oncogene, a transcriptional regulator and a well validated cancer drug target. However, targeting MYC has been challenging. Because MYC function is controlled by signaling proteins, one approach is to discover critical regulators of MYC and inhibit MYC using protein-protein interactions (PPI) disruptors. Towards this goal we utilized a high-throughput PPI technology and identified a novel MYC partner, an epigenetic regulator, NSD3S which is amplified in multiple cancers and functions as an oncogenic driver. We demonstrated that NSD3S interacts with MYC under physiological conditions in cancer cells. We defined the interaction interface between a 26-amino acid region on NSD3S and MYC internal region. Overexpression of NSD3S increases MYC protein stability and transcriptional activity. We designed and developed a time-resolved-fluorescence energy transfer (TR-FRET) assay in a 1536-well ultra-high-throughput-screening (uHTS) format to identify PPI inhibitors. We have screened a library of 130 thousand compounds for NSD3S-MYC PPI disruption with a positive rate of 0.3%. This study identifies a critical link between the epigenetic modulator NSD3S and the MYC oncogene and potential chemical modulators for further analysis. The study suggests a novel regulatory axis between NSD3S and MYC and a novel therapeutic approach for treating patients with MYC-driven tumors.

Katie Ponder, CB **4:30PM**

ROLE OF THE PRODOMAIN OF CASPASE-3 IN APOPTOTIC ACTIVITY

Katelyn G. Ponder[1] and Lawrence H. Boise[2]

[1]Cancer Biology Graduate Program, Emory University, Atlanta, GA; [2]Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA

Caspase-3 (C3) is a protease that is activated at the end of the apoptotic pathway. Previous studies demonstrated that complete removal of the prodomain enhances activity. No studies have determined if activity is due to removal of complete prodomain or a specific region. We created deletion constructs that remove 10 (Δ10) and up to 28 amino acids from the N-terminus. We conducted apoptosis and C3-cleavage assays to determine which region regulates activity. Results show Δ10 have activity like that of $C3^{-/-}$ MEFs. Therefore, the first 10 amino acids are required for activity. We discovered $C3^{-/-}$C3 D9A do not have activity. Therefore, cleavage at D9 could be important. We compared the activation of $C3^{-/-}C3^{WT}$ and $C3^{-/-}$ by looking at C3 cleavage via western blot. $C3^{-/-}C3^{WT}$ have a 17 kDa cleavage product after apoptotic induction (interdomain-linker cleavage and removal of prodomain). Δ10 also has a cleavage product, however it is 20 kDa. This shift demonstrates the linker is cleaved, but the prodomain is not removed. We also hypothesize that the catalytic site, C163, is responsible for removing the prodomain as $C3^{-/-}C3^{C163A}$ results in the same 20 kDa fragment. Further work is being done to determine the cleavage sequence required remove the prodomain.

Travis Loya, BCDB **4:45PM**

CONDITIONAL SUBCELLULAR LOCALIZATION OF THE YEAST TERMINATION FACTOR NAB3 REQUIRES ITS LOW COMPLEXITY DOMAIN

Travis Loya[1,2], Thomas O'Rourke[2], Dr. Daniel Reines[2]

[1]BCDB Program, Laney Graduate School, Emory University, [2]Department of Biochemistry, Emory University

Until recently, much of the focus on amyloids and proteins containing amyloid-like domains has centered upon disease states where amyloid formation is thought to drive pathogenesis, *e.g.*, Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Creutzfeldt-Jakob disease. Recent work has shown that many RNA-binding proteins possess domains with a biased amino acid content that normally assemble into an ordered amyloid-like form. These domains are referred to as low complexity domains (LCDs). In response to environmental factors, these RNA-binding proteins, in an LCD-dependent manner, are differentially localized to subcellular compartments in which RNA metabolism is focused. Yeast Nab3, an essential RNA-binding protein, contains RNA-binding domains and a low complexity, glutamine/proline-rich, amyloid-like domain that can self-assemble. It is known that in response to sugar deprivation, Nab3 localizes to a specialized subcellular compartment. We are currently exploring the LCD-mediated subcellular localization of wild-type and mutant Nab3's in response to sugar deprivation to determine the role the LCD plays in localization, possible components of the subcellular compartment, and the effect of loss of LCD function on the cell. This work will expand our understanding of Nab3's essential role in transcription termination and the biological function of LCDs in RNA-binding proteins.

Arielle Valdez, NS **5:00PM**

NOVEL ROLE OF CDH1-APC AS A MOLECULAR SWITCH FOR PROTEIN SYNTHESIS AT THE SYNAPSE

Arielle N. Valdez[1,2], Austin Lai[1], Gary J. Bassell[1]

Institution: [1]Department of Cell Biology, [2]Medical Scientist Training Program, Emory University, Atlanta GA 30322

Purpose: For learning and memory to occur, neurons synthesize synaptic proteins in response to stimulation; this process can be regulated via ubiquitination. Disrupted ubiquitination can lead to several neurodevelopmental disorders, suggesting a shared mechanism amongst these diseases. One neurodevelopmental disease with no FDA-approved treatment is Fragile X Syndrome (FXS). FXS is caused by the loss of one protein, the Fragile X Mental Retardation Protein (FMRP). FMRP has been observed to repress translation; however, it is unclear how the repressive activity of FMRP is regulated. Results: Neuronal stimulation leads to an increase in the ubiquitination of FMRP. This suggests that ubiquitination may be a mechanism of regulating the repressive activity of FMRP. The Cdh1 subunit of the E3-ubiquitin ligase anaphase-promoting complex (APC) binds to FMRP, and thus may play a role in ubiquitinating FMRP. Mass spectrometry analysis of Cdh1 reveals a novel function of Cdh1 as a translational regulator, beyond its well-characterized role in ubiquitination during mitosis. This biological relevance is emphasized as expression of Cdh1-APC increases steady-state protein synthesis. Conclusions: Our data identify a novel role of Cdh1-APC as a regulator of translation and support the novel hypothesis that ubiquitination serves as a dynamic mechanism to regulate FMRP.

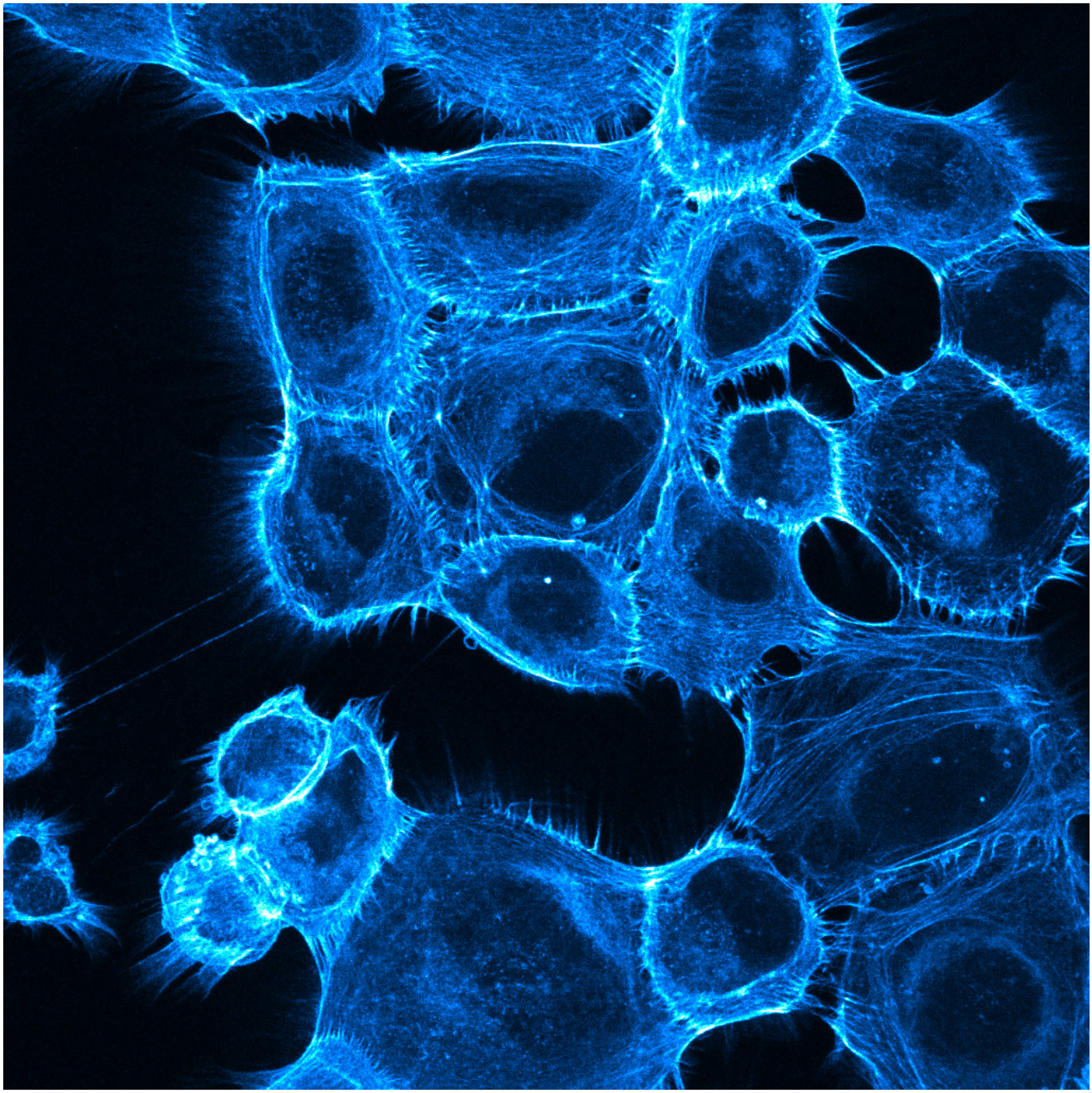
A NOVEL FUNCTION OF THE MIR126/MAPK PATHWAY IN ETV2-INDUCED FLK1^{+} MESODERM GENERATION FROM MOUSE EMBRYONIC STEM CELLS

***Ju Young Kim*,[1,2,4]** Dong Hun Lee,[1,4] Changwon Park[1,2,3,4]

[1]Department of Pediatrics, [2]Molecular and Systems Pharmacology Program, [3]Biochemistry, Cell Biology and Developmental Biology Program, [4]Children's Heart Research and Outcomes Center, Emory University School of Medicine, Atlanta, GA

ETV2, an ETS transcription factor, has been identified as an essential player for cardiovascular system development. However, the detailed molecular mechanism behind ETV2-regulated endothelial and hematopoietic cell generation remains largely unclear. In this study, we showed that ETV2 regulates the generation of FLK1/VEGFR2^{+} cells, a multipotent progenitor of cardiovascular lineage, through the miR126/MAPK pathway. From miRNA sequencing analysis, we found miR126 as a potential downstream of ETV2 and revealed that ETV2 was able to induce the expression of miR126 through a direct binding on the promoter of *Egfl7*, which is co-transcribed with miR126. Overexpression of ETV2 increased the generation of FLK1^{+} cells with concomitantly decreased expression of SPRED1, a suppressor of the MAPK pathway and target of miR126. Consistently, MAPK activity was positively regulated by ETV2, and inhibition of MAPK activity led to impaired ETV2-induced FLK1^{+} cell generation. Further, we showed that the downstream of the MAPK pathway JUN/FOS activated the enhancer of *Flk1* through AP1 responsive elements. In addition, we found that introduction of miR126 into ETV2$^{-/-}$ cells augmented the generation of FLK1^{+} cells. Taken together, our findings strongly suggest that the miR126/MAPK pathway plays an important function of ETV2-mediated FLK1^{+} cell generation from mouse embryonic stem cells.

Poster Presentation Abstracts



3rd Place, ICI Image Contest
Brian Pedro, Cancer Biology
H1299 lung cancer cells stained for actin

Poster Presentations

Session 1: 1:00 - 1:45PM - Odd-numbered posters
Session 2: 1:45 - 2:30PM - Even-numbered posters

Poster	Name	Program	Poster	Name	Program
1	Zane Laughlin	BCDB	**35**	J. Christopher Rounds	GMB
2	Sabrina Lynn	BCDB	**36**	Alyssa Scott	GMB
3	Kelsey Maher	BCDB	**37**	Alyse Steves	GMB
4	Elizabeth Minten	BCDB	**38**	Sarah Suciu	GMB
5	Raven Peterson	BCDB	**39**	Victor Band	IMP
6	Samantha Schwartz	BCDB	**40**	Lynette Chea	IMP
7	Mwangala Akamandisa	CB	**41**	Ching-wen Chen	IMP
8	Jameson Berry	CB	**42**	Elina El-Badry	IMP
9	Alex Chen	CB	**43**	Bijean Ford	IMP
10	Jamie King	CB	**44**	Madelyn Houser	IMP
11	Allyson Koyen	CB	**45**	Andrew Jones	IMP
12	Yixiang Li	CB	**46**	Michael La Muraglia	IMP
13	Brian Pedro	CB	**47**	Tiger Li	IMP
14	Briana Rackley	CB	**48**	Julia McBrien	IMP
15	Cara Schiavon	CB	**49**	Anna Morris	IMP
16	Emily Summerbell	CB	**50**	Madeline Price	IMP
17	David Weir	CB	**51**	Alexandra Wolfarth	IMP
18	Matthew Armstrong	GMB	**52**	Sarah Anderson	MMG
19	Ognenka Avramovska	GMB	**53**	Kelsie Brooks	MMG
20	Edwin Corgiat	GMB	**54**	Kara Phipps	MMG
21	Sarah Curtis	GMB	**55**	Roxana Rodríguez Stewart	MMG
22	Christine Doriono	GMB	**56**	Edgar Sherman	MMG
23	Salma Ferdous	GMB	**57**	Aimee Paulk Tierney	MMG
24	Sara Fielder	GMB	**58**	Sara Bramlett	MSP
25	Stephanie Grewenow	GMB	**59**	Kirsten Cottrill	MSP
26	George Inglis	GMB	**60**	Lauren Fleischer	MSP
27	Anna Kania	GMB	**61**	Cameron Herting	MSP
28	Christy Kinney	GMB	**62**	Akram Salam	MSP
29	Kari Mattison	GMB	**63**	Darian Williams	MSP
30	Jasmine Moody	GMB	**64**	Rachel Branco	NS
31	Trenell Mosley	GMB	**65**	Erica Ahkter	NS
32	Dillon Patterson	GMB	**66**	Desiree De Leon	NS
33	Rebecca Pollak	GMB	**67**	Stephanie Foster	NS
34	Juan Rodriguez	GMB	**68**	Eduardo Gigante	NS

69	Mary Herrick	NS	**77**	Rachel Pearcy	NS
70	Michelle Johnson	NS	**78**	Lindsey Shapiro	NS
71	Erin King	NS	**79**	Archana Venkataraman	NS
72	Erica Landis	NS	**80**	Lahiru Wimalasena	NS
73	Laura Butkovich	NS	**81**	Nate Jacobs	PBEE
74	Dan Li	NS	**82**	Ellie Maino	PBEE
75	Neeti Mehta	NS	**83**	Diana Vera-Cruz	PBEE
76	Amielle Moreno	NS	**84**	Signe White	PBEE

Zane Laughlin, BCDB **Poster #1**

MECHANISM OF BACTERIAL RIBOSOME 30S AND 50S SUBUNIT RECOGNITION AND MODIFICATION BY TLYA

Zane Laughlin[1,2] and Graeme Conn[1,2]

[1]Biochemistry, Cell and Developmental Biology (BCDB) Program, Emory University. [2]Department of Biochemistry, Emory University School of Medicine, Atlanta, GA.

Mycobacterium tuberculosis (*Mtb*) infected ~10.4 million people worldwide in 2015 which resulted in ~1.8 million deaths. *Mtb* can become resistant to second-line drugs like capreomycin through the loss of activity of the ribosomal RNA methyltransferase TlyA which methylates the ribose 2'-OH of C1409 of the 16S rRNA of the small ribosome subunit (30S) and C1920 of the 23S rRNA of the large ribosome subunit (50S). Previous research suggests that the C-terminal domain of TlyA is responsible for its methyltransferase activity while the N-terminal domain may control specific target site recognition. Additionally, the flexible interdomain linker was found to be able to adopt two different conformations and is speculated to be a "molecular switch" capable of altering the interaction between TlyA's two domains and thus controlling TlyA activity. However, TlyA's molecular mechanisms of substrate recognition and modification are currently not well understood. We set out to determine the mechanism of 30S or 50S recognition and site-specific methylation of TlyA's two distinct target nucleotides. Defining these molecular details will help complete the picture of TlyA activity and its role in drug resistance in *Mtb*, as well as furthering our general understanding rRNA modification processes that are prevalent in all domains of life.

Sabrina Lynn, BCDB **Poster #2**

IMPACT OF TIGHT JUNCTION REMODELING ON LUNG EPITHELIAL BARRIER FUNCTION

K. Sabrina Lynn, Barbara Schlingmann, Rachel Vance, Max Cornely, Michael Koval[1]

[1] Department of Medicine, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine and Department of Cell Biology

Survival of acute respiratory distress syndrome (ARDS) is chiefly attributed to the ability to maintain airspace fluid balance. The severity and risk of ARDS is magnified with chronic alcohol abuse. Currently, our lab is investigating the molecular mechanisms behind increased incidence of ARDS, with particular interest in the effects on tight junctions. Previous work in the Koval lab determined that chronic alcohol ingestion increases expression of tight junction protein claudin-5 by the alveolar epithelium, which is necessary and sufficient to decrease alveolar epithelial barrier function. This impairment of the alveolar epithelial barrier correlated to molecular rearrangement of claudin-18 into spike-like structures perpendicular to the cell junction interface. These "tight junction spikes" (TJ spikes) appear to be active areas of junction remodeling driven by increased endocytosis of tight junction proteins. Treatment with the endocytosis inhibitor Dynasore, which targets the actin-binding protein dynamin, significantly reduces the number of TJ spikes. This suggests a role for clathrin-mediated, dynamin-dependent endocytosis in TJ spike formation. The long-term goal is to identify novel therapeutic targets to improve barrier function by redirecting spike-associated claudin-18 into barrier forming tight junctions.

