Two faces of anti-NMDA receptor antibody encephalitis in toddlers

Objective: A case series exploring two very different presentations of N-methyl-D-aspartate (NMDA) receptor encephalitis in two-year-old boys.

Background: Pediatric patients comprise 37 - 40% of NMDA receptor encephalitis cases. The disease entity in toddlers is exceedingly rare, however, and often diagnosed retrospectively as part of a comprehensive encephalitis work-up.

Method: The first patient is a 34-month-old boy presenting for EEG monitoring after sudden onset of mutism and aggression following two brief generalized tonic-clonic seizures. His presentation is contrasted with that of a 25-month-old boy presenting with recurrent focal seizure clusters with return to baseline mental status in between episodes.

Results: A 34-month-old boy presented with acute onset of generalized seizures, mutism, anorexia, and aggressive behavior. Physical exam was significant for orobuccal dyskinesia, poor eye contact, and emotional lability with aggression. EEG showed prominent diffuse slowing with delta brush. This is contrasted with a 25-month-old boy presenting with difficulty to control brief focal seizures, often clustering, but with return to normal functional status in between episodes. Physical exam was non-focal. Both children were positive for anti-NMDA receptor antibodies in CSF and serum. The 34-month-old patient responded well to a 3-day course of IV Methylprednisolone followed by one 2 gram/kg dose of IVIG with resolution of his aggression and anorexia, as well as gradual improvement in his verbal capabilities. Seizures resolved in the 25-month-old patient with a titrated dose of oxcarbazepine without recurrence.

Conclusion: NMDA receptor encephalitis is uncommon in toddler age children, and with such a diverse array of associated symptoms, diagnosis can be difficult. This case series explores two very different clinical presentations of NMDA receptor encephalitis in toddlers to highlight variations in symptomology associated with such a critical diagnosis.

Improving Anticipatory Guidance and Preventing SIDS in an Ambulatory Setting

Sleep-related infant deaths, including sudden infant death syndrome (SIDS) remain one of the leading causes of death in newborns. In 1992, the American Academy of Pediatrics (AAP) issued a “Back To Sleep” campaign as evidenced by findings that the supine sleeping position correlates to decreased incidence of SIDS. The AAP has since added further guidelines in 2016 to further reduce its incidence. We designed a questionnaire to survey the sleeping habits of the newborns seen at the Pediatric Resident Continuity Clinic at Kings County Hospital Center (KCHC) and the University Hospital of Brooklyn (UHB). We aim to identify the aspects of the AAP Safe Sleep Guidelines that have decreased adherence and improve anticipatory guidance in those aspects. Sixty-three parents with children between 4 days to 6 months of age were asked to fill out a questionnaire; 7 surveys were invalid. In adherence to the AAP Safe Sleep Guidelines, majority of the children were placed in the supine position (80.4%). Almost all babies slept on an AAP-approved sleep surface such as the crib, bassinet or playpen (96.4%) and slept in their parents’ room (98.0%). However, there remains a significant percentage of parents that have extraneous items on the baby’s sleep surface (41.1%), such as a blanket (n=17) and a pillow (n=6). A significant percentage of parents placed the baby to sleep at least once on a non-approved sleeping position (55.4%) or surface (33.9%). The results of this questionnaire will help improve the quality of anticipatory guidance given by the residents to their patients regarding safe sleep practices. By emphasizing anticipatory guidance pertaining to the aspects of the AAP Safe Sleep Guidelines that have a lower adherence within our community, we can aim to increase compliance to these guidelines and further lower the incidence of SIDS in our population.
HPV Vaccination Rates at Downstate Pediatrics

Despite the availability of an approved HPV vaccine introduced more than ten years ago, vaccination rates remain low in many parts of the country with a national average vaccination rate of 60%. HPV 16 and 18 are responsible for 70% or worldwide cervical cancers, with an additional 20% caused by HPV 31, 33, 42, 52, and 58. These serotypes are all targeted by the 9-valent vaccine, which can be given starting at 9 years of age and is recommended between ages 11 and 12. Misconceptions about the HPV vaccine are prevalent, and lack of education regarding the benefits of the vaccine is a common reason for parent refusal. This study attempted to quantify rates of HPV vaccination at Downstate and elucidate reasons for vaccine refusal among parents.

Data for this study was collected through chart review of all patients ages 9 and above who came to general pediatrics clinic from August 1 to 31 2018. Qualitative data was obtained through individual patient interviews in this same time frame. Overall, the HPV vaccination rate of children above age 11 at Downstate Pediatrics was 83%, with 74% of females and 93% of males vaccinated. The only age group in which more girls were vaccinated than boys was between the ages of 9 and 11. This perhaps provides evidence that parents are more open to vaccinating their daughters at a younger age. Deferrals and misunderstanding about the utility of the vaccine and side effects of vaccine were the most common reasons we found for vaccine refusal. The HPV vaccination rate of 83% found at Downstate Pediatrics compares to a national HPV vaccination rate of 60% and a rate of 70% in NY state, indicating good overall adherence to national standards, but with room for vaccination rate improvement especially among females.

Authors: Lesje Atkinson and Emily Carbaugh

CPR at Downstate: Attitudes Among Providers at Downstate Pediatric Clinics

An estimated 16,000 children die each year of unexpected Pediatric out-of-hospital cardiac arrest (OCHA), with the overall population based incidence of non-traumatic pediatric OHCA being 8/100,000 person years. A disproportionate number of pediatric OHCAs occur in minority populations, with black children accounting for approximately 51.6% and hispanic children 26.6% of all cases. Black children have also been shown to have twice the risk of OHCA, possibly due to increased incidence of SIDS in this population. Despite the high percentage of OHCAs occurring in minority children, CPR by a bystander is more likely to be performed on white children than on black or hispanic children. As bystander CPR is associated with increased survival to discharge and favorable neurological outcomes, minority children are further placed at a disadvantage. The Downstate pediatric population is at a disproportionate risk for OHCA due to racial and socioeconomic factors. Determining the attitude and practices of Downstate pediatric providers (DPPs) in the pediatric clinics towards CPR is necessary to introduce BLS/CPR to this vulnerable population. It was found that DPPs rarely discuss CPR with new parents, except for rare mentions of discussions with parents of patients discharged from the NICU, reflecting a lack of communication regarding CPR. Despite the low number of DPPs addressing CPR within their patient population, the overwhelming majority of providers interviewed believe CPR is an important topic and should be a skill for all parents and children of varying ages. While providers had no consistent recommendations for parent CPR training, they expressed a strong interest in intervention following interview. Suggestions for intervention were made and an information sheet was developed to provide available BLS/CPR training options to members of the local community.
C5: Vivek Shukla  Advisor(s): Sukhvinder Ranu

**Novel Association of Antenatal Corticosteroid and Neonatal Indomethacin Therapy with Spontaneous Intestinal Perforation and Necrotizing Enterocolitis in Extremely Low Birth Weight Neonates**

**Background:** Administration of Indomethacin and steroids in extremely low birth weight neonates (ELBW, birth weight < 1000 gm) has been shown to increase the risk of spontaneous intestinal perforation (SIP) and necrotizing enterocolitis (NEC). Objective: To assess association between maternal antenatal corticosteroids (ANS) treatment followed by Indomethacin treatment in ELBW neonates and SIP/NEC by case-control study design.

**Methods:** The study was conducted at neonatal intensive care unit at Kings County Hospital, Brooklyn, New York. All ELBW neonates born between 1/1/2009 - 06/31/2016 who received Indomethacin for patent ductus arteriosus treatment were identified and antenatal, perinatal and neonatal variables were collected from EMR. Data was analyzed using SPSS. Relevant variables were expressed as means and standard deviations, means and interquartile ranges (IQR) and percentages. Categorical data was analyzed by Chi-square test or Fisher exact test as applicable. Continuous data was analyzed by t-test or Mann-Whitney U test as applicable.

**Results:** Total of 133 ELBW neonates were studied. N=11(8.2%) participants had SIP and 35(26.3%) had NEC. There was significantly higher mortality in the participants who had NEC or SIP (cases) (43.7% vs 4.8 %, P-value <0.001). C-section delivery was also significantly higher in cases who had NEC or SIP (76.0% vs. 44.8%, P=0.001). The neonates who developed NEC or SIP received antenatal steroids closer to delivery vs. controls (6(1-49) vs. 26(6-106) hours, P=0.003). The infants with NEC/SIP received Indomethacin sooner after ANS as compared to controls (37(14-110) vs. 85(44-173) hours, P=0.0003). Neonatal steroid therapy (P-value <0.001) and number of blood transfusions (P=0.01) were also significantly associated with NEC/ SIP.

**Conclusion:** Short interval between antenatal steroid therapy and neonatal indomethacin therapy was found to be associated with an increased risk of SIP and NEC in the current study.

---

C6: Jenny Paredes  Advisor(s): Laura Martello-Rooney

**Immune Checkpoints and Inflammation in Colon Tumors from African Americans**

Colorectal cancer (CRC) is the third most common cancer among African Americans (AA) and when compared to Caucasian Americans (CA), they present more advanced CRC disease and lower survival rates. Recent findings suggest that this may be related to the differential expression in genes linked to inflammation and immune response. Therefore, we aimed to investigate if tumors from AA colon cancer patients diverge in their immunologic profile from CA and if these differences play a role in the health disparities observed between these populations.

**Methods:** Using DESeq2 we evaluated the differential gene expression pattern by whole transcriptome sequencing (Illumina) of 20 CRC tissues (and 20 matching adjacent non-tumor tissue) from AA and CA individuals and validated significantly expressed genes by qPCR. We also examined by ELISA the secretion of cytokines associated with T cell activation (Th1/Th2/Th17) in plasma from these AA CRC patients and analyzed the microsatellite (MSI) status and MMR mutations in colon tumors from AA at Downstate. Results: The genomic data revealed that AA and CA tumors had a significant difference of expression in 221 genes associated with immune-oncology pathways, with 20 genes exclusively expressed in AA including IL17A, CD80 and FOXP3. The cytokine concentrations in plasma of these AA patients revealed a differential expression between early stages (I, II) and late stage (III) with a significant reduction of cytokines’ secretion in the late stage group. Lastly, we demonstrated that up to 19% of our AA colon cancer patients have MSI and/or MMR mutations who could potentially benefit from immunotheraphy.

