Colbourn, Robert Advisor(s): Sabina Hrabetova

Dynamic Volume Changes of the Brain's Extracellular Space Underlying Seizures

The brain's extracellular space (ECS) is known to play a critical role in determining the excitability of neurons, and through this function, promote or inhibit seizure activity. It has been established that the ECS undergoes a long lasting shrinkage of about 30% during a seizure. However, this project investigates a previously unreported phenomenon: the ECS undergoes a fast shrinkage, then slow expansion back to baseline volume during each synchronous neuronal discharge that occurs during epileptiform activity. The goal of this project is to establish these dynamic volume changes (DVCs) as a mechanism that promotes seizure activity and determine if manipulation of this phenomenon halts seizures. The first experiments that characterized DVCs during drug-induced epileptiform activity in mouse neocortical slices revealed that DVCs lead to a transient 22% reduction in ECS volume. This observation has also been repeated in vivo through rat neocortical measurements of ECS volume during drug-induced epileptiform activity. Because water transport between the intra- and extra-cellular compartment is likely responsible for DVCs, pharmacological blockade of osmotic and ionic transport proteins was performed, revealing several protein dependencies of seizures and their DVCs. These channels and others yet to be investigated may represent new therapeutic targets to treat seizures.

Edokpolo, Leonard Advisor(s): Dennis Dimaculangan

Comparing 'Readiness for discharge' in Colonoscopy after Sedation with only Propofol vs Sedation with Propofol and Dexmedetomidine combined

Approximately 15 million colonoscopies are performed per year in the United States. Usually done in the ambulatory setting, propofol is commonly used alone for sedation due to its rapid onset and fast recovery. However, propofol can cause significant hypotension, tachycardia and respiratory depression in some patients. Enhanced recovery protocols propose the use of multimodal anesthesia, which involves combining several medications with different mechanisms to achieve the desired sedation level. This strategy, decreases the amount of each drug and minimizes their respective side effects. Dexmedetomidine can be combined with propofol because it may decreases the amount of propofol required and has minimal respiratory depression. However, dexmedetomidine alone may prolong post-operative recovery and cause hypotension with bradycardia. We found no studies that have assessed whether the combination of propofol and dexmedetomidine prolongs discharge after ambulatory colonoscopy. The objective of this study was to prospectively compare hemodynamic variables and 'discharge readiness' in two groups of patients randomized to receive either propofol-only, or a combination of propofol with dexmedetomidine during ambulatory colonoscopy. This was a 2-arm, randomized, double-blind, non-inferiority trial. All patients undergoing ambulatory colonoscopy were randomized (50 patients per group) to receive sedation with either propofol and placebo (Group P) or a combination of propofol and dexmedetomidine (Group D). Readiness for discharge was assessed every 10 minutes, using the Modified Postanesthetic Discharge Scoring System (MPDASS), until discharge criteria was met. The primary outcome was the percentage of patients in each group meeting discharge criteria within 30 minutes from the procedure end time.

We plan to present our findings of percentage of patients meeting discharge criteria within 30 minutes, and report the hemodynamic findings in each group.

Evrard, Matthew Advisor(s): Sheryl Smith

The role of $\alpha 4 \beta \delta$ GABAA receptors in triggering synaptic pruning in the medial prefrontal cortex of female mice during adolescence

Many psychological disorders such as anxiety and depression target dysfunction in the prelimbic (PL) medial prefrontal cortex. Interestingly, these disorders have a higher prevalence amongst women and symptoms begin to emerge in early adolescence. Studies have documented changes in spine density of pyramidal cells of this region during adolescence which may underlie the etiology of these disorders. This study investigates if the emergence of $\alpha 4 \beta \delta$ GABAA receptors (GABARs) initiates adolescent synaptic pruning in Layer 5 PL, as our lab has previously reported in CA1 hippocampus. Initially , we used Golgi staining to assess spine density comparing prepubertal (PND 35) vs. postpubertal (PND 56) female mice. Individual neurons were viewed using a 100x oil objective on a Nikon Eclipse Ci-L microscope and spine density/typing accomplished using Z-stack projection photomicrographs (0.1 - 0.9 μ m steps) which were taken using a Nikon DS-U3 camera mounted on the microscope and were analyzed using NIS-Elements D 4.40.00 software. Spine density decreased 40%~ across adolescence (8.9 $\pm$ 0.73 spines/10 μ m, pub vs. 5.5 $\pm$ 0.38 spines/10 μ m, post-pub, P<0.05) with mushroom spines showing the greatest decrease (, ~62%, 1.8 $\pm$ 0.23 spines/10 μ m, pub; 0.66 $\pm$ 0.12 spines/10 μ m, post-pub, P<0.05). Then, we determined that $\alpha 4 \beta \delta$ GABAR expression increases at the onset of puberty (~PND 35, assessed by vaginal opening) reflected by the response of pyramidal cells to 100 nM gaboxadol, a GABAR agonist selective for $\alpha 4 \beta \delta$, assessed using whole cell patch clamp recordings. This response was 10-fold greater at puberty compared to pre-puberty (P<0.05). In order to determine the role of pubertal $\alpha 4 \beta \delta$ GABARs in pruning of this region, we compared spine density/spine types from pubertal and post-pubertal $\alpha 4$ knock-out mice. Unlike wild-type mice, there were no significant differences in spine density or type across adolescence. Taken together these data suggest that in Layer 5 of the PL adolescent synaptic pruning is initiated by the emergence of $\alpha 4 \beta \delta$ GABARs.