Kelsey Maher, BCDB **Poster #3**

PROFILING OF ACCESSIBLE CHROMATIN REGIONS ACROSS MULTIPLE PLANT SPECIES AND CELL TYPES REVEALS COMMON GENE REGULATORY PRINCIPLES AND NEW CONTROL MODULES

Kelsey A. Maher[1,2], Marko Bajic[1,3], Roger B. Deal[1]

[1] Department of Biology, Emory University, Atlanta, GA, [2] Biochemistry, Cell, and Developmental Biology Program in the Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA, [3] Genetics and Molecular Biology Program in the Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA

The transcriptional regulatory structure of plant genomes remains poorly defined relative to animals. It is unclear how many *cis*-regulatory elements exist, where these elements lie relative to promoters, and how these features are conserved across plant species. We employed the Assay for Transposase-Accessible Chromatin (ATAC-seq) in four plant species (*Arabidopsis thaliana*, *Medicago truncatula*, *Solanum lycopersicum*, and *Oryza sativa*) to delineate open chromatin regions and transcription factor (TF) binding sites across each genome. Despite 10-fold variation in intergenic space among species, the majority of open chromatin regions lie within 3 kb upstream of a transcription start site in all species. We find a common set of four TFs that appear to regulate conserved gene sets in the root tips of all four species, suggesting that TF-gene networks are generally conserved. Comparative ATAC-seq profiling of *Arabidopsis* root hair and non-hair cell types revealed extensive similarity as well as many cell type-specific differences. Analyzing TF binding sites in differentially accessible regions identified a MYB-driven regulatory module unique to the hair cell, which appears to control both cell fate regulators and abiotic stress responses. Our analyses revealed common regulatory principles among species and shed light on the mechanisms producing cell type-specific transcriptomes during development.

Elizabeth Minten, BCDB **Poster #4**

REGULATION OF BRCA1 BY SIRT2

Elizabeth Minten[1], Hui Zhang[1] MD/PhD, Chunyang Li[1], PamelaSara Head[1], and David Yu[1], MD/PhD.

[1]Emory University, Department of Radiation Oncology

Breast Cancer 1 (BRCA1) is a protein necessary for the proper repair of DNA double-stranded breaks (DSBs) through the homologous recombination (HR) pathway. Defects in BRCA1 have been linked to different types of cancer in both men and women, including breast, ovarian, and pancreatic cancer. However, the regulation of BRCA1 is not yet well understood, and in many cases, how defects in BRCA1 function lead to an increased risk of developing cancer is also unknown, making preventative care and treatment of resulting cancers more difficult. Our lab has discovered that SIRT2, a histone deacetylase and putative human tumor suppressor, plays a crucial role in the DNA damage response and repair of DNA DSBs, where depletion of SIRT2 impairs HR and increases cell sensitivity to IR in a deacetylase-dependent manner. A mass spectrometry analysis showed SIRT2 interacts with BRCA1, an interaction we validated. We also found SIRT2 deacetylates BRCA1 both *in vitro* and in cells. Depletion of SIRT2 and subsequent deacetylation of BRCA1 decreases BRCA1 protein levels in cells and impairs HR. Our results show SIRT2 is a novel regulator of BRCA1 and is critical for the repair of DNA DSBs through HR.

Raven Peterson, BCDB **Poster #5**

REGULATION OF TIGHT JUNCTIONS BY ANTI-INTEGRIN NANOWIRES

Raven J. Peterson[1,2], Colin R. Zamecnik[3], Tejal A. Desai[3], Michael Koval[1,2,4]

[1]Biochemistry, Cell and Developmental Biology Graduate Program, [2]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University, [3]Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, [4]Department of Cell Biology, Emory University

Epithelial cells form tight junctions (TJs) which serve as selective barriers that regulate the paracellular route between cell-cell contact sites creating an obstacle for the delivery of large macromolecular drugs. We have determined that stimulation of epithelial cells in contact with nanostructured films (NSFs) increases TJ permeability to large macromolecules, specifically through stimulation of apically expressed integrin ®1. The drawback of using NSFs to study integrin-dependent regulation of TJ permeability is that they interact with large patches of the apical surface of a monolayer all at once rather than just integrin ®1. To address the specific role that integrins play in regulating TJ permeability, we developed an anti-integrin nanowire system. These anti-integrin nanowires serve as a platform for us to further study the roles for apical integrins in regulating the barrier function of epithelial cells, of which very little is presently known. Treatment of epithelial monolayers with anti-integrin nanowires significantly decreased the transepithelial resistance of the monlayer, increased paracellular flux, promoted changes in the localization of TJ scaffolding protein zonula occludens-1, and promoted changes in actin organization, suggesting that apical integrins play a role in regulating paracellular permeability through the TJ.

Samantha Schwartz, BCDB **Poster #6**

REGULATION OF 2'-5'-OLIGOADENYLATE SYNTHETASE 1 (OAS1) BY SMALL DOUBLE-STRANDED RNAS

Samantha L. Schwartz[1, 2] and Graeme L. Conn[1, 2]

[1]Biochemistry, Cell and Developmental Biology (BCDB) Program, Emory University.

[2]Department of Biochemistry, Emory University School of Medicine, Atlanta, GA.

The innate immune system is a collection of critical, first line intracellular and extracellular processes that limit viral infectivity. This system must accurately distinguish "self" from foreign molecules, and its misregulation can cause increased susceptibility to infection and other diseases, such as interferonopathies. The 2'-5'-oligoadenylate synthetase (OAS) enzymes are important sensors of cytosolic double-stranded (ds)RNA. X-ray crystal structures have given some insight into how dsRNA activates OAS1, but we still understand little about how specific dsRNA features control the level of activation. To address this gap, we designed duplexes to test the impact of changes within a strongly activating dsRNA. Remarkably, while a single mutation on one strand resulted in *complete loss* of OAS1 activity, the equivalent change on the opposite strand led to *increased* OAS1 activity, despite both dsRNAs binding OAS1 with similar affinity. Given these findings, I hypothesize that dsRNAs contain competing OAS1 binding sites with remarkably different capacities to activate the protein. However, the molecular signatures and their contexts that define such sites as activating or non-activating are unknown. Clearly defining these features will enhance our understanding of host-pathogen interactions, such as how viruses might circumvent the OAS1/RNase L pathway by masking activating RNA motifs to evade detection.

Mwangala Akamandisa, CB **Poster #7**

MECHANISMS OF PPM1D-MEDIATED TUMORIGENESIS IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

***Mwangala Akamandisa*[1,4]**, Kai Nie[1], Jing Wen[1], Rita Nahta[2,3, 4], Dolores Hambardzumyan[1,3,4], Robert C Castellino[1,3,4]

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Diffuse intrinsic pontine glioma (DIPG) has a dismal prognosis with a five-year survival of less than 2%. It is unamenable to surgical resection, is not responsive to conventional chemotherapy, and responds only temporarily to radiation therapy (XRT). New and effective treatments of DIPG are needed. Up to 25% of DIPGs contain a *PPM1D* mutation, which results in C-terminal-truncated Ser/Thr protein phosphatase. Normally, PPM1D negatively regulates activation of the DNA damage response proteins p53, ATM/ATR, H2AX and CHK1/2. Recent studies suggest a role for mutated PPM1D in radio-resistance. We examined the role of mutated *PPM1D* in the growth and radio-sensitivity of DIPG using patient-derived DIPG cells. Mutated *PPM1D* promoted DIPG cell proliferation, while knock-down suppressed DIPG cell growth. Treatment with a small molecule PPM1D inhibitor similarly suppressed the growth of DIPG cells containing a mutant PPM1D, and, PPM1D inhibition augmented the efficacy of radiation *in vitro* and *ex vivo* on brain tissue slices. Our results establish PPM1D as a promoter of tumorigenesis in DIPG and provide pre-clinical evidence of the efficacy of PPM1D inhibition alone and in combination with radiation therapy against DIPG.

Jameson Berry, CB **Poster #8**

TARGETED DELIVERY OF DOXORUBICIN VIA CONJUGATION AND COMBINATION WITH ONCOLYTIC REOVIRUS IN TRIPLE-NEGATIVE BREAST CANCER

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Treatment of triple-negative breast cancer (TNBC), which lacks expression of estrogen and progesterone receptors, along with HER2, is largely limited to cytotoxic chemotherapy. One approach to increase treatment efficacy is combination therapy. Reovirus is an oncolytic virus which preferentially infects and kills transformed cells. In a chemical screen of Phase I – III-tested small molecule inhibitors, doxorubicin hydrochloride robustly enhanced reovirus infectivity while inducing potent cytotoxicity of MDA-MB-231 TNBC cells. Doxorubicin is a topoisomerase II inhibitor that causes DNA double-strand breaks and cell death. To circumvent off-tumor cytotoxic effects of doxorubicin, drug-conjugated reovirus will be assessed for increased reovirus cytopathic efficacy with enhanced selective delivery of doxorubicin to TNBC cells. Preliminary results indicate that conjugated virus attachment to MDA-MB-231 cells is slightly diminished. However, conjugation does not hinder virus infectivity of MDA-MB-231 cells. Additionally, the amount of doxorubicin bound to reovirus positively correlates with overall cytopathicity. Future studies will determine if conjugated reovirus induces similar DNA damage response as doxorubicin alone, the intracellular location of doxorubicin delivery, and the effect of doxorubicin treatment on infection kinetics. Conjugation of small molecule inhibitors to reovirus may be an effective new method to directly target and kill cancer cells in a multi-faceted combinatorial approach.

Alex Chen, CB **Poster #9**

UNDERSTANDING THE MECHANISM OF RIOK2 FUNCTION IN GLIOBLASTOMA

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Glioblastoma multiforme (GBM) is the most aggressive and prevalent form of primary brain cancer and is incurable. Amplification, mutation, and/or overexpression of the EGFR receptor tyrosine kinase and activating mutations in components of the PI3K pathway are common in GBM tumors, although the pathways that act downstream of EGFR and PI3K to drive tumorigenesis remain poorly understood. To better understand the underlying biology of tumorigenesis, we use a *Drosophila melanogaster* GBM model in which malignant neoplastic tumors arise from glial progenitor cells overexpressing activated oncogenic versions of EGFR and PI3K and identified Right-Open-Reading-Frame-2 (RIOK2), an atypical serine-threonine kinase, as a possible driver of EGFR-PI3K-dependent GBM. To elucidate downstream targets of RIOK2, we conducted preliminary immunoprecipitation experiments of RIOK2 from patient-derived GBM cell cultures coupled with proteomics and identified several novel RNA-binding proteins (RBPs) as binding partners and potential substrates of RIOK2. Subsequent experiments using our *Drosophila* GBM model show that RBP knock-down drastically reduced aberrant glial cell proliferation and invasion, similar to RIOK2 knock-down. Based on our preliminary results, we hypothesize that RIOK2 drives tumorigenesis by modulating the activity of RBPs, and that this promotes the translation of RBP target mRNAs to drive tumor cell proliferation and survival.

Jamie King, CB **Poster #10**

TTK AND KLF5 SIGNALING MODULATE EMT IN TRIPLE NEGATIVE BREAST CANCER.

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Triple negative (TN) breast tumors are a significant health disparity because they disproportionally affect African-American and Latin women. Effective treatment is a challenge partially due to aggressive cell behavior. TTK kinase is correlated with the TN subtype and overexpressed in TN cells while the KLF5 transcription factor is downregulated in mesenchymal stem cell like TN cells. TTK and KLF5 are regulated by TGF-β and we hypothesized that high TTK expression may regulate KLF5, and contribute to the epithelial to mesenchymal transition (EMT) in TN breast cancer. In preliminary tests, we found the mesenchymal TN cell lines were most sensitive to TTK inhibition. Next, silencing TTK or preventing TTK kinase activity decreased mesenchymal markers and cellular phenotypes in MDA-MB-231 and Hs578t cells, while also increasing KLF5 expression. Conversely, when TTK and KLF5 were silenced simultaneously, mesenchymal phenotypes were rescued. Furthermore, targeting TTK decreased expression of micro RNA 21 (miR-21), an oncomir in the TGF-β pathway. Overexpressing wild type KLF5 in MDA-MB-231 cells also decreased miR-21 expression and altered apoptotic responses to TTK inhibition. These results suggest targeting TTK could decrease invasive behavior in TN breast cancer cells and provides support to develop TTK inhibitors to improve treatments for TN breast cancer.

Allyson Koyen, CB **Poster #11**

EZH2 MEDIATES CISPLATIN RESISTANCE IN SMALL CELL LUNG CANCER THROUGH NUCLEOTIDE EXCISION REPAIR

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Small cell lung cancer (SCLC) is the most aggressive form of lung cancer, with a five-year survival rate of 7%. Cisplatin-based chemotherapy is the first line treatment for SCLC; however, many patients develop treatment resistance and experience tumor recurrence. Targeting proteins critical to the repair of cisplatin DNA crosslinks is a strategy for overcoming acquired cisplatin resistance in SCLC, but many proteins that mediate crosslink repair have yet to be identified. To address this issue, we performed a synthetic lethal siRNA screen in cisplatin resistant SCLC cells, and identified EZH2 as one of the strongest mediators of cisplatin resistance. EZH2 localizes to sites of DNA damage which are induced by UVA-crosslinking laser microirradiation and interacts in a complex with DDB1, and XPC, members of the nucleotide excision repair (NER) pathway. Loss of EZH2 sensitizes SCLC cells to UV damage, and further, loss of EZH2 and DDB1 together are epistatic in the sensitization of SCLC to cisplatin, confirming a role for EZH2 in NER. Finally, we found EZH2 expression correlates with cisplatin resistance across SCLC cell lines. Together, this data suggests that EZH2 functions as a novel regulator of NER, and that EZH2 is a promising target for cisplatin resistant SCLC.

Yixiang Li, CB **Poster #12**

ACETYLATED KRUPPEL-LIKE FACTOR 5 AND TRANSFORMING GROWTH FACTOR-B MEDIATED DRUG RESISTANCE IN PROSTATE CANCER

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Prostate cancer is the second leading cause of cancer related death in the United States. As the most aggressive form of prostate cancer, metastatic Castration Resistant Prostate Cancer (mCRPC) is primarily treated with chemotherapy including docetaxel. However, the effect of chemotherapy is limited by development of lethal drug resistant diseases in almost all patients. Human Krüppel-Like Factor 5 (KLF5) was identified as a tumor suppressor in prostate cancer and underwent acetylation by P300 acetyltransferase recruited by Transforming Growth Factor-β. We found that acetylated KLF5 induced docetaxel resistance in DU145 and PC3 prostate cancer cell lines and xenograft mouse model. Moreover, we found that the induction of docetaxel resistance depends on TGF-βsignaling. RNA-seq analysis identified several potential downstream targets. Among them, Aldo-Keto Reductase 1C3 and 1B10 are pivotal antioxidant enzymes with detoxification function. In addition, ChIP-seq analysis revealed that NFE2L1, a master antioxidant regulator, is a direct binding target of KLF5. These suggested that acetylated KLF5 mediated drug resistance through orchestrating antioxidant enzyme detoxifying network. Our study introduced a novel mechanism of acetylated KLF5 mediated docetaxel resistance in prostate cancer and contributed to an advanced therapy combination for advance prostate cancer patients.

Brian Pedro, CB **Poster #13**

DEFINING LEADER CELL BIOLOGY IN COLLECTIVE INVASION

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Metastasis is responsible for the vast majority of cancer deaths, yet the mechanisms by which this process occurs are still poorly understood. Solid tumors, including lung cancer, often metastasize by collective invasion, in which groups of cancer cells invade and migrate together in cohesive packs. We have previously shown that these packs contain distinct leader and follower cells, which act cooperatively to facilitate collective invasion. Now, RNA-seq analysis has revealed a number of leader- and follower-specific gene mutations, potentially providing new insight into the biology and function of these phenotypically distinct cells. Included among this list are genes involved in cell motility, metabolism, post-translational modification, and other key biological processes. Importantly, we identified a leader-specific point mutation in ARP3, a major component of the Arp2/3 complex that regulates actin dynamics during cell motility. This lysine-to-arginine point mutation has been identified as a predicted ubiquitination site in the ARP3 protein, and introduction of this mutation into follower cells confers increased ability to invade and lead collective chains, indicating a potential role for this mutation in leader cell function and emergence. Overall, these findings provide us with a new window into the biological mechanisms underlying lung cancer collective invasion and metastasis.

Briana Rackley, CB **Poster #14**

AN IN VIVO MOSAIC APPROACH TO DEFINE THE MOLECULAR PATHWAYS REQUIRED FOR THE INVASIVE BEHAVIOR OF THE LKB1 METASTASIS SUPPRESSOR

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The LKB1 serine/threonine kinase is a prolific metastasis suppressor, and is commonly co-mutated with KRAS. At a functional level, myriad downstream kinases of the AMPK family are phosphorylated by LKB1 to control energy homeostasis, cell polarity, and cell adhesion signaling, however; the biologic process and molecular players required for LKB1-mutant cells to cross the basement membrane and ultimately disseminate remain elusive. To answer these questions in vivo, we have created the first oncogenic Kras, Lkb1-mutant Drosophila model. Loss of Lkb1 in imaginal disc epithelial clones expressing varying levels of oncogenic Kras leads to alterations in cell signaling and over-expression of MMP1, a hallmark of JNK-driven basement membrane invasion. Intriguingly, while moderate levels of Kras overexpression leads to hyperplasia of surrounding wild-type tissue due to both increased growth and proliferation, higher levels of Kras overexpression causes a neoplastic switch and more severe basement membrane invasion. These data suggest that loss of polarity may not underlie the aggressive nature of LKB1-mutant tumors in vivo but may be dependent on a different aspect of LKB1/KRAS biology. Currently, we are using both a genetic approach and cutting-edge light sheet microscopy to define the behavior and biologic pathways required by this aggressive molecular subtype.