**Conclusions:** Our results suggest that the immune profiles of the tumors from AA patients differ from CA. The lower expression of immune-related genes in AA when compared to CA suggest an impairment of the immunological defense mechanism in this population that may contribute to the cancer health disparities among CRC patients.
Drug-loaded microparticles as a treatment approach for pancreatic cancer

Pancreatic cancer is the fourth leading cause of cancer death in the United States with only 7% of diagnosed patients surviving 5 years. Most pancreatic cancer patients are not surgical candidates due to advanced stage at diagnosis. Current systemic chemotherapies have not been very effective at decreasing tumor burden. Drug-loaded microparticles (MPs) are a promising tool for localized drug delivery within the tumor due to their biocompatibility and extended drug release. We investigated whether gemcitabine-loaded microparticles (GMP), paclitaxel-loaded microparticles (PMP) or sequential treatment of both, in comparison with blank MPs, systemic treatments and no treatment controls, are able to promote cancer cell killing and modulate drug resistance in vitro and in vivo. We were able to complete the MPs studies with two human pancreatic cancer cell lines, PANC-1 and MIAPaCa-2. In both cases, we tested the effect of the treatments on two resistance markers for gemcitabine, ribonucleotide reductase catalytic subunit M1 and cytidine deaminase, as well as the promotion of cell death measuring cleaved caspase-3 (CC3). When treated with GMP alone, both markers went up suggesting an increase in resistance against gemcitabine. Interestingly, the sequential treatment showed an increase in CC3 and a significant decrease in the expression of resistance markers. Subsequently, we tested the in vivo efficacy of MPs by direct injection into subcutaneous MIAPaCa-2 tumors in nude mice. Following four weeks of treatment, the tumors were excised, biopsied for protein analysis and frozen in OCT to detect apoptosis. Currently, we are analyzing the potential increase of reactive oxygen species in the MPs groups. In conclusion, we observed a decrease in cell viability and drug resistance proteins in vitro using the MPs in two high grade pancreatic cancer cell lines. The described drug delivery method has the potential to be an efficient treatment modality against pancreatic cancer.

Novel Mechanisms of Initiation on Nedicistrovirus-like IRESs

Many viral mRNAs utilize internal ribosome entry sites (IRESs) to initiate translation in a 5' end-independent manner. The most streamlined mechanism is used by the ~200 nt-long intergenic region (IGR) in dicistrovirus genomes, e.g., Cricket Paralysis virus (CrPV). The IGR's triple pseudoknot (PK) structure binds ribosomes directly and mediates factor-independent initiation at a non-AUG codon by mimicking an authentic tRNA-mRNA interaction. PKI binds in the 40S ribosomal subunit's A site and must be "pseudotranslocated" to the adjacent P site by elongation factor (eEF) 2 for eEF1A/ami noacyl-tRNA (aa-tRNA) to bind and start translation.

Advances in metagenomics have revealed novel dicistroviruses such as Nedicistrovirus (NedV) and Antarctic picorna-like virus 1 (APLV1). Their IGRs have CrPV-like structures but are ~40 nt shorter and lack motifs critical for canonical IGR IRES function. In vitro reconstitution showed that both novel IGRs mediate factor-independent formation of elongation-competent 80S ribosomes on a non-AUG codon, GCU. The NedV IGR promoted translation in rabbit reticulocyte lysate at high [Mg2+] after preincubation with ribosomal subunits.

These IGRs differ from CrPV-like IRESs in key mechanistic respects: they bind 80S ribosomes (but not 40S subunits) and place the initiating GCU codon in the A site such that eEF2 is not needed for subsequent binding of A-site ligands (e.g., eEF1A-GTP/aa-tRNA, the bacterial toxin RelE, or, if the GCU codon is appropriately mutated, termination factors eRF1/3). We generated structural models using bioinformatics approaches and tested them by mutagenesis to destabilize and then restore base-pairing by second-site mutations coupled with ribosome binding assays of IRES function. Our data show that NedV-like IRESs bypass the eEF2-mediated "pseudotranslocation" step and thus initiate translation by a mechanism even simpler than that used by CrPV-like IRESs and thereby constitute a novel IRES subclass.
PTSD and comorbid AUD: Neurocognitive influences in adolescent and young adult offspring from families enriched with Alcohol Use Disorders

Trauma exposure can have many consequences, including subsequent posttraumatic stress disorder (PTSD) or related disorders, such as alcohol use disorder (AUD). It is hypothesized that shared risk factors for these disorders exist, such as family history of AUD (FH-AUD) and neurocognitive factors. Few studies have examined the influence of FH-AUD together with trauma exposure on risk for PTSD and comorbid AUD incorporating neurocognitive factors, and no study to our knowledge has examined this using prospective assessments throughout adolescence/young adulthood. Using data from the Collaborative Study on the Genetics of Alcoholism (COGA) prospective study, we investigated whether trauma-exposed adolescents/young adults who report a FH-AUD have increased risk for comorbid PTSD/AUD or display neurocognitive deficits, than those without a FH-AUD. COGA’s prospective study is comprised of offspring from AUD high-risk and comparison families who were aged 12-22 at enrollment and were interviewed every 2 years since 2004 (N=3812). Traumatic exposures were collected using the Semi-Structured Assessment for the Genetics of Alcoholism, which assesses 20 potentially traumatic events. We investigated interaction effects of FH-AUD and trauma exposure (assaultive, non-assaultive, and sexual assaultive) on DSM-IV PTSD/AUD, as well as on two aspects of behavioral task performance (Tower of London test (TOLT) and Go/NoGo (GNG)), after controlling for race, sex, age, and socioeconomic factors. Significant interaction effects were observed among sexual assaultive trauma and FH-AUD such that having both a sexual assaultive trauma and FH-AUD increased risk for comorbid PTSD/AUD (β=0.133, p<0.001). In addition, preliminary data suggest differences in TOLT and GNG task performance as a function of trauma. Understanding the influence of FH-AUD on the risk for PTSD/AUD could inform early intervention and treatment strategies aimed at reducing the severity and endurance of both disorders.

Targeting of α4βδ GABA-A receptors to select spine types: Importance for pruning and optimal learning flexibility

During puberty, a period of synaptic pruning of occurs in the hippocampus. This process is thought to be necessary for normal brain function. Excitatory synapses of hippocampal pyramidal cells are localized to dendritic spines where they underlie learning and memory formation. We have previously shown that α4βδ GABA-A receptors are necessary for pubertal pruning and that mushroom and stubby spines are particularly targeted for removal. α4βδ GABA-A receptors are pubertally expressed on dendritic spines of CA1 hippocampal cells of female mice. We have begun preliminary experiments using a novel Golgi-immunohistochemistry (IHC) technique to see if these receptors are shuttled to specific spine types. In pubertal CA1 hippocampus, α4 expression is increased on mushroom spines by 100% (p<.05), while in CA3 hippocampus there was a trend for increased expression of α4 on both mushroom and stubby spines, by 150% (p<.06) and 100% (p<.07), respectively.

In order to assess the role of the various spine types in learning processes, we analyzed Golgi-stained neurons from separate groups of mice before and after multiple trials of object relocation in the hippocampal-dependent multiple placement object recognition task (MPORT). Mushroom and stubby spine-types were significantly increased by 150% and 200% (p<0.05) after a single object relocation (“learning”) compared to naïve mice, while a 50% increase (p<0.05) in mushroom spines was observed after the second object relocation (“re-learning”) when thin spine density also decreased. Under conditions where synaptic pruning was prevented by picrotoxin treatment (3mg/kg) and mushroom spines were already plentiful, mushroom spines still increased after learning, which was normal, but not after relearning, which was impaired in these animals. Thus, α4 localization to the mushroom spines at puberty may explain how these receptors trigger pruning of this spine type which is essential for normal learning flexibility in adulthood.
C11: John Hessburg Advisor(s): Joseph Francis

**Reward and Aversion Representation in the Primary Somatosensory, Primary Motor, and Dorsal Premotor Cortices of Non-Human Primates Completing a Motor Task**

Signals of reward and aversion have been recorded in a number of areas in the brain, from the midbrain to the cortex. This work explores how these variables are represented in the hand and arm regions of the primary motor cortex (M1), primary somatosensory cortex (S1), and dorsal premotor cortex (PMd). Two non-human primates (NHPs) were trained to complete a gripping task on a virtual robotic arm, where the animal manually gripped and held a given level of force for a specified period of time. Prior to each trial, visual cues were displayed to inform the NHP if the trial would result in a juice reward if completed successfully, a punishment consisting of a five-second timeout if completed unsuccessfully, or no reward or punishment, where the task would move immediately to the next trial. Subsets of trials with no cues and with catch trials, where a cue was presented but no reward or punishment delivered, were included to investigate reward and punishment prediction and error. Multiple levels of reward and punishment were incorporated to investigate how reward and punishment magnitude were represented in these regions, and how the interplay between the two was represented as motivation and/or value. Investigating the intricacies of these signals in M1, S1, and PMd will allow future brain-machine interfaces (BMI) to capture the breadth of these signals in a limited number of cortical regions that also contain sensorimotor information, rather than requiring multiple implants in multiple regions. Taking full advantage of the range of information in these regions will be useful in creating algorithms for more robust, nuanced, and naturalistic BMI control.

