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Research Advisor: Girardin Jean-Louis

Insufficient Sleep Derived from Seven-Day Diary Habitual Sleep Time and Actigraphy

Introduction: Mixed results have been reported regarding the prevalence of insufficient sleep (<6 hours) in the population. This may be in part attributable to use of varying assessment tools (e.g., sleep diary, time-use estimate, and actigraphy). This study compared estimates of insufficient sleep derived from three measurement techniques.

Methods: Data emanated from a sample of postmenopausal women (mean age = 67.71±7.87 years) participating in the Women's Health Initiative study. It included Non-Hispanic White=72%, Hispanic=14%, Black=9%, and Other =5%. At the beginning of the study, volunteers estimated their habitual sleep time (HST). Thereafter, sleep was continuously recorded for 7 days using the Actillum (ACT) while maintaining a seven-day diary (SDD). Actigraphic data was recorded every minute and quantified based on the MAXACT modality. Data were analyzed using ACTION3 .

Results: Based on SPSS analysis, 20.6% of the sample reported insufficient sleep based on SDD; 15.6% reported insufficient sleep based on HST; and 47.4% experienced insufficient sleep based on ACT. We also ascertained associations of each of these estimates of insufficient sleep with obesity. For SDD, odds ratio [OR] was 1.03 (95% CI: 0.52-2.06, NS). For HST, OR was 2.26 (95% CI: 1.18-4.29, p<0.01). For ACT, OR was 2.13 (95% CI: 1.29-3.50, p<0.001).

Conclusion: Our study shows that estimates of insufficient sleep derived from sleep diaries, time-use estimates, and actigraphy are markedly different from each other. Of interest, insufficient sleep derived from actigraphy yielded the greatest odd of being obese, followed by time-use estimates. Estimates of insufficient sleep from sleep diary did not show significant association with obesity.

Dana Addison

Research Advisor: Girardin Jean-Louis

Associations of Insufficient Sleep and Obesity with Life Satisfaction

Introduction: Prevalence of insufficient sleep (≤ 6 hours) and obesity (BMI ≥ 30 kg/m²) have substantially increased over the last 40 years. Yet, it is unknown how these factors influence level of satisfaction with life, which is associated with general health and essentially well-being. This study examined whether insufficient sleep and obesity are independently associated with life satisfaction.

Methods : Analysis was based on the 2009 Behavioral Risk Factor Surveillance System (BRFSS) data. BRFSS is a CDC-sponsored study, which represents the world's largest ongoing, state-specific, randomized survey gathering behavioral risk factors among adults living in households in the United States [mean age=56 ± 16 years; female=63%]. Analysis focused on phone interviews conducted in six representative states, soliciting sociodemographic, health, and sleep data, yielding data for 37,328 respondents. Respondents were classified as being dissatisfied with life if they indicated "dissatisfied" or "very dissatisfied" during the survey. Data analysis was performed using SPSS 19, applying appropriate BRFSS weights to adjust for use of complex design.

Results : Of the sample, 88% were white and 12% were black; 63% were female, 92% completed HS education, 66% reported yearly income >35K, and 58% were married. Based on logistic regression analyses, individuals reporting insufficient sleep had nearly four-fold greater odds of being dissatisfied with life, relative to those sleeping 7-8 hours (OR=3.70, 95% CI: 3.32-4.12, p<0.001). Individuals who were obese were 58% more likely to be dissatisfied with life (OR=1.58, 95% CI:1.44 -1.74, p<0.001), compared with those of normal weight. Further analyses adjusting for sociodemographic and medical confounders (such as diabetes and hypertension) showed no significant interactions of insufficient sleep and obesity with life satisfaction.

Conclusion: Our study showed that both insufficient sleep and obesity were inversely related to life satisfaction. Although insufficient sleep was a stronger predictor of life satisfaction, it did not mediate associations between obesity and life satisfaction.

Christie Racine

Research Advisor: Girardin Jean-Louis

Associations between Short Sleep and Healthful Practices: Role of Race/Ethnicity

Background: Antidepressant treatments (electroconvulsive shock and fluoxetine) increase dentate gyrus neurogenesis in nonhuman primates. Conversely, irradiation of the temporal lobe ablates neurogenesis and abolishes efficacy of fluoxetine in a nonhuman primate of depression. Following early life stress [maternal variable foraging demand (VFD)], macaque neurogenesis is reduced but not ablated. We examined susceptibility for distressed behavior following temporal lobe irradiation in VFD-reared subjects versus controls.

Methods: Sixteen adult female subjects served as subjects, eight were reared under VFD conditions and eight were normally reared. Following baseline observation for six weeks, four subjects from each group received bilateral temporal lobe irradiation whereas four subjects received a sham condition. Subjects were observed post-irradiation for 10 weeks. Behavioral measures reflective of affective distress were assessed – “Affiliation”, “Anhedonia” and “Detachment”.

Results: Affiliation increased specifically in VFD-reared irradiated subjects versus irradiated healthy subjects and sham-treated VFD and controls [rearing x irradiation interaction; $F(1;10) = 26.80$; $p = 0.0004$]. Anhedonia was increased following irradiation versus sham [$F(1;10) = 9.17$; $p = 0.02$] without rearing effect. Detachment was increased specifically in VFD-reared irradiated subjects but not in irradiated controls or sham-treated VFD or control subjects [rearing x irradiation interaction; $F(1;10) = 84.45$; $p < 0.0001$]. Effects were not attributable to age, weight or baseline differences.

Conclusions: Following early life stress, ablation of suppressed neurogenesis may interact with a vulnerable biological substrate to induce affective distress. Ablating healthy neurogenesis in normally-reared subjects produces limited effects because compensatory mechanisms putatively maintain behavioral homeostasis.

Ernest Yushvayev

Research Advisor: Jason Lazar

Use of Capsaicin as an agent in assessing vasodilatory responses

Introduction: Capsaicin is a component of chili peppers of the genus *Capsicum*. It is a topical cream for pain relief. Capsaicin is an agonist for TRPV1 expressed in vascular smooth muscle and arteriolar endothelial cells and helps regulate microvascular tone. The use of capsaicin as a provocative agent in assessing vasodilatory responses is unknown. Pulse wave velocity (PWV) is a measure of arterial stiffness. We assess topically applied capsaicin on forearm vasodilation using carotid to radial artery PWV measurements.

Methods: PWV was measured by applanation tonometry before and at intervals of 5, 10, 15, 25, and 30 min. after topical administration of 0.5 inch Capsaicin cream to the forearm over the radial artery. For comparison, PWV was measured without capsaicin application in a subset of the original group of subjects (control group). The responses of 42 healthy subjects were compared to that of 22 controls.

Results: In the capsaicin group PWV decreased from 8.3 ± 1.1 m/s at baseline to 8.0 ± 1.1 m/s at 5 min. ($p=0.04$) whereas PWV was unchanged without capsaicin (8.3 ± 1.4 m/s vs. 8.3 ± 1.4 m/s, $p=0.64$). In a subgroup of 11 subjects asked to identify onset time of local burning sensation and to grade it on Likert pain scale from 0-10, time to burn onset was 7.1 ± 3.3 min., and burn Intensity was 3.4 ± 0.5 out of 10. The 5 min. PWV decline (%) was correlated with time to burn onset ($p < 0.05$) but not with burn intensity ($p=ns$). Healthy subjects exhibit a time dependent decrease in PWV with and without capsaicin. After application of topical capsaicin the PWV decline occurs earlier, with a 4% decrease in PWV at 5 min. vs. no change (0%) without capsaicin.

Conclusions: These pilot data suggest capsaicin induces forearm vasodilation as evidenced by a more rapid decrease in PWV. Decrease of PWV precedes local burning sensation (5mins vs. 7.1 min). The 5 min PWV decline is related to the time of onset but not to the intensity of subjective burning sensation.

Stephanie Lauw

Research Advisors: Jason Lazar and Louis Saliccioli

Cerebrovascular Reactivity and Cognitive Dysfunction in Patients with Heart Failure

Introduction: Cerebrovascular disease may contribute to the cognitive dysfunction seen in patients with left ventricular systolic dysfunction (LVSD) and low ejection fraction (EF). Impaired cerebrovascular reactivity (CVR) has been found associated with cognitive dysfunction in a variety of disease states but not yet in the setting of LVSD. The objectives of this study are to determine whether CVR is impaired in patients with LVSD and the relationship with measures of cognitive function.

Methods: CVR was assessed by the breath holding index (BHI) by transcranial Doppler, which uses changes in middle cerebral artery Doppler velocities with permissive hypercapnea. We measured the BHI in 24 patients with LVSD (EF = 25±11) and 30 normal controls (age 58±9 vs. 40±13 respectively; $p < 0.001$). Tests for cognitive function were the color block time test (CBT), BW time (BWT) and color interference test (CIT).

Results: The cognitive function tests were worse in the LVSD group before but not after adjustment for age. In the LVSD group, both age and BHI were independent predictors of CBT test ($p = .02$, $p = .007$ respectively) and CIT test ($p = .002$, $p = .055$, respectively), while age was the only predictor of BWT test ($p = .03$). In the LVSD group the BHI was correlated with EF ($r = .41$, $p = .05$). There was a trend toward lower BHI in the LVSD group ($r = -.25$, $p = .07$). In normal subjects only the CIT correlated with BHI ($p = .03$).

Conclusions: Cognitive dysfunction appears related to age and CVR as measured by the BHI in those with LVSD. Further studies in a larger population are warranted to assess CVR in patients with LVSD.

Andrew Lee

Research Advisors: Louis Saliccioli and Jason Lazar

Wave Intensity Analysis via Pressure and Velocity Waveforms in Subjects with Reduced Left Ventricular Function

Introduction: Wave intensity (WI) is the product of the time derivatives of the blood pressure (dp/dt) and velocity (du/dt). Changes in pressure and velocity are acquired using measurements by invasive techniques, or arterial ultrasound with pressure-arterial size assumptions. WI measurements may allow for the evaluation of arterial-ventricular hemodynamics. We evaluated the reproducibility of WI from the carotid and brachial arteries using Doppler and applanation tonometry and compared WI values in subjects with and without heart failure (HF).

Methods: Doppler velocity was acquired with an ultrasound probe (Philips Sonos 5500) while arterial pressure waveforms were acquired simultaneously using applanation tonometry (Atcor Medical). Pressure, velocity, and ECG readings were digitally acquired for 10 seconds and analyzed by customized software to generate WI. There were 27 healthy subjects and 23 with HF (EF = 31±9). The forward traveling compression wave was derived into W1 and W2 while the reflected wave was derived into the negative wave (NA). Ejection time was obtained from the WI curve and ECG. Augmentation pressure (AP) and index (AI) were obtained from the pressure curves.