Cara Schiavon, CB **Poster #15**

A ROLE FOR THE ARL2 GTPASE ACTIVATING PROTEIN (GAP), ELMOD2, IN MITOCHINDRIAL FUSION

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ARL2, a member of the ARF family of regulatory GTPases, is highly conserved across eukaryotes. It is ubiquitously expressed in eukaryotes and is an essential gene in several model organisms. We previously reported that ARL2 plays an important role in mitochondrial morphology, demonstrating that expression of dominant activating or negative point mutants of ARL2 results in mitochondrial elongation and fragmentation, respectively. Furthermore, we discovered that expression of dominant active ARL2 partially rescued mitochondrial fragmentation in *mfn1*$^{-/-}$ or *mfn2*$^{-/-}$ MEFs. Our lab identified and purified a family of ARL2-specific GTPase activating proteins (GAPs), termed ELMOD1-3. Of these only one, ELMOD2, was found in mitochondria. ELMOD2 siRNA also resulted in mitochondrial fragmentation. Data from CRISPR knockouts in cultured cells are consistent with loss of ELMOD2 leading to mitochondrial fragmentation. Recent data show that expression of ELMOD2 also partially reverses the fusion defect observed in *mfn 1*$^{-/-}$ or *mfn2*$^{-/-}$ MEFs. Mitochondrial fusion assays reveal that expression of ELMOD2 results in increased mitochondrial fusion. These data suggest that ELMOD2 acts downstream of ARL2 in mitochondria to promote mitochondrial fusion. This is consistent with other ARF family GAPs, which also serve as effectors of biological responses, in addition to regulators/terminators of their respective GTPase activities.

Emily Summerbell, CB **Poster #16**

LEADER CELLS ARE DEFINED BY DNA HYPERMETHYLATION AND ABERRANT GENE EXPRESSION DURING COLLECTIVE LUNG CANCER INVASION

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Collective cancer cell invasion is found in most solid tumors and directly contributes to cancer metastasis. Within these collective invasion packs, highly-invasive leader cells pioneer migration and invasion while highly-proliferative follower cells travel behind them. Since epigenetic mechanisms, such as DNA methylation, regulate phenotypic plasticity and cell differentiation in many cellular contexts, we hypothesize that leader and follower cell phenotypes emerge through epigenetic reprogramming of lung cancer cells. Using a DNA methylation array, lung cancer-derived leader cells showed significant global DNA hypermethylation compared to both follower cells and the parental population. Integrating DNA methylome analysis with RNAseq analysis identified unique gene expression and enhancer signatures that correlated with these DNA methylation changes and that were enriched for gene ontology pathways critical for collective cancer invasion, including VEGF/angiogenesis signaling. Differentially methylated promoters correlated with significant gene silencing or overexpression of 59 genes in leaders, including putative tumor suppressors (HTATIP2) and oncogenes (MYO10). Inhibition of DNA methylation using 5-aza-2'-deoxycytidine (DAC) significantly abrogated leader-dependent collective invasion and rescued expression of the tumor suppressor HTATIP2. Our data suggest a mechanism wherein global DNA hypermethylation can drive the leader cell phenotype and wherein DNA methylation regulates gene expression critical for leader cell behavior.

David Weir, CB **Poster #17**

PROCASPASE-3 REGULATES THE APOPTOTIC THRESHOLD OF THE CELL THROUGH MODULATION OF FIBRONECTIN SECRETION

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Mounting evidence indicates caspases have non-apoptotic functions. Our laboratory recently demonstrated the zymogen procaspase-3 negatively regulates fibronectin secretion. This function is distinct from the executioner caspase function of caspase-3. Additionally, we showed procaspase-3 regulates adhesion in the absence of a supplied ECM through control of fibronectin secretion. Furthermore, we demonstrated procaspase-3 regulates survival in an adhesion-dependent manner. However, it remains unclear whether fibronectin secretion is required for procaspase-3 to regulate survival. We hypothesize procaspase-3 regulates survival through modulation of fibronectin secretion. Fibronectin knockdown ablates the resistance of caspase-$3^{-/-}$ mouse embryonic fibroblasts (MEFs) to serum withdrawal. Furthermore, supplying exogenous fibronectin to these cells restores resistance. Death due to serum withdrawal is blocked by Q-VD-OPh in WT MEFs, but not $C3^{-/-}$ MEFs subjected to fibronectin knockdown. Thus, $C3^{-/-}$ MEFs subjected to fibronectin knockdown and serum withdrawal die in a caspase-independent fashion. Procaspase-7 is cleaved and activated in $C3^{-/-}$ MEFs subjected to serum withdrawal, implying that MOMP is occurring. However, inhibition of caspase-7 activity has no effect on death. This is consistent with our previous findings that caspase-3 is crucial this cell death while caspase-7 is dispensable. These data demonstrate procaspase-3 regulates the apoptotic threshold of the cell through modulation of fibronectin secretion.

Matthew Armstrong, GMB **Poster #18**

SEX-SPECIFIC COGNITIVE–BEHAVIOURAL PROFILES EMERGING FROM INDIVIDUAL VARIATION IN NUMEROSITY DISCRIMINATION IN GAMBUSIA *AFFINIS*.

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The relationship between an individual's cognitive abilities and other behavioral attributes is complex, yet critical to understanding how individual differences in cognition arise. Here we use western mosquitofish, Gambusia *affinis*, to investigate the relationship between individual associative learning performance in numerical discrimination tests and independent measures of activity, exploration, anxiety and sociability. We found extensive and highly repeatable inter-individual variation in learning performance ($r = 0.89$; $ICC = 0.89$). Males and females exhibited similar learning performance, yet differed in sociability, activity and their relationship between learning and anxiety/exploration tendencies. Sex-specific multivariate behavior scores successfully predicted variation in individual learning performance, whereas combined sex analyses did not. Female multivariate behavior scores significantly predict learning performance across females ($\rho = 0.80$, $p = 0.005$) with high-performing female learners differentiated from female non-learners and low-performing learners by significant contributions of activity and sociability measures. Meanwhile, males of different learning performance levels (high-, low- and non-learners) were distinguished from each other by unique behavioral loadings of sociability, activity and anxiety/exploration scores, respectively. Our data suggest that despite convergence on learning performance, the sexes diverge in cognitive–behavioral relationships that are likely products of different sexual selection pressures.

Ognenka Avramovska, GMB **Poster #19**

MECHANISTIC INSIGHTS IN POLYPLOID GENOME STABILITY AND IMPLICATIONS FOR ADAPTATION TO FLUCONAZOLE IN AN OPPORTUNISTIC PATHOGEN

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Candida albicans, a human fungal pathogen, rapidly acquires resistance to the limited number of antifungal drugs available for treatment, especially fluconazole (FLU). The *C. albicans* genome is highly labile and tolerates genomic perturbations such as aneuploidy and loss of heterozygosity (LOH), which are vital for acquiring resistance to FLU. Indeed, 50% of FLU-resistant clinical and laboratory strains carry aneuploidy (Selmecki 2006) and LOH events are common in regions containing genes implicated in FLU-resistance (Ford 2015). Preliminary data suggests that overexpression of the conserved centromeric H3 variant, *CSE4,* may stabilize the genome of polyploid cells, which readily undergo genomic perturbations (Hickman 2015). Through this observation, we hypothesize that wildtype centromere and kinetochore structure results in chromosome mis-segregation in polyploid backgrounds and generates aneuploidy. To determine how the ability to generate aneuploidy contributes to FLU resistance in C. *albicans*, we will manipulate the degree of genome stability via *CSE4*-overexpression in diploid, triploid and tetraploid backgrounds. Experimental evolution will be performed with these strains in the presence and absence of fluconazole to track adaptation dynamics to antifungal drugs. A clear understanding of the mechanisms C. *albicans* utilizes in FLU adaptation will drive the development of more effective antifungals and treatment regimens for *Candida* and other fungal pathogens.

Edwin Corgiat, GMB **Poster #20**

DEFINING LINKS BETWEEN AN INTELLECTUAL DISABILITY-ASSOCIATED RNA-BINDING PROTEIN AND PLANAR CELL POLARITY IN NEURODEVELOPMENT

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The human *ZC3H14* gene encodes a ubiquitously expressed zinc-finger polyadenosine RNA-binding protein. Mutations in *ZC3H14* that impair function have been linked to an inherited form of intellectual disability (ID). We developed a *Drosophila melanogaster* model of ZC3H14 ID by deletion of *dNab2*, the fly ortholog of *ZC3H14*. These *dNab2*-deficient animals display defects in survival, locomotion, and memory which correlate at a cellular level with neurodevelopmental defects. Importantly, pan-neuronal expression of human ZC3H14 in *Drosophila* neurons can rescue several phenotypes of *dNab2*-deficient flies, suggesting that dNab2 and ZC3H14 serve conserved roles in neurons. To probe this role, we used a dominant-modifier approach to identify alleles of genes that interact with *dNab2*. This approach has uncovered genetic interactions between *dNab2* and multiple components of the planar cell polarity (PCP) pathway that can rescue dNab2-deficient neurodevelopmental defects. Here we show that dNab2 null flies and ZC3H14 knockout mice both show classic PCP-like orientation defects in wing hairs and organ of Corti, respectively. Furthermore, loss of function alleles of PCP components can rescue a portion of dNab2 null neuro-morphology defects observed in structures analogous to the mammalian hippocampus. These data suggest that dNab2 may regulating mushroom body neurodevelopment through the PCP pathway.

Sarah Curtis, GMB **Poster #21**

DIFFERENCES IN EPIGENETIC MARKS ASSOCIATE WITH EXPOSURE TO AN ENDOCRINE-DISRUPTING COMPOUND

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In the 1970's, Michigan residents were exposed to an industrial mixture of polybrominated biphenyl (PBBs), an endocrine-disrupting compound, when it was added to farm animal feed during a factory accident. Exposed individuals and their children have numerous health problems, though the underlying mechanism behind these health problems remains unknown. Other endocrine-disrupting compounds have been linked to epigenetic differences, but no epigenetic studies have been done for PBB. Therefore, DNA from the blood of individuals with current (N = 659) PBB was interrogated with the MethylationEPIC BeadChip. Associations between each of the ~850,000 CpG sites and serum PBB levels were tested with a linear regression that controlled for age, sex, and cell type proportion. After multiple test correction (FDR <0.05), 412 CpG sites associate with total PBB levels. While many of the CpGs that associated with total PBB levels are in genes important for endocrine function, there was no enrichment for specific biological pathways. Further analyses will be needed to interrogate whether PBB acts more stochastically on the genome, and whether the CpG sites found in this analysis associate with the development of health problems in exposed individuals.

Christine Doriono, GMB **Poster #22**

EPIGENETIC CONTRIBUTIONS TO HOMOLOGOUS CHROMOSOME RECOGNITION IN MEIOSIS

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During meiosis, homologous chromosomes must correctly identify one another in order for proper alignment and recombination to occur. Improper pairing can lead to chromosomal rearrangements that result in defective embryonic development. Currently, little is known about how homologs identify each other to the exclusion of other chromosomes. During meiosis distinct patterns of transcription are produced on each chromosome and are associated with epigenetic modifications such as the methylation of Lysine 36 on Histone H3 (H3K36me). In humans, H3K36me is recognized by the chromodomain containing protein MRG15. Pairing defects were observed in *C. elegans* lacking the MRG15 homolog, *mrg-1*. The specific role of MRG-1 in homolog recognition is unknown. Our hypothesis is that histone modifications that result from meiotic transcription, including H3K36me, provide an "epigenetic barcode" used to distinguish chromosomes during homolog searching, and is facilitated through MRG-1. We are examining the role of H3K36me in homolog recognition in germlines lacking *mes-4* and *met-1,* the histone methyltransferases responsible for H3K36me. Our recent data demonstrates that germ cells lacking H3K36me exhibit increased sterility and synaptic delay. Similar observations are seen in *mrg-1* mutants. These results suggest that epigenetic modifications such as H3K36me may play an important role in homolog recognition during meiosis.

Salma Ferdous, GMB **Poster #23**

THE ROLE OF LSD1 IN RETINAL DEVELOPMENT AND RETINOBLASTOMA DIFFERENTIATION

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The purpose of this study was to determine the role of lysine specific demethylase 1 (Lsd1) in proper retinal differentiation. Proper retinal differentiation is necessary for normal visual function, but aberrantly occurs in retinoblastoma. Additionally, we investigated Lsd1 role in human retinoblastoma tumors, specifically rosette and fleurette features, which mimic photoreceptor differentiation. We conducted immunohistochemistry (IHC) and western blotting (WB) on C57BL/6J and DBA/2J mice and performed several techniques on Lsd1 heterozygous mice, including electroretinogram (ERG), SDOCT, Fundus photography, IHC, WB, and H&E staining to assess ocular health. Additionally, we conducted IHC on enucleated human eyes from retinoblastoma patients. At post-natal day 7, a developmentally critical time, show higher Lsd1 protein levels in DBA mice, but shows similar localization pattern. In mature retinas, Lsd1 is expressed in most cells but depressed in rods. Lsd1 heterozygous mice do not display morphological retinal defects in SDOCT, Fundus photos, IHC, or H&E staining and ERGs appear normal. Within retinoblastoma tumors, Lsd1 is highly expressed in differentiated areas, but absent in undifferentiated areas. These experiments show Lsd1 involvement in the differentiation of certain retinal cell subtypes and possible contribution to the differentiation and aggression of retinoblastoma tumors.

Sara Fielder, GMB **Poster #24**

SEX SPECIFIC DYNEIN REQUIREMENT IN *C. ELEGANS* MEIOSIS

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Homologous chromosome pairing and meiotic synapsis are essential processes in both oogenesis and spermatogenesis to prevent aneuploidy and developmental defects in offspring. Despite the importance and high conservation of synapsis, not every aspect is the same between the two sexes. My preliminary results indicate that male and female *C. elegans* have different requirements for dynein motor proteins in the initiation of synapsis. Dynein dependent forces have been proposed to test whether a potential homolog match is correct, and once a match is established, synapsis (SYP) proteins are loaded between the homologs. Knockdown of the dynein light chain (DLC-1) at an elevated temperature results in abnormal SYP polycomplex formation away from chromatin in females. Unexpectedly, DLC-1 depletion in males at the same temperature shows grossly normal synapsis. Even more surprisingly, mutants in the heavy chain and dynactin components of dynein also do not show SYP polycomplexes. This indicates that there is a previously undescribed function for DLC-1 in synapsis initiation. A consensus binding motif for the mammalian DLC-1 ortholog has been reported, and we identified a potential binding motif in a SYP protein. This suggests that DLC-1 directly interacts with SYP proteins and may have a role in polycomplex dynamics.

Stephanie Grewenow, GMB **Poster #25**

IDENTIFYING THE GENETIC DRIVERS OF 3Q29 DELETION SYNDROME

Stephanie Grewenow[1,2], Timothy Rutkowski[2], Jason Schroeder[2], Georgette Gafford[2], Tamika Malone[2], Stephen Warren[2], Jennifer Mulle[2], David Weinshenker[2], Tamara Caspary[2]

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3q29 deletion syndrome patients display a variety of symptoms including intellectual disability, anxiety, dental abnormalities, and stunted growth. 3q29 deletion confers the largest identified genetic risk (>40 fold) for schizophrenia. The 1.6 megabase deletion contains 22 coding genes in which the causal gene(s) is not known. This limited number of genes provides a tractable region in which to determine causal gene(s) and potential mechanisms responsible for distinct phenotypes, such as schizophrenia, that manifest in the patients. Using CRISPR/Cas9 technology, we deleted the syntenic region on mouse chromosome 16, *Del16*$^{+/Bdh1\text{-}Tfrc}$. Our preliminary behavioral characterization of *Del16*$^{+/Bdh1\text{-}Tfrc}$ mice identified sensorimotor gating and learning/memory deficits indicating neurological defects comparable to those identified in patients. To further dissect the molecular mechanisms underlying the neurological deficits and possibly identify the causal gene(s), we generated a proximal and a distal subdeletion of 11 genes apiece. Upon behavioral characterization, we may identify specific *Del16*$^{+/Bdh1\text{-}Tfrc}$ behavioral phenotypes segregate with a single subdeletion, providing rationale for future work identifying the critical region. Alternatively, if the *Del16*$^{+/Bdh1\text{-}Tfrc}$ behavioral phenotypes are only seen when the subdeletions are in trans, heterozygosity of multiple genetic elements within the two subdeletions underlie the phenotype.

George Inglis, GMB **Poster #26**

INVESTIGATION OF NONCODING GENETIC ELEMENTS IN THE REGULATION OF *SCN1A* AND *SCN8A*

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Epilepsy is a common neurological disorder that affects over 50 million people worldwide, and is characterized by recurrent, unprovoked seizures. Heterozygous loss-of-function mutations in the VGSC gene *SCN1A* (encoding the protein $Na_v1.1$) are responsible for 70-80% of cases of Dravet syndrome (DS), a severe, treatment-resistant form of childhood epilepsy. Restoring *SCN1A* expression, or reducing *SCN8A* expression (encoding the VGSC $Na_v1.6$) is predicted to be therapeutic in these cases, though we have limited knowledge about the genetic elements or factors responsible for transcriptional regulation of either gene. By analyzing genomic markers of open chromatin across multiple neuronal cell types, we have identified several genetic elements in *SCN1A* and *SCN8A* with putative transcriptional regulatory ability. We have cloned these elements into a vector upstream of a human *SCN1A* promoter driving luciferase reporter expression. A number of these constructs resulted in altered luciferase activity relative to vector with just the *SCN1A* promoter, suggesting the cloned elements have functional significance. Given that disease-associated SNPs are also known to alter or create binding motifs for transcription factors, we are also investigating epilepsy-associated SNPs that fall within these regions of open chromatin.