---

C12: Veronica Sebastian Advisor(s): Todd Sacktor and Panayiotis Tsokas

**Hippocampal PKMzeta expression in mouse models of Alzheimer's disease**

Alzheimer's Disease (AD) is a neurodegenerative disorder, which results in severe cognitive and behavioral deficits characterized by progressive memory loss. Over 5 million Americans currently suffer from AD, with an estimated 13.8 million cases projected by 2050. One possible mechanism that could explain the memory deficits seen in AD is disruption of PKMzeta expression. PKMzeta is a nervous system-specific, persistently active PKC isoform that is necessary for maintaining long-term memory. Work in our lab has shown a decrease in PKMzeta expression in the dendrites of CA1 neurons in three separate transgenic mouse models of AD (Tg-SwDI, J20 and APP/PS1), compared to age-matched controls. We also see abnormal increased PKMzeta expression in non-neuronal cells, which strongly co-localizes with the astrocytic marker, glial fibrillary acidic protein (GFAP). These results suggest that PKMzeta may play a dual role in AD, involving both loss-of-function in neurons and excessive signaling in astrocytes, which may be related to astrogliosis and glial activity affecting neuronal function.
C13: Timothy Morello  Advisor(s): Mark Stewart and Helen Durkin

T memory cells for human ragweed specific IgE responses express receptors for complement. A role for complement in memory IgE responses?

**Rationale:** CD4+IL-4+ T cells are required for human and murine IgE responses. We reported that CD4+ T cells and CD8+CD60+ T cells and six cytokines (IL-2,4,6,10,12,IFN α ,IFN γ ) are required for induction of ragweed specific memory IgE responses. Antigen cleaves complement and human CD4+ T cells express receptors for CSP. Receptors for CSP C3a and C5a on CD8+CD60+ T cells have not been reported.

**Methods:** CD4+CD3+ and CD8+CD60+CD45RO±CD45RA±IL-4±IFN γ ± T cells in blood of serum IgE+ (fluoroimmunoassay) ragweed sensitized (RS) and IgE- nonallergic humans expressing receptors for CSP C3a and C5a (CD88) (n=2-3/group) were determined by flow cytometry. Data expressed as mean % total lymphocytes and % subset.

**Results:** Blood of IgE+ RS humans contained increased numbers of CD4+ and CD8+CD60+ T cells expressing receptors for C3a (36, 85%, respectively), compared with IgE- nonallergic humans (16, 36%, respectively). Further, in IgE+, but not IgE- humans, both T cell subsets expressed greatly increased C3a receptors/cell (MESF). In IgE+ humans, virtually all CD8+CD60+ T cells were CD45RO+CD45RA- and IL-4+IFN γ -; in IgE- humans they were virtually all IL-4-, with CD45RA+ cells predominating. Neither CD4+ nor CD8+CD60± T cells of either IgE+ or IgE- humans expressed receptors for CSP C5a (CD88) (&lt;1%).

**Conclusions:** The presence of receptors for C3a on CD4+ and CD8+CD60+CD45RO+ IL-4+ T cells required for induction of ragweed specific memory IgE responses suggests that C3a may play an important role in induction of these responses.

C14: Elena Nikulina  Advisor(s): Peter Bergold

Minocycline plus N-Acetylcysteine prevents neuronal loss and repairs dendrites after experimental traumatic brain injury with a clinically useful time window

Traumatic brain injury (TBI) is an acute, heterogeneous injury that produces long term cognitive and behavioral impairments. There are presently no treatments for TBI. Clinical trials to treat TBI may have failed since most drugs rapidly lose efficacy with increasing time to treatment. Drugs that treat brain injury either prevent damage or induce repair. TBI can be induced by a blunt impact, a penetrating object, or by a blast wave. We use a closed head injury (CHI) model that mimics blunt head trauma. Following CHI, brain damage begins rapidly at the impact site and spreads to distal brain regions over time. Brain damage decreased when the drugs minocycline plus N-acetylcysteine were first dosed 72 hours (MN72) after CHI. To determine if MN72 worked by preventing injury or inducing repair, we examined the time course of injury progression proximal and distal to the impact site in saline and MN72-treated mice.

Neuronal loss was seen 3 days post-CHI in the hippocampus ipsilateral, but not contralateral to the impact site. MN72 was neuroprotective since the drugs prevented this loss at 14 days post-CHI. The expression of dendritic protein MAP2 was reduced in both hippocampi at both 3 and 14 days post-CHI. At 14 days post-CHI, MN72 increased MAP2 expression in the contralateral hippocampus suggesting repair of dendrites distal to the impact site. Our results suggest that CHI caused loss of hippocampal neurons and dendritic proteins that was seen as early as 3 days and continued at 14 days post-injury. MN72 prevented neuronal loss and repaired dendrites in regions distal to the impact site. These data suggest that MN72 works by both preventing injury and inducing repair with a clinically useful time window.
**C15: Kristen Whitney**

**Advisor(s): Peter Bergold**

**Minocycline plus N-acetylcysteine limits injury and restores synaptic plasticity distal to the impact site in experimental traumatic brain injury**

Traumatic brain injury (TBI) is a world-wide health problem and a major cause of death and disability. To be clinically useful, drugs to treat TBI must retain potency when first dosed hours to days after injury. This long window is necessary due to lack of access to immediate medical care or delays in seeking treatment. Brain injury develops over time following TBI; the risk of long-term neurobehavioral changes increases as damage spreads to brain regions distal to the initial impact site. We are developing therapeutic interventions that repair damaged tissue at the impact site, and protect more distal regions. With this goal, we examined the efficacy of MINO plus NAC when first dosed 72 hours after injury (MN72) to improve morphological and behavioral outcomes after experimental TBI using a clinically relevant closed head injury (CHI) model. Similar to TBI, the CHI model produces a heterogeneous injury to gray and white matter that leads to cognitive and behavioral deficits. The efficacy of MN72 was examined at brain regions both proximal and distal to the impact site. CHI damaged both the ipsilateral and contralateral hippocampus. CHI also impaired acquisition of Barnes maze, a long term potentiation (LTP)-dependent spatial memory task that requires one functioning hippocampus. MN72 treatment improved Barnes maze performance and maintained neuronal structure and synaptic density in the contralateral hippocampus. The atypical protein kinase C, PKMζ, is essential for synaptic plasticity. CHI decreased PKMζ expression and impaired LTP in both hippocampi. MN72 treatment restored PKMζ expression and LTP in the contralateral hippocampus. These data show that MN72 restores PKMζ expression, synaptic plasticity, and spatial memory performance. PKMζ activity mediates these outcomes, suggesting that PKMζ is a potential key target of MN72. These data also show that MN72 limits brain injury distal to the impact within a clinically useful time window.

---

**C16: Michael Tekin**

**Advisor(s): Sheryl Smith**

**Role of α4βδ GABAA receptors in adolescent synaptic pruning of primary motor cortex of the female mouse**

Pubertal synaptic pruning is thought to play an important role in refining memories. Proper neurodevelopment in M1 is essential for motor learning and coordination. Synaptic plasticity in layer 5 (L5) of the primary motor cortex (M1) decreases after puberty. Previous research has shown that α4βδ GABAA receptors regulate pubertal synaptic pruning in the prefrontal cortex and hippocampus but has not been studied in M1. Autism Spectrum Disorder has been linked to abnormalities in the α4 GABAA receptor subunit, motor deficits and difficulty with motor learning. Thus, the following experiments were used to test the hypothesis that adolescent selective synaptic pruning in L5 pyramidal cells of M1 is regulated by α4βδ GABAA receptors. Golgi staining was used to assess spine density and spine types in each group from z-stack projection (0.3 μm) photomicrographs taken with a Nikon DS-U3 camera mounted on a Nikon Eclipse Ci-L microscope using a 100xoil objective. Spine density of the basilar dendrites of pubertal vs. post-pubertal mice were compared using either wild-type (P35WT vs. P56WT) or α4 knockout mice (P35α4KO vs. P56α4KO). We found no significant difference in total spine density between P35WT and P56WT. However in the proximal region of the dendrite there was a significant decrease in mushroom spines (P<0.05), and increase in thin (P<0.05) and long thin spines (P<0.05) in L5. These changes were not observed in L5 when comparing P35α4KO and P56α4KO. Moreover, immunohistochemistry was performed to detect α4 expression using confocal microscopy (alpha 4 antibody, Santa Cruz) on tissue collected from pre-pubertal wild-type (P28WT) mice and P35WT. Preliminary data suggest a 24% increase of α4 subunit expression at the onset of puberty (P<0.05). These results indicate that selective pruning of mushroom spines in the proximal region of M1 L5 pyramidal cells occurs during puberty and the emergence of α4 is responsible for this selective pruning.
Expanding NEURON extracellular reaction-diffusion support: simulation of ischemic stroke

The NEURON simulation platform, featured in over 1900 publications, traditionally focused on models of neurons and networks of neurons. NEURON’s reaction-diffusion module (rxd) expanded support for 1D and 3D intracellular reaction-diffusion models. These have been used to probe intracellular calcium dynamics in dystonia, impedance mismatch and persistent neuronal activity via HCN channels.

Originally rxd provided only limited extracellular support with isolated compartments around each segment. Recently rxd has been extended to include coarse-grained macroscopic models of the extracellular space. NEURON thus allows detailed cell models to be embedded in a 3D macroscopic model of tissue. Extracellular diffusion is implemented using the Douglas-Gunn alternating direction implicit method, an efficient scheme which supports parallelization. Reactions are now implemented using Just-In-Time compilation, allowing numerical integration to use faster compiled code rather than slower interpreted code.

Ischemic stroke modeling requires multiscale coupling of electrophysiology with complex intracellular molecular alterations, and consideration of network properties in the context of bulk tissue alterations mediated by extracellular diffusion. Occlusion of a blood vessel in the brain triggers a cascade of changes, including: 1. synaptic glutamate release, related to excitotoxicity; 2. elevated extracellular potassium, leading to spreading depression; 3. cell swelling, reducing the extracellular volume and increasing the tortuosity; 4. production of reactive oxygen species, which give rise to inflammation. These cascades occur over multiple time-scales, with the initial rapid changes in cell metabolism and ionic concentrations triggering several damaging agents that may ultimately lead to cell death.

Acknowledgments: Research supported by NIH grant 5R01MH086638
Tissue Doppler Imaging on transthoracic ECHO to assess prevalence of HIV-associated Pulmonary Hypertension

Introduction: Pulmonary Artery Hypertension (PAH) in patients with human immunodeficiency virus (HIV) has mortality that is higher than the general population. Despite this poor prognosis, no evidence exists to support routine screening for HIV-associated PAH.