Malakhov, Nikita Advisor(s): David Schreiber

Patterns of Care and Outcomes for Glioblastoma in Patients with Poor Performance Status

Background: Glioblastoma (GBM) is the most common and aggressive primary CNS tumor with dismal survival outcomes. The treatment with tumor resection followed by chemoradiation (CRT) is generally the accepted standard of care, however the best treatment for patients with poor performance status remains uncertain. Thus, we sought to examine patterns of care and survival outcomes among patients with poor performance status utilizing the National Cancer Database. Methods: Patients with GBM and Karnofsky Performance Status (KPS) <60 between 2010-2013 were included. Data was collected regarding surgery, radiation therapy (RT) and chemotherapy. Logistic regression was used to analyze predictors for utilization of chemoradiation (age, race, surgery, facility type, year of diagnosis, and MGMT status). Kaplan-Meier survival curves were generated and compared using the log-rank test between those who received CRT to RT alone. Cox regression analysis was performed to assess covariates associated with overall survival (OS). Results: There were 488 patients included in the analysis of which 51.2% received CRT and 46.1% underwent subtotal or gross total resection. None of the factors analyzed were significantly associated with increased likelihood of receiving CRT over RT alone. Survival data was available for 236 patients that received RT with and without combination chemotherapy. The median OS for those receiving RT alone was 3.6 months and 8.7 months in those who received CRT (p<0.001). On multivariable Cox regression, older age (HR 1.80-2.10, p=0.001) was associated with worse survival and subtotal/gross total resection compared to no surgery (HR 0.60, p=0.003) was associated with improved survival. Conclusion: Even patients with poor performance status had better survival outcomes when they received treatment with CRT over RT alone. Therefore, treatment with CRT could be an acceptable treatment option and should be considered for select patients with low performance status.

Marwa, Albara Advisor(s): Vivian Chin

Effectiveness of Downstart Healthy Lifestyle Program for Childhood Obesity

Introduction: Downstart Healthy Lifestyle Program (DHLP) is a three-month comprehensive program that addresses childhood obesity using thrice weekly nutrition and behavioral counseling, and supervised aerobic activity. The purpose of this study was to evaluate the effectiveness of DHLP at improving metabolic parameters and weight reduction for the past 7 years.
Methodology: Retrospective chart review of 126 patients included socio-demographic characteristics, medical history, BMI, vitals, exam, and chemistries. Chi-square, Fisher's exact, Spearman's correlation, independent and paired T-tests were used.
Results: From 103 patients with mean 10.94 Â± 3.035 (SD) years, 60.2% were females, 84 (81.6%) attended five or less visits, and 23 patients (22.3%) repeated participation. There was a statistically significant decrease in mean BMI z-score (pre 2.31 Â±0.50, post 2.25 Â±0.55, change BMI: 95% CI 0.02 - 1). There was no difference in delta BMI Z-scores or attendance between boys and girls. No correlation was found between number of sessions attended and delta BMI z-score. Metabolic parameters such as blood pressure, hemoglobin A1C, or lipid panel remain unchanged.
Conclusion: DHLP helped reduce BMI z-score, even with low attendance rates. Longer term follow-up is needed to evaluate changes in metabolic parameters.