Anna Kania, GMB **Poster #27**

INHIBITION OF H3K27ME3-SPECIFIC DEMETHYLASES PROMOTES PLASMA CELL FORMATION

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B cell terminal differentiation must be properly regulated to ensure robust humoral immune responses. In additional to the well-established role of key transcription factors, there is a growing interest in the epigenetic regulation of B cell differentiation. However, the epigenetic remodeling that occurs to suppress the B cell and promote the plasma cell fate is still poorly understood. Histone H3 lysine 27 trimethylation (H3K27me3) is a modification associated with a repressive chromatin state and gene silencing. H3K27me3 is established by EZH2 (component of PRC2) and was shown to be essential in the formation and maintenance of germinal centers. To further evaluate the role of H3K27me3 in B cell differentiation, we evaluated the effects of pharmacological inhibition of UTX and JMJD3 (H3K27me3-specific demethylases) in B cells stimulated ex vivo with LPS, IL2, and IL5. Our preliminary data suggest that retention of those silencing histone modifications nearly doubles the number of B220+ CD138+ plasma cells after 3-day ex vivo culture as assayed by flow cytometry. We also evaluated viability, gene expression profile, and functionality of the plasma cells treated with or without the inhibitor. Taken together, the collected data provide us with more insight into the role of H3K27me3 dynamics in B cell terminal differentiation.

Christy Kinney, GMB **Poster #28**

THE RNA BINDING PROTEIN NAB2 MAY FUNCTION IN CONTROL OF TELOMERE LENGTH: A COMING OF AGE TAIL

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RNA-binding proteins (RBPs) play critical roles in modulating the expression of both coding and non-coding RNAs (ncRNAs). We have employed a budding yeast model to study the function of a conserved polyadenosine RBP termed ZC3H14 in humans and Nab2 in yeast. To identify RNAs regulated by Nab2, we performed RNA-Seq analysis on *nab2* mutant cells and have identified a number of critical ncRNAs that show decreased steady-state levels. The most affected RNA identified is *TLC1,* the RNA component of the telomerase holoenzyme. Telomerase, which is responsible for maintaining the telomeres at chromosome ends, is implicated in both aging and cancer. Budding yeast cells lacking *TLC1* show telomeres shortened by ~40 basepairs and clonal senescence by 100 generations. In contrast, wildtype yeast cells can proliferate indefinitely. As little as a two-fold decrease in *TLC1* promotes senescence; however, the *nab2* mutant cells show a five-fold decrease. We will test the hypothesis that *nab2* mutant cells display shortened telomeres and more rapid senescence than wildtype cells and extend this analysis to determine how Nab2 modulates levels of *TLC1* and other critical ncRNAs. Ultimately, this work will provide mechanistic insight into how this conserved class of RBPs modulates post-transcriptional regulation of gene expression.

Kari Mattison, GMB **Poster #29**

FUNCTIONAL ANALYSIS OF *SLC6A1* VARIANTS IDENTIFIED IN EPILEPSY PATIENTS

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Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures caused by an imbalance in neuronal excitability and inhibition. At EGL Genetics, patients referred for genetic testing are screened using a library of approximately 5000 evidence-based disease genes. Utilizing this rich resource of sequence data, we have examined 460 unselected epilepsy patients referred for genetic testing. Through this examination, we identified eight variants in the *SLC6A1* gene. *SLC6A1* encodes the voltage-gated GABA transporter, GAT-1. GAT-1 regulates GABA concentration at the synapse through the reuptake of GABA. Recently, *SLC6A1* variants were reported in patients presenting with Myoclonic-Astatic Epilepsy (MAE); however, the functional effect of these variants on GAT-1 activity was not determined. We have performed functional assays to demonstrate the impact of our eight variants on GAT-1 activity. Missense and in-frame deletion variants were functionally tested through a GABA transport assay in HeLa cells. Additionally, a minigene vector was used to determine the splicing pattern caused by a splice site variant. Our data suggest that *SLC6A1* variants observed in epilepsy patients result in loss of GAT-1 transporter function, likely disrupting the balance between neuronal excitation and inhibition.

Jasmine Moody, GMB **Poster #30**

IDENTIFICATION OF A RHO-GEF THAT DIRECTS SITE-SPECIFIC ASSEMBLY OF INTEGRIN ADHESION COMPLEXES IN STRIATED MUSCLE

Jasmine Moody, Hiroshi Qadota, April R. Reedy, Yohei Matsunaga, and Guy M. Benian

The adhesion of cells to extracellular matrix is mediated by “integrin adhesion complexes” (IACs) consisting of integrin and a several associated proteins. Although much is known about their composition and molecular mechanisms that initiate assembly, little is known about what determines where such assemblies will form. Nematode striated muscle has 3 types of IACs; M-lines, dense bodies and attachment plaques at muscle cell boundaries. From a screen for mutants that disrupt the localization of PAT-6 (a-parvin), we discovered a gene that as a loss of function mutant results in the absence of PAT-6 at muscle cell boundaries, but not at the other IACs (M-lines and dense bodies). This gene encodes PIX-1, the nematode ortholog of vertebrate bPIX. In both swimming and crawling assays, pix-1(gk299374), moves more slowly than wild type, suggesting that the muscle cell boundaries consisting of cell-ECM-cell contacts is important for proper transmission of lateral forces between muscle cells that occur during whole-animal locomotion. We hypothesize that PIX-1 either is located exclusively at muscle cell boundaries, or that it is localized at all three IACs in muscle, but is only activated (by an unknown mechanism) as a RhoGEF at muscle cell boundaries

Trenell Mosley, GMB **Poster #31**

IDENTIFICATION OF CANDIDATE VARIANT FOR SHORT STATURE AND INSULIN RESISTANCE

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We identified two Middle Eastern sibling probands presenting with short stature, particularly of the hands and feet, and insulin resistance. The probands are offspring of unaffected consanguineous parents. We hypothesized the phenotypes are the result of a novel autosomal recessive disorder and predicted both probands should be homozygous for the same identical-by-descent allele. To uncover putative disease-causing mutations, we performed whole-genome sequencing and two orthogonal variant analyses: 1) a genome-wide search for rare, high-CADD (MAF≤0.001; CADD≥15) variants homozygous in both cases, and 2) rare, high-CADD variants located in runs of homozygosity where both probands were homozygous for the same allele. The analyses converged on nine variants. One variant in the *DUSP7* gene (*g.*52050873:T>C; hg38) is rare in the general population (MAF = 0) and is predicted to be a tyrosine to cysteine missense mutation (p.Tyr401Cys). *DUSP7*, a dual-specificity phosphatase, interacts with the growth hormone receptor (GHR) and MAP kinase (MAPK) pathway, both of which interact with the insulin pathway. We independently show that the *DUSP7* variant is heterozygous in both parents and is not homozygous in any of the unaffected siblings. Future steps include testing whether the observed mutation functionally and/or structurally disrupts the DUSP7 protein.

Dillon Patterson, GMB **Poster #32**

PURIFICATION OF HOMEMADE TN5 TRANSPOSASE FOR EPIGENETIC ASSESSMENT OF RARE IMMUNE CELLS

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Accumulating evidence reveals that changes in the epigenome regulate gene expression profiles of developing, differentiating, and effector immune cells. Importantly, disturbances in this developmental road map may contribute to aberrant immune responses. The recent development of the Assay for Transposase Accessible Chromatin sequencing (ATAC-seq) allows for the epigenetic programming of rare immune cells to be determined. This method utilizes the Tn5 transposase to simultaneously fragment and tag genomic DNA by inserting Illumina sequencing adapters. Unique sequencing indexes are then added to the adapter-modified genomic fragments during the PCR enrichment step of sample preparation. This tagmentation-based approach has emerged as a popular approach to generating sequence-ready libraries. Here, we describe a method to purify adapter-loaded Tn5. Importantly, in-house purification of Tn5 allows for innovation, such as customizing the tagmentation process by adding pre-indexed adapters. This method would allow for a more efficient analysis of samples which increases experimental throughput while significantly reducing sequencing cost.

Rebecca Pollak, GMB **Poster #33**

THE NEUROPSYCHIATRIC AND BEHAVIORAL PHENOTYPES OF 3Q29 DELETION SYNDROME

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3q29 deletion syndrome (3q29DS) is a rare (~1:30,000) genomic disorder caused by a 1.6 Mb deletion on chromosome 3, and is associated with intellectual disability, anxiety, Autism Spectrum Disorder (ASD), and schizophrenia. We used Emory University's 3q29DS registry (3q29deletion.org) to collect data on 3q29DS patients, including medical and demographic data (n=88); Achenbach Behavior Checklists (CBCL/ABCL, n=45); Social Responsiveness Scale (SRS, n=48); and the Social Communication Questionnaire (SCQ, n=30). Self-report data shows increased prevalence of ASD diagnosis versus the general population (30.7% vs. 1.47%, $p<2.2e-16$). Scores on the SRS are elevated among all individuals with 3q29DS; 3q29DS patients without an ASD diagnosis scored significantly higher on the SRS ($p=2.03e-8$), SCQ ($p=0.00016$), and CBCL/ABCL ($p=1.31e-9$) as compared to non-ASD, non-3q29DS children. ASD diagnosis is similar between 3q29DS males and females, unlike in the general population. This 3q29DS sample is enriched for ASD diagnosis and ASD features; however, several individuals scored in the clinical range on all scales, despite reporting no diagnosis of ASD. This implies that either ASD is underdiagnosed or not adequately assessed in 3q29DS patients, or additional psychopathology is present that may be independently elevating scores. This finding has implications for the care and long-term management of individuals with 3q29DS.

Juan Rodriguez, GMB **Poster #34**

DEVELOPMENTAL CONSEQUENCES OF THE INAPPROPRIATE TRANSGENERATIONAL INHERITANCE OF HISTONE METHYLATION IN *SPR-5;MET-2* MUTANT WORMS

Juan Rodriguez, Dave Katz

Genetic and epigenetic information are transmitted from one generation to the next through the germline. While heritability of genetic information across generations is stable, epigenetic information is highly modified within each generation in order to regulate proper gene expression. Reestablishing the epigenetic ground state of the *Caenorhabditis elegans* (*C. elegans*) zygote is required for normal development and ensures that information is transferred properly from one generation to the next. Two epigenetic enzymes, the H3K4me2 demethylase, SPR-5, and the H3K9 methyltransferase, MET-2, are maternally deposited into the oocyte and cooperate to reestablish the epigenetic ground state by modifying histone methylation. Progeny of worms lacking *spr-5* and *met-2* rapidly accumulate H3K4me2, resulting in somatic expression of spermatogenesis genes and sterility (maternal effect sterile phenotype). However the mechanism underlying this germline/soma defect in embryos is unclear. To interrogate the mechanism underlying this defect, we are using confocal imaging to perform automated lineage tracing experiments. The *C. elegans* embryonic lineage is normally invariant. Thus, by identifying defects in the embryonic lineage we hope to gain mechanistic insight into the germline/soma defect, and uncover how the inappropriate transgenerational inheritance of H3K4 methylation affects embryonic development.

J. Christopher Rounds, GMB **Poster #35**

THE CONSERVED INTELLECTUAL-DISBILITY-ASSOCIATED RNA-BINDING PROTEIN DNAB2 REGULATES NEURONAL MORPHOLOGY AND SPECIFIC NEURONAL TRANSCRIPTS IN CONJUCTION WITH ATAXIN-2

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Intellectual disability refers to a common class of etiologically heterogeneous neurodevelopmental disorders. Recently, we have shown that one form of intellectual disability is caused in humans by loss-of-function mutations in *ZC3H14*, a gene encoding a ubiquitously expressed polyadenosine-RNA-binding protein whose molecular functions are largely unknown. To better understand the function of human ZC3H14, we have begun to dissect the function of its *Drosophila* ortholog dNab2. We find evidence that dNab2 may play a crucial role in controlling neuronal morphology and specific neuronal transcripts through, in part, its interactions with Ataxin-2 (Atx2), a neuronal translational regulator which is mutated in the neurodegenerative disease spinocerebellar ataxia type 2. Loss-of-function alleles of *Ataxin-2* ameliorate effects of dNab2 loss or overexpression on mushroom body and retinal morphology, implying that dNab2 and Atx2 may interact in nuanced ways to regulate these processes. Moreover, we find that neuronal, FLAG-tagged dNab2 associates with endogenous *Ca^{2+}/calmodulin-dependent kinase II* (*CaMKII*) RNA, an Atx2 target, suggesting dNab2 and Atx2 may regulate shared target RNAs. Taken with other preliminary results, these data provide insight into ZC3H14-linked intellectual disability, supporting a role for the ZC3H14 ortholog dNab2 in regulating neuronal morphology and specific neuronal transcripts through, in part, molecular interactions with Atx2.

Alyssa Scott, GMB **Poster #36**

MATERNALLY PROVIDED LSD1 ENABLES THE MATERNAL-TO-ZYGOTIC TRANSITION AND PREVENTS DEFECTS THAT MANIFEST POSTNATALLY

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Somatic cell nuclear transfer has established that the oocyte contains maternal factors with epigenetic reprogramming capacity. However, the identity and function of these maternal factors during the gamete to embryo transition remains poorly understood. In *C. elegans*, LSD1 (lysine specific demethylase 1) enables this transition by removing H3K4me1/2 and preventing the transgenerational inheritance of transcription patterns. Here we show that loss of maternal LSD1 in mice results in embryonic arrest at the 1-2 cell stage, with arrested embryos failing to undergo the maternal-to zygotic transition. This suggests that LSD1 maternal reprogramming is conserved. Moreover, partial loss of maternal LSD1 results in striking phenotypes weeks after fertilization, including perinatal lethality and abnormal behavior in surviving adults. These maternal effect hypomorphic phenotypes are associated with alterations in DNA methylation and expression at imprinted genes. To further characterize these heritable defects we are currently using CRISPR to engineer an allelic series of maternal hypomorphic LSD1 mice. Our goal is to discover how subtle defects in LSD1-mediated epigenetic reprogramming at fertilization can give rise to long-term behavioral consequences.

Alyse Steves, GMB **Poster #37**

ACUTE HBCDD AND TBBPA EXPOSURE TARGETS SPERMATOGONIA AND PRIMARY SPERMATOCYTES IN A HUMAN STEM-CELL DERVIED MODEL OF SPERMATOGENESIS

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Sperm counts have rapidly declined in the Western male over the past four decades. This rapid decline remains largely unexplained. Exposure to environmental toxicants provides one potential explanation for this alarming decline. Flame retardants are highly prevalent and persistent in the environment, but many have not been assessed for their effects on human spermatogenesis. Using a human stem cell-based model of spermatogenesis, we evaluated two major flame retardants, HBCDD and TBBPA, under acute conditions simulating occupational-level exposures. Here we show that HBCDD and TBBPA are human male reproductive toxicants *in vitro*. While not specifically impacting the survival of haploid spermatids, these toxicants affect spermatogonia and primary spermatocytes through mitochondrial membrane potential perturbation and ROS generation, ultimately causing apoptosis. Taken together, these results show that HBCDD and TBBPA affect human spermatogenesis *in vitro* and potentially implicate this highly prevalent class of toxicants in the decline of the Western males' sperm counts.

Sarah Suciu, GMB **Poster #38**

THE CILIARY PROTEIN ARL13B REGULATES AXON GUIDANCE IN THE MOUSE HINDBRAIN

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The ciliopathy Joubert Syndrome (JS) presents with physical anomalies, intellectual disability, and is diagnosed by the molar tooth sign (MTS). The MTS results from cerebellar hypoplasia in conjunction with axon guidance defects in the white matter tract known as the superior cerebellar peduncles (SCPs). Mutations in cilia-associated genes including *ARL13B* cause JS. ARL13B regulates transcription-dependent Shh signaling, which requires cilia to regulate cell-fate specification and cerebellar precursor proliferation. *Arl13b* mutations in mice lead to constitutive but low-level transcription-dependent Shh signaling, which is consistent with cerebellar hypoplasia in JS. Shh signaling uses a distinct, transcription-independent pathway to regulate axon guidance, and so we hypothesized that aberrant Shh signaling might provide a common mechanism for the MTS. To examine Arl13b's potential role in transcription-independent Shh signaling, we examined SCP guidance in mouse brains lacking either Arl13b or all Shh signaling in projection neurons. We observed significant guidance defects in SCPs lacking Shh signaling or Arl13b. These data indicate Arl13b regulates axon guidance in projection neurons that use Shh as a guidance cue, implicating a cilia-associated gene in axon guidance. Taken together, our data suggest that disruption of Shh signaling may be a common mechanism underlying the MTS phenotype seen in JS.

Victor Band, IMP **Poster #39**

COLISTIN HETERORESISTANCE OF CARBAPENEM RESISTANT ENTEROBACTERIACEAE IN US HOSPITALS: A RETROSPECTIVE PREVALENCE STUDY

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Antibiotic resistance is a major public health threat, significantly increasing patient mortality and healthcare cost. This issue is further complicated by unexplained failures of antibiotic therapy caused by bacteria that appear antibiotic susceptible. The phenomenon of heteroresistance, where a small resistant subpopulation of bacteria exists within a larger susceptible population, has been shown to mediate failure of antibiotic therapy while avoiding detection in the clinic. We sought to characterize the extent of heteroresistance within US hospital populations in a retrospective prevalence study of highly antibiotic resistant pathogens. We screened 409 carbapenem resistant Enterobacteriaceae isolated from 2012-2015 within 7 US states, assessing the heteroresistance of these isolates to the last-line drug colistin. We found that overall >10% of isolates were heteroresistant to colistin, a rate higher than that found for conventional colistin resistance. Even more concerning, the majority of these isolates were identified as colistin susceptible by routine clinical testing. When these heteroresistant isolates are included, the rate of colistin resistance is actually double what is detected in the clinic, indicating a major shortfall of clinical antibiotic resistance testing. Additionally, these heteroresistant isolates, misclassified as susceptible, could subsequently be treated with colistin and lead to unexplained treatment failures.