Transthoracic echocardiography (ECHO) is an accepted noninvasive screening tool to assess for possible PAH, though its limitations are well understood. Studies using ECHO in symptomatic patients have shown a prevalence of PAH between 0.5-2% in the HIV-positive population. By using advanced echocardiographic techniques like tissue doppler imaging (TDI), the accuracy of ECHO as a screening tool may improve.

This study was designed to understand the clinical utility of screening asymptomatic HIV-positive patients for PAH, allowing for earlier surveillance and intervention.

Methods: A retrospective review was performed on all HIV-positive patients that were seen in the HIV clinic between January 2015 to September 2016 at the Brooklyn VA. Patients with pulmonary arterial systolic pressure (PASP) > 35mmHg as assessed by ECHO were suggestive of PAH; these patients were then reassessed using Tissue Doppler Imaging (TDI) to estimate the pulmonary capillary wedge pressure (PCWP). Other variables were also collected.

Results: Of 96 HIV-positive patients who received an ECHO from January 2015 to September 2016, 15 had a PASP > 35mmHg with a PCWP < 15mmHg. This suggests a prevalence of PAH of 15.6% (95% CI 9%-24%) in this population. Out of these patients, only 13.3% were noted to have uncontrolled viral load.

Conclusion: A higher prevalence of PAH was found in the HIV-positive population at our institution. Given the mortality of this disease, all HIV-positive patients should be screened with ECHO for elevated PASP with TDI estimations of PCWP to improve the sensitivity of this screening test. This should be used to pursue guideline-directed diagnostic workup at the time of screening.

HIV and Bronchiectasis, a case series

Background: Bronchiectasis is a permanent distortion of airways characterized clinically by cough productive of sputum and diagnosed with the presence of bronchial wall thickening and luminal dilatation on computed tomographic (CT) scan of the chest. The relationship between HIV and bronchiectasis is not completely understood, however, preliminary analyses suggest that bronchiectasis may be more prevalent in the HIV-positive population than previously thought. We describe here, several cases of bronchiectasis in HIV-positive patients seen at our institution.

Subjects and Methods: 14 patients were identified with bronchiectasis and HIV infection seen at Kings County Hospital Center or SUNY Downstate Medical Center from 1999 to present. Details of their care over time was collected and compiled.

Discussion: With the advent of newer anti-retroviral therapy, there has been a decline in pulmonary infections that were typically thought to be the inciting factor for bronchiectasis in HIV patients. Thus, it is not clear if HIV-positive patients develop bronchiectasis as result of an opportunistic infectious insult or if an independent inflammatory insult from the HIV infection itself is to blame.

In our small sample, we noted that patients are routinely connected to the pulmonary service somewhat late in the course of their disease and sometimes are inappropriately treated for alternate and seemingly incorrect diagnoses. Importantly, patients were uniformly not offered bronchodilator therapy after diagnosis. We identified many reasons for this, but ultimately this was often due to the patients’ primary providers not being fully aware of the diagnosis.

Given the under recognition of bronchiectasis in our 14 patients we posit that the prevalence of bronchiectasis in HIV patients may be grossly underestimated. Improving recognition and management of bronchiectasis in our population could help diminish rehospitalization rates.
Clinical utility of electromagnetic navigation bronchoscopy in the diagnosis of lung cancer

**Introduction:** Lung cancer remains the leading cause of mortality from malignancy in the United States despite significant advances. With the recent validation of low dose helix computed tomography (LD-CT) as a screening modality, there have been an increased number of diagnosed peripheral lung nodules that require evaluation. Electromagnetic navigation bronchoscopy (ENB) has emerged as a novel diagnostic modality that is purported to be equivalent to CT transthoracic needle aspiration (CT-TTNA) in diagnostic yield with a superior safety profile. We set out to evaluate the diagnostic yield and the number of adverse events of ENBs performed at the Brooklyn Veterans Affairs Hospital.

**Methods:** A retrospective chart review was done of all ENB cases performed from 2012 until present. 45 completed cases were identified and chart review was done to identify nodule size and location, distance to the pleura, PET-CT standardized uptake value (SUV), pathological yield, and clinical course following procedure. Two cases were excluded due to patients having been diagnosed with malignancy prior to ENB, thus 43 cases were included for final analysis.

**Results:** 12 patients were identified with false negative biopsies (negative biopsy from ENB with subsequent positive pathologic diagnosis from either repeat ENB surgical biopsy). Given that 14 patients were found with disease, sensitivity of this test was calculated at 53.9%. 19 patients were found to have positive initial biopsies, thus negative predictive value (NPV) was calculated at 61.3%. There was an incidence of 0.04% of pneumothoraces in our patient population.

**Discussion:** We demonstrated that ENB in our institution is not as sensitive a modality in ruling out malignancy as previously thought. While this raises the question of the clinical utility of ENB as a diagnostic tool, it still remains significantly safer than CT-TTNA in the evaluation of peripheral lung nodules.

Patterns of Care and Outcomes in Patients with Squamous Cell Carcinoma of the Buccal Mucosa

**Purpose/Objective(s):** Primary buccal mucosa squamous cell carcinoma represents 2% of all oral cavity cancer cases in the United States annually. The purpose of this study was to examine patterns of care and outcomes for squamous cell carcinoma of the buccal mucosa.

**Materials/Methods:** Using the National Cancer Data Base (NCDB) we identified 5,786 patients with buccal mucosa squamous cell carcinoma diagnosed between 2004-2014. Patients who lived less than 3 months from diagnosis or who had stage 0 or IVC disease were excluded. Patient and treatment factors were compared between patients who received surgery alone (S), postoperative radiation therapy (S+RT), postoperative chemoradiation (S+CRT) or definitive chemoradiation (CRT) using the Chi-square test. Univariate and multivariate Cox proportional hazards regression models were used for covariate survival analysis.

**Results:** The final cohort analysis included 2,570 patients. Median age and median follow-up were 69 years and 44 months, respectively. 1068 patients had stage I/II disease and 936 stage III-IVB. 1,468 (57.1%) patients received surgery alone (S), 605 (23.5%) received S+RT, 300 (11.7%) S+CRT, and 197 (7.7%) definitive CRT. Median radiation dose was 64 Gy for those that received RT. The 3-year overall survival was 71.8%, 58.4%, 52.6%, and 35.8% for the S, S+RT, S+CRT, and CRT arms, respectively. The 3-year survival by stage was 71.3% (I-II), 54.5% (III) and 38.7% (IVA-IVB). Charlson/Deyo score of 2, overall stage III-IVB disease, and presence of ECE were associated with worse survival on MVA. Higher number of neck nodes removed was associated with improved survival.

**Conclusion:** Nearly 60% of buccal mucosal cancers present with stage III-IVB disease. Consistent with national guidelines, more than 90% of patients were treated with surgery with or without adjuvant therapy rather than definitive chemoradiation. Patients with stage IVA-IVB disease have a very poor prognosis, with a 3 year overall survival of 38%.
Patterns of Care and Comparison of Outcomes Between Primary Anal Squamous Cell Carcinoma and Anal Adenocarcinoma

**Purpose/Objective(s):** To compare and analyze the patterns of care and survival outcomes of patients with anal squamous cell carcinoma (SCC) and anal adenocarcinoma (AC).

**Materials/Methods:** The National Cancer Database was explored to identify patients diagnosed with primary stage II or III SCC or AC of the anus from 2004-2014. Patients were treated with surgery alone (S), neoadjuvant chemoradiation followed by surgery (CRT+S), surgery followed by adjuvant chemoradiation (S+CRT), or definitive chemoradiation (CRT). S was defined as abdominal perineal resection while CRT was defined as starting either modality within 14 days of each other. Median radiation dose was 5400cGy. Overall survival (OS) was obtained and treatment groups compared via the log-rank test after stratifying by histology. Univariate and multivariate Cox proportional hazards regression models were performed to assess the impact of covariates on survival.

**Results:** 19,539 patients were included, 18,346 (93.9%) with SCC and 1,193 (6.1%) with AC of the anus. Median follow-up was 47.6 months. Of the SCC group, 96.2% received CRT alone (p<0.001). The 5-year OS by treatment for SCC was 48.2% for S alone, 46.3% for CRT+S, 60.8% for S+CRT, and 67.8% for CRT alone (p<0.001). For the AC group, 38.8% received CRT alone, 44.5% received CRT+S, and 12.5% received S alone (p<0.001). The 5-year OS by treatment for AC was 57.6% for S alone, 64.6% for CRT+S, 51.7% for S+CRT, and 39.2% for CRT alone (p<0.001). The 5-year OS for stage II SCC was 69.2% and for AC was 54.2% (p<0.001). Five-year OS for stage III SCC was 55.2% and for AC was 32.9% (p<0.001).

**Conclusion:** Primary anal AC when compared to primary anal SCC had a lower 5-year OS stage for stage. Anal AC appears to be treated similarly to the rectal cancer paradigm, with frequent use of neoadjuvant chemoradiation followed by surgery. When definitive chemoradiation was used, outcomes were very poor, with a 5-year OS of 39%.

Patterns of Care of Adjuvant Radiation Therapy After Lumpectomy and Survival in T1N0M0 Estrogen Receptor Positive Breast Cancer

**Background:** Given the excellent outcomes in early stage breast cancer, there is an increased focus on de-escalation of treatment, particularly for estrogen receptor (ER) positive breast cancer who receive endocrine therapy. We sought to examine patterns of care of adjuvant radiation therapy (RT) after lumpectomy and outcomes in these most favorable breast cancer patients using the National Cancer Database.

**Methods:** Patients diagnosed with ER positive pathologic T1N0M0 breast cancer from 2010-2013 who received lumpectomy with negative margins followed by adjuvant RT and endocrine therapy were identified. Those with human epidermal growth factor receptor 2 positive status were excluded. Patient- and clinical-related factors were compared between those who received adjuvant RT versus those who did not. Logistic regression was performed to assess for predictors of RT use. The Kaplan-Meier method was used to assess overall survival (OS) and Cox regression to assess impact of covariates on OS.