Results: The intraclass coefficients for WI measurements were significant with values from .51 to .92 except for the carotid NA area. Carotid W1 amplitude was not different between normal and HF ($p = .41$). There was a trend in HF patients for lower W1 area ($p = .12$), W2 amplitude (1.9 vs. 1.3, $p = 0.06$) and W2 area ($p = 0.09$). There was a correlation between ejection time and EF ($r = .44$, $p = .04$) in the HF group. AP and AI showed correlation with brachial NA wave ($r = 0.32$, $p = .03$ and $r = .32$, $p = .04$, respectively.)

Conclusion: WI using this method showed general reproducibility and may allow for evaluation of arterial hemodynamics, wave reflection and ventricular-arterial coupling. Further analysis in a larger population is warranted.

Josef Brejt

Research Advisor: Louis Saliccioli

The relationship of the carotid artery gray scale median to anatomic and functional measures of cardiovascular risk

The Grey scale median (GSM) is a measure of echogenicity on ultrasound images and has been used to characterize carotid plaque and intima-media density, and to assess cardiovascular (CV) risk. Few studies have evaluated the relationship of intima-media echogenicity to other CV risk factors. Bone demineralization, carotid intima-media thickness and functional measures such as arterial stiffness are associated with higher CV event rates. We evaluated the relationship of the carotid GSM to these CV risk measures and to the standard Framingham risk score.

We measured carotid GSM in 41 African-American women who also had measurements of bone density (BMD) using DEXA scan, the arterial stiffness measures of pulse wave velocity and augmentation index using applanation tonometry, and carotid intima-media thickness by vascular ultrasound. Lipid profile and Framingham risk scores were available in a subset.

The mean age was 58 ± 16 yrs. The BMI was 29.9 ± 7.2 . GSM inversely correlated with Framingham risk ($r = -.39$, $p = .05$), total cholesterol ($r = -.39$, $p = .03$) and LDL cholesterol ($r = -.39$, $p = .03$). There was no correlation between GSM and CIMT, bone density, pulse wave velocity or augmentation index ($p = \text{NS}$ for all). There was significant correlation between CIMT and Framingham risk ($r = .54$, $p = .004$). On multivariate analysis CIMT ($R^2 = .36$) and not GSM was an independent predictor of Framingham risk.

In summary GSM predicts Framingham risk and does not correlate with bone density, CIMT or arterial stiffness. However GSM does not predict risk when CIMT is added to the multivariate model. Further studies are needed to assess the incremental value of GSM measurements in predicting CV risk.

Jane Yee

Research Advisors: Helen Durkin and Rauno O. Joks

C5a increases human CD4+ phosphorylated p38 MAP kinase+ T cell numbers linking innate immune responses to IgE production.

Background: We previously demonstrated that adult IgE+ allergic asthmatic subjects (1) had increased levels of complement proteins, C5a and C3a, and their respective receptors in blood/plasma; C5a and C3a are activated by pollen and dust mite allergens; (2) increased plasma C5a and C3a levels correlate with concurrent pollen counts and C5a correlates with asthma severity and QOL scores; (3) increased phosphorylated p38 MAP kinase+ lymphocytes (phos-p38 MAPK) were present in their PBMC, compared with IgE- nonallergic counterparts; and (4) CD4+ phos- p38 MAPK+ T cells numbers correlate with serum IgE levels. Phos-p38 MAPK is a central signal for upregulation of IL-4, the key cytokine associated with IgE production, allergies and asthma. The effect of C5a on human blood lymphocyte phos-p38 MAPK expression not been studied.

Methods: PBMC (CD4+CD3+ and CD8+CD3+ T cells, CD19+ B cells, CD14+ monocytes) of adult IgE+ allergic ($n = 5$) (serum IgE 817.8 ± 534.4 IU/ml) and IgE- non-allergic subjects ($n = 7$) (< 100 IU/ml) were incubated with phorbol myristate acetate (PMA), C5a, or both for 15 min, and the numbers of leukocyte+ phos- p38 MAPK+ subsets determined (flow cytometry).

Results: PMA treatment significantly increased CD4+ phosphorylated p38 MAP kinase+ T cell and CD14+ phosphorylated p38 MAP kinase+ monocyte numbers in IgE- nonallergic humans ($p = 0.05$, 0.06 , respectively). Interestingly, in IgE+ allergic humans, PMA had virtually no effect on these subsets ($p = 0.15$, 0.22 , respectively). C5a treatment had no effect on phos-p38 MAPK+ numbers ($p = \text{ns}$). However, C5a with PMA significantly increased CD4+ phos- p38 MAPK kinase+ T cell ($p < 0.001$), but not CD14+ phos-p38 MAPK kinase+, numbers. ($p = 0.06$).

Conclusion: The results suggest that allergens may activate complement (C5a), which, in turn, directly upregulates CD4+ phos-p38 MAPK+ T cells (with IL-4 production) for induction of human IgE allergic responses.

Kanwaljit Brar

Research Advisor: Rauno O. Joks

Contact hypersensitivity to shea butter

Background: Although indigenous to Africa, shea (*Butyrospermum parkii*) butter is increasingly being used in the American health and beauty industry as a fatty emollient found in cosmetics, lotions, and baby products. There are no known reported allergic reactions to shea butter. We report of a 51-year-old male who complained of onset of erythema and swelling in the beard area after 3 weeks of use of a shaving cream containing shea butter. Allergic contact dermatitis (ACD) was suspected.

Methods: Patch testing (Finn chamber) was performed on our patient using raw yellow shea butter, and the implicated shave cream, Soft Sheen Carson with Shea Butter®. Both normal and razor abraded skin was tested. Possible allergens and saline control were placed in Finn chambers and affixed to intact as well as abraded skin. The chambers were kept in place for 48 hours and reactions measure at 48 and 72 hrs.

Results: At 48 hours, only erythema was noted at the sites of raw shea butter application (abraded and non-abraded), and at the abraded site of Soft Sheen Carson shaving cream. At 72 hours; erythema, edema, and papule formation; a 2+ reaction was seen at the sites of raw shea butter application (abraded and non-abraded) and again at the abraded site of Soft Sheen Carson shaving cream. This confirmed the presence of allergic contact dermatitis to shea butter in our patient.

Conclusions: This is the first case of contact dermatitis to shea butter. Shea butter contains minimal protein, and a previous study failed to demonstrate IgE binding to shea butter or shea nut. Therefore, the contact hypersensitivity demonstrated might be due to lipid hapten-protein binding, as is seen with poison ivy contact dermatitis.

Lihua Yang

Research Advisors: Jack Moallem and Rauno O. Joks

Evaluation of People with Atopic Dermatitis Applying Patch Test with Mites Cockroach and Mouse Extracts

Rationale: Atopic dermatitis (AD) may be exacerbated by exposure to aeroallergens and might improve by elimination of the allergen. Many inner-city dwellings are infested with dust mites, cockroaches, and mice, but there is limited information on the role of these allergens in triggering AD.

This study investigated the role of Dust mite (DM), Cockroach (CR) and mouse in AD, and evaluated the diagnostic value of patch testing (PT) with these antigens in AD in terms of cell mediated (Type4) reactions.

Methods: Patients diagnosed with AD using Hanifin and Rajka criteria (n=6, 4 children, 2 adults) following IRB approval, underwent skin patch test using Finn Chambers individually prepared with DM (Glycerinated Dermatophagoides pteronyssinus & Dermatophagoides farinae), American cockroach and mice allergen (ALK-Abello, 15, 000 BAU, 1/20 w/v, 1/20 w/v, respectively, 0.08ml/test). The patches were applied to uninvolved skin on the back, removed at 48 hours, and read at 48 hours and 72 hours. Interpreting and recording reactions to patch test was based on T.R.U.E. test guidelines. Patients' Skin Prick Test (SPT) results or serum allergen specific IgE levels were collected from the medical record.

Results: Five out of six (5/6) AD patients had positive patch tests to both DM and CR, and none had reactions to mice.

Three out of four (3/4) AD patients with negative SPT & or serum IgE to DM showed positive patch test to DM.

Two out of three (2/3) AD patients with negative SPT & or serum IgE to CR showed positive patch test to CR.

Discussion & Conclusions: We demonstrated that DM, cockroach, but not mouse extract can induce positive cell mediated reactions in our patients with AD. Diagnosis and removal of allergens from the environment may play an important role in the treatment of these patients. The evaluation of cell-mediated response through patch testing may seem to be a valuable additional tool in the diagnostic work-up of patients with atopic dermatitis.

Edward Kleiman

Research Advisors: M. Vastardi, I. Katayeva, R. Joks

The Impact of Ethnicity on Incidence Rates for Development of Allergic Disease in Immigrants to Brooklyn

Rationale: Inner city areas including Brooklyn, New York suffer disproportionately from allergies and asthma. As Brooklyn has ongoing immigration from regions of low allergy / asthma prevalence, we determined the incidence rates of allergy and asthma for immigrant resident groups including Asians (Chinese), Hispanic and Afro Caribbean.

Methods: Asian, Hispanic, and Afro-Caribbean immigrants (n=637) were surveyed to determine for onset of asthma or allergic rhinoconjunctivitis (ARC) after their immigration to Brooklyn to determine incidence rates. This was done using Poisson regression. The effect of individual ethnicity on incidence rates was evaluated by Kaplan-Meier analysis using the log-rank test and bootstrap adjustment for pair-wise multiple comparisons.

Results: Incident asthma cases were: 7/166 in Asian (4%), 25/77 in Afro-Caribbean (32%), and 45/394 in Hispanic (11%). The incidence rates (95% CI) per 100 person-years for asthma were: Afro-Caribbean 1.69 (1.14, 2.50), Hispanic 1.06 (0.79, 1.42), and Asian 0.47 (0.22, 0.98). There was a significant overall effect of ethnicity (p=0.010) on development of asthma. Incident cases for ARC were: 56/162 in Asian (35%), 68/72 in Afro-Caribbean (94%), and 120/391 in Hispanic (31%). The incidence rates were: Afro-Caribbean 6.19 (4.88, 7.85), Asian 4.57 (3.51, 5.93), and Hispanic 2.99 (2.50, 3.58). There was a significant overall effect of ethnicity (p<0.001) on development of ARC in immigrants to Brooklyn.

Conclusion: Ethnicity significantly impacts development of respiratory allergic disease and may contribute to the allergy/asthma epidemic, which deeply affects inner city populations.