Lynette Chea, IMP **Poster #40**

IMPEDING APOPTOSIS ACTIVATION AUGMENTS MVA VACCINE-INDUCED HUMORAL RESPONSES

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Developing an HIV vaccine to protect from infection is critical to prevent the spread of HIV/AIDS. Modified vaccinia Ankara (MVA) is an attenuated poxvirus being developed as a vector for multiple vaccines. However, MVA-infected cells undergo rapid apoptosis leading to faster clearance of antigens. A possible reason could be the fragmentation of the anti-apoptotic gene B13R in MVA. Here, we replaced the fragmented B13R with a functional copy and tested its effects on immunogenicity. MVA infected cells were monitored for caspase-3 activation and cell membrane permeability as apoptosis markers. MVA-B13R infected Hela cells were protected from induced apoptosis confirming functionality of B13R. Infection of Hela cells and a human muscle cell line demonstrated the ability of MVA-B13R to delay caspase-3 activation compared to MVA. To determine immunogenicity, BALB/c mice were immunized intramuscularly with recombinant MVA/SHIV or MVA-B13R/SHIV expressing SIV Gag, Pol and HIV Env (SHIV) at weeks 0 and 4. We observed 3.5-fold higher Env-specific antibody secreting cells and 2-fold higher Env-specific serum antibodies in MVA-B13R/SHIV compared to MVA/SHIV mice. MVA-B13R/SHIV mice also had 2.5-fold higher Env-specific memory B cells. These results demonstrate that B13R functionality significantly delays MVA-induced apoptosis and this is associated with augmented anti-HIV Env antibody responses.

Ching-wen Chen, IMP **Poster #41**

TUMOR ANTIGEN-SPECIFIC T CELLS EXHIBIT LESS DYSFUNCTION DURING SEPSIS AND MODULATE SEPSIS SURVIVAL

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Cancer patients have a ten-fold greater risk of developing sepsis. However, the impact of sepsis-induced immune-dysregulation on tumor immunity is unknown. To investigate the impact of sepsis on tumor antigen-specific CD8+ T cell responses, ovalbumin-expressing lung cancer cells (LLC-OVA) were implanted in B6 mice, and OVA-transgenic T cells were adoptively transferred into animals to function as tumor-specific T cells. After three weeks, animals were subjected to sham surgery or cecal ligation and puncture (CLP) to induce polymicrobial sepsis. Results indicated that compared to sham, CLP animals displayed significantly fewer OTI and endogenous CD8+ T cells T cells in both spleen and tdLN. However, in TILs, the significant cell loss was detected only in the endogenous CD8+ T cell compartment and OTI numbers were unchanged. Moreover, flow analysis revealed that sepsis resulted in four significant clusters changes in splenocytes, but not in TILs. Futhermore, depletion of tumor antigen specific T cells resulted in a significant improvement in sepsis survival ($p=0.043$, $n=39$). Thus, these data suggest that tumor-specific T cells are more resistant to sepsis-induced phenotypic changes, and that the tumor microenvironment can reduce the impact of sepsis-induced dysregulation. However, these tumor antigen-specific CD8+ T cells may contribute to increased sepsis mortality.

Elina El-Badry, IMP **Poster #42**

ZAMBIAN WOMEN EXHIBIT AN EXACERBATED INFLAMMATORY RESPONSE TO EARLY HIV INFECTION COMPARED TO MEN

Elina El-Badry[1], Gladys Macharia[2], Daniel Claiborne[1], Jill Gilmour[2], Susan Allen[1,3] and Eric Hunter[1]

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Women infected with HIV have been reported in several studies to have significantly lower viral loads than men, although the reason for this discrepancy has yet to be identified. We analyzed viral loads longitudinally in a cohort of heterosexual Zambian individuals and observed significantly lower viral loads in women throughout infection as well as higher CD4+ T cell counts in women which subsequently decreased at a higher rate than in men. In order to understand the immunological basis of these disparate clinical parameters we analyzed cell markers in PBMC of 47 HIV-infected individuals at between 1 and 30 months post-infection. Early in infection, CD8+ T cells and NK cells isolated from women expressed higher levels of CD107a than those isolated from men. Cells isolated from women also produced higher levels of IFNL1. Finally, the plasma of HIV-infected women contained higher levels of certain inflammatory proteins. Several immunological markers differed between men and women at 1 and 9 months post-infection, indicating that men and women exhibited a differential acute and early chronic immune response to infection with HIV. These observations suggest a more robust inflammatory response to early HIV infection which may control viral load but exacerbate CD4+ T cell death.

Bijean Ford, IMP **Poster #43**

IN VITRO CHARACTERIZATION OF PRO-INFLAMMATORY MONOCYTES WITHIN THE CYSTIC FIBROSIS AIRWAY ENVIRONMENT

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Cystic fibrosis (CF) disease most commonly manifests itself in the lungs as a combination of airway obstruction, microbial infection, and chronic inflammation. Although extensive work has been done on the contributions of neutrophils, macrophages, and T cells to the inflammatory milieu present in the CF airway, there has been little work done to elucidate the role of monocytes upon entry into this environment. Our lab has developed an *in vitro* transmigration model that has been utilized to analyze the effects of chemotaxis on different cell types isolated from whole blood and allowed to pass into the healthy and/or CF airway. As has been shown in previous studies, 3 different subsets of monocytes exist in the circulation, and understanding how their proportion, phenotype, and function may be altered upon transmigration into the CF airway is of primary interest, potentially uncovering additional therapeutic targets of airway inflammation.

Madelyn Houser, IMP **Poster #44**

FROM THE GUT TO THE BRAIN: INTESTINAL INFLAMMATION AS A DRIVER OF PARKINSONIAN NEUROPATHOLOGY

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Parkinson's disease (PD) is a progressive disorder caused by degeneration of dopaminergic neurons in the brain. The etiology of PD remains uncertain, and by the time the characteristic motor impairments manifest, extensive, irreversible neurodegeneration has already occurred. Gastrointestinal problems are also common features of PD, however, and they frequently manifest years before the development of motor symptoms. This has led to the theory that PD pathology initiates in the intestine and progresses to neurodegeneration in the central nervous system. We hypothesize that intestinal inflammation could mediate the progression from digestive dysfunction to neurodegeneration in PD. We first investigated whether PD patients exhibit signs of intestinal inflammation. We identified elevated levels of specific inflammatory mediators in stool from PD patients compared to controls. In colonic biopsies from PD patients, we found evidence of increased immune cell infiltration, proinflammatory activity, and oxidative stress compared to controls. We then utilized rodent models to evaluate the effects of colonic inflammation on neuron health in the brain. We determined that damage and inflammation in the intestine could impair the functionality of dopaminergic neurons and could augment the effects of neurotoxic agents. Our findings support the involvement of gastrointestinal inflammation in the pathogenesis of PD.

Andrew Jones, IMP **Poster #45**

SUBLINGUAL AND BUCCAL DELIVERY OF MVA/PROTEIN HIV-1 VACCINATION WITH A NEEDLE-FREE INJECTOR INDUCES ROBUST SYSTEMIC AND MUCOSAL ANTIBODY RESPONSES IN RHESUS MACAQUES

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Immediately post mucosal transmission, HIV-1 is considered to be at a vulnerable state due to localized replication and low or unestablished viral reservoirs. Thus, HIV vaccines should induce a strong mucosal immune response and mucosal vaccination would be an ideal route to achieve this. Here we evaluate the sublingual and buccal tissue (SL/B) as a route of oral mucosal vaccination in rhesus macaques. We utilized a modified needle-free injector, designed for use in dentistry, to deliver immunizations across the oral epithelium. Animals were immunized twice with modified vaccinia Ankara (MVA) expressing HIV-1 Gag, Pol and envelope antigens, followed by two immunizations with a recombinant trimeric gp120 immunogen along with the mucosal adjuvant dmLT. A second group was immunized via topical oral application of the vaccines, and a third group received the immunizations via the conventional intradermal and subcutaneous routes. Impressively, needle-free oral immunization generated robust HIV Env-specific antibody responses both in blood and mucosal compartments significantly higher compared to intradermal/subcutaneous immunized animals. Topical application resulted in very low or undetectable antibody responses. Our results show that needle-free injection of the sublingual and buccal tissues acts as an effective and practical route to generate both systemic and mucosal antibodies via vaccination.

Michael La Muraglia II, IMP **Poster #46**

CIRCULATING FOLLICULAR T CELLS: A POTENTIAL BIOMARKER CANDIDATE FOR THE GENERATION OF DONOR SPECIFIC ALLOANTIBODY FOLLOWING TRANSPLANTATION.

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It is well-recognized that donor-specific antibodies (DSA) play a significant role in the development of chronic renal allograft rejection. T follicular helper (T_{FH}) and regulatory (T_{FR}) cells are distinct subsets of $CD4^+$ T cells functioning primarily within secondary lymphoid organ germinal centers, rendering them elusive targets for immune monitoring in transplant recipients. Recent studies have identified circulating T_{FH} (cT_{FH}) cells that correlate with ongoing antibody responses after vaccination and in autoimmune disease, however little is known about the existence of cT_{FH} cells during transplantation. To determine the kinetics and magnitude of circulating follicular cells during transplant, we utilized a major MHC mismatch BALB/c-to-B6 transplant model. Flow cytometric analysis of the peripheral blood revealed a 3-fold and 2-fold expansion of $CD4^+CXCR5^+Foxp3^-$ cT_{FH} and $Foxp3^+$ cT_{FR} cells, respectively, following BALB/c skin transplantation as compared to controls. These graft-elicited changes also correlated with the initiation of anti-BALB/c IgG DSA generation. CD28 costimulation pathway blockade abrogated all components of the donor-reactive GC response, DSA formation, and expansion of cT_{FH} and cT_{FR} cells. These data support continued investigations aimed to develop cT_{FH} cells as a biomarker for the clinical assessment of humoral alloimmunity to guide DSA management for improvement of kidney long-term transplant outcomes.

Tiger Li, IMP **Poster #47**

AN ALTERNATIVE EXPLANATION TO THE LOW EVOLUTIONARY RATE OF CD8 T CELL EPITOPES OF INFLUENZA A VIRUSES: A THEORETICAL MODEL

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The relative conservation of CD8 T cell epitopes of human influenza A viruses compared to antibody epitopes may be explained by three mechanisms: (1) Mutations on CD8 T cell epitopes are constrained by their potential to decrease viral fitness, (2) the overall selective advantage of 'escaping' mutation is limited by the breadth of MHC polymorphisms among human population, or (3) CD8 T cell epitopes are under lower selection pressure because CD8 T cells contribute to the reduction of pathology and transmission instead of blocking infection. We developed a population genetics model incorporating the fitness cost, selective advantage, and frequency of HLA alleles that indicated certain combinations of these three parameters determined the fate of a CD8 T cell-escaping mutant. To account for genetic drift and the scenario where a mutant escapes from pre-existing immunity but meanwhile induce new CD8 T cell populations, we employed an ordinary differential equation (ODE) model with stochastic simulation using Gillespie's tau-leaping algorithm to analyze the time required for introduction and emergence of the CD8 T cell-escaping mutant. We concluded that human MHC polymorphism can result in the observed low evolutionary rate even if no fitness cost is accompanied with the mutation.

Julia McBrien, IMP **Poster #48**

ANTIVIRAL ROLE OF CD8+ T CELLS IN SIV-INFECTED, ART-TREATED RHESUS MACAQUES WITH EFFECTOR ENHANCMENT VIA ALT-803, AN IL-15 SUPERAGONIST COMPLEX

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The main obstacle to develop a functional cure for HIV infection and AIDS is the presence of a persistent viral reservoir of latently infected cells that is established early during the course of infection and is maintained even in the presence of successful ART. Recent approaches to target the viral reservoir include the "shock and kill" strategy, where the viral reservoir under ART is "shocked" out of latency using latency-reversing agents (LRA), and then the antiviral response is heighted with a "kill" strategy to eliminate the exposed reservoir. A recent study by our group (Cartwright et al., 2016 *Immunity*) showed that CD8+ lymphocyte depletion of short-term ART-treated macaques results in a transient rebound of viremia despite ongoing ART. In this study, we are investigating the ability of CD8+ lymphocyte depletion to "shock and kill" the SIV viral reservoir. The ability of a promising LRA, IL-15 superagonist complex ALT-803, to further augment a "shock and kill" response will also be investigated.

Anna Morris, IMP **Poster #49**

FcγRIIB IS A NOVEL COINHIBITORY MOLECULE ON EFFECTOR CD8$^+$ T CELLS

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T cells are critical mediators of transplant rejection, and as such, are important targets for anti-rejection therapies. Costimulatory and coinhibitory molecules on CD8$^+$ T cells provide necessary secondary signals for activation. FcγRIIB, the only inhibitory Fcγ receptor, is known to be expressed by many immune cells, but has not been described on T cells. In an *in vivo* murine model of transplantation, we monitored survival of minor-mismatched skin grafts on WT and FcγRIIB$^{-/-}$ animals and found that FcγRIIB$^{-/-}$ exhibit accelerated costimulation-blockade resistant rejection relative to WT controls (MSTs of 20 and 33 days, respectively ($p= 0.0002$)). Furthermore, we detected a high frequency of FcγRIIB$^+$ cells within the CD8$^+$effector memory population, compared to central memory and naïve populations (10% vs 3% vs 0.1%), that increases to 30% on antigen-specific CD8$^+$ T cells on day 14 following skin transplantation. When we pharmacologically inhibit FcγRIIB using a monoclonal antibody, we observed a significant increase in the frequency of donor-reactive CD8$^+$ T cells in the spleen at day 14 post-transplant ($p<0.05$). Based on these experiments, we conclude that FcγRIIB is a novel coinhibitory molecule expressed on CD8+ T cells that is crucial in modulating T cells, and therefore an important target for rejection therapies.

Madeline Price, IMP **Poster #50**

PROGRESSIVE UPREGULATION OF OXIDATIVE METABOLISM FACILITATES PLASMABLAST DIFFERENTIATION TO A T-INDEPENDENT ANTIGEN

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Immune cell differentiation requires a transition in metabolic programming to achieve effector function. Using in vivo and ex vivo LPS driven models of B cell differentiation, metabolic changes were investigated. Naïve B cells are quiescent, and activated B cells shift their metabolic program to use oxidative phosphorylation, but maintain a large spare respiratory capacity. In contrast, differentiated plasmablasts use oxidative phosphorylation at their maximal ability, with no spare respiratory capacity, suggesting unique metabolic changes are programmed upon differentiation. Next, an adoptive transfer model system that utilizes cell-trace violet labeled B cells was used to distinguish molecular events during the proliferative versus the differentiation phase. Analysis of transcriptome data in the two phases identified a subset of metabolic genes that underwent differentiation-specific programming. Additionally, the roles of cell division and differentiation on metabolic function were uncoupled using conditional Blimp1 knock-out (cKO) mice, which divide normally but fail to differentiate to plasmablasts. Comparing wild-type and cKO mice suggests that metabolism is programmed during differentiation and is largely independent of cell division. These results provide novel insights into how changes in metabolism are programmed as quiescent B cells differentiate into antibody-secreting plasmablasts.

Alexandra Wolfarth, IMP **Poster #51**

PRAP1: A NOVEL EPITHELIAL SECRETED PROTEIN

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Proline rich acidic protein-1 (PRAP1) is a 17 kDa secreted intrinsically disordered protein encoded in higher chordates with no known function or recognizable sequence homology. In the course of evaluating transcriptional activation in murine gut by members of the Lactobacilli taxon, we found PRAP1 induced in the colon within 4 hours of oral gavage with 10^8 Lactobacilli. To define the physiological role of PRAP1, we have made polyclonal antibodies, PRAP1 recombinant protein and *Prap1* null mice. Measurement of PRAP1 expression by qPCR and western blot reveal PRAP1 expression is highest in the proximal small intestine, and interestingly, in a hormonally dependent manner in uterine endometrial cells of female mice. Preliminary *in vivo* data shows *Prap1* null mice have increased inflammation in the gastrointestinal tract and uterus, along with increased systemic inflammation. Given the localization of PRAP1, its secretion into the lumen of the small intestine and uterus, and its effect on local and systemic inflammation, we hypothesize that PRAP1 is a novel intrinsically disordered protein that contributes to the intrinsic defenses of mucosal epithelial surfaces.

Sarah Anderson, MMG **Poster #52**

VARIATIONS IN AN OPACITY AND VIRULENCE SWITCH IN *ACINETOBACTER BAUMANNII*

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The Gram-negative pathogen *Acinetobacter baumannii* undergoes high-frequency opacity variation. This phenomenon occurs in a density-dependent manner, with switching frequencies in a 24-hour colony approaching 30%. Opaque (O) and translucent (T) variants exhibit several differential phenotypes, and O variants exhibit enhanced virulence. The O to T switching phenotype is variable, with *A. baumannii* capable of forming low-switching O (LSO) colonies that have dramatically reduced rates of switching to T. LSO and normal O variants can interconvert, and whole genome sequencing and methylome analysis indicate that LSO variants do not arise due to mutation or changes in methylation. To determine the mechanism by which LSO variants occur, preliminary suppressor screens were performed. The LSO phenotype can be rescued by overexpression of a TetR-family transcriptional regulator, and by disruption of the DNA mismatch repair gene *mutS*. RNA-sequencing has revealed a number of genes that are differentially expressed between LSO and normal O variants, indicating that these subpopulations differ in several cellular processes in addition to their switching rate. Our laboratory has also shown that the O to T switching rate in colonies can be strongly influenced by agar concentration, suggesting that extracellular signaling or surface sensing may be important for this process.

Kelsie Brooks, MMG **Poster #53**

PROVIRAL SEQUNECS OF THE RESERVOIR DEMONSTRATE ARCIVIHING OF TRANSMITTED/FOUNDER VIRUS-LIKE VARIANTS

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The majority of heterosexually transmitted HIV infections are initiated by a single viral variant identified as the transmitted/founder virus (TFV). The subject of persistence of the TFV in chronic untreated infection and the reservoir of latently infected CD4+ T cells is understudied. In a group of 13 HIV+ individuals, we have investigated TFV persistence through sequencing of the HIV *env* gene during chronic, untreated infection. Chronic sequences demonstrated ongoing mutation from the TFV, with the time since infection significantly correlated to an increased median diversity from the TFV ($p<0.05$). We additionally sequenced *env* genes from the reservoir in five individuals. The mean genetic distance of reservoir sequences from the TFV was not significantly different than the mean distance of chronic sequences from the TFV ($p>0.3$), indicating that the reservoir is seeded throughout untreated infection. However, in all five individuals, the single closest genetic variant to the TFV was amplified from the reservoir. These variants may represent archiving of viruses that were present early in infection; archiving in the reservoir indicates that earlier treatment initiation, known to improve treatment outcomes, may additionally limit viral diversity of the reservoir and lead to a more homogenous population for targeting with HIV cure strategies.