**Results:** There were 21,312 (54.4%) patients who received adjuvant RT and 18,887 (45.6%) who did not. Median follow-up for living patients was 48.4 months (IQR 37-61). Five-year OS for those who did and did not receive RT was 96.3% and 92.9% (p<0.001). On multivariable survival analysis, older age (HR 1.96-4.85, p<0.001) and 10-20mm (T1c) tumor size (HR 1.55, 95% CI 1.20-2.00, p=0.001) were associated with worse survival. Treatment at an academic facility (HR 0.90, 95% CI 0.67-1.21, p<0.001) and receipt of postop RT (HR 0.66, 95% CI 0.55-0.79, p<0.001) were associated with improved survival. Race, grade and receipt of boost were not associated with any differences in survival. When stratifying by age group, there was still a survival benefit in all groups with postop RT, including among those over 70 years (log-rank p<0.001).

**Conclusion:** Nearly half of patients with T1N0M0 ER-positive breast cancer did not receive post-lumpectomy RT though it was associated with a survival benefit.
C25: Virginia Osborn

The Impact of Treatment Order in Trimodality Therapy for Malignant Pleural Mesothelioma

**Purpose:** To assess the impact of timing of chemotherapy in trimodality therapy for malignant pleural mesothelioma (MPM) using the National Cancer Database (NCDB)

**Methods:** The NCDB was queried to identify patients diagnosed with nonmetastatic MPM 2004-2014. Two cohorts receiving trimodality therapy were then selected for comparison: 1) patients receiving neoadjuvant chemotherapy (NAC) initiating chemotherapy >30 days prior to surgery with adjuvant radiation started within 12 weeks (84 days) of surgery, and 2) patients receiving only adjuvant therapy (ADJ), having had no therapy prior to surgery and then receiving both adjuvant chemotherapy and radiation (in any order). ADJ patients must also have begun their first adjuvant therapy within 84 days of surgery and their second adjuvant therapy within 180 days of surgery. Patients were stratified according to age, gender, race, Charlson-Deyo Comorbidity Index, cT stage, cN stage, clinical stage grouping, facility type, insurance status. Characteristics were compared between the groups using Chi-Squared and Fisher’s Exact Tests. Kaplan-Meier and multivariable Cox regression analysis were performed to assess for factors affecting overall survival (OS) outcomes.

**Results:** 259 patients were identified, 119 (45.9%) ADJ, and 140 (54.1%) NAC. Median age was 63 and median follow up was 20.9 months. Patient characteristics were well balanced between the groups. Median and 2-year OS were 20.9 months and 40.6% for ADJ compared to 23.7 months and 47.6% for NAC, respectively (p=0.90). Multivariable Cox regression analysis also demonstrated no survival difference between the treatment groups HR 0.878 (p=0.414) for NAC compared with ADJ. Women had higher OS, HR 0.568 (p=0.002). cN3 and cNX patients had worse OS compared to cN0, HRs 8.728 (p=0.001) and 1.845 (p=0.040), respectively.

**Conclusion:** The delivery of neoadjuvant chemotherapy was not associated with any OS difference in patients receiving trimodality therapy for MPM.

C26: Niki Sheth

Hepatocellular Carcinoma: Patterns of Care and Outcomes for Patients receiving Stereotactic Radiotherapy

**Purpose:** This study aims to analyze the patterns of care, including fractionation and utilization, of hypofractionated stereotactic body radiotherapy (SBRT) in the treatment of hepatic cellular carcinoma

**Methods:** The NCDB was queried for patients diagnosed with hepatocellular carcinoma (HCC) in 2004-2014 and treated with radiotherapy in 3, 4, or 5 fractions in 15-20, 10-13, or 6-12Gy per fraction respectively. Patients with stage IV and Charlson-Deyo Comorbidity Index &gt; 0 were excluded in order to avoid bias resulting from selection of poorer prognosis patients. The patients were then stratified based on several characteristics including Biologically Equivalent Doses (BEDs) of &gt;100 Gy and &lt;100 Gy to determine whether there was an association with overall survival (OS) benefit and a multivariable analysis (MVA) was performed to assess for potential confounding factors.

**Results:** There were 462 patients identified in whom the most common SBRT fractionation regimen was 10Gy x 5 fractions (25.3%), followed by 8Gy x 5 (17.7%), and 15-16Gy x 3 (26.4%). 152 patients were treated to a BED &lt;100Gy which was associated with a median overall survival (OS) of 20.8 months (95% CI 14.551-27.109. 310 patients were treated to a BED &gt;100Gy which was associated with a median overall survival (OS) of 30.8 months (95% CI 5.251-32.083. On MVA, BED &gt;100Gy was not significant associated with improved OS (HR 0.852 CI 0.638-1.137, p=0.277). Factors that were associated with significantly worse survival were tumor size in the largest quartile (HR 2.197 CI 1.440-3.354, p&lt;0.0001) and T3a disease (HR 2.474 CI 1.472-4.158, p=0.001 compared to T1).

**Conclusion:** The most common SBRT fractionation regimen was 10Gy x 5 fractions. BED dose &gt;100Gy was not associated with a significant survival benefit. However, local control data are not available within the NCDB.
C27: Joseph Kim

**Long Term Outcomes and Prognostic Factors of Head and Neck Soft Tissue Sarcoma (HNSTS) Treated with Definitive Therapy**

**Purpose:** We reviewed long term outcomes of HNSTS patients treated at a tertiary cancer center with definitive intent.

**Methods:** The study included adult (>18 yo) patients with biopsy-proven HNSTS treated at our institution between 1990-2016. Local progression free survival (LPFS) and overall survival (OS) were evaluated with the Kaplan-Meier method. Chi-square and Cox proportional hazards were used to identify clinicopathologic predictors of survival and compare treatment groups.

**Results:** Our study had 127 patients with a median age of 53 years (19-86) and 58% male. 58 (46%) received radiation therapy (RT): 16 were treated definitively, 42 (33%) definitive surgery + RT, and 16 received concurrent chemoradiation (CRT). 91 patients received definitive surgery, of which 49 were surgery alone. 104 patients had sufficient data for outcome analysis: 2-year OS and LPFS were 76.9% and 63.0%, respectively. In multivariable analysis, non-white race (HR 3.51, 95%CI 1.47-8.35) and high grade (HR 3.20, 95%CI 1.04 -9.83) were associated with worse LPFS. Compared to surgery only, definitive RT/CRT (HR 0.18, 95%CI 0.05-0.66) and definitive surgery + RT/CRT (HR 0.23, 95%CI 0.1-0.57) were associated with better LPFS. Age ≥60 and high grade were associated with worse OS. In the surgical subset, non-white race was associated with worse LPFS and surgery + RT/CRT was associated with increased LPFS compared to surgery alone. There was no difference in OS between treatment groups in both the entire cohort and the surgical subset.

**Conclusions:** In patients with HNSTS, surgery alone was associated with worse LPFS than RT/CRT alone and surgery with RT/CRT groups. Non-white race and high grade were also associated with decreased LPFS. Factors associated with worse OS included older age and high grade. In the surgical subgroup, non-white race and surgery alone were associated with worse LPFS. There was no difference in OS between treatment groups in the main cohort and the surgical subset.

C28: Tenya Steele


The Text4baby™ mobile health (mhealth) program has received national attention and is acclaimed to provide pregnant women with greater access to prenatal healthcare resources and information. However, without sufficient piloting, little is known whether urban and immigrant women are receptive to mobile health communication methods, or of the cultural and systematic barriers that inhibit their behavioral intent to use Text4baby. In our study, we aimed to understand the lived experiences of urban and immigrant pregnant women with accessing prenatal health care and information in Brooklyn New York, and to utilize behavioral and technology assimilation theoretical constructs to measure their knowledge, perceptions and behavioral intent towards the use of the Text4baby program.

This exploratory mixed methods study first used a phenomenological approach to explore and describe the lived experiences of pregnant women. Data from the qualitative arm led to the development of a survey instrument that was then used in a repeated measures pre-post test design to evaluate changes in participants’ knowledge, attitudes, beliefs and perceptions of Text4baby after a minimum of four weeks exposure to the program’s message.

Findings showed that inadequate patient provider engagement often left many participants with feelings of indifference regarding the prenatal care and information they received. In contrast, these women displayed strongly positive attitudes towards the use of technology for accessing prenatal health information, and many indicated heavy use of the internet and mobile apps for health information-seeking and increased support. Both qualitative and quantitative data indicated positive interest in the use of Tex4baby. Nearly 60% of survey respondents reported strong agreement in the compatibility of Text4baby as a mode of communication, while 63.3% reported strong agreement that Text4baby provided them extra support during their pregnancy.
Perceptions of Facilitators and Barriers for Physical Activity among Adolescents Living with Obesity

**Background:** Childhood obesity is a serious public health problem in NYC. Central Brooklyn one of the poorest areas in NYC, where the majority are Black, experiences a disproportionate burden of obesity-related diseases. Obesity in children 5-14 years old in Central Brooklyn (23.1-26.5%) are among the highest in NYC. One in three adults are obese, exceeding the NYC average.

**Objective:** Qualitative study was used to explore the understanding of physical activity, perceptions of their ideal body type, and the facilitators and barriers for physical activity among adolescents with obesity.

**Method:** Twenty-two (22) adolescents with BMI >85th or > 95th percentile, 12-18 years of age, and 14 of their parents from Central Brooklyn were recruited at an obesity clinic and exercise sites from June to November 2017. Data was collected using focus groups and semi-structured in-depth interviews, followed by Interpretative Phenomenological Analysis (IPA) of the transcripts.

**Results:** The adolescents wanted to “lose some weight” but not to be “thin” or “look hungry.” Most females desired a “slim-thick” figure, - which was “a flat stomach with big thighs, and curvy.” Fun and support from parents and peers, facilitated their activity. Barriers included their low self-efficacy, inactive families, fear of neighborhood gangs and crime, and perceptions that the parks were small and overcrowded with limited physical activity options for adolescents.

**Conclusion:** These findings highlight the need to consider local norms concerning body image when designing obesity interventions. To seriously tackle childhood obesity in NYC, policy should center on the promotion of public safety, improvement of neighborhood parks, and increasing options for physical activity.