Nath, Sridesh Advisor(s): Patrick Geraghty

Protein Phospholipid Transfer Protein and Alpha-1 Antitrypsin Regulate Neutrophil Immune Responses

Introduction/rationale: Excessive neutrophil degranulation is a common feature of many inflammatory disorders, including alpha-1 antitrypsin (AAT) deficiency. Phospholipid transfer protein (PLTP) prevents neutrophil degranulation but serine proteases cleave PLTP in the airways. We propose that PLTP can prevent degranulation of neutrophils isolated from AAT deficient subjects, and PLTP deficiency enhances neutrophil degranulation responses in mice.
Methods used: Neutrophils were isolated from venous peripheral blood of PiMM and PiZZ AAT genotype subjects (n=14/group). Neutrophils were exposed to PLTP prior to stimulation with leukotriene B4 (LTB4) and neutrophil degranulation was recorded. Degranulation was also examined in neutrophils isolated from Pltp knockout mice and wild type control mice.
Results of the study: Stimulation with LTB4 induced degranulation of primary, secondary and tertiary granules in neutrophils isolated from both AAT genotypes. However, neutrophils from PiZZ subjects had heighted degranulation responses. PLTP treatment reduced degranulation responses in neutrophils from both groups. Loss of Pltp expression resulted in enhanced degranulation in neutrophils from mice compared to wild type mice.
Conclusions of the study: PLTP mediates neutrophil responses and loss of PLTP function, via enhanced serine protease responses and reduced AAT, could contribute to elevated neutrophil associated signaling in the lung.

Sapozhnikov, Milana Advisor(s): Louis Salciccioli

Characterization of Microvascular Disease In Patients With Sickle Cell Disease Using Nailfold Capillaroscopy

Sickle cell disease (SCD) is a chronic disorder characterized by repetitive vaso-occlusive crises occurring when erythrocytes and leucocytes are trapped in the microcirculation causing vascular obstruction, tissue ischemia and pain. Repeated microvascular obstruction often heralds chronic multi-organ ischemic sequellae. Nailfold videocapillaroscopy (NFC) is a non-invasive imaging technique used clinically to directly visualize capillaries located near the fingertip in patients with Raynaud's phenomena. NFC is increasingly performed in recent years to assess the microvasculature in various non-rheumatic conditions but has not been well studied in SCD. Accordingly, the objective of this study was to characterize NFC abnormalities in the setting of SCD. We studied 71 SCD patients and 70 age matched controls. NFC was performed on 8 digits using a video capillaroscope. Images were analyzed to determine mean capillary number and final capillary score (capillary dropout which is inversely related to capillary density), capillary dilation, neovascularization and micro-hemorrhages. As compared to controls, the mean capillary number was lower and the final capillary score higher in the SCD group. On multivariate linear analyses, both mean capillary number and final capillary score were each independently associated with SCD after adjusting for age, BMI, and gender. SCD was also associated with greater numbers of dilated capillaries and more extensive neovascularization, but a similar number of micro-hemorrhages. In conclusion, SCD is associated with lower capillary density, more dilated capillaries and increased neovascularization on NFC. These changes appear unrelated to the frequency of sickle crises, number of transfusions, HbS level, and other markers of disease severity in our SCD cohort. The relation between microvascular structure, markers of target organ involvement and severity of SCD merits further study.

Seger, Edward Advisor(s): Raj Wadgaonkar

Prediction of disease progression in mycosis fungoides using the immune microenvironment

One of the challenges in caring for patients with mycosis fungoides, the most common cutaneous T-cell lymphoma (CTCL), is early identification of patients who will develop progressive disease. While TNM staging is prognostic, identification of high-risk patients earlier in their disease remains an unmet clinical need. We hypothesized that the balance between anti-tumor CD8+ T cell and anti-inflammatory FOXP3+ T regulatory cell infiltration in the initial CTCL skin biopsy could be predictive of disease progression. To examine this, a cohort of 33 CTCL patients (9 I, 4 II) with a median follow-up of 78 months were divided into two groups depending on whether they developed progressive disease (n=13). We studied their skin biopsy specimens by multiplexed tyramide signal amplification based staining for CD4, CD8, FoxP3, PD-1 and DAPI expression, followed by image deconvolution and automated cell analysis. Patients with greater CD8+ T cell infiltration had significantly improved progression-free survival in univariate (HR=0. 6, CI 0. 4-0. 97, p=0. 04) and multivariate analysis (HR 0. 4, CI 0. 2-0. 7, p=0. 01). When we restricted the analysis to early stage patients, this finding remained significant (HR=0. 6, CI 0. 4-0. 98, p=0. 04) and did not correlate with malignant clone frequency or age. The number of FoxP3+ regulatory T cells, PD-1+ T cells and total CD4+ T cells were not associated with improved survival. Ratios between these cell types were also examined for potential associations with prognosis. We found that an increased ratio of CD4+ T cells:FoxP3+ T cells was associated with worse PFS (HR 1. 02, CI 1. 0-1. 03, p=. 01) but this result did not remain significant in multivariate analysis (p=0. 7). We are in the process of confirming this finding in a larger cohort. In summary, CD8+ T cell density in the lesional skin of CTCL patients is predictive of disease progression and may be a useful adjunct in risk-stratifying early stage patient.