Kara Phipps, MMG **Poster #54**

DEVELOPMENT OF REOVIRUS AS AN ONCOLYTIC THERAPEUTIC AGAINST INCOMPLETE GENOME LEVELS OF INFLUENZA A VIRUS VARY BY VIRUS STRAIN AND CELL TYPE

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The influenza A virus (IAV) genome is partitioned into eight, negative-sense RNA segments. Segmentation enables genetic diversification by reassortment, which occurs when two IAVs co-infect the same cell and exchange segments. Segmentation also imposes constraints, however, as all eight segments must be delivered to the cell successfully for productive infection. The frequency with which IAV genomes of fewer than eight segments are delivered, and the conditions which dictate this frequency, remain to be characterized. We used a single cell assay to experimentally measure incomplete genome levels produced by infection of A/Panama/2007/99 virus in MDCK cells. Results accurately accounted for observed reassortment frequency, demonstrating that reassortment is a useful indicator of incomplete genome levels. Reassortment was then measured for human and avian IAV strains in multiple host cell types. When the same IAV strains were used to infect different cell types, differing reassortment levels resulted. Reassortment levels also differed by virus strain. Characterization of chimeric viruses revealed the viral polymerase was a major determinant of reassortment levels. Together, these findings indicate that reassortment levels, and thus, the frequency of incomplete IAV genomes, are determined through interactions with the host cell, with particular importance for the viral polymerase.

Roxana Rodríguez Stewart, MMG **Poster #55**

ENGINEERED REOVIRUS INDUCES ENHANCED TRIPLE-NEGATIVE BREAST CANCER CELL DEATH

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Triple-negative breast cancer (TNBC) constitutes approximately 15% of all breast cancer and is associated with worse prognosis when compared to other subtypes. There is a need for targeted therapeutics to treat this type of breast cancer, as current therapies are largely limited to cytotoxic chemotherapy. Mammalian orthoreovirus (reovirus) has great potential as an oncolytic therapeutic given infection is mostly asymptomatic and it preferentially kills transformed cells. To engineer reovirus with enhanced infective and cytopathic properties against TNBC cells, we coinfected TNBC cell line MDA-MB-231 with parental reoviruses T1L, T2J, and T3D. Following serial passage, we isolated reassortant reovirus r2Reovirus. r2Reovirus has genomic segments predominantly from T1L with one gene segment from T3D and synonymous and nonsynonymous point mutations. Infection of MDA-MB-231 cells with r2Reovirus is more efficient and induces greater cell death than parental reoviruses. Infection of MDA-MB-231 cells with r2Reovirus results in cell death by caspase-dependent and caspase-independent mechanisms. We aim to identify the type of cell death r2Reovirus is inducing in these cells to understand differences in infection outcome between r2Reovirus and parental viruses.

Edgar Sherman, MMG **Poster #56**

MCR-1 CONFERS CROSS-RESISTANCE TO THE CATIONIC HOST ANTIMICROBIAL LYSOZYME

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The mobile colistin resistance gene *mcr-1* has become an increasing concern due to the risk of global resistance to one of our last-resort antibiotics. Colistin is one of the remaining therapeutic option available to treat serious Gram-negative bacterial infections resistant to most or all other classes of antibiotics. Few studies have focused on characterizing the impact of *mcr-1* within the context of the host. Due to the cationic charge of colistin, we hypothesized that resistance conferred by *mcr-1* also affects positively-charged host antimicrobials, including lysozyme. We removed *mcr-1* containing plasmids from *E. coli* clinical isolates to create *mcr-1* negative strains and measured survival in lysozyme killing assays. We also measured growth rates between *mcr-1* positive and negative strains. *mcr-1* positive isolates showed a 5 to 20-fold increase in survival rate when compared to their negative counterparts during lysozyme treatment. We saw no differences in growth between *mcr-1* positive and negative strains, suggesting that *mcr-1* may not confer a fitness cost. Resistance to host antimicrobials and the absence of a fitness cost may provide an advantage that could enhance the spread of mobile colistin resistance in the host even without antibiotic selection.

Aimee Paulk Tierney, MMG **Poster #57**

A RODZ ORTHOLOG IN *ACINETOBACTER BAUMANNII* REGULATES PHENOTYPIC HETEROGENEITY

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Acinetobacter baumannii is a multidrug resistant, Gram-negative nosocomial pathogen that exhibits two forms, termed opaque (O) and translucent (T) due to the appearance of colonies under a dissecting scope with oblique lighting. O and T variants can interconvert, and they exhibit multiple phenotypic differences, have different patterns of gene expressions, and most importantly, only the O variant is virulent. Our attempts to elucidate the genetic mechanisms underlying the O to T switch have led to the discovery of a RodZ ortholog that plays a role in the regulation of the phenotypic switch. RodZ is a transmembrane protein containing a helix-turn-helix motif. The primary function of RodZ is to bind and secure MreB (actin) near the cell membrane. Cells of a *rodZ* deletion mutant switch to the T variant at levels reduced over 4,000-fold compared to wild-type cells. Concordant with the role of *rodZ* in other bacterial species, the deletion results in a round, bloated cell phenotype. Interestingly, full complementation of switching can be achieved with no or only partial complementation of cell morphology, indicating that the altered cell morphology is not responsible for the decrease in O to T switching.

Sara Bramlett, MSP **Poster #58**

EFFECTS OF ADVERSE MATERNAL CARE ON THE DEVELOPMENT OF HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS FUNCTION IN NONHUMAN PRIMATES

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Early life stress (ELS) is a known risk factor for psychopathology, including anxiety and depressive disorders. The mechanisms underlying this association remain poorly understood. A likely link is the impact of ELS on development of the hypothalamic-pituitary-adrenal (HPA) axis. Our group used a translational and well-established ELS model of infant maltreatment by the mother in rhesus macaques. Infant macaques (n=43) were cross-fostered at birth and randomly assigned to either control (n=21) or maltreating (MALT; n=22) foster mothers. We assessed the developmental impact of adverse care on HPA axis function longitudinally since birth through adolescence using measures of (1) hair cortisol (CORT) accumulation, (2) diurnal CORT rhythm, (3) glucocorticoid negative feedback via dexamethasone (DEX) suppression tests, and (4) stress reactivity via human intruder tests. We observed differences in: accumulated hair CORT during infancy, diurnal CORT rhythm and DEX suppression during the early juvenile period, and a trend in stress reactivity during adolescence. Differences observed during infancy and the early juvenile period disappeared by late juvenile period. Although HPA axis activity seems to recover over time, chronic exposure to high levels of CORT during the first 12 months of life are expected to have long-term consequences for brain, physiological and behavioral development.

Kirsten Cottrill, MSP **Poster #59**

DETERMINING THE MECHANISM OF SMASE-MEDIATED INHIBITION OF CFTR

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Cystic Fibrosis (CF) is a common, lethal genetic disease caused by insufficient activity of the ion channel CF Transmembrane conductance Regulator (CFTR). The predominant cause of death for CF is pulmonary insufficiency due to persistent infection and inflammation of the airways. Interestingly, many of the infectious bacteria common in CF secrete the virulence factor sphingomyelinase (SMase), which degrades membrane sphingomyelin into phosphocholine and ceramide, a pro-inflammatory molecule. Our lab has shown that bacterial SMase applied to the serosal side of patient bronchial epithelial cells inhibits CFTR current (Stauffer et al. 2017). However, the mechanism by which this SMase-mediate inhibition of CFTR occurs is yet uncharacterized. Furthermore, inflammation causes a release of endogenous SMase from cells on the serosal side of bronchial epithelial cells. This inflammatory SMase response and the effect of endogenous SMase on CFTR activity has yet to be characterized. The work presented herein begins to explore the mechanism by which SMase inhibits CFTR current, and outlines the future directions of this project. This is important, as it will inform how bacterial virulence factors may need to be targeted to prevent further inhibition of the already deficient CFTR to improve treatment for CF patients.

Lauren Fleischer, MSP **Poster #60**

ENGINEERING CD5-TARGETED CHIMERIC ANTIGEN RECEPTORS AND EDITED T CELLS FOR THE TREATMENT OF T-CELL LEUKEMIA

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Treatment of relapsed/refractory T-cell malignancies to induce a second remission poses a great challenge. Chimeric antigen receptor (CAR) T-cell therapy has demonstrated great success in the treatment of relapsed B-cell malignancies. However, the same approach is difficult to apply to the treatment of T-cell malignancies due to the lack of T-lymphoblast-specific antigens. Therefore, CAR-T cells target themselves, resulting in fratricide. We have been investigating mechanistic approaches to evade fratricide-based limitations of CAR therapy for T-cell leukemias. Since the majority of T-cell leukemias express CD5, we hypothesized it would be a suitable target. We used CRISPR/Cas9 to knock out CD5 expression in CD5-positive Jurkat T cells, resulting in CD5-negative Jurkat T cells that were used as CAR-expressing effector cells. Here, we compare non-CRISPR T cells to CD5-edited T cells when modified with a CD5-CAR. Our *in vitro* studies show CD5-edited CAR-modified T cells have limited self-activation, increased activation in the presence of CD5-positive target cells, and increased CD5-CAR expression compared to those of non-edited CAR-modified T cells. Overall, our data show an advantage to using CD5-edited effector T cells when utilizing CAR-T cell therapy to target difficult to treat relapsed T-cell malignancies, leading to more potent and durable anti-leukemia effects.

Cameron Herting, MSP **Poster #61**

DELINEATING THE THERAPEUTIC MECHANISM OF DEXAMETHASONE IN GLIOBLASTOMA-RELATED CEREBRAL EDEMA

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Glioblastoma is the most common and aggressive primary brain tumor. During disease progression, nearly all patients will develop cerebral edema. Standard treatment for cerebral edema has been the corticosteroid dexamethasone for over 50 years. Although efficacious, recent data indicates that dexamethasone administration is associated with reduced median survival and that it interferes with radiation and chemotherapy. Therefore, it is necessary to develop an alternative therapy for glioblastoma-related cerebral edema. The inflammatory cytokine IL-1β has been referred to as the master regulator of neuroinflammation. It is primarily produced by macrophages; a cell population that can constitute up to 30-50% of the tumor in glioblastoma. This work demonstrates the ability of dexamethasone to inhibit IL-1β expression in primary, bone marrow-derived macrophages following stimulation with lipopolysaccharide and interferon gamma. Moreover, it illustrates the ability of dexamethasone to suppress induction of inflammation-related genes following stimulation with recombinant IL-1α and IL-1β. Ongoing investigations utilizing RCAS/tv-a modeling of glioblastoma in IL-1R$^{-/-}$ and IL-1β$^{-/-}$ mice will elucidate the role of IL-1 in development of cerebral edema *in vivo*. Overall, this project demonstrates the role of IL-1 in the therapeutic efficacy of dexamethasone for treating cerebral edema and lays the groundwork for therapies that specifically target IL-1 signaling.

Akram Salam, MSP **Poster #62**

FRACTIONATION OF ENRICHED *CASTANEA SATIVA* LEAF EXTRACT 224C-F2 YIELDS QUORUM QUENCHERS WITH ENHANCED BIOACTIVITY

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Methicillin-resistant *Staphylococcus aureus* (MRSA) presents one of the most serious health concerns worldwide. With the spread of antibiotic resistance due to the survival pressure exerted by conventional antibiotics, the use of anti-virulence strategies has been recurrently proposed as a therapeutic approach. In MRSA, virulence is chiefly controlled by quorum sensing (QS); QS inhibitors are called quorum quenchers (QQ). In *S. aureus*, most components of QS are coded by a gene locus called the accessory gene regulator (*agr*). Previously, we reported the non-bactericidal QQ activity of *Castanea sativa* leaf extract, 224C-F2. This extract impaired MRSA pathogenesis in a mouse skin infection model without manifesting local or systemic toxicity and demonstrated no detectable resistance after 15 days of serial passaging. Recently, we found that 224C-F2 exerted virulence inhibition in an *agr*-dyfunctional MRSA strain. This indicates that components of this extract targets non-*agr* systems. A portion of 224C-F2 called 224C-F2c was fractionated via reverse phase preparative HPLC to yield 51 prep fractions (PFs). Among these, PF44 exhibited markedly improved inhibition of all *agr* subtypes over parent compositions. Our results identified PF44 as a source of QQs which, once isolated, hold promise for development into highly effective anti-virulence drugs against all MRSA *agr* subtypes.

Darian Williams, MSP **Poster #63**

ROLE OF KLK10 IN ENDOTHELIAL BIOLOGY AND ATHEROSCLEROSIS

Darian Williams[1] and Hanjoong Jo[1,2]

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Atherosclerosis is a chronic inflammatory disease of the arterial blood vessels that underlies the occurrence of heart attack, peripheral artery disease, and ischemic stroke; the leading causes of death worldwide. Currently cholesterol lowering statin drugs and stents are the most commonly used therapies for the prevention and treatment of atherosclerosis, however, despite their success, atherosclerosis is still the leading killer. Therefore, new therapeutics are needed to treat atherosclerosis. It is well-known that atherosclerosis preferentially occurs in areas of disturbed blood flow (d-flow) while areas of stable flow (s-flow) are protected from developing atherosclerosis. Dysfunction of the endothelial cells in lesion-prone areas is an important contributor to the development of atherosclerosis, however, the underlying mechanisms by which blood flow regulates endothelial dysfunction and atherosclerosis are still unclear. We have sought to understand the molecular mechanisms of flow-dependent atherosclerosis in order to develop novel therapeutics. Interestingly, we have identified over a thousand endothelial genes that change in response to blood flow that may acts as novel therapeutics, termed flow-sensitive proteins. My research looks to characterize one of the most flow-sensitive proteins, Kallikrein Related Peptidase 10 (KLK10), and its effects on atherosclerosis.

Rachel Branco, NS **Poster #64**

LEVODOPA AND DOPAMINE DYNAMICS IN PARKINSON'S DISEASE METABOLOMICS

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We used mass spectrometry metabolomics to characterize and compare over 10,000 plasma metabolites from older adults with and without Parkinson's disease in an untargeted way. We perform a network analysis that demonstrates that the presence of the PD drug levodopa influences variation observed between PD and control patients. We also perform metabolome wide t-tests, OPLS-DA, and PCA analyses. These analyses show a significant differentiation in the metabolomics profile of older adults with and without PD. Notably, 15 metabolites (ten of which we putatively identified) were significantly different between PD and control adults. Furthermore, 13 metabolic networks were identified to be functionally different between PD and disease patients. Lastly, dopaminergic toxic intermediates (DOPAL, m/z 153.0548) differed between patients populations, supporting the dopaminergic sequestration model of PD. These individual metabolites and metabolic networks have been implicated in past PD pathogenesis models, including the beta-carboline harmalol (m/z 223.0846) and the glycosphingolipid metabolism pathway (including the ganglioside GM2, m/z 1427.752). We recommend that future studies take into account the confounding effects of levodopa in metabolic analysis of disease versus control patients, and encourage validation of several promising metabolic markers of PD.

Erica Ahkter, NS **Poster #65**

RESTORATION OF MOTONEURON KCC2 FOLLOWING PERIPHERAL NERVE INJURY IS DEPENDENT ON SUCCESSFUL MUSCLE REINNERVATION

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Following peripheral nerve injury (PNI), axotomized motoneurons undergo many changes within the spinal cord that are not well understood. One such change is the disappearance of the potassium-chloride cotransporter-2 (KCC2) from the membrane of motoneuron somata and proximal dendrites. In the dorsal horn, KCC2 is downregulated within interneurons due to microglial release of brain-derived neurotrophic factor (BDNF). However, this is not the case for motoneurons that are themselves axotomized after PNI. We illustrate that the microglia-specific deletion of BDNF does not prevent the removal of KCC2 from the proximal somatodendritic membrane of motoneurons. We also investigate alternative mechanisms regulating motoneuron KCC2 after PNI, including a possible role of BDNF from non-microglial sources. In addition, we illustrate that KCC2 is only restored in animals that have undergone successful nerve repair, not those that have had regeneration prevented by tightly ligating their axons. Based on these results we suggest that the regulation of KCC2 on motoneuron proximal cell membranes cannot be entirely explained by cell autonomous mechanisms or release of BDNF from microglia. Instead it is likely that a retrograde signal from the periphery plays an important role in regulating this significant intrinsic motoneuron property.

Desiree De Leon, NS **Poster #66**

PERIPHERAL METHYLATION OF MACAQUE OXT AND OXTR GENES, OXYTOCIN LEVELS IN CEREBROSPINAL FLUID, AND SOCIAL BEHAVIOR

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Oxytocin (OXT) and its receptor (OXTR) are encoded by *OXT* and *OXTR*, respectively. Variable methylation of these genes has been linked to variability in sociability and neuroendophenotypes. Here we examine whether *OXTR* or *OXT* methylation in blood predicts concentrations of OXT in cerebrospinal fluid (CSF) and social behavior in rhesus macaques. We report a similarity between human and rhesus CpG sites for *OXT* and *OXTR*. We did not detect a statistically significant association between methylation of these CpG sites and CSF OXT concentration that survived Bonferroni corrections. Before corrections, methylation of the *OXTR* CpG closest to the start codon explained 4.1% of OXT CSF variance ($p=0.008$) and was associated with pro-sociability and decreased anxiety. Because no associations survived statistical corrections, if there is any relationship between blood-derived methylation of these genes and OXT CSF or social behavior, the effect size is too small to be detected reliably with this sample size. These results do not support the hypothesis that blood methylation of *OXT* or *OXTR* is associated with CSF OXT concentration or social behavior in rhesus. It is possible, though, that methylation of these loci in the hypothalamus or in cheek epithelia may be associated with central OXT release and behavior.