---

Unsolved mystery: 11-year-old boy with idiopathic immune-mediated necrotizing myopathy

Immune-mediated necrotizing myopathy is a poorly known, relatively newly recognized disease, and has very rarely been reported in pediatric age group.

We present an 11-year-old boy who was brought in by his mother with 3-week history of progressive proximal symmetrical weakness in upper and lower limbs and neck flexion with no associated rash or previous illness. He had elevated CK of 13000. An extensive investigation including blood work, MRI, and muscle biopsy lead to diagnosis of idiopathic immune mediated necrotizing myopathy. The patient initially had poor response to steroid treatment, however showed some improvement with subsequent IVIG treatment.

A high index of suspicion is necessary to diagnose immune mediated necrotizing myopathy as it is a very rare entity in children and earlier recognition can prevent rapid and severe progression.
A Rare Case of Rapidly Progressive Stiff Leg Syndrome Refractory to Treatment

**Introduction:** Stiff person syndrome (SPS) is a rare neurological disorder that affects 1-2 people/million. It is characterized by progressive muscle stiffness of the trunk and extremities and elevated Anti-Glutamic Acid Decarboxylase (GAD) antibodies. Here, we report a rare variant of SPS: stiff limb syndrome (SLS).

**Case Report:** 70-year-old Haitian woman with HTN and T2DM presented with bilateral lower extremity pain for 5 days. The pain started in the lower back and progressed to lower extremities leading to sudden inability to ambulate. Physical exam showed bilateral lower extremity hyperreflexia and spastic paraparesis with peripheral edema worse on the left, rest of the physical exam was normal. Initial vitals were T 99.5F, BP 164/95, HR 100, RR 20, O2 96% and remained stable over hospital course. Doppler studies and total spine MRI revealed no DVT or cord compression, respectively. CPK level was 325 and SPEP, B12, copper, zinc levels were normal. Anti-GAD antibodies were elevated, confirming the diagnosis of SPS.

Baclofen 20mg and Clonazepam 1mg was started, then a 5-day course of IVIG and Dantrolene 25mg, no clinical improvement was noticed with treatment.

**Discussion:** Classical SPS presents with truncal rigidity progressing to distal limbs, affecting balance and gait. Anti-GAD antibodies are elevated leading to decreased GABA in the CNS and sustained co-contraction of antagonist muscles. SPS is treated with benzodiazepines or baclofen (GABA agonists), IVIG is reserved for severe disease.

Stiff Leg Syndrome (SLS) is a rare form of SPS that spares the trunk and affects one or both legs. It has a worse prognosis and is more resistant to treatment than SPS. One study following 23 SLS patients found that half of them became wheelchair bound in 3.5 years. We report a case of SLS with an incredibly fast deterioration in ambulation, with only 5 days from walking without assistance to being wheelchair bound. Progression of disease was also refractory to treatment.
**A Diagnosis of Neuromyelitis Optica Spectrum Disorder in a Patient with Systemic Lupus Erythematosus presenting with sudden Acute Transverse Myelitis**

Acute transverse myelitis (TM) is a rare neuro-inflammatory spinal cord disorder that presents with the rapid onset of weakness, sensory alterations, and bowel and bladder dysfunction. The differential for TM can be broad including compressive and non-compressive spinal cord pathologies. In this case, we describe a 28 year old African American male with a known history of SLE who presented with a high grade fever and sudden onset bilateral lower extremity weakness, profound sensory deficits, and urinary and fecal incontinence. The leading differentials initially included Guillain Barre syndrome, CNS infectious processes, and Lupus Transverse Myelitis. A CT head was unrevealing for a causative pathology followed by a MRI of the Brain and total spine which showed extensive longitudinal T2- enhancing changes from C2-T4. Infectious work up including a lumbar puncture were negative for common and opportunistic infectious causes. The patient received high dose steroids and immunomodulation as initial treatment for Lupus transverse myelitis with poor clinical response as well as IVIG and plasmapheresis for possible Guillain-Barre Syndrome. Lab results later showed gross seropositivity with NMO-IgG antibodies consistent with Neuromyelitis Optica (Devic’s disease). Ophthalmologic evaluation and imaging however did not reveal evidence of optic neuritis. This case illustrates a rare occurrence of SLE in conjunction with clinical, radiologic and serum antibody positivity consistent with Neuromyelitis Optica (NMO) in the absence of optic neuritis. Optic neuritis is currently believed to be a defining feature of this demyelinating disease. A recently modified spectrum of NMO like disorders, namely NMO spectrum disorders (NMOSD) is congruent with this patient’s findings in the scarce setting of a previous SLE diagnosis.

---

**Eyes on the Line: CLABSI evaluate at UHB**

Central Line Associated Bloodstream Infection (CLABSI) is a growing concern among hospitalized patients due to high patient mortality, non-reimbursable hospital costs at ~$50,000 per case, and it’s use as a Core Measure of hospital competency by Center of Medicare and Medicaid Services (CMS) and The Joint Commission. Rates of CLABSI have been monitored at University Hospital Brooklyn (UHB) and demonstrate wide ranges between 2015 to 2017. CLABSI rates have been shown to decrease with increasing awareness of central venous catheter (CVC) indication and maintenance.

This study aimed to evaluate CVC indication, duration and review prevention techniques in order to implement an interdisciplinary approach to reduce CVC placement and maintain increased line awareness, thus improving patient care and, in turn, a reduction in CLABSI, patient morbidity and mortality and hospital costs. This quality improvement project evaluated rates of CLABSI in hospitalized patients through chart review, documenting line indications, dates, line types and duration of hospitalization.

PICC’s demonstrated highest CLABSI rate at 46%, with mediport lowest at 8%. Difficult access was commonest line indication at 30%, prolonged therapy at 25%, hemodialysis 24%, critical illness at 21%. Mean line duration was 44.7 days with median of 20 days. Mean line duration prior to CLABSI was 39 days. Average total days hospitalization for patients with CLABSI was 54.4 days, median 43.5 days.

Results indicate a high rate of CLABSI in PICC line with indication of difficult venous access. Through the implementation of an algorithmic approach to determine appropriate venous line access type and reduction of PICC placement, with consideration of midline catheter, initiation of a multidisciplinary team including nursing staff, residents and Infection Control staff for increased line awareness, monitoring and maintenance, CLABSI rates at UHB show potential for significantly decreased rates in the upcoming year.
C35: Sara Wertenteil
Advisor(s): Steven Levine

**Bringing Recognition and Awareness to Inner-city Neighborhoods about Stroke (BRAINS)**

**Introduction:** Children are exposed to individuals at risk for stroke and when properly educated may recognize stroke and call 911. We evaluated baseline stroke knowledge of an underserved, inner-city community to assess the need and optimize future educational interventions.

**Objective:** To assess beliefs and concepts of pre-teens (9-12 year olds), teens (13-18 year olds), and adults (19+) about stroke and determine variation in stroke knowledge with age.

**Methods:** In a cross-sectional study we recruited and surveyed participants in Central Brooklyn aged >9 years about stroke symptoms, prevention, risk factors, and urgent responses (5 multiple-choice and 5 fill-in questions). For multiple-choice responses, chi-square test was used for association between categorical variables and ANOVA compared mean number of correct answers between 3 age groups. Fill-in answers were categorized and described.

**Results:** Of 81 subjects completing surveys 82% were Black, Caribbean, or both, and 11% Hispanic. Freeform responses revealed misconceptions participants had about stroke causes, symptoms, and prevention strategies. Our analysis of multiple-choice responses revealed the mean numbers of correct answers were 2.0(0.9 SD), 2.8(1.2) and 3.8(1.3) for age groups of 9-12 (n=27), 13-18 (n=23) and >18 (n=31) years, respectively (p<0.001). Of these respective groups, 11%, 52%, and 87% (p<0.001) identified the brain as the site of stroke, and 11%, 26%, and 58% (p<0.001) correctly identified stroke symptoms. For response to stroke, 89%, 96%, and 100% (p=0.14) of each group chose “call 911â€” . Thirty (37%) reported having a close relative/family friend with a stroke, and it did not predict the number of correct answers (p=0.30) after controlling for age.

**Conclusions:** Stroke knowledge was lowest among children, yet still low among teens and adults in Central Brooklyn. Public health initiatives should focus on educating more children/teens about stroke symptoms to enhance stroke recognition.

C36: Peiqi Ou
Advisor(s): Chongmin Huan

**Sphingomyelin synthase 2 protects against lupus pathogenesis via regulating the B cell tolerance**

Systemic lupus erythematous is an autoimmune disease characterized by the presence of anti-double stranded DNA antibodies produced by self-reactive B cells. Lupus remains a clinical challenge due to lack of a treatment that specifically targets the pathogenic mechanism of the disease. Recent studies indicate that failed clearance of self-reactive B cells generated by somatic hypermutation in the germinal center is the primary source of autoreactivity in lupus. However, the protective mechanism of B cell tolerance that normally eliminates self-reactive B cells in the germinal center is unknown.

Sphingomyelin synthase 2 (SMS2) is a sphingolipid enzyme that catalyzes the synthesis of sphingomyelin and diacylglycerol on the plasma membrane. We found that SMS2 deficient mice have a lupus-like phenotype due to failure of the elimination of self-reactive B cells in the germinal center. SMS2 induces apoptosis in germinal center B cells via activation of PKC delta, a recognized mediator of B cell apoptosis that prevents the pathogenesis of lupus in both humans and mice. Activation of SMS2 was able to inhibit the production of anti-double stranded DNA antibodies in NZBWF1 mice, an established animal model of lupus. Thus, our findings provide significant insight into the mechanism of B cell tolerance that protects against the pathogenesis of lupus, and could lead to development of an effective therapeutic approach to target the pathogenic mechanism of lupus.
Comparison of Renal Cell Carcinoma Characteristics Among Distinct Populations of Black Patients

Introduction: Previous studies have shown differences in Renal Cell Carcinoma (RCC) subtypes, stage and comorbidities between non-African American (non-AA) and African American (AA) patients. This study aims to elucidate what type of relationships exist when these populations are compared to an underserved, primarily Afro-Caribbean population.