Maria-Anna Vastardi

Research Advisor: Rauno O. Joks

Correlation of development of asthma to previous infections in Chinese and Hispanic immigrant populations residing in Brooklyn

Rationale: The hygiene hypothesis suggests infections may be protective against development of allergy/asthma. We determined the relationship of previous infections to development of asthma in foreign-born subjects who were asthma-free when immigrating from areas with low allergy/asthma.

Methods: Immigrants residing in Brooklyn ± allergy/asthma [Chinese (n=157) and Hispanic (N= 55); n=205, respectively] were surveyed for previous infections and history of onset of asthma after immigration (n=29). Serologies were obtained for: H pylori, T. gondii, H. simplex virus 1, C. pneumoniae, and C. trachomatis (ELISA, IgG). Serum IgE and exhaled nitric oxide levels were measured (ELISA; eNO, Aerocrine). Statistical analysis: Fisher's exact test, T-test, Mantel-Haenszel Chi-Square for test of trend, and logistic regression.

Results: Asthmatic immigrants reported significantly greater frequency of past infection with chickenpox (p=0.02), measles (p=0.04), tuberculosis (p=0.05), but not hepatitis (p=0.13). None of the infections surveyed were protective (p=NS). Increasing number of reported or confirmed infections was associated with greater probability for presence of asthma (p=0.04). The odds ratio for developing asthma was higher for Hispanics (OR 10.75; 95%CI 2.1-52.8, p=0.004) and for subjects with a history of hepatitis (OR 5.2; 95%CI 1.5-18.6, p=0.009). Asthmatic immigrants had significantly higher IgE levels (138.5 ± 143.5 vs. 92.8 ± 92.5, p=0.02) and exhaled NO levels (32.9 ppb ± 22.9 vs. 21.4ppb ± 12.5, p<0.001) than controls.

Conclusions: None of the infections surveyed were protective against development of asthma in Chinese and Hispanics after immigration to Brooklyn.

Ashlei Mathew

Research Advisor: Rauno O. Joks

Seasonal Variation in Angioedema and Urticaria in an Inner-City Minority Population

Rationale: Seasonal variation in respiratory allergy has been attributed to allergen exposure. Whether there is a correlation between season and the hospital presentation of urticaria or angioedema has not been determined in pediatric or adult populations.

Methods: An IRB approved retrospective EMR chart review was conducted of pediatric and adult patients treated at Kings County Hospital Center for urticaria and/or angioedema, from January 2007 to July 2012. The dates of occurrence of urticaria or angioedema were obtained for emergency department patients and inpatients, in order to determine whether there was a seasonal distribution in presentation.

Results: We identified 407 patients (281 women, 126 men, mean age 48 years) who were diagnosed with angioedema or urticaria. Angioedema occurred in 285 patients, urticaria occurred in 127 patients, and angioedema and urticaria concurrently occurred in 5 patients. Statistical analysis of angioedema, which occurred most commonly in the summer (34% of cases), resulted in a significant association across seasons ($P < 0.001$) and months ($P = 0.017$). Urticaria presented most commonly in the summer as well (31%), however this finding was not significant across seasons ($P = 0.677$) or months ($P = 0.677$).

Conclusions: We found seasonality in the presentation of angioedema in our predominantly African American cohort. Studies have determined that angioedema is relatively common and there has been an increase in hospitalizations for angioedema in New York State. African Americans are known to have an increased rate of hospitalizations for angioedema and angiotensin-converting-enzyme inhibitor-induced angioedema. There may be seasonal IgE-mediated physical urticaria and angioedema contributing to our finding. Further examination will give us better insight to the seasonal variation in the presentation of cases of angioedema.

Bryan McCarthy

Research Advisor: Helen Durkin

Magnetic stimulation of left TPO (temporo-parieto-occipital) cortex of IgE producing allergic humans increases blood/serum substance P levels and CD4+ and CD8+ T cell numbers while suppressing ongoing IgE responses. Substance P suppresses CD4+ phosphorylates p38 MAP kinase (p38 MAPK)+ T cells and memory IgE responses *in vitro*.

Rationale: Magnetic/electrical stimulation of left, but not right, TPO cortex of IgE+ allergic humans or BPO-KLH sensitized rats increased serum substance P levels and blood CD4+ and CD8+ T cell numbers, while suppressing IgE responses. This did not occur in rats with spinal cords cut at T1 (level of innervation of thymus) or in thymectomized rats, but did occur if cords were cut at T6 or T12 (innervation of other lymphoid organs). Our other studies demonstrated that substance P suppresses specific IgE responses of BPO-KLH sensitized mice. Others demonstrated a relationship between phosphorylated p38 MAPK and IL-4, which is required for IgE production. The effect of substance P on phosphorylated p38 MAPK expression by human lymphocytes in conjunction with IgE responses has not been studied.

Methods: Serum substance P levels of IgE+ allergic humans were determined before and 2-4 hr after left TPO stimulation (enzyme immunoassay). The effect of substance P on (1) CD45+ phosphorylated p38 MAPK+ lymphocytes and CD4+ phosphorylated p38 MAPK+ T cell numbers was determined before and after PBMC were incubated for 15-30 min +/- PMA or PMA + substance P (flow cytometry); and (2) memory IgE responses was determined by culturing PBMC for 0-12 days +/- ragweed antigen or ragweed antigen + substance P, and measuring IgE in supernatants (ELISA).

Results: Left, but not right, stimulation of TPO cortex increased serum substance P (4-7 fold). Treatment of PBMC with substance P suppressed PMA-induced increases in CD45+ phosphorylated p38 MAPK+ lymphocyte and CD4+ phosphorylated p38 MAPK+ T cell numbers (30-50%), and prevented induction of memory IgE responses by PBMC (>95%).

Conclusions: Taken together, our results indicate that brain regulates IgE responses, probably by release of substance P. This is the first demonstration that substance P suppresses CD4+ phosphorylated p38 MAPK+ T cells and human memory IgE responses.

Sumit Baral

Research Advisor: Samuel Marquez

Sex and Racial Population Differences in the Arthro-kinematics of the Carrying Angle: Potential Clinical Implications

The carrying angle (CA) of the elbow is defined as the angle between the long axis of the extended forearm as it lies lateral to the long axis of the arm. It develops in response to pronation of the forearm and keeps the swinging upper extremity away from the side of the pelvis during locomotive gait. Larger CA's may be a risk factor leading to elbow instability and pain. This study compares the CA between males and females and between Euro-Americans (EA) and African Americans (AA). 10 male (5 EA, 5 AA) and 10 female (5 EA, 5 AA) volunteers drawn from an urban population with no past history of elbow pathology had their CA's measured via goniometer. Results showed that males had an average CA of 12.32 degrees compared to an average 15.08 degrees in females. EA and AA had less discrepant angles of 13.68 degrees and 13.72 degrees, respectively. Student's t-test revealed that the angles of females were significantly ($p < 0.05$) larger than those of males, while no significant variation was shown in the angles between EA and AA. The cultural role of females in rearing children typically involve the carrying of their young, which generates a significant amount of stress on the proximal muscle attachments of the medial and lateral epicondyles of the elbow. Our results suggest that CA may be a predisposing factor of the female predilection to epicondylitis particularly in eccentric contraction during routine activities.

Elizabeth Tam

Research Advisor: Tamar Smith-Norowitz

IgE Anti-Hepatitis B Surface Antigen Antibodies Detected in Serum From Inner City Serum IgE Positive Asthmatic and Serum IgE Negative Nonasthmatic Children

Rationale: The previously reported production of IgE specific to different viruses (HIV-1, Parvovirus B19, Varicella Zoster Virus (VZV), Influenza Virus) in humans and the ability of IgE anti-HIV-1 to suppress HIV-1 production by human PBMC suggest important roles for IgE and/or anti viral specific IgE in viral pathogenesis in health and disease. However, the presence of IgE anti-Hepatitis B surface antigen antibodies in inner city children without asthma or with moderate to severe asthma has not been studied.

Methods: Specific IgE and IgG Hepatitis B surface antigen antibodies were studied in serum IgE + (> 100 IU/mL) asthmatic (N=20) and serum IgE negative (< 100 IU/mL) nonasthmatic (N=13) children (m/f 0-19y/o; Brooklyn, NY) who were vaccinated with Hepatitis B vaccine (>45 years to study) (ELISA).

Results: IgE and IgG specific Hepatitis B surface antigen antibodies were detected in sera of asthmatic children (40%, 50%, respectively). Interestingly, these antibodies also were detected in sera of nonasthmatic children. Further, the numbers of nonasthmatic children producing IgE anti-Hepatitis B were higher than those producing IgG anti-Hepatitis B (46%, 38%, respectively).

Conclusions: IgE anti-Hepatitis B joins the growing list of IgE antibodies directed against viruses, including HIV-1, Parvovirus B19, VZV, and Influenza, indicating that anti-viral activity is a principal evolutionary role of IgE, and that long term persistence of IgE anti viral responses might contribute to protective immunity. Hepatitis B vaccination induces IgE responses in serum IgE negative nonasthmatic children.

Elizabeth Garay

Research Advisor: Abraham Wu

Prognostic factors for post-resection recurrent NSCLC treated with definitive radiotherapy

After curative surgery for non-small cell lung cancer (NSCLC), some patients develop localized recurrence. Radiotherapy (RT) can be given with definitive intent, but it is unclear whether outcomes are comparable to primary NSCLC and whether similar prognostic factors apply. We examined 152 such patients treated at MSKCC between 1994 and 2012 and identified prognostic factors for survival and further disease recurrence. Kaplan-Meier and Cox regression analyses were used for overall survival (OS) and competing-risk regression was used to examine locoregional failure (LF), distant metastasis (DM), and overall recurrence rates. Median follow-up was 25 months for living patients. 133 patients were treated with conventional fractionation (median 66Gy, range 45-90Gy) and 19 received stereotactic body RT (SBRT) (median 45Gy, range 24-60Gy). Two and 5-year OS were 49% and 28% respectively. Two and 5-year LF, DM, and overall recurrence rates were 40%/45%, 33%/37%, and 53%/57%, respectively. Initial stage, stage at recurrence, location of recurrence (nodal vs. lung nodule) and KPS were independently prognostic for OS. SUVmax of the recurrence, interval from surgery to recurrence, and use of chemotherapy were not associated by UVA. For non-SBRT patients, use of intensity-modulated RT (IMRT) and dose >60Gy were independently associated with increased OS. There was a trend towards association of higher recurrent stage with risk of LF. Adenocarcinoma was associated with a higher risk of DM. This is the largest reported series of post-resection recurrent NSCLC treated with definitive RT. Both initial and recurrent stages are independently prognostic for survival. Similar to primary NSCLC, performance status is a significant prognostic factor, but use of chemotherapy is not. IMRT and higher RT doses were associated with improved survival, suggesting that optimizing RT is important. The promising survival of this cohort supports a definitive approach to RT in these patients.