Stephanie Foster, NS **Poster #67**

THE D3 ANTAGONIST PG01037 AND D2 ANTAGONIST L741626 EXERT OPPOSING EFFECTS ON SENSITIZATION OF COCAINE-INDUCED LOCOMOTOR ACTIVITY IN MICE

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The dopamine D3 receptor may be a therapeutic target for drug addiction. In this study, we tested the effect of the D3-selective antagonist, PG01037 (PG), against the D2-selective antagonist, L741626 (L7), on cocaine-induced locomotor sensitization in mice. We hypothesized that PG, but not L7, would enhance sensitization of cocaine-induced locomotion. The sensitization paradigm consisted of 3 days of habituation, 5 days of cocaine treatment, and 10 drug-free days followed by a cocaine (7.5 mg/kg) challenge day. This paradigm was repeated in another cohort to test 10 mg/kg L7 on 15 mg/kg doses of cocaine. There was a significant interaction between induction day and treatment group 30 minutes after cocaine treatment ($F(12, 104) = 3.015$, $p = 0.00120$). PG significantly enhanced locomotion on days 4 ($p<0.0001$) and 5 ($p<0.05$) compared to vehicle, but had no effect on challenge day. L7 treatment also generated a significant interaction between induction day and treatment group ($F(12, 96) = 9.503$, $p<0.0001$). L7 attenuated cocaine-induced locomotion on days 2 through 5 ($p<0.05$), but had no effect upon challenge. Overall, PG enhanced, and L7 attenuated, acute sensitization of cocaine-induced locomotion. This finding highlights the need for high-specificity receptor ligands for new drug addiction therapies.

Eduardo Gigante, NS **Poster #68**

INEFFICIENT ENRICHMENT OF SMO IN CILIA DISRUPTS THE HIGHETS LEVEL OF SHH ACTIVITY

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Sonic hedgehog (Shh) signaling is a tightly regulated developmental pathway that requires the G-protein coupled receptor Smoothened (Smo) and the primary cilium. Smo acts as the obligate transducer of the Shh signal and is normally enriched in cilia when the pathway is stimulated. While the Shh pathway and Smo are well studied, the biological mechanisms surrounding Smo have yet to be fully characterized. Using an ENU-induced forward genetic screen in mice, we identified a novel recessive allele of *Smo* carrying a missense mutation, called *cabbie* (*cbb*). Despite a reduction in Shh signal transduction, the Smo^{cbb} embryo survives longer than the *Smo* null, suggesting it is a hypomorph. We characterized Smo^{cbb} for defects in craniofacial and skeletal development, as well as neural tube patterning, and showed Smo^{cbb} affected processes that require the highest levels of Shh activity. We determined Smo fails to properly localize to the primary cilium in Smo^{cbb} neural tube and MEFs. Taken together, our data argue Smo^{cbb} perturbs Shh signaling, leading to aberrant craniofacial, neural tube and limb development.

Mary Herrick, NS **Poster #69**

THE ROLE OF LRRK2 IN REGULATION OF IMMUNE CELL FUNCTION AND INFLAMMATORY RESPONSES IN G2019S BAC TRANSGENIC MICE

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Mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) are the greatest contributor to dominantly inherited Parkinson's disease (PD) and are associated with sporadic PD. G2019S, the most prevalent LRRK2 mutation, results in increased kinase activity; therefore, therapeutic intervention has focused on the development of LRRK2 kinase inhibitors to dampen kinase activity. While much attention has focused on the role of LRRK2 in neurons and neuronal toxicity, LRRK2 is highly expressed in immune cells. Recent work from our group revealed immune cells from PD patients have increased LRRK2 levels compared to age-matched healthy controls. Given that increased brain and peripheral inflammation have been associated with the pathophysiology of PD, we hypothesize LRRK2 regulates inflammatory responses to reduce the risk for sporadic PD. To directly investigate the role of LRRK2 in immune cells, we are using flow cytometry to perform immunophenotyping of immune cells from BAC transgenic mice overexpressing WT or G2019S mLRRK2. We will use the LRRK2 kinase inhibitor PF-360 to test the hypothesis that peripheral immune cell populations are altered through increased G2019S mediated kinase activity. Completion of these studies will further reveal the effects that LRRK2 kinase inhibitors afford to immune system function in familial and sporadic PD.

Michelle Johnson, NS **Poster #70**

DETERMINING THE MECHANISMS THROUGH WHICH PHOSPHORYLATION OF FUS CAUSES CYTOPLASMIC ACCUMULATION

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Frontal temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are two types of neurodegenerative disorders that exhibit robust RNA/DNA dysfunction. FTD and ALS share many genetic and neuropathological markers of diseases. One such neuropathological marker that occurs in about 5-10% of cases is the abnormal cytoplasmic aggregation of the Fused in Sarcoma (FUS) protein. FUS is a RNA/DNA binding proteins involved in gene transcription, mRNA splicing, DNA-repair pathways, and mRNA transport. To accomplish its many roles in the cell, FUS shuttles between the nucleus and cytoplasm carrying mRNA transcripts to distinct locations in the cell body and dendrites. However, in FTD and ALS with FUS pathology, nuclear/cytoplasmic shuttling is disrupted resulting in an accumulation of cytoplasmic FUS into insoluble inclusions. Recently, studies have shown that DNA-PK mediated phosphorylation of FUS (p-FUS) at N-terminal residues triggers cytoplasmic aggregation of FUS. Nonetheless, it remains unclear 1) what mechanism mediates p-FUS mislocalization to the cytoplasm and 2) how p-FUS aggregation may affect disease progression. CLM is a potent trigger of double strand DNA breaks and induces FUS to accumulate in the cytoplasm. Therefore, I used cytoplasmic/nuclear fractionation to determine where FUS was being phosphorylated in the cell following CLM treatment.

Erin King, NS **Poster #71**

MYELIN STATUS IS ASSOCIATED WITH CHANGE IN FUNCTIONAL MOBILITY FOLLOWING SLOPE WALKING IN PEOPLE WITH MULTIPLE SCLEROSIS

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The level of myelin disruption in Multiple Sclerosis (MS) patients may impact the capacity for training-induced neuroplasticity and the magnitude of therapeutic response to rehabilitation interventions. Downslope walking has been shown to increase functional mobility in individuals with MS, but it is unclear if myelin status influences therapeutic response. The current study aimed to examine the relationship between baseline myelin status and change in functional mobility after a walking intervention. The Timed Up and Go (TUG) Test was used to measure functional mobility before and after completion of a repeated, 6-session slope walking intervention in 16 participants with relapsing-remitting MS. Multi-component T2 relaxation imaging was used to index myelin water content expressed as a fraction (MWF) of overall water content in brain tissue compartments. Results demonstrated that the ratio of the MWF in lesion to normal-appearing white matter (NAWM) (MWF ratio) significantly predicted 39% of the variance in change in TUG score after the downslope walking intervention, where less myelin disruption was associated with greater intervention response. MWF ratio may offer a neural biomarker of myelin to identify potential responders to interventions targeting functional impairments in MS.

Erica Landis, NS **Poster #72**

POTENTIAL MYOPIA PREVENTION WITH ENVIRONMENTAL LIGHT

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The prevalence of myopia has reached epidemic levels around the world leading to a pressing need for prevention techniques which could stop the progression of myopia and prevent later stage vision loss. Research suggests that bright light exposure as a possible prevention since children who spend more time outdoors in bright sunlight are less myopic. Here, we tested the effects of light to prevent myopia. Male C57BL/6J mice were housed in either bright (10,000 lux), intermediate (50 lux), or low (0.005 lux) light from post-natal day 23 (P23). Monocular lens defocus (-10D) myopia was induced in a subset starting at P28. By P35, mice in bright or dim light showed a smaller myopic response (treated-control shift, bright: -2.60±0.54D, dim: -1.81±0.61D), compared to intermediate light (-4.74±0.61D, $p<0.005$). To determine the clinical relevance of dim light protection, the light exposure patterns of 82 children, aged 12-15 years old were monitored over two weeks. As expected, children with myopia spent less time in bright light ($p<0.01$). Additionally, increased time in dim light showed a nonsignificant association with decreased myopia. Here we show the importance of both bright and dim environmental light for the prevention of myopia in a mouse model and humans.

Laura Butkovich, NS **Poster #73**

A NOVEL TRANSGENIC MOUSE MODEL TO INVESTIGATE PARKINSON'S DISEASE-LIKE α-SYNUCLEIN PATHOLOGY IN NORADRENERGIC NEURONS

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While cell loss and α-synuclein (αsyn) aggregates in the substantia nigra pars compacta (SNpc) are a major hallmark of Parkinson's disease PD, pathology in the locus coeruleus (LC) is commonly more severe, and may even precede that found in the SNpc and contribute to nigrostriatal loss. While most PD research has focused on the SNpc, we have lacked suitable models to understand how αsyn pathology specifically affects noradrenergic neurons in PD, and whether noradrenergic neurons are vulnerable to αsyn pathology. Transgenic models of αsyn expression have previously been unable to selectively target LC neurons, limiting our understanding of how αsyn pathology affects noradrenergic neurons. To examine this question, we have developed a BAC-transgenic mouse model expressing wild-type human αsyn under the control of the noradrenergic-specific dopamine β-hydroxylase promoter. These animals express human αsyn in LC neurons, and enteric neurons derived from the neural crest. Preliminary analysis revealed human αsyn immunoreactivity and mRNA expression in noradrenergic neurons of the LC in transgenic mice, but not non-transgenic littermates. We are currently evaluating age- dependent LC neuron loss and fiber degeneration in these mice. Our preliminary findings indicate that this novel transgenic mouse model could provide insight into the mechanisms underlying PD- like αsyn aggregation.

Dan Li, NS **Poster #74**

APPLICATION OF IFENPRODIL FOR DRUG VULNERABILITIES DUE TO ADOLESCENT COCAINE EXPOSURE

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Adolescent cocaine exposure increases the risk of cocaine abuse, dependence, and relapse and decreases the likelihood that individuals will seek treatment for problematic drug use at any point in the lifespan. We aim to understand how developmental cocaine durably impacts decision-making. We observe that cocaine self-administration in adolescent mice is highly heterogenous, with some mice stably responding, while others demonstrate an escalatory response, possibly mirroring episodic, recreational use versus pathological drug seeking in humans. In adulthood, mice with a history of escalatory responding develop biases towards habit-based behaviors at the expense of goal-directed actions. We find that escalatory adolescent cocaine exposure results in long-term synaptic marker loss in the prefrontal cortex (PFC), and that the stable cocaine-response phenotype is associated with decreased expression of the NR2B subunit of N-methyl-D-aspartate receptors (NMDARs). Based on these findings, we assessed the potential therapeutic-like efficacy of ifenprodil, an NR2B-selective NMDAR antagonist that attenuates cocaine-induced locomotor sensitization, as well as heroin-, nicotine-, and alcohol-associated reinstatement. Ifenprodil pretreatment in adolescence blocked the development of cocaine-induced habits and other perseverative behaviors in adulthood. Together, these findings suggest that downregulation of NR2B-mediated activity may be protective against certain long-term behavioral consequences of cocaine exposure.

Neeti Mehta, NS **Poster #75**

NEOTROPICAL BATS THAT CO-HABIT WITH HUMANS FUNCTION AS DEAD-E INFLAMMATION IS ASSOCIATED WITH DECREASED AMYGDALA TO VENTROMEDIAL PREFRONTAL FUNCTIONAL CONNECTIVITY IN ASSOCIATION WITH SYMPTOMS OF ANXIETY IN PATIENTS WITH DEPRESSION

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Increased inflammation is reliably observed in patients with depression and/or fear and anxiety-related psychiatric disorders and is thought to contribute to symptom severity. Previous work shows that administration of inflammatory stimuli affects brain regions involved in fear, anxiety and emotional processing such as the amygdala. However, whether increased inflammation affects the amygdala and its functional connectivity with other brain regions in patients with depression and/or anxiety-related disorders is only beginning to be explored. Using resting-state functional MRI, we investigated whether increased inflammation in patients with depression was associated with altered functional connectivity of the amygdala to whole brain in relation to symptoms of anxiety. Results indicated that increased inflammation (plasma C-reactive protein) was associated with decreased functional connectivity between the right amygdala and left ventromedial prefrontal cortex (vmPFC; corrected $p<0.05$), which was in turn correlated with increased symptoms of anxiety ($r=-0.33$, $df=46$, $p=0.022$). Of note, the relationship between decreased amygdala-vmPFC connectivity was strongest in patients with a secondary diagnosis of PTSD compared to those with no PTSD, and was significant only in females. These findings suggest that increased inflammation compromises amygdala to prefrontal circuitry in association with increased anxiety in patients with depression, and particularly in those with comorbid PTSD.

Amielle Moreno, NS **Poster #76**

BEHAVIOR AND PLASTICITY ASSOCIATED GENE EXPRESSION

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Recent research suggests long-term changes at a mother's site of cortical auditory processing, the auditory cortex (AC), leads to enhanced recognition and response to infant vocalizations. However, it is currently unknown what immediate molecular mechanisms are enacted during infant experience to lead to this enhanced neural response. The parturition hormone estrogen (E2) is associated with maternal behavior as well as learning and memory through the expression of the plasticity related gene, brain derived neurotrophic factor (*bdnf*). Here, we use a mouse maternal model to investigate the effect of the social neuromodulator E2 on both behavior and the transcription of *bdnf* in the AC of virgin mice in response to acute infant pup-caring experience. As expected, E2 leads to increases in maternal behavior during pup exposure. Additionally, we found a significant effect of both pup ($F_{(3,9)} = 53.42$, $p = 0.0003$) and E2 ($F_{(3,9)} = 11.46$, $p = 0.0148$) exposure on the transcription of *bdnf* in the AC one hour after acute pup-caring experience. By examining changes in *bdnf* expression and behavior, we investigate the molecular underpinnings associated with the early stages of AC plasticity which might be responsible for enhancing future infant stimuli processing.

Rachel Pearcy, NS **Poster #77**

IMMUNOHISTOCHEMICAL AND BEHAVIORAL CHARACTERIZATION OF MICE LACKING GALANIN IN NORADRENERGIC NEURONS

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The neuropeptide galanin is expressed throughout the brain and body, with the exact pattern of expression varying between species. However, the locus coeruleus (LC), the main noradrenergic nucleus in the brain, consistently shows high galanin expression among humans and rodents, indicating that LC-derived galanin may play a conserved biological role in normal brain function. Disruptions in the galaninergic system have been widely associated with disorders such as depression, anxiety and addiction, yet the source of the critical galanin has not been identified. In order to examine the functional role of LC-derived galanin in behavior, conditional knockout mice (Gal cKO) were generated by crossing mice expressing Cre recombinase under control of the noradrenergic-specific dopamine β-hydroxylase promoter with a floxed galanin line of mice. Immunohistochemical analysis confirmed a selective loss of galanin in brain noradrenergic neurons of Gal cKO mice, and preliminary behavioral analysis indicates that these animals show greater anxiety-like behavior in some tasks compared to their wild-type littermates, consistent with galanin's previously reported anxiolytic properties. Future studies will work to determine the mechanisms by which LC-derived galanin may influence anxiety-like and other behaviors.

Lindsey Shapiro, NS **Poster #78**

INVESTIGATING THE ROLE OF THE CANNABINOID 2 RECEPTOR IN EPILEPSY

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Epilepsy affects fifty million individuals worldwide, and 30% of these individuals do not achieve adequate seizure control with currently available medications, highlighting the need to develop more effective treatment strategies. The Cannabinoid 2 Receptor (CB2Rs) can modulate processes that are dysfunctional in epilepsy, but we know very little about the function of CB2Rs in epilepsy models. CB2Rs are upregulated in models of neurological diseases with pathological similarities to epilepsy, and their activation is anti-inflammatory and neuroprotective in these models. CB2Rs can inhibit microglia, thereby reducing the release of pro-inflammatory markers and improving neurological and inflammatory phenotypes. Importantly, neuroinflammation is a key feature of refractory epilepsies, indicating a potential role for CB2Rs in the treatment of epilepsy. Here, we show that Cannabinoid 2 receptor knockout Mice (*Cnr2*$^{-/-}$) are not susceptible to seizures induced acutely by the chemiconvulsants flurothyl and kainic acid, electroconvulsive seizures, or hyperthermia (febrile) induced seizures. This evidence suggests a role for CB2Rs is more likely in chronic models of refractory epilepsy, such as mesial temporal lobe epilepsy (MTLE), as a response to the epileptogenic changes which occur over time following an initial insult.

Archana Venkataraman, NS **Poster #79**

ZONA INCERTA MODULATES FEAR RESPONSES IN MICE AND HUMANS

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The ability to inhibit fear in neutral, non-aversive conditions is crucial for adaptive functioning of an organism. Dysregulation of fear inhibition is associated with a wide range of psychopathological conditions. In the mammalian brain, the sub-thalamic Zona Incerta, typically considered a sensorimotor relay is gaining attention for its role in behaviors like sleep and modulates behavioral responses in a state-dependent manner. However, very little is known about its role in modulating fear. Using Designer Receptors Exclusively Activated by Designed Drugs (DREADD)-based manipulation of cellular activity, we found that the medial zona incerta (mZI) bi-directionally modulates fear inhibition in mice. Reducing activity of the mZI leads to impairments in fear inhibition and stimulating the mZI rescues these impairments. Moreover, in humans, functional magnetic resonance imaging (fMRI) revealed ZI activity to be associated with individual differences in fear inhibition. Our data suggest a role for the ZI in fear inhibition that is conserved across species and future studies will examine afferent and efferent circuitry associated with the ZI.