Methods: Clinical and pathologic data were collected retrospectively from 65 Afro-Caribbean patients with RCC who underwent a nephrectomy at Kings County Hospital Center (KCHC) (6/24/2003 - 12/29/2016). We performed a chi-squared analysis to compare our data with previously published data of AA and non-AA patients from Vanderbilt University Medical Center (VUMC) (Lipworth et. al. 2016), Kaiser Permanente Northern California (KPNC) health system (Mafolasire et.al. 2016) and Duke University Medical Center (DUMC) (Qi et. al. 2014).

Results: RCC subtype distribution (Clear cell vs Papillary vs Other) was different in the Afro-Caribbean population from KCHC when compared to non-AA populations (p<.001) with a higher percentage of Papillary and Other RCC (Table 1). KCHC subtype distribution was also different from the AA patients with a higher percentage of Other RCC in the KCHC patients (p=.004, 27.7% vs 12.8%). T stage was non-significantly earlier in KCHC patients compared to non-AA patients (p=.068, T1-T2 80% vs 69.5%) and AJCC stage was significantly earlier compared to KPNC non-AA patients (p=.031, stage I-II 75.4% vs 62.2%).

Conclusion: In this retrospective comparative analysis, our population was found to have a higher proportion of non-clear cell/non-papillary RCC when compared to AA patients from other studies. This may signify a difference of how RCC affects the Afro-Caribbean patients when compared to the general AA population. Furthermore, previous studies have shown that AA patients were diagnosed at an earlier stage than non-AA patients, which our data validates.

Relationship of nocturnal polyuria and combination anti-hypertensive drug therapy

Introduction and Objective: Nocturia due to nocturnal polyuria is a prevalent problem in middle-aged and elderly patients. Most patients find no improvement from current therapies. The mechanism of nocturnal polyuria is believed to be multifactorial, including a change in the circadian release of natriuretic peptides and anti-diuretic peptide, and possibly blunting of the normal nocturnal dip in blood pressure (which can drive pressure-natriuresis). This study attempts to identify an association between anti-hypertensive (AHT) drug therapy and nocturnal polyuria.

Methods: We performed a retrospective analysis of voiding diaries taken from male patients at a Veterans-Affairs based urology clinic. Inclusion criteria were patients with a baseline actual nocturnal voids (ANV) ≥1 and age ≥ 50. Patients were excluded who had a diagnosis of obstructive sleep apnea, diabetes insipidus, congestive heart failure, or chronic renal failure. Patients were split into 3 groups based on number of AHT’s taken (0, 1, or 2 or more), which were limited to thiazide diuretics, calcium-channel blockers, and ACE-I’s/ARB’s. Patients were also broken down by age into 4 groups (50-59, 60-69, 70-79, and 80+). An ANOVA model was used to test for significance.

Results: Patients taking 0, 1, 2 or more AHT’s had a nocturnal polyuria index (NPI) of 37% (n=93), 40% (n=58), and 49% (n=26) respectively. Along the same group breakdown, patients had an ANV of 2.7, 2.7, and 3.5 respectively. NPI was found to be significantly associated with AHT’s (p=0.007) and age (p=0.002). ANV was also shown to be significantly associated with AHT’s (p=0.04), but no relationship was found between ANV and age (p=0.42). There was no interaction found in the model between AHT’s and age for NPI (p=0.48) or ANV (p=0.93).

Conclusion: Combination drug therapy for hypertension, as compared with untreated hypertension or monotherapy, was shown to be associated with much more nocturia and nocturnal polyuria. The steepest increase in these outcomes was seen between monotherapy and combination antihypertensive drug therapy. Patients requiring multiple blood pressure drugs are likely to have more severe and long-standing hypertension, with impairment of both nocturnal dipping of blood pressure and renal tubular sodium and water transport, resulting in greater nocturnal polyuria. Further research is warranted.
History of the "sontimeter" and its role in medical education

Students of medicine in English-speaking countries will encounter “sontimeter”, a variant pronunciation of centimeter. This variant is notable in that it is heard exclusively in the medical field, resulting in confusion for the learner. This article describes the history of “sontimeter”, explains its continued use, and enables educators to consider the implications of using the pronunciation. “Sontimeter” is a partially anglicized pronunciation coexisting with “centimeter” since at least the 1880s. The persistence of “sontimeter” demonstrates a sociological concept, the medical habitus—dispositions that facilitate membership in the medical culture. The issue of “sontimeter” reveals social forces at work within medical education and challenges medical teachers to consider their high degree of influence on students.

Patterns of Care and outcomes for Early Stage Anal Squamous Cell Carcinoma

**Purpose/Objective(s):** Standard of care treatment for squamous cell carcinoma (SCC) of the anus is concurrent chemoradiation (CRT) however it is unclear whether CRT is necessary for very early stage, T1-2N0 anal cancer. We therefore sought to assess for predictors of use of CRT and its impact on overall survival (OS) in patients with early stage node negative SCC of the anus with favorable characteristics in a large hospital-based database.

**Materials/Methods:** The National Cancer Database (NCDB) was queried to identify patients who received CRT, or RT alone for cT1-2N0M0 Anal SCC. The cohort was limited to patients less than 70 years old with Charlson-Deyo Comorbidity Index of 0. Patients were stratified by age (<60, ≥60), gender, race, stage, facility type, and insurance status. Univariable and multivariable logistic regression were performed to assess for predictors of CRT usage. 5-year OS was analyzed using the Kaplan Meier method with the log rank test both for the full cohort and then on the subsets of T1 and T2 patients. Univariable and multivariable logistic regression were used to assess for covariables associated with survival differences.

**Results:** There were 8,914 patients included in the present study, of whom 8,223 patients received chemoradiation and 691 received radiation alone. Median follow up was 46.2 months overall. Multivariable logistic regression indicated that patients were more likely to receive chemoradiation if they were <60 years old, had better performance status, were of white race, or had T2 disease. 5-year OS was 80.1% for chemoradiation and 54.4% for radiation alone. There was also a significant association between survival and chemoradiation us (HR 0.431, P<.0001).

**Conclusion:** The vast majority of patients under age 70 without significant comorbidities are treated with chemoradiation over radiation alone for early stage squamous cell carcinoma of the anus, with better survival associated with chemoradiation.
Regulation of CD4 T cells by MiT family of proteins

The MiT family of transcription factors consists of four members: TFE3, TFEB, MiTF and TFEC. TFE3 and TFEB have been shown to be involved in the control of two genes which are critical for CD4 T cell function: CD40L and FoxP3. CD40L is necessary for protective antibody responses and cellular immunity because it activates B cells and macrophages, respectively, via the receptor for CD40L, CD40. FoxP3 is necessary for the generation of regulatory CD4 T cells (Tregs), which have an essential role in suppressing autoreactive and other undesirable immune reactions. My research will focus on establishing a clearer picture of the physiological importance and regulation of CD40L and FoxP3 by TFE3 and TFEB. To this end, I will be studying T cell function, such as in models for CD40L-dependent cellular immunity, in mice that are deficient in TFE3, TFEB or both. In addition, I will be using mouse models for spontaneous and induced mucosal inflammation to test the importance of TFE3-dependent FoxP3 expression, because Tregs are important for preventing this process. I will also compare the phenotype observed in WT mice and mice lacking either TFE3 or both TFEB and TFE3 in the induced colitis model. In complementary studies, I will be examining TFE3- and TFEB-dependent CD40L and FoxP3 expression in primary human and mouse naive CD4+ T cells to examine under what conditions TFE3 and TFEB are needed. Through my work I hope to provide greater insight into the cause of autoreactive disorders.

The Role of the C1q Domain of Otolin1 in Otolith Morphogenesis

Otolin1 is an extracellular matrix protein of otoliths ("ear stones" of fishes), and otoconia ("ear dust" of higher vertebrates). These acellular biominerals are essential for the sense of balance; dislodging results in the most common human balance disorder, benign paroxysmal positional vertigo. Otolin1 comprises of a collagen and a C1q domain, similar to atypical collagens VIII and X. We propose that Otolin1 forms a scaffold to which other otolith proteins, Ca2+ and CO2- ions bind during otolith morphogenesis, with C1q trimers as hubs and collagen triple-helices as spokes. To test this model, we investigated whether the Otolin1 C1q domain is necessary and sufficient to form trimers and higher complexes in vitro. The zebrafish Otolin1a C1q domain was expressed in bacteria either alone or fused to thioredoxin. Multimerization of affinity purified recombinant proteins was assessed by size-exclusion chromatography and gel electrophoresis. Under denaturing conditions, recombinant C1q proteins formed monomers and trimers, but not dimers or higher-order complexes. Under native conditions, they formed only higher-order complexes. In contrast, thioredoxin alone only appeared as a monomer. Our results are consistent with the proposed ability of the Otolin C1q domain to form trimers that, in turn, assemble into higher-order complexes. Experiments are underway to characterize the various complexes in more detail and to test whether the C1q domain is necessary to trimerize of full-length Otolin1a.
C43: Scott Schoninger

Nanoparticle-Mediated Delivery of Alt Brk Protein in Human Breast Cancer Cells and its Impact on Cell Cycle Arrest

Introduction: p27Kip1 regulates cyclinD-cdk4 activity, and has both oncogenic and tumor suppressor properties [1]. Breast tumor related kinase (Brk) has been shown to phosphorylate p27Kip1 at tyrosine 88 (Y88), which is associated with cellular proliferation [2]. An alternatively spliced but catalytically inactive form of Brk (Alt), is believed to compete for the binding site of Brk on p27Kip1, thereby inhibiting its activity. The Blain lab has focused on mechanisms to increase intracellular Alt, with the hypothesis that this will inhibit p27Kip1 Y88 phosphorylation and progression through the cell cycle. Prior work has shown that overexpression of Alt in a tetracycline-inducible MCF-7 breast cancer cell line inhibits cellular proliferation. In order to study the biological activity of Alt in different cell lines and evaluate its potential use as a pharmacologic agent, we packaged Alt into cationic liposomal nanoparticles (NP1-Alt). The primary aim of my project was to create dosereresponse curves for three breast cancer cell lines using NP1-Alt.