Shunpei Okochi

Research Advisor: Chongmin Huan

Identification of PAP2 as a novel endogenous tissue protector in experimental acute pancreatitis

Introduction: Acute pancreatitis (AP) is a state of pancreatic inflammation and injury that can initiate fatal systemic inflammation. The mechanisms that mediate AP progression are not completely understood. The Pancreatitis-Associated Protein family of proteins (PAP1, 2 and 3) are small proteins secreted by acinar cells during AP. Our previous studies showed that blocking the expression of the entire PAP family in rat pancreata results in increased inflammation and tissue necrosis in AP. Interestingly, others have reported that in mouse AP, PAP1 deficiency in fact reduces tissue injury, despite causing increased inflammation. This suggests that the PAP proteins may have different functions in AP despite the similarity in their sequences. To understand the role of PAP2, we studied AP in PAP2^{-/-} mice.

Methods: AP was induced in paired PAP2^{-/-} and wild type mice following established cerulein and L-arginine AP models. Serum was collected for lipase and amylase assays and pancreata were harvested for histological studies of tissue injury and inflammation. Western blot was used to analyze Stat3 activation in pancreatic tissues and NFκB activation in cultured AR42J acinar cells incubated with recombinant PAP proteins.

Results: 1) In contrast to PAP1^{-/-} mice, PAP2^{-/-} mice showed increased pancreatic edema and inflammatory infiltrates and higher serum amylase and lipase levels, demonstrating more tissue injury and inflammation than their WT controls. 2) Levels of pancreatic active Stat3 were unchanged in PAP2^{-/-} mice, unlike attenuated Stat3 activation observed in PAP1^{-/-} mice. 3) Exogenous PAP2, but not PAP1, activated NFκB in cultured AR42J cells. Since NFκB in acinar cells inhibits tissue necrosis in AP, this finding supports a protective role of PAP2 in AP.

Conclusion: In this premiere study of PAP2^{-/-} mice, we demonstrate a tissue protective function of PAP2 in AP, distinct from that of PAP1. This study suggests the potential role of PAP2 in AP treatment.

Micah Meltzer

Research Advisor: Robert Schulze

Psychosomatic Effects of Stretching in the Wilderness Setting

Introduction: Much research has been done on the effects of static and/or dynamic stretching on muscle strength and flexibility. Others have looked at the psychosomatic effects (i.e. fatigue, soreness) in various populations. It is less clear what the psychosomatic effects of stretching may have after endurance exercise activities, such as hiking. Objective: To assess the psychosomatic effects of stretching on endurance exercise in the context of hiking.

Methods: 21 medical students were given a questionnaire immediately before and after a 4-mile moderately difficult hike. Questions asked about prior hiking experience, general level of fitness, and relative levels of perceived fatigue and soreness. 10 individuals were assigned to the non-stretch control group and 11 individuals were allowed to participate in an approximately 10 minute stretching session. Analysis of p-values was done using the two-sample t-test.

Results: There was a 67% higher level of perceived soreness ($p=0.02$) immediately finishing the hike in the control group as compared to the subject group. The average level of perceived fatigue (on a scale of 1 to 5) in the control group increased from 2.7 to 3.7 ($p=0.049$) whereas the level of reported fatigue in the subject group increased to a lesser extent from 2.36 to 3 and this increase was not statistically significant ($p=0.216$).

Conclusions: Perceived soreness immediately following hiking can potentially be lessened by stretching. A larger study examining the different types of stretching (dynamic vs. static) could be useful to further examine the psychosomatic effects of stretching on hiking.

Alexandra Chudner

Research Advisor: Robert Shulze

Greatest Risk for Mortality after Repeat Gun Violence in First Year

Background: Victims of recurrent violent injury are at increased risk for morbidity and mortality. The purpose of this study was to determine if mechanism of initial and recurrent injuries affected mortality in patients with RVI.

Methods: All cases of recurrent violent injury for patients with initial injury during a five-year study period at an urban trauma center were reviewed retrospectively. Kaplan-Meier analysis was performed to determine survival.

Results: There were 314 patients seen for RVI during the study period. Overall 5-year survival was 97%. There were no statistically significant differences in survival by age, gender, race, or injury severity. Survival was significantly lower (86%) for patients who sustained gunshot wounds on both the first and second intentional injury visit ($p<0.001$) equating to a 6-times the risk of death compared to patients with other violent injury mechanisms. Overall survival was not significantly affected by any other combination of mechanisms. For those patients with multiple visits for gunshot wounds, all of the mortalities occurred within eight months of the initial injury.

Conclusion: For patients with recurrent violent injury, those who sustained gunshot wounds on both the initial and recurrent visit have 6-times the mortality compared to patients who sustained other mechanism combinations. Furthermore, these mortalities all occurred within 8-months of the initial injury, suggesting there is a golden period during which intervention may be most effective in reducing mortality from gun violence.

Lidie Lajoie

Research Advisor: Robert Schulze

Mortality from Recurrent Violent Injury in an Urban Trauma Setting

Introduction: Recurrent violent injury is a significant problem in urban communities. Despite this, little contemporary evidence exists regarding the impact of recurrent violent injury on mortality. The purpose of this study was to evaluate the effect of recurrent violent injury on 5-year survival among youths in an urban setting.

Methods: A retrospective cohort study was conducted on all patients ages 15-25 seen at an urban trauma center for initial intentional violent injury from 2004-2009. Patients were followed for incidence of recurrent violent injury through 2012. Chi-squared, Kaplan-meier, and logistic regression were used to analyze effects of recidivism on mortality.

Results: Of the 1300 subjects included in analysis, 183(14%) were recidivists. Recidivists had a significantly higher five-year mortality than non-recidivists (5.7% versus 2.5%, $p=0.029$). This increased risk remained significant at the $P<0.05$ level when included in logistic regression analysis with gender, race, mechanism, and injury severity score (adjusted-OR 8.65, CI 2.8-26.7). Furthermore, among recidivists, 5-year survival declined dramatically with number of admissions for violent injury: 96% after one admission for violent injury, 95% for patients with two violent injury admissions, and 75% after the third violent injury admission.

Conclusion: Recurrent violent injury is an independent predictor of mortality among urban youth, and survival declines significantly with successive admissions for violent injury. Programs that target at-risk youth in an effort to reduce recidivism can play a significant role in decreasing both recurrent violent injury and mortality.

Gregory Grimberg

Research Advisor: Vijaya L. Nacharaju

Maternal-fetal stress: Relationship in obese mothers between cord serum cortisol and offspring birthweight

Background :Obesity is epidemic globally, associated with multiple comorbidities including risk to mother, fetus and growing child, transmitted between generations. Food insecurity, a common stressor in our neighborhood, is related to obesity and comorbidities. Serum cortisol (s-cort) is a biomarker of psychosocial stress. It is elevated in normal pregnancy and hyper responsive in obesity. We have recently reported an inverse relationship between maternal body mass index (BMI) and placental 11β -Hydroxysteroid dehydrogenase type 2 (11β - HSD2 normally inactivates cortisol to cortisone, limiting fetal exposure to maternal cortisol) activity. Here we study relationships between umbilical cord s-cort, birthweight and pre-gravid maternal body mass index (BMI) in a convenience sample of 42 obese (BMI: 34.5 ± 5.9 SD),pre-dominantly Caribbean black women, aged 17-45 delivering 22 female and 20 male neonates with birthweights ranging 1710 – 4625 g (mean 3110 ± 550 g).

Methods :Self-reported pre-gravid BMI, measured BMI, cord serum cortisol (ELISA), offspring birthweight, chart review.

Results :Cord s-cort was significantly related to birthweight ($r=0.65$; $p<0.0001$), particularly in offspring with severely obese mothers ($BMI\geq 35$; $r=0.82$; $p<0.0001$). There was no relationship between maternal BMI and cord s-cort ($r=0.02$).

Conclusions :This is the first report relating cord-blood cortisol to offspring birthweight in obese mothers, implying abnormalities in fetal-placental steroid metabolism in obesity potentially contributing to developmental origins of adult disease.

Daniel Fein

Research Advisor: Olcay Batuman

Profile of multiple myeloma in the inner city: Disease presentation and clinical course.

Multiple myeloma (MM) is the most common hematologic neoplasm in blacks in the US. Based on SEER data the disease is more common in men, has a median diagnosis age of 70 and median survival of 6 years. The subclinical syndrome MGUS precedes MM, and blacks have a higher risk of developing MGUS and MM. To gain new insight into pathogenesis and care we characterized the largely Caribbean-African MM patients at Downstate, in terms of presentation and course of MM. Patients were identified by tumor registries based on histopathology. Data including survival were collected from patient records of 2001-2011 (n=242).

Results: Median age was 64 (range 35-91), male:female ratio was 0.70. The most common presenting pathology was multiple skeletal lesions with fractures (67% of patients). Spinal cord compression and spinal compression fractures occurred in 33% and 32% of patients respectively. Renal disease was present in 26% indicated by serum creatinine >2 mg/dL. Consistent with advanced stage and renal failure, median serum beta-2 microglobulin was 4.25 (range 0.96-82.8). Chromosome banding and FISH was available on 133 patients and showed no cytogenetic abnormalities in 53%; hyperdiploidy (30.4%). Common trisomies included chr 1,5,15 and 19. Other abnormalities included del13p (n=17), t chr14 (n=15), del17p. Comorbidities include hypertension (65%), diabetes (35%) and high BMI (26.7%). As of October 1, 2012 36% of all patients are living. Survival analyses are underway.

Conclusions: MM presents at an advanced stage affecting younger female AA's in the Downstate community. Studying patients for cytogenetic and cell markers that could identify progression in early disease stages may enhance survival.

Logan Jardine

Research Advisors: Makini Chisolm-Straker and Peter Shearer

Experience Matters: What Happens When Transgender Patients Seek Emergency Care?

Background: Transgender people face discrimination in their daily lives. Fear of discrimination may act as a barrier for this population in seeking emergency medical care. This study aims to identify if transgender (TG) people avoid seeking emergency medical care. The study also aims to illuminate the experiences of TG people in the emergency department (ED) so that TG positive policies and resident education programs may be developed. There have been no studies of the experience of TG individuals in the ED.