Lahiru Wimalasena, NS **Poster #80**

IMPROVED DECODING PERFORMANCE OF UNSTRUCTURED MOTOR TASK USING DEEP LEARNING METHODS

***Lahiru Wimalasena*[1],** Anil Cherian[2], Lee Miller[2], Chethan Pandarinath[1]

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It has long been sought after to decode various kinematic (position, velocity, etc.) and kinetic (muscle activation, joint rotations, etc.) outputs from neural activity. For the field of brain-machine interfaces (BMI), the solution to this problem is limited by the necessity for simple, efficient methods for real-time execution of desired movements. Furthermore, the decoded output must mimic similar dynamics of natural movement. In order to decode natural movement, we must study neural populations during motor tasks that are unstructured to probe various movement dynamics. Analysis of these unstructured tasks is not a trivial task. Here we aimed to utilize deep learning methods to generate a learned representation of the neural data that could improve decoding performance of kinematic and kinetic outputs. Using the Latent Factor Analysis of Dynamical Systems (LFADS), a deep learning tool developed to study neural populations, we analyzed neural data from a monkey performing an unstructured motor task. Using basic linear regression, we show increased prediction accuracy for kinematic (position, velocity) and kinetic (EMG) outputs using LFADS-inferred variables in comparison to traditional methods of neural data processing such as Gaussian smoothing and Principle Component Analysis (PCA).

Nate Jacobs, PBEE **Poster #81**

INCOMPLETE GENOMES PROMOTE ABUNDANT REASSORTMENT AND DIVERSIFICATION IN INFLUENZA A VIRUS POPULATIONS

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Rapid evolution allows RNA viruses to evade immunity and antimicrobial therapies. Beyond mutation, viruses with segmented genomes, such as influenza A viruses, may produce progeny with novel gene combinations by reassortment. Influenza virions often fail to replicate all 8 genome segments, however, with most singly infected cells expressing only some viral proteins, which suggests that the infectious dose comprises multiple virions, making replication dependent on co-infection. Using a single cell assay, we observed that each genome segment of influenza A/Panama/2007/99 (H3N2) virus has only a 56% probability of being present in singly infected cells, which predicts the frequent reassortment observed in co-infection experiments and suggests that an average of 3 particles are required for productive infection. The presence of each RNA segment in individual cells was largely independent, with only 4 weak associations observed between segments. Without complementation, incomplete viral genomes are readily degraded, with 51% of segments lost by 4 hours post-viral entry. Computational modeling predicts that incomplete genomes impair spread but promote reassortment, which like sexual reproduction in eukaryotes may hasten adaptation. Thus, a reliance of influenza viruses on co-infection may have important implications for viral adaptation to novel environments like new hosts following cross-species transmission.

Ellie Mainou, PBEE **Poster #82**

PARSING A CROWD OF NEAR BEST FITS: CONSENSUS RANGES FOR DRUG-RESISTANT TUBERCULOSIS MODELING

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According to WHO, one third of the world's population is infected with tuberculosis (TB), with drug resistance posing a major challenge to the management of TB. Strains resistant to the most common drugs for treatment (e.g. isoniazid, rifampin) are already widespread. To address the issue, we constructed a mathematical compartmental model described by differential equations depicting the transmission of TB in the US. The model encompasses four strains of different resistance to antibiotics, while taking into consideration immigration, which greatly contributes to the excessive transmission of latent TB. A set of 27 parameters was fitted to recent CDC data on TB morbidity and mortality, using a genetic algorithm to minimize an error function. producing reliable fits, by generating random parameter values within the ranges obtained from real-world data. Local minima were identified and multiple sensitivity analysis tests were performed to identify which parameters the model is sensitive to.

Diana Vera-Cruz, PBEE **Poster #83**

IMPACT OF IMMUNE RESPONSES ON VIRAL DIVERSITY AND VIRAL LOAD DYNAMICS IN A MONKEY MODEL FOR CONGENITAL CYTOMEGALOVIRUS INFECTION.

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Congenital CMV infection is the leading infectious cause of birth defects worldwide, including severe neurologic damage, hearing loss, and microcephaly in the developing fetus. For this reason, interventions to prevent congenital transmission are needed. In this work, we investigate how pre-existing anti-CMV antibodies shape the maternal viral population and their effects on intrauterine transmission. We analysed genomic data from a newly-defined rhesus monkey model of congenital rhesus CMV (RhCMV) infection to examine the effects of pre-infection, passively-infused hyperimmune globulin (HIG) on viral population genetics in both maternal and fetal compartments. Three different strains of RhCMV were simultaneously inoculated intravenously into CD4+ T cell-depleted rhesus monkeys following prior treatment with either a standard HIG preparation or a high-neutralizing potency preparation. Samples were collected weekly after infection and utilized for targeted amplicon deep sequencing of the glycoprotein L (gL) and B (gB) genes. Here, we quantify the relative abundances of these three strains in maternal and fetal samples, as well as the nucleotide diversity present in these strains over time. We also investigate the case of transmission between maternal and fetal fluids by analyzing shared haplotypes and their recurrence in time.

Signe White, PBEE **Poster #84**

DAUER ALTERS BACTERIA PREFERENCE IN CAENORHABDITIS ELEGANS

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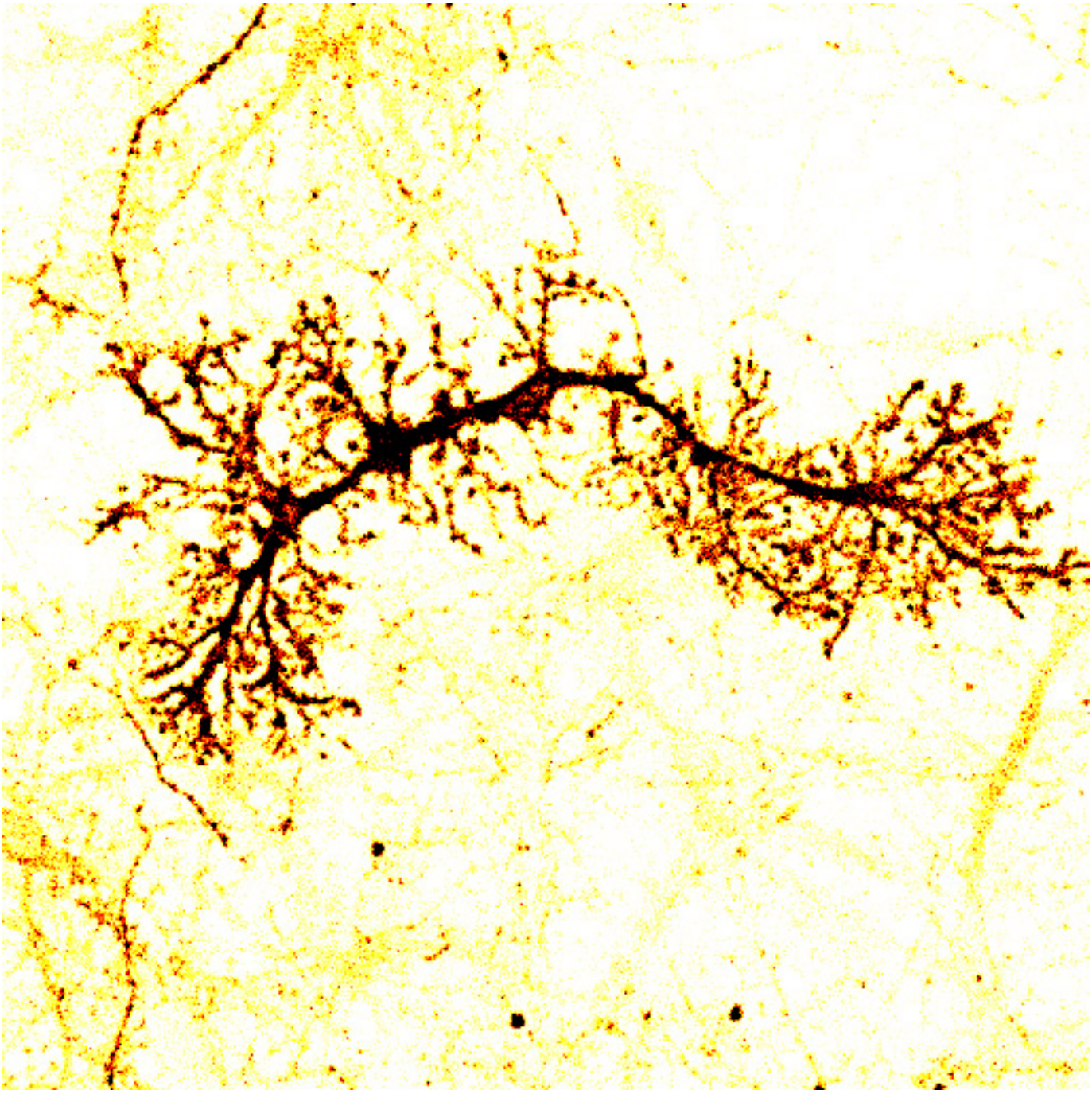
Pathogenic microbes are ubiquitous in nature and hosts must be able to mitigate the negative effects of these pathogens. Hosts often use avoidance as the first line of defense against pathogenic bacteria in order to prevent infection. *Caenorhabditis elegans*, a commonly used nematode in experimental biology, exists with a large diversity of bacterial species in nature, many of which serve as the worm's primary food source. While previous studies have shown that adult worms are unexpectedly attracted the pathogenic bacteria *Serratia marcescens*, these studies do not take into account an important nematode life stage known as "dauer." Dauer is known to be an important phenotype in nature as most natural isolates are found and collected in this stage. Dauer serves as a developmental arrest when external conditions become stressful. In our experiments, we found that dauer larvae do not choose *S. marcescens* as seen in adult worms and instead prefer *Escherichia coli*, a benign food source. Our experiments suggest that behavioral differences may allow dauer worms to better discriminate between bacterial species, thus providing them with a potential fitness advantage relative to non-dauer worms.

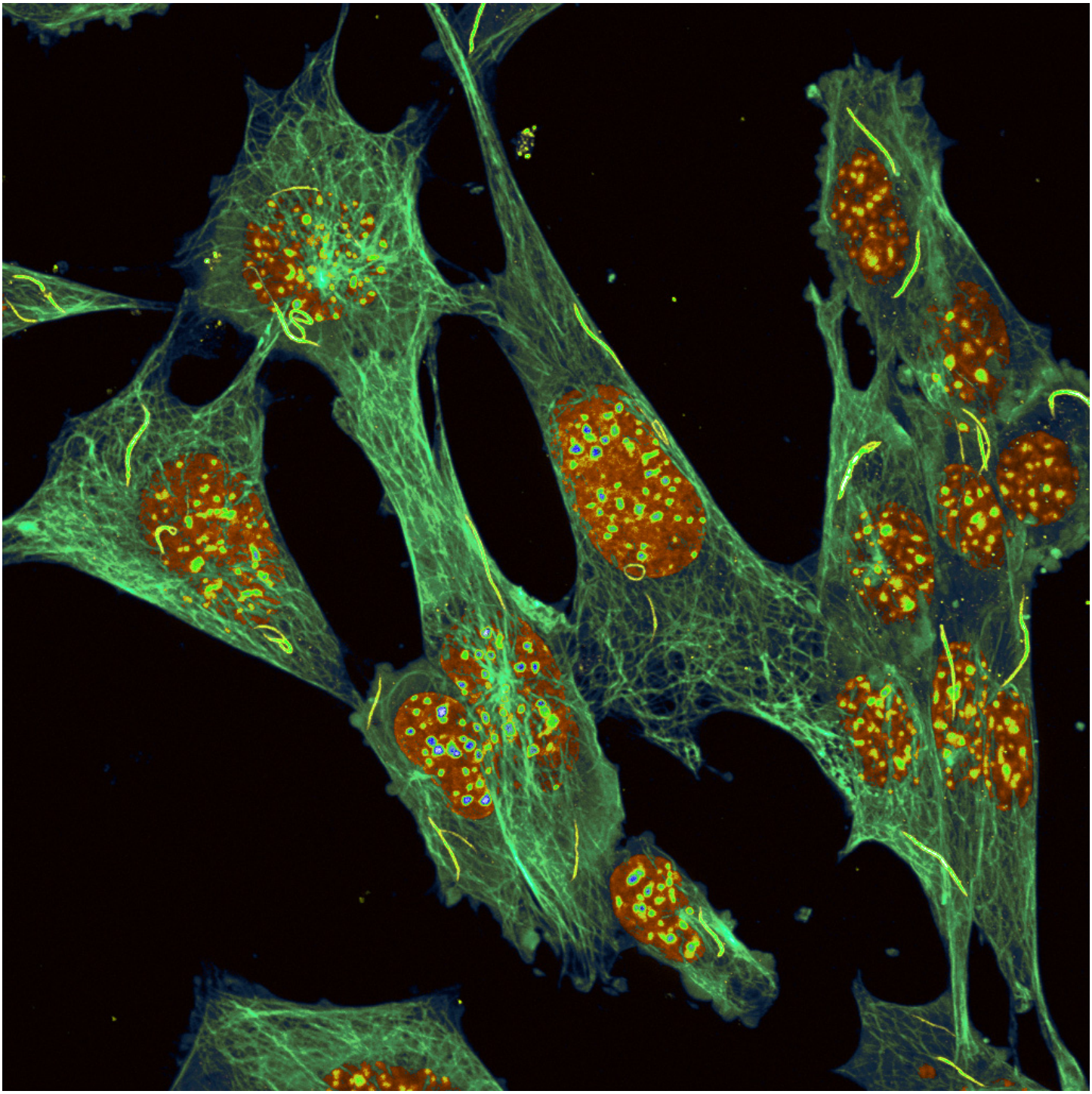
Runner Up, ICI Image Contest



Stephanie Pollitt, Neuroscience

Transfected hippocampal neuron in culture

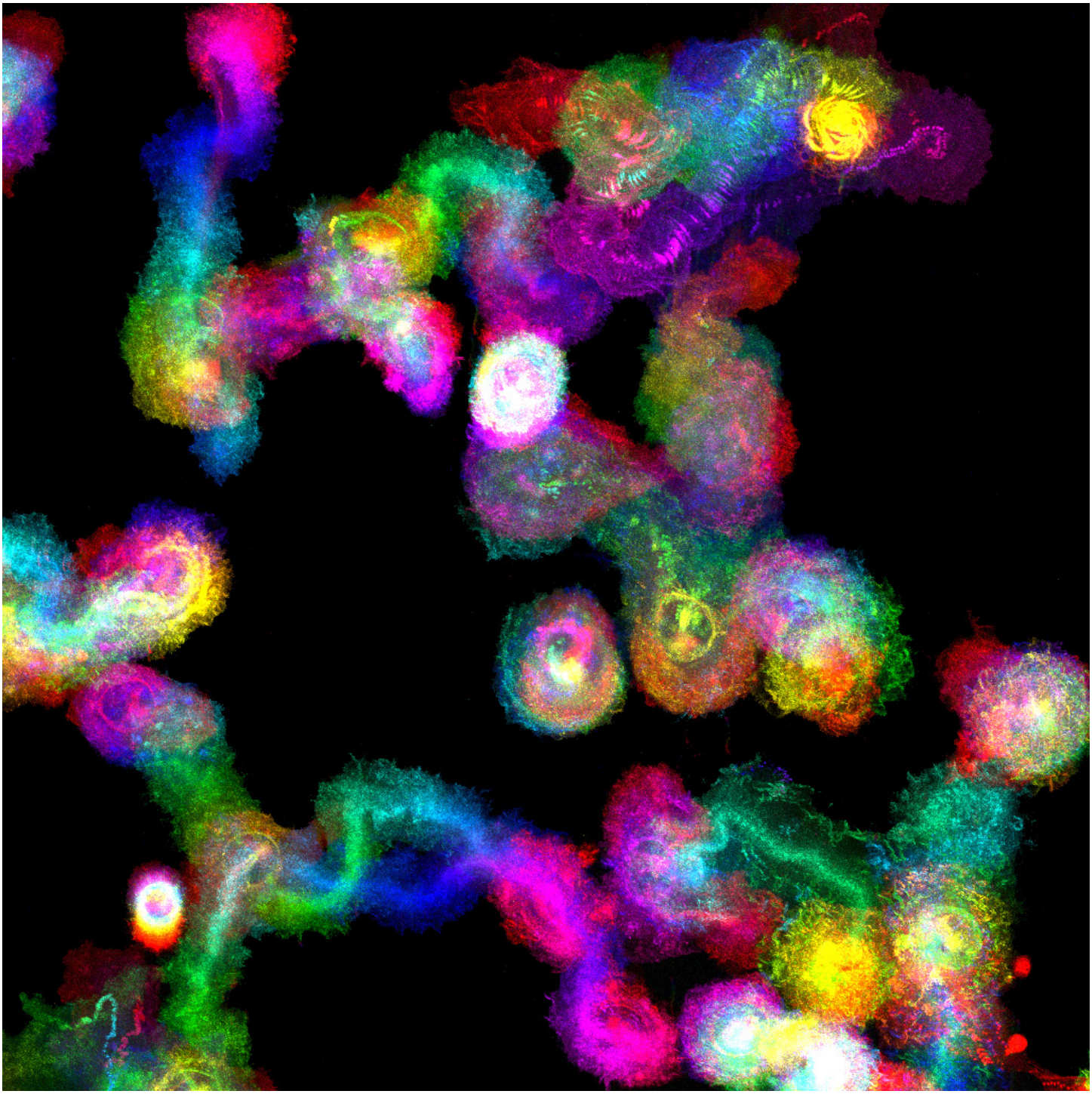
Runner Up, ICI Image Contest



Cara Schiavon, Cancer Biology

MEFs stained for the nucleus, microtubules, and mitochondrial “Rods and Rings” (RRs)

Runner Up, ICI Image Contest



Emily Summerbell, Cancer Biology

A color-coded time lapse of several GFP-expressing lung cancer cells moving over the course of about 24 hours, taken using confocal microscopy (1 frame = 2.5 minutes). In this compilation of all time points, the earliest time points are in red, and as time progresses, the color of the moving cells shifts through the spectrum of the rainbow and then ultimately ends with magenta.