Materials & Methods: Nanoparticles were produced by combining Alt protein with empty liposomes via sonication. Day 0: 5.0 x 10^4 cells were plated for the MCF-7 and MB231 cell lines, and 7.5 x 10^4 cells for the HCC1954 cell line. Day 2: NP1-Alt or empty lipoparticles, in serum-free media, were applied to each well for 6 hrs. Day 4: The cells were counted using a hemocytometer, and assessed for viability with trypan blue.

Results/Conclusions: Liposomal nanoparticles are a viable strategy for delivering Alt into human breast cancer cell lines in vitro. MB231, MCF-7, and HCC1954 human breast cancer cell lines all exhibited a dose-dependent response to Alt treatment, with the MB231 cell line being the most responsive. MB231 responded similarly to both the 10:1 & 20:1 formulations, while MCF-7 responded better to 10:1, and HCC1954 better to 20:1. The 10:1 formulation will be used in future experiments.

C44: Albert Palileo

Treatment With Paclitaxel Causes Upregulation in Resistance Protein Beta III Microtubulin in a Beta III Microtubulin Negative Type 2 Endometrial Cancer Cell Line

Introduction: Type 2 uterine cancers are associated with chemoresistance and poor outcome. Poly(lactic-co-glycolic acid)-based (PLGA) microparticles (MPs) are a promising new tool for delivery of cytotoxic chemotherapies. These MPs have a benefit of eluting drugs over a period of days for sustained pharmacokinetic effect. The current study serves to test the hypothesis that paclitaxel encapsulated microparticles is a feasible cytotoxic treatment modality in an in vitro model of a Type 2 uterine carcinoma cell line. Part of this evaluation included evaluating the cell line for resistance to paclitaxel. Overexpression of beta 3 microtubulin (TUBB3) has been linked to paclitaxel resistance in many cancers including uterine carcinomas.

Materials and Methods: PLGA MPs were prepared using established laboratory procedure to encapsulate paclitaxel in DMSO (PMPs). Blank microparticles (BMPs) were created by repeating the process with DMSO only and were used as controls. Endometrial adenocarcinoma cells from type 2 cell line KLE were plated in 6 well plates at a density of 2x10^5 cells and treated with BMPs and varying volumes of the 15 mM PMPs (20, 40, and 60 uL). Cells incubated with BMPs and PMPs for 6 days then harvested and underwent western blot analysis.

Results: Cells treated with PMPs showed decrease in cell density with morphologic changes consistent with apoptosis. Western Blot analysis for cleaved-PARP, a byproduct of apoptosis, showed significant increase in cells treated with PMPs compared to the control group. WB analysis also revealed an absence of TUBB3 in the controls, indicating no baseline resistance to paclitaxel. After treatment with PMPs, there was a statistically significant increase in TUBB3 for 40 and 60uL.

Discussion: This endeavor represents the first demonstration biochemically of upregulation of a resistance marker for paclitaxel as a response to treatment in a cell that is negative for beta 3 microtubulin prior to treatment.
Testing EAAT2 and glutamine synthetase as potential targets for epileptiform activity inhibition via ECS volume changes

Because numerous forms of epilepsy remain resistant to classical anticonvulsant drugs, hints toward new therapeutic approaches must be actively pursued. Such a lead was recently observed when introduction of gliotoxin DL-alpha-aminodipate (DL-AA) during an induced epileptiform activity in a mouse cortical brain slice led to inhibition of epileptiform activity and concurrent spikes of extracellular space (ECS) marker, tetramethylammonium ion (TMA+), suggesting a rhythmic water movement between the ECS and glial cells as a potential component in the generation of epileptic activity.

To further explore the observed phenomenon, this study tested 2 key targets of DL-AA, excitatory amino acid transporter 2 (EAAT2) and glutamate synthetase, with their respective antagonists, dihydrokainate (DHK) and methionine sulfloximine (MSO), to see which of these is responsible for the effects seen with DL-AA. Epileptiform activity was induced using a potassium channel blocker 4-aminopyradine (4-AP). Its frequency and ECS shrinkage before, during, and after application of each drug from multiple experiments were measured using ion selective microelectrodes (ISMs) and application of the Nikolsky equation. These were then compared using one-way ANOVA, followed by a post-hoc Tukey HSD test when a statistically significant difference was detected.

As expected, results of the statistical analysis with DL-AA showed a statistically significant reduction in frequency of epileptiform activity and ECS shrinkage with the drug and a return once it was washed out [F(2,3) = 79.392, p = 0.003 and F(2,3) = 21.589, p = 0.017, respectively]. However, frequency and ECS shrinkage had no statistically significant change with either DHK [F(2,6) = 0.107, p = 0.900 and [F(2,6) = 0.709, p = 0.529, respectively] or MSO [F(2,6) = 0.043, p = 0.958 and F(2,3) = 0.088, p = 0.918, respectively]. Hence, neither EAAT2 nor glutamate synthetase, when targeted separately, seem to account for DL-AA’s effects.

Correlation of Exhaled Nitric Oxide Levels with Salivary Melatonin Levels in Adults With and Without Allergy/Asthma

Rationale: We have previously reported that longer duration of sleep is associated with lower AM FeNO levels. As melatonin, a photoneurohormone which regulates sleep-wake cycles, can have anti-inflammatory effects, we sought to determine whether salivary melatonin levels correlate with FeNO.

Methods: IgE+ adults with allergy/asthma (n=10, IgE:554.7 IU/ml ±54.1) and IgE- nonallergic adults (n=10, IgE:48.8 IU/ml ±38.4) had FeNO levels measured and salivary samples obtained for melatonin levels (Niox Vero, Circassia; EIA, Salimetrics, State College, PA) at 9-10 AM (> 1hr post meal) and 6 hrs later. Saliva was collected by unstimulated passive drool technique and frozen at -20°C until assay. Salivary melatonin levels (pg/ml) were determined with a competitive immunoassay using HRP and tetramethylbenzidine. Pearson correlation coefficients and T-test were used in analysis.

Results: There was no intraday variability in FeNO levels for either the IgE- (AM: 16.2 ppb ±7.5, PM: 15.8 ppb ±8.0) or IgE+ (AM: 40.7 ppb ±40.8, PM: 33.5 ppb ±27.3) group (p=ns). While there was no significant change in melatonin from AM to PM for the IgE+ group (AM: 6.8 pg/ml ±8.2, PM: 18.1 pg/ml ±34.2)(p=0.3), there was a significant increase in salivary melatonin for the IgE- group (AM: 6.5 pg/ml ±9.8, PM: 31.6 pg/ml ±26.52)(p=0.02). There was no correlation between FeNO and salivary melatonin level for either group, in either AM or PM (p=ns).

Discussions/Conclusions: Daytime FeNO levels in IgE+ and IgE- adults are independent of circadian effects on salivary melatonin levels. Sleep has been likened to a shifting balance between Th1 and Th2 cytokine activity toward Th1 dominance. This may suppress allergic inflammation and decrease FeNO levels. The data from this study does not associate this with salivary melatonin levels.
C47: Hui Jiang  
Advisor(s): Xian-cheng Jiang

**Prodomain of furin promotes phospholipid transfer protein proteasomal degradation in hepatocytes**

Background—PLTP is one of the major modulators of lipoprotein metabolism and atherosclerosis development, however, very little is known about the regulation of PLTP. The effect of hepatic profurin expression on PLTP processing and function is investigated. Methods and Results—We utilized adenovirus expressing prodomain of furin (profurin) in mouse liver to evaluate PLTP activity, mass, and plasma lipid levels. We co-expressed PLTP and profurin in Huh7 cells and studied their interaction. We found profurin expression significantly reduced plasma lipids, plasma PLTP activity and mass in all tested mouse models, compared with controls. Moreover, the expression of profurin dramatically reduced liver PLTP activity and protein level. We further explore the mechanism using in vivo and ex vivo approaches. We found that profurin can interact with intracellular PLTP, and promote its ubiquitination and proteasomal degradation, resulting in less PLTP secretion from the hepatocytes. Furin does not cleave PLTP, instead it forms a complex with PLTP, likely through its prodomain. Conclusions—Our study reveals that hepatic PLTP protein is targeted for proteasomal degradation by profurin expression, which could be a novel post-translational mechanism underlying PLTP regulation. Keywords: PLTP, profurin, furin (PCSK3), hepatocytes, ubiquitination, proteasomal degradation.

C48: Adriana Nozima  
Advisor(s): Stephen Macknic

**An Objective Classifier of Expertise in United State Marine Corps Combat Aviators**

We and others have previously shown that oculomotor dynamics serve as a valid biomarker for fatigue and high mental workload, and other brain states—measured in applied environments—and neural disease, such as parkinsonian diseases and Alzheimer’s disease. Here we obtained eye movements from both instructor and trainee United States Marine Corps (USMC) combat aviators to determine the differences in dynamics as a function of expertise. The pilots flew different simulated mission types and we determined their ocular kinematics—as a function of mission type and cohort—across many dimensions. We observed that there are differences in specific eye movement signals between novice and expert helicopter pilots. From this data we created a classifier of expertise, which performed with an accuracy of 70.5%. We then studied whether novice pilots benefit more from viewing movies of experts performing emergency procedures or the same movies with the expert’s eye position scanpaths overlaid. As an innovation, we did not measure the benefit to novices as a function of performance, but instead measured their oculomotor dynamics as a function of the expert scanpaths—assessed by our objective expertise discriminator. We tasked novice pilots with repeatedly resolving an Emergency Procedure (dual engine failure cascade), followed by watching a video with the expert eye position indicated, and the other half watched the video without the eye movements superimposed. Pilots who were given access to the expert’s scanpaths significantly changed, in comparison to pilots who saw the same movies without scanpaths. These results suggest that physiological biomarkers—such as oculomotor dynamics—may provide a rich source of data—in short amounts of time—even within challenging operational environments, and that our oculomotor systems learn fast to use eye tracking information—even without being instructed to—very quickly.