Methods: An online survey was used to assess the experiences of TG people in EDs. This observational study collects both quantitative data and qualitative narratives of past ED visits. The survey was advertised at an LGBT primary care center in New York City and on Facebook. The target population is self-identified transgender individuals 18 years and older. The study began on June 1st, 2012 and is ongoing.

Results: 103 surveys have been completed. 75% of respondents wanted to use an ED. 90% of those who wanted to use an ED did. 21% of respondents had positive experiences related to their gender in the ED; 29% had negative experiences; and 14% had mixed experiences. The remaining 46% only reported their chief complaint. 56% of respondents recommended that providers ask about and use their chosen pronouns and name. 42% recommended that providers only discuss TG status when it is relevant to their chief complaint.

Conclusion: Only a small percentage of TG respondents avoided using the ED, but 29% of those who did use the ED had negative experiences. Our study reflects a biased sample population: 84% graduated from college, and the majority were well connected to primary care. Further research is necessary to sample the experiences of TG populations not as well connected to primary care. TG-affirming policies and residency education programs should be developed to improve the experience of TG people in the ED.

Yousra Yusuf

Research Advisor: Nadia Islam

Gender Differences in Self-Efficacy and Behavior Outcomes among Diabetic Bangladeshis in NYC

Background: South-Asians have the highest prevalence of diabetes compared to other Asian subgroups. Self-efficacy plays a role in diabetes management, yet few studies have examined this concept among South-Asian diabetics, particularly among Bangladeshis.

Objective: To examine gender differences in health-related self-efficacy and diabetes outcomes among Bangladeshi individuals participating in a diabetes management community health worker (CHW) intervention.

Methods: Eligible diabetic Bangladeshis were randomized into treatment (n=47) and control (n=37) groups. Treatment group participants received monthly group educational seminars and one-on-one visits from a CHW, while control group participants received an introductory seminar only. Surveys were collected at baseline, midpoint, and endpoint (6-months). Quantitative analyses using paired sample t-tests were performed to reveal trends in self-efficacy overall, by gender, and by study group. Changes in clinical outcomes, including HbA1c and weight were also examined. Additionally, field notes collected by CHWs were examined to help understand and explain observed trends.

Results: A significant increase in overall self-efficacy among the intervention group was seen ($p < 0.10$) while there was no significant change in the control group. Furthermore, results stratified by gender showed improvement in self-efficacy among females in the treatment group ($p < 0.05$); females felt more comfortable going to the doctor alone at endpoint compared to baseline. No significant changes in self-efficacy were seen among males in either group, or among females in the control group. Moreover, females in the intervention group demonstrated a significant decrease in weight at 6-months ($p < 0.10$).

Discussion: Results provide insight on the role of self-efficacy in diabetes management for Bangladeshis, especially among women. Further research is needed to help understand and address cultural and social norms to improve health care access.

Ali Mir Ahmed

Research Advisor: Frank Gress

A Prospective Single Center Comparison of EUS-guided Core Biopsy and EUS-guided Fine Needle Aspiration for Suspected Upper GI Lesions

EUS-guided fine needle aspiration (FNA) is employed for tissue acquisition with a diagnostic accuracy of 60-90% and a false positive rate of 5%-7%. FNA is limited by the inability to aspirate quality cellular elements and optimized by on-site cytopathology which is neither available, nor feasible for all practitioners. The EUS histology needle (FNB) was recently developed to procure core specimens for tissue architecture. FNB has demonstrated a diagnostic accuracy of 89-93%. However, none of the studies compared samples obtained by FNA and FNB in the same patient. This study prospectively compares sample adequacy, technical yield and diagnostic accuracy of EUS-FNA and FNB.

Patients were referred for EUS evaluation of suspicious GI lesions. Pathology was then reviewed at our institution without the aid of an on-site cytopathologist. A final diagnosis of malignancy was based upon surgical pathology, positive FNA, or by clinical evidence of malignancy.

75 patients (61% female, 77% black), median age 65 underwent 79 upper EUS procedures identifying 83 lesions. The average lesion was 3cm predominantly in the pancreas (65%) and stomach (17%). The most common diagnoses were pancreatic cancer (49%) and GIST (10%). The average EUS FNA needle passes was 3.7 as compared to 1.7 for FNB. Sample adequacy was comparable in both groups with FNA 76% and FNB 71% as was technical failure rates (FNA 0%, FNB 2%). The Kappa value for FNA and FNB results was 0.45 demonstrating moderate agreement. Diagnostic accuracy was greater in the FNA patients (78%) than FNB (57%). Overall outcome measures of both needles were similar in sensitivity (FNA 75%, FNB 68%) and specificity (100%, both).

This represents the first direct comparison of EUS FNA and FNB sampling obtained in the same subject. The study demonstrates moderate agreement of FNA and FNB for sample adequacy, diagnostic accuracy and outcome measures consistent with the published literature.

Robin Brehm

Research Advisor: Philippe Amstislavski

Pharmacy deserts? Using GIS (geographic information systems) to map potential disparities in US pharmacy access

Introduction: “Deprivation amplification,” the pejorative effect of environmental disparities on individual level disparities, is associated with poor access to health-care and food. Pharmacy access may be subject to analogous forces. Small population-level studies suggest a scarcity of pharmacies in rural and poor areas, but no large-scale spatial analysis project has been completed. We use GIS to investigate continental US pharmacy access by road.

Methods: Geospatial techniques, including geographic information systems (GIS), permit us to assess distance as experienced by pharmacy customers, quantifying it as transportation along roads. County level data was obtained from Census 2010 and the North American Roads network (ESRI), and was mapped with ArcMap10.1. Pharmacy locations were mapped using the Business Analyst 2011 geodatabase. Population weighted centroids (PWC) were calculated based upon census tract population to provide an average location of county inhabitants and mapped to the road network for 3089 counties. Pharmacies within 1 mile by road of the PWC, “walking distance,” were counted as accessible for counties with lowest car ownership (>2 standard deviations below mean). For all other counties, accessible pharmacies were within 10 miles by road of the PWC, or “driving distance.”

Results: Maps of accessible pharmacies were produced. Number of pharmacies accessible to the PWC ranged from 0 in many rural counties, to 721 in Manhattan, NY. 457 counties had no accessible pharmacy.

Conclusions: Counties without accessible pharmacies are potential “pharmacy deserts.” Many counties without pharmacy access are adjacent, suggesting spatial clustering, potentially leading to additional increases in travel distances.

Alexander Davies and Caitlin Date

Research Advisor: Christopher Lange

An Analysis of Cancer Stem Cells in a Hybrid Spheroid System

Cancer stem cells are an important target for future oncological therapies, unfortunately many of the current and recent research efforts revolve around studying cancer stem cells *in vitro* in systems that don't well mimic the natural stem cell niche that exists in tumors. Our goal was to create a system that efficiently and effectively replicates that niche while allowing us to continually monitor tumor growth. Our resulting round bottom plate hybrid spheroid assay is significantly more streamlined than previous spheroid attempts and easier to monitor than *in vivo* tumor assays, allowing for a greater volume of data collection as well as more consistent results from experiment to experiment. We first showed that pure fibroblast (non-tumor) spheroids decayed at a predictable and reproducible rate down to a consistent fraction of the original size. We then showed that the proportion of stem cells in a tumor population could be derived by observing the number of spheroids that failed to decay as predicted. We used our assay to measure the proportion of cervical tumor cells exhibiting the properties of cancer stem cells yielding 0.265%, congruous with previously published data. This assay will be invaluable not only in future *in vitro* cancer stem cell experiments, but also as a modality to help deliver individualized chemotherapeutic and radiologic care based on the characteristics of each patients unique tumor milieu.

Anthony Collado

Research Advisor: Girardin Jean-Louis

Lipid-Related Cardiovascular Disease Markers and Sleep Apnea

Investigations based on controlled samples revealed mixed results regarding associations between dyslipidemia and sleep disturbances. This study explored the relationship between lipid markers, which are predictors of cardiovascular disease, and sleep disorders in a nationally representative US adult population. Analysis was based on the 2007-2008 National Health and Nutrition Examination Survey. Physical examinations and laboratory tests were performed in mobile medical facilities to collect medical and physiological data. Insomnia was defined either as a reported diagnosis or by any of the 3 common symptoms: trouble falling asleep, waking up during the night or early in the morning. Sleep Apnea was defined either as a reported diagnosis or by any of the 3 common symptoms: snoring, breathing cessation, or excessive daytime sleepiness. Short (<6 hours) and long (>8 hours) sleep were also assessed. Cardiovascular disease risk prediction was determined by total cholesterol (≥ 200 mg/dL) and high-density lipoprotein cholesterol (<40 mg/dL). 6,546 respondents (mean=45.8 years; female=51%) answered questions about sleep disturbances. The prevalence of self-reported diagnosed sleep apnea and insomnia was 2.76% and 1.05% and of short and long sleep 10.28% and 5.28%. Prevalence of symptoms of insomnia and sleep apnea was 33.23% and 23.15%. Multivariate-adjusted logistic regression analysis showed total cholesterol (OR=1.18, 95% CI: 1.01-1.37) and HDL-C (OR=1.26, 95% CI: 1.05-1.51) were the most important lipid related markers associated with sleep apnea symptom. Our analysis of epidemiologic sleep and lipid data suggest individuals reporting proxy symptoms of sleep apnea have a higher risk for lipid related cardiovascular disease markers.

David Solomon

Research Advisor: Lidie Lajoie

Predictors of Recurrent Violent Injury

Background: A significant number of patients who present after intentional violent injury will endure multiple traumas resulting from violence, resulting in potentially avoidable utilization of healthcare and municipal resources. This study aims to identify those most at risk for recurrent violent injury (RVI).

Methods: A retrospective cohort study was conducted of all victims of initial intentional violent injury presenting to an urban trauma center from 2004-2009. Patients were followed for incidence of RVI through 2012.

Results: During our 5-years study period, a total of 2748 patients survived initial violent injury and were included in analysis. Of these, 314 (11%) returned with RVI. Five characteristics were found which together predicted a 10-fold increased risk for RVI in logistic regression analysis: age < 25 years (adjusted OR 1.8, CI 1.4-2.3), having medical insurance (adjusted OR 2.4, CI 1.8-3.1), residence in a >85% black neighborhood (adjusted OR 1.7, CI 1.1-2.6), mechanism of physical assault (adjusted OR 1.5, CI 1.2-2.1), and discharge home from emergency department (adjusted OR 2.3, CI 1.8-3.0). All five predictors were significant at the $p < 0.01$ level. Gender, race, and injury severity score were not statistically significant predictors in our analysis.