Yusupov, Denis Advisor(s): Andrew Chang

FIT vs Colonoscopy: Using Shared Decision Making to Optimize Colorectal Cancer Screening in an Urban Underserved Population

Although colorectal cancer (CRC) is the third most common cancer among men and women and is projected to cause more than 50,000 deaths in 2017, only 62.6% of adults 50 years and older were screened. Access, insurance/immigration status, education, burden of preparation and ethnicity impact cancer screening. Urban underserved populations are disproportionately affected by these barriers.

The purpose of this study was to evaluate whether shared decision making, discussing the pros and cons of FIT and colonoscopy testing, with eligible patients, would improve colorectal cancer (CRC) screening completion rates in underserved populations.

The study population consisted largely of Afro-Caribbean patients, 50 years and older with average risk factors. A retrospective analysis reviewed baseline CRC screening rates in resident clinic patients between January and February 2017. As an intervention, residents were encouraged to discuss the pros and cons of FIT and colonoscopy for CRC screening, allowing patients to make a more informed decision when choosing their preferred modality. A prospective cohort study reviewed charts from September 1 to December 31st, 2017 to assess completion of screening.

By engaging our patients in the decision making process, we witnessed an increase in FIT testing and improved overall colon cancer screening rates. Subjects who chose FIT testing were more likely to complete screening compared to those who chose colonoscopy. While colonoscopy is often offered as a first line for CRC screening, it may not be ideal for patient populations that have more socioeconomic barriers. The U.S. Preventive Services Task Force Guidelines consider both modalities equally valid for CRC screening. This study demonstrates that improving shared decision-making between patients and providers can decrease barriers to screening, and improve CRC screening.

Zinoviev, Alexandra Advisor(s): Tatyana Pestova

Release of ubiquitinated and non-ubiquitinated nascent chains from stalled ribosomal complexes

Aberrant translation induces mRNA and protein quality control systems to ensure the fidelity of gene expression. No-go and non-stop decay mRNA surveillance mechanisms target mRNAs, on which elongation complexes (ECs) are stalled by stable secondary structures, rare codons or the lack of a stop codon. Nascent chain (NC) peptides arising from interrupted translation are, in turn, degraded by the ribosome-associated quality control (RQC) pathway. The process starts with the endonucleolytic cleavage of mRNA near the stall site. After that, ECs are disassembled by ABCE1/Pelota/Hbs1 into 40S subunits, NC-tRNAâ€¢60S ribosome-nascent chain complexes (RNCs), and mRNA cleavage products that are degraded by Xrn1 and the exosome. Dissociation of 40S subunits exposes the P site peptidyl-tRNA and intersubunit interface on the 60S subunit, allowing binding of NEMF which recruits Listerin, the E3 ubiquitin ligase that ubiquitinates NCs, targeting them for degradation. The mechanism of subsequent steps, which would free Ub-NCs from 60S subunits and culminate in their degradation, is unclear. Strikingly, we found that Ptrh1, a putative peptidyl-tRNA hydrolase, can release non-ubiquitinated NCs from 60S and even 80S RNCs formed on non-stop mRNAs, suggesting the existence of an additional pathway involving release rather than ubiquitination of NCs. To investigate whether Ptrh1 is also involved in RQC, we reconstituted ubiquitination in vitro. We found that TCF25, a poorly characterized component of RQC, specifically stimulated formation of the K48 Ub linkage. Ptrh1 did not release Ub-NCs from Listerin/NEMF-bound 60S RNCs, arguing against its role in RQC. However, Ub-NC release that led to proteasomal degradation was promoted by puromycin, indicating that NEMF/Listerin induced accommodation of NC-tRNAs in the peptidyl transferase center. This suggests the existence of an additional as-yet unidentified factor that associates with the ribosomal A site and releases Ub-NCs from 60S subunits.