Conclusion: Five criteria of patients who present with initial violent injury can be used to predict those who are most likely to return with RVI: age, insurance, neighborhood, mechanism, and disposition. We hope that using these criteria for enrollment in our community-based violence prevention program will direct resources toward patients most likely to benefit from intervention.

Polina Advolodkina

Research Advisors: Robert DiRaimo, Mark Song and Samuel Marquez

A Survey of Vein Anatomy in the Brachium and Antebrachium of 24 Cadavers

Background: Current National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) guidelines support the placement of arteriovenous fistulas (AVF) in hemodialysis patients over the placement of grafts. However, long-term outcomes of AV fistulas are variable and access site failure continues to be a major problem in hemodialysis patients. Preoperative sonographic mapping may help to prolong the success of native AV fistulas.

Materials and Methods: This study looked at the venous architecture in the upper limbs of 48 cadavers. The cadavers were anatomical specimens used for medical students at SUNY Downstate. Following dissection of subcutaneous skin and fat, we compared vessel diameters in the cephalic and basilic veins of cadavers with normal versus variant venous anatomy, and in male versus female cadavers.

Results: Our study group consisted of 22 male and 20 female cadaver limbs. Of these, 55% showed normal anatomy. The duplicate cephalic system was the most frequently encountered variant. More males than females showed variant anatomy. Females exhibited statistically significantly smaller veins than males. Likewise, we found that anatomical variants exhibited smaller vein diameters than those cadavers that had normal anatomy. This relationship was stronger in the basilic than in the cephalic vein.

Conclusions: In our study, we found statistically significant differences in vein diameters in male versus female cephalic and basilic veins. This is an important consideration for the surgical planning of native AVFs as it may explain the greater failure rates observed in female hemodialysis patients. Our finding that anatomical variants were more likely to have smaller vein diameters emphasizes the importance of preoperative venous mapping prior to the construction of an AVF. This finding may also prompt further clinical studies to investigate whether patients with anatomical variations have inferior outcomes in AVF construction.

Anupriya Gogne

Research Advisor: Roger P Worthington

Cultural aspects of primary care in India: A case based analysis

Delivering quality primary care to large populations is always challenging, and that is certainly the case in India. While the sheer magnitude of patients can create difficulties, not all challenges are about logistics. Sometimes patient health-seeking behavior leads to delays in obtaining medical help for reasons that have more to do with culture, social practice and religious belief. When primary care is accessed via busy state-run outpatient departments there is often little time for the physician to investigate causes behind a patient's condition, and these factors can adversely affect patient outcomes. We consider the case of a woman with somatic symptoms seemingly triggered by psychological stresses associated with social norms and familial cultural expectations. These expectations conflict with her personal and professional aspirations, and although she eventually receives psychiatric help, initially, psycho-social factors underlying her condition posed a hurdle in terms of accessing appropriate medical care. While for many people culture, belief and social norms exert a stabilizing, positive influence, in situations where someone's personal expectations differ significantly from accepted social norms, individual autonomy can be directly challenged, and in which case, something has to give. The result of such challenges can negatively impact on health and well-being, and for patients with immature defense mechanisms for dealing with inner conflict, such an experience can be damaging and ensuing somatic disturbances are often difficult to treat. Patients with culture-bound symptoms are not uncommon within primary care in India or in other Asian countries and communities. We argue that such cases need to be properly understood if satisfactory patient outcomes are to be achieved. While some causes are structural, having to do with how healthcare is accessed and delivered, others are about cultural values, social practices and beliefs.

Sean Galligan

Research Advisor: Louis Saliccioli

Comparison of Passive Leg Raising and Hyperemia on Macrovascular and Microvascular Responses

Introduction: Passive leg raising is a simple diagnostic maneuver that has been proposed as a measure of arterial vasodilator reserve and possibly endothelial function. While passive leg raising has previously been shown to lower blood pressure, increase flow velocity and cause brachial artery dilation, its effects on microvascular flow has not been well studied. Also, passive leg raising has been directly compared previously to upper arm but never to lower arm occlusion of blood flow induced hyperemia responses.

Method: We compared changes in macrovascular indices measured by brachial artery ultrasound and microvascular perfusion measured by Laser Doppler Flowmetry induced by passive leg raising to those provoked by upper arm and lower arm induced hyperemia in 37 young healthy subjects.

Results: Upper arm induced hyperemia increased mean flow velocity by 398%, induced brachial artery dilatation by 16.3%, and increased microvascular perfusion by 246% ($p < .05$ for all). Lower arm induced hyperemia increased flow velocity by 227%, induced brachial artery dilatation by 10.8%, and increased microvascular perfusion by 281%. Passive leg raising increased flow velocity by 29% and brachial artery dilatation by 5.6% ($p < .05$ for all), but did not change microvascular perfusion (-5%, $p = ns$).

Conclusion: In conclusion, passive leg raising increases flow velocity orders of magnitude less than does upper arm or lower arm induced hyperemia. Passive leg raising-induced brachial artery dilatation is less robust than either of these hyperemic techniques. Finally, although upper arm and lower arm hyperemia elicits macrovascular and microvascular responses, passive leg raising elicits only macrovascular responses.

Atif Afzal

Research Advisor: Jason Lazar

The Relationship of Self Measured Home Blood Pressure Variability With Arterial Stiffness

Purpose of Study: Home blood pressure monitoring (HBPM) by patients using automated devices has grown in clinical and research settings. HBPM is superior to office measurements for testing antihypertensive medications, titration of medical therapy and to enhance adherence to therapy. HBPM variability (Var.) has been found to be related to increased cardiovascular risk, however the reason for this is unknown. Accordingly, the objective of this study was to study a potential relation between HBPM Var. with arterial stiffness.

Methods: We retrospectively studied 74 hypertensive patients (age 63.9 ± 13.8) who were evaluated for management of hypertension at an academic cardiology practice. Most were African American. All had >10 BPs recorded over a period of 2 to 52 weeks while stable. The accuracy of the automated devices was determined by comparison with the office sphygmomanometer. The HBPM Var. was obtained by calculating the standard deviation of systolic BP of all the blood pressure measurements for each patient. Arterial stiffness was evaluated by measuring pulse wave velocity (PWV) and augmentation index (AI) by applanation tonometry using sphygmocor apparatus (AtCor Medical). Univariate associations between study variables were analyzed using Spearman's correlation coefficients. Multivariate linear regression analysis was performed with HBPM Var. as the dependent variable.

Results: HBPM Var. correlated directly with age ($r=0.35$, $p<0.001$). There was a trend towards higher HPBM Var. with higher PWV ($r= 0.19$, $p= 0.11$). There was no correlation of HBPM Var. with the AI ($r= 0.045$, $p= 0.69$). On multivariate regression analysis, PWV was found to be an independent predictor of higher HBPM Var. when age and the Framingham risk score were included in the enter model ($B=1.173$, $p=0.017$).

Conclusion: Higher HBPM variability is related to greater arterial stiffness. This association might explain the prognostic value of HBPM variability.

Edirin Obasare

Research Advisors: Jason Lazar and Louis Saliccioli

Determinants of Post-Ischemic Reactive Hyperemia Tissue Oxygen Saturation in Normal Subjects

Purpose of Study: Large artery endothelial function is evaluated by changes in brachial artery dimension post hyperemia whereas microcirculatory function is less commonly assessed. Tissue oxygen saturation (StO₂) is derived from near-infrared spectroscopy (NIRS). StO₂ is a measure of tissue perfusion and changes in StO₂ represent oxygen delivery in regional tissue where capillary, arteriolar and venular beds are located. Oxygen delivery and possibly microcirculatory function may be evaluated by StO₂ changes post hyperemia. The clinical determinants of StO₂ changes post hyperemia are not known.

Methods Used: We evaluated the determinants of StO₂ changes in 73 normal subjects (40 males; age 30±7) after the provocative maneuver of upper arm occlusion to induce ischemia followed by release of occlusion to induce hyperemia. StO₂ was measured in the thenar eminence of the hand using the Inspectra Oxygenation NIRS Monitor. StO₂ parameters measured at rest and post 5 minute brachial artery occlusion included baseline StO₂, occlusion slope (OS), recovery slope (RS) and hyperemic recovery curve area (HYRA).

Summary of Results: Baseline StO₂ was 85.9 ± 4.7%. There was no significant difference between females and males in body mass index (26±13 vs. 26 ±4, p=ns), mean blood pressure (86±6 vs. 85±7, p=ns), or age (30±7 vs. 30±7, p=ns). There was a significant difference in heart rate between female vs. male subjects (75±11 vs. 68 ± 10, p=0.014). On multivariate analysis the RS was predicted only by HR (B= -0.06; p=0.02, R² = 0.23). The HYRA was predicted by gender (B= 6.6, p=0.009, R² = 0.25) with females having greater HYRA. The RT was predicted by mean blood pressure (B=-4.4, p=0.005, R² = 0.25). There were no independent predictors of the OS.

Conclusions: StO₂ variables post hyperemia may be affected by gender, heart rate and mean blood pressure.

Andrew Persits

Research Advisors: Jason Lazar and Louis Saliccioli

Effects of Ischemic Reperfusion Injury and Remote Conditioning on Passive Leg Raising Induced Brachial Artery Dilation

Passive leg raising (PLR) has been proposed to assess arterial vasodilator reserve and possibly endothelial function. Since endothelial function is sensitive to ischemic-reperfusion (I-R) injury, we determined the effects of I-R injury and ischemic conditioning on PLR induced brachial artery dilation (BAD). We induced PLR-BAD before and after ipsilateral arm I-R injury (7.5min occlusion) in 20 healthy males, age 29 ± 6 years. The protocol was repeated in combination with remote conditioning stimuli (3 x 30s contralateral arm occlusions). PLR resulted in significant BAD (3.85%, p<.001) before but not after prolonged ischemia (0.25%, p=0.38). I-R injury along with either pre or post ischemic conditioning restored the PLR induced BAD response (pre: 3.11%, p<0.001; post: 3.74%, p<0.001). In conclusion, I-R injury blunts the BAD induced by PLR. Remote pre and post-conditioning restore this response. These findings are similar to those previously reported using hyperemia and ultrasound to assess BAD.

Stefan Kenel-Pierre

Research Advisor: Mark Song

Outcomes of Pediatric Vascular Trauma in the Endovascular Era

Objectives: Vascular injuries in the pediatric population have historically been managed with open surgical repair (OR), though the use of endovascular techniques (EV) has become more common. This study is among the first to compare the outcomes of OR and EV modalities in the management of pediatric vascular trauma.

Methods: A retrospective review was performed of all pediatric patients (age < 18 years) treated over a 9-year study period at an urban trauma center for vascular injury. Patients with iatrogenic or isolated intracranial injuries were excluded.

Results: During the study period, 60 patients suffered a total of 80 traumatic vascular injuries. Though most patients were treated with OR (84%), a significant number were managed with EV (16%). Mechanism, age, injury severity score, anatomic region of injury and time to intervention were comparable between groups. Females, however, were more likely to undergo EV than males (56% vs 17%, $p=0.02$). This difference could not be attributed to injury severity. EV modalities used included embolization (77%), stent (15%) or stent-graft (8%) placement. There were no stents placed in patients under 13 years old. After an average follow-up of 6-weeks, analysis revealed no statistically significant differences in amputation rate or mortality between OR and EV, but patients treated with EV were significantly more likely to require reintervention (38% vs 7%, $p=0.01$).

Conclusion: Though the mortality and limb salvage rates between operative and endovascular management of pediatric trauma were comparable, EV treated patients were more likely to require reintervention. EV was also more likely to be chosen as the initial approach in female patients. In properly selected patients, EV modalities can have similar early outcomes to OR in the management of pediatric vascular trauma. Further study is needed to determine any long-term disparity in outcomes.

Penina Dienstag

Research Advisor: Deena Zimmerman

Tay Sachs and the Orthodox Jewish Community: a Model How a Traditional Culture Can Deal With a Terminal Genetic Illness

Introduction: Epidemiological data has often shown a significant discrepancy in the utilization of prenatal screening in traditional and religious communities (Jaber 2000).

Methods: A PubMed search on prolife or traditional patients and prenatal testing excluding articles discussing prolife health practitioners, was performed.

Results: Prenatal testing is widely available in many countries. Testing may reassure anxious parents. In the event testing indicates the fetus is afflicted with an incurable condition testing allows for the parents to decide whether to continue or terminate the pregnancy (Mishori 2008; Jorde 2006).

While parental attitudes towards abortion have been demonstrated to be a major factor in the decision to test, factors such as level of education and interactions with children with disability have also been connected with decision to perform prenatal testing (Santalahti 1998; Li 2008; Gottfreodottir 2009). Reasons women refused testing included opposition to abortion, skepticism as to the usefulness of the test, influence of family members, low education level, willingness to keep a malformed fetus, failure to use providers as a useful source of information, and misunderstanding the purpose of the test (Li 2008; Mushen 2010).

Even in some cultures where termination of pregnancy (TOP) is disapproved of, or is unavailable, some couples still perform prenatal testing (Paolini 2009; Gadow 2006). Even in religious communities, prenatal diagnosis is often not pursued for reasons other than religion (Ahmed 2006). Reasons given to perform prenatal testing in an area with no availability for TOP included decreasing parental fears, allowing for better health care during pregnancy and for the newborn; as well as to improve parental disposition to receive a malformed child (Gadow 2006).

Conclusions: Studies suggest that factors apart from religion contribute to the decreased rates found in many traditional societies (Ahmed 2006; Jaber 2000).

Subash Chandra

Metal detector in CPEP: does it increase safety or violates civil rights?

Objective: This review of literature was done to find if the metal detectors in psychiatric emergency department makes our patients and mental health professionals feel that their civil rights are violated; they are being discriminated or it makes them feel safe and secure.

Method: A systematic literature search was done using MEDLINE (via PubMed), Medscape, Psychiatryonline, and Bureau of labor statistic. The key words were civil rights, psychiatric emergency, violence and metal detector.

Result: Nearly 60 percent of all nonfatal assaults and violent acts in U.S. workplace settings occurred in the health care industry, there were 73 murders in health care settings, including 20 in hospitals from 1997 through 2009. Over the past year, 23 percent of hospitals reported an overall increase in attacks and assaults. The annual rate for nonfatal violent crime for psychiatrists was 68.2 per 1,000. Violence against psychiatric residents ranges from 19% to 64%. There had been serious impact of the hospital violence on mental health professional. Many of them took days off, no longer working in the emergency department, or had left the job. Studies reported that in a 6 month period in a psychiatric emergency service using a metal detector arch and a hand wand, 1,324 knives, 97 cans of mace and 33 handguns were discovered. There was approx. 50% decline in confiscation after the security system was installed. The majority of the persons surveyed felt safe (75%) in the ED and were satisfied with the level of security (68%). Vast majority of patients responded favorably to the metal detector. Overall, 80% of the patients and 85% of the employees said they liked it.

Conclusions: Metal detector is reportedly well accepted by most of the patients and mental health professional, only a few of them feel it is violation of their civil rights. However to most of them it gives a sense of safety, security and peace with a reasonable cost and effort.

Kobkul Chotikanatis

Research Advisor: Stephan Kohlhoff

***Chlamydia pneumoniae* - induced *in vitro* interferon gamma and interleukin 2 Responses of PBMC from asthmatics**

Rationale: Infection with Cpn can lead to exacerbation of asthma but there is also a potential for development of persistent Cpn infection in asthmatics which may contribute to asthma symptoms. Pathogen-specific effector memory T lymphocytes (T_{EM}) are commonly found in patients with persistent viral infections. Identification of Cpn-specific T_{EM} in asthmatics may help diagnose patients with persistent Cpn infection. T_{EM} produce effector cytokines such as IFN- γ while central memory T lymphocytes produce IL-2 but not effector cytokines.

Methods: PBMC from stable allergic asthmatics (n=22) and healthy non-atopic controls (n=11) were either infected with Cpn strain AR-39 at multiplicity of infection of 0.1 or not and cultured up to 10 days. IFN- γ , IL-2 were assayed in supernatants by ELISA. Cytokine levels of uninfected were subtracted from those of infected PBMC in each subject. Direct detection of Cpn from nasopharyngeal swabs by quantitative PCR and serum anti-Cpn IgG antibody by microimmunofluorescence were performed.

Results: The Cpn-induced production of the following cytokines was found: IFN- γ only, IFN- γ and IL-2, IL-2 only in 14%, 27%, 32% of asthmatics, compared to 0%, 0%, 55% of healthy controls, respectively. We found significantly more subjects with IFN- γ production in asthmatics than healthy controls (41% vs 0%; p=0.015). Cpn PCR was not detected in any of the subjects who had cytokine responses.

Conclusion: The finding of Cpn-induced effector cytokine responses in asthmatics without evidence of acute Cpn infection is consistent with the presence of Cpn-specific T_{EM} lymphocytes, which suggests persistent infection.

Christina Maxis

Research Advisor: Erin Stevens

Defining Practice Patterns: What is “Standard” Postoperative Care? A Survey of the SGO Membership

Objective: To determine practice patterns of the SGO membership regarding “standard” postoperative management.

Methods: A survey was sent to SGO members with questions regarding feeding after laparotomy and laparoscopy, and nasogastric tube (NGT) use after bowel resection.

Results: 294 members of SGO completed the survey from 1,345 eligible members with a response rate of 22.4%. There was a statistically significant difference in advancing diet after laparotomy based on extent of surgery ($\chi^2 = 105.806$, $p < 0.001$). Compared to an uncomplicated TAH/BSO, respondents were less likely to advance diet if a lymph node dissection (LND) or if LND/infracolic omentectomy (O) was performed with TAH/BSO ($p < 0.001$). Additionally, respondents were less likely to advance diet in the case of TAH/BSO/LND/O when compared to a TAH/BSO/LND ($p < 0.001$). After laparoscopy respondents were more likely to immediately feed a laparoscopic hysterectomy (LH) alone when compared to a LH/LND ($p < 0.001$). Respondents were more likely to feed higher order diet to LH on POD#0 than TAH/BSO on POD#1 ($p < 0.001$) as well as to LH/LND rather than TAH/BSO/LND ($p < 0.001$). 50.8% of respondents did not keep an NGT in after small bowel (SB) resection, while 71.5% of respondents did not keep an NGT in after a large bowel (LB) resection ($p < 0.001$). Most respondents (41.3% SB, 41.7% LB) await passage of flatus prior to discontinuing the NGT.

There was no statistically significant difference with regards to postoperative feeding or NGT use based on membership category or practice setting. Similarly, there was no difference in management styles when stratifying by years in practice.

Conclusions: Despite randomized controlled trials in gynecology oncology showing the safety of regular diet after laparotomy, most gynecologic oncologists do not give regular diet as the first meal especially with more extensive surgery.

Genevieve von Walstrom

Research Advisor: Erin E. Stevens

Clinical Utility of a Drug Response Assay for Gynecologic Malignancies

Objective: To assess the utility of ChemoFx® in the treatment planning for gynecologic malignancies.

Methods: Patients were identified at 3 institutions from 11/2008-7/2012 with tumor sent to Precision Therapeutics for ChemoFx®. Data included demographics, cancer type, time to result, chemotherapy prescribed and concordance, response to treatment, and outcomes. Descriptive statistics and Kaplan Meier survival plots were used.

Results: 74 specimens were sent and patients treated with at least one cycle of chemotherapy were analyzed ($n=39$). 18 were treated with a responsive regimen (RR), 8 with an intermediate regimen (IR), and 13 with a non-responsive regimen (NR). There was a mean survival benefit in patients treated with RR (39.6 mo) over IR (21.3 mo) or NR (18 mo) ($p=0.03$). Figure 1A. Given 1/3 of patients were treated with NR, we examined the subset of patients treated with first-line carboplatin/paclitaxel (C/T), the standard of care and most often used regimen ($n=23$). No significant difference was found in overall survival based on stage, disease type (ovary or endometrial) or residual disease. There was a trend towards significance ($p=0.068$) of prolonged overall survival when C/T was RR when compared to those when C/T was IR or NR. Figure 1B. ChemoFx® results were available in 33 +10.4 days (range 15-80). 43.6% patients began treatment before available ChemoFx® results, of whom 58.8% were treated with RR; 29.4% were treated with IR, and 11.8% were treated with NR. Of the 22 patients with available results prior to starting treatment, 8 were treated with RR, 3 were treated with IR, 11 were treated with a NR.

Conclusion: A responsive chemotherapy regimen on ChemoFx® is associated with an improved overall survival in patients with a gynecologic malignancy regardless of stage of disease, disease type, or residual disease. Prospective studies to evaluate use of ChemoFx® to determine initial chemotherapy after primary surgery should be investigated.

Camilla Guitarte

Research Advisors: Erin Stevens, Ovadia Abulafia, Yi-Chun Lee

Glassy Cell Carcinoma of the Cervix: a systematic review and meta-analysis

Objective: To report the incidence, clinical features, and survival of patients with glassy cell carcinoma of the cervix (GCCC).

Methods: A retrospective chart review was performed at two academic centers from 1990-2011 and combined with a PubMed database search to retrieve all English published abstracts and papers from 1976-2011 regarding GCCC. Patient demographics, stage, treatment, and follow-up data were obtained. Descriptive statistics and Kaplan-Meier plots for overall survival (OS) were used for analysis.

Results: A total of 39 studies of 279 patients and 13 patients from our chart review were included. The incidence at our institutions was 1.6% of all cervical cancers in the study period, which was comparable to the literature (0.2-9.3%). Overall, the average age at the time of diagnosis was 46.9 years, with the majority of patients in early stage (50.3% Stage I).

The median OS from all combined cases with follow-up data (n=148) is 25.0 months (mo) (95%CI 8.4-41.6). This was not significantly different from the OS of our institutional cohort (p=0.39). There was a significant difference in survival by stage (p<0.01). The median OS for Stage I was not reached. The mean OS for Stage 1 (n=61) was 233.9 mo (95%CI 182.7-285.1). Median OS for Stage 2 (n=54) was 25.0 mo (95%CI 10.7-39.3), for Stage 3 (n=24) was 18.0 mo (95%CI 7.1-28.9) and Stage 4 (n=7) was 3.0 mo (95% CI 1.7-4.3). There appeared to be a survival benefit in early stages when treated with surgery and/or chemotherapy as primary treatment (p<0.01).

Conclusions: GCCC is a rare subgroup with historically poor prognosis and limited response to treatment. This meta-analysis found median OS to be 25 mo with decreased survival in more advanced disease and more favorable results when early stage disease is treated with surgery and/or chemotherapy.

Tanya Menard

Research Advisor: Cathryn Galanter

Strategies for Improved Classification of Pediatric Bipolar Biobank Participants

Objective: As part of a pediatric bipolar (BD) biobank, co-investigators conducted a study to improve diagnostic classification. We supplemented the KSADS, the diagnostic research standard, with clinical narratives to provide more detail. We used the task of standardizing the narrative to examine how co-investigators varied in their interpretation and application of BD diagnostic criteria and differential diagnoses.

Method: We solicited 4 narratives ranging from prototypical to ambiguous BD. Narratives were de-identified, revised, and distributed to the steering committee that rated confidence for mania criteria and typical comorbidities from highly unlikely to highly likely (-6 to 6) using a visual analogue scale. Responses were characterized descriptively, and interclass correlations (ICC) were conducted to estimate the reliability of the raters to a larger sample.

Results: 11 investigators participated. Confidence in a manic episode ranged from high (4.67 + 1.41) for prototypical BD to low (-4.75 + 0.91) for ambiguous BD. ICC demonstrated excellent agreement for ADHD (.88, CI: .70-.99), acceptable agreement for mania (.61, CI: .31-.96) and hypomania (.51, CI: .21-.94) and unacceptable agreement for BD NOS (.03, CI: 0.5-.62). ICC agreement for symptoms ranged from high (increased speech, .60, CI: .30-.96) to modest (elevated mood, .60 CI: .30-.96), to unacceptable (irritability, .37 CI: .11-.90).

Conclusion: Ratings for manic symptom confidence varied depending on case ambiguity. Rater agreement on diagnoses and symptoms also varied. Limitations included small sample size and limited generalizability to non BD researchers.

Asif Karim

Research Advisor: Jeremy D. Coplan

Ablation of Neurogenesis by Temporal Lobe Irradiation produces Affective Distress only in Nonhuman Primates reared under conditions of Early Life Stress

Background: Antidepressant treatments (electroconvulsive shock and fluoxetine) increase dentate gyrus neurogenesis in nonhuman primates. Conversely, irradiation of the temporal lobe ablates neurogenesis and abolishes efficacy of fluoxetine in a nonhuman primate of depression. Following early life stress [maternal variable foraging demand (VFD)], macaque neurogenesis is reduced but not ablated. We examined susceptibility for distressed behavior following temporal lobe irradiation in VFD-reared subjects versus controls.

Methods: Sixteen adult female subjects served as subjects, eight were reared under VFD conditions and eight were normally reared. Following baseline observation for six weeks, four subjects from each group received bilateral temporal lobe irradiation whereas four subjects received a sham condition. Subjects were observed post-irradiation for 10 weeks. Behavioral measures reflective of affective distress were assessed - “Affiliation”, “Anhedonia” and “Detachment”.

Results: Affiliation increased specifically in VFD-reared irradiated subjects versus irradiated healthy subjects and sham-treated VFD and controls [rearing x irradiation interaction; $F(1;10) = 26.80$; $p = 0.0004$]. Anhedonia was increased following irradiation versus sham [$F(1;10) = 9.17$; $p = 0.02$] without rearing effect. Detachment was increased specifically in VFD-reared irradiated subjects but not in irradiated controls or sham-treated VFD or control subjects [rearing x irradiation interaction; $F(1;10) = 84.45$; $p < 0.0001$]. Effects were not attributable to age, weight or baseline differences.

Conclusions: Following early life stress, ablation of suppressed neurogenesis may interact with a vulnerable biological substrate to induce affective distress. Ablating healthy neurogenesis in normally-reared subjects produces limited effects because compensatory mechanisms putatively maintain behavioral homeostasis.

Sasha Rai

Research Advisor: Jason Hershberger

Differences in the implementation of AOT (assisted outpatient treatment) in New York City

Introduction: Assisted Outpatient Treatment (AOT) or Kendra’s Law is a New York state law passed 12 years ago. AOT petitions are filed at vastly different rates by different mental health systems. This project attempts to quantify those differences.

Methods: Data was obtained from the NYC DOHMH regarding the total number of AOT petitions filed from 1999 to 2010 by each mental health system (private hospitals, public hospitals and state hospitals) and that was compared to the total number of inpatient psychiatric beds available at each of these health systems. Furthermore the staff resources were compared between four hospitals representing these health systems.

Results: Public, private and state hospitals represented 23%, 33.3% and 43.6% of the total inpatient psychiatric beds respectively and accounted for 56.3%, 21% and 22.6% of all AOT initial petitions filed from 1999 to 2010 respectively. 97% of all petitions filed were granted AOT. The DOHMH filed mostly renewals of existing AOT petitions. Both Public and State hospitals had legal and staffing costs defrayed by the government unlike the private hospitals.

Conclusion: The authors recommend funding private hospitals systems for the costs of filing AOT petitions to better serve the severely mentally ill cared for in that setting.

Hassan Fathy

Research Advisor: Jeremy D Coplan

Behavioral Neuropeptide and Neuroplastic Correlates of Amygdala Volume : Relationship To Early Life Stress and Serotonin Transporter

Objective: Adoptees with severe early institutional deprivation have large amygdala volumes on MRI in comparison to non-institutionalized controls. We explored the correlation between amygdala volume and biological measures relevant to early life stress (ELS) in nonhuman primates including: the serotonin transporter gene, CSF corticotrophin releasing factor (CRF), hippocampal neurogenesis and diffusion tensor imaging (DTI) of white matter.

Methods: 14 variable foraging demand (VFD)-reared and 9 normally reared monkeys were studied. Unpredictability of foraging conditions prevents VFD mothers from attending to their infants achieving the early-life stress paradigm. Amygdala volume was determined on MRI. Serotonin transporter gene status, CSF CRF concentrations, fractional anisotropy, and hippocampal neurogenesis rates had been previously determined.

Results: Mean amygdala volume was larger in VFD versus control macaques ($p = 0.03$). A gene by environment effect ($p = 0.04$) was noted whereby VFD-reared macaques expressing the short allele of the serotonin transporter gene had larger amygdala volume compared to ELS subjects with the long allele and unstressed controls. Higher CSF CRF concentration associated with larger amygdala volume. Amygdala volume correlated inversely with hippocampal neurogenesis and inversely with anterior limb internal capsule white matter fractional anisotropy.

Conclusion: ELS produced increased amygdala volume but this effect was driven by subjects expressing the short arm of the serotonin transporter gene. Amygdala volume increase was associated with previous markers of early life stress - increased CRF, decreased white matter integrity and suppressed neurogenesis. Amygdala development is sensitive to ELS, is moderated by vulnerability genes and occurs within the context of altered diverse stress-related neurobiological parameters.

Ryan Hashem

Research Advisor: Thomas Brouette

The Caribbean population could represent a variance: the relationship between schizophrenia and cannabis.

Introduction: Cannabis is known to have pro-psychotic effect (1) and its relationship to schizophrenia has been studied with a wide range of results (2). It's effect on positive, negative and cognitive symptoms has been variable and debated extensively of late. This variability could elucidate a further understanding of the neuropsychological bases of the disorder. One of those variables has been reported in the Afro-Caribbean population, which has shown increased rates of schizophrenia diagnosis in those who abuse Cannabis (3).

Aim: The aim of this literature review is to describe this variance and find out if there is a consensus about it. Methodology: We used Pubmed and Elsevier Science direct to search for key words and phrases associated with Cannabis, Schizophrenia and the Afro-Caribbean population (ACP).

Results: Cannabis' effects were different for different domains of symptoms with the most published data pertaining to positive symptoms. There were higher rates of positive symptoms in subjects who used cannabis (4). For the ACP schizophrenia rates were higher in those from West-Indian population who used cannabis (5). Several theories were proposed for the results including migration theory and genetic preloading. However, there was no consensus about the theory. The majority of the studies were from the United Kingdom and no research in the United States has been reported.

Conclusion: It is possible that the higher rates are associated with both genetic predisposition and environmental interaction. More research is needed to discuss the possibility of a genetic variable interacting with Cannabinoid receptors, as the literature is scant in this population.

Aryeh Dienstag

Research Advisor: Dahlia Weitzman

Literature Review of Prenatal Testing in Traditional Communities

Introduction: Epidemiological data has often shown a significant discrepancy in the utilization of prenatal screening in traditional and religious communities (Jaber 2000).

Methods: A pubmed search on prolife or traditional patients and prenatal testing excluding articles discussing prolife health practitioners, was performed.

Results: Prenatal testing is widely available in many countries. Testing may reassure anxious parents. In the event testing indicates the fetus is afflicted with an incurable condition testing allows for the parents to decide whether to continue or terminate the pregnancy (Mishori 2008; Jorde 2006).

While parental attitudes towards abortion have been demonstrated to be a major factor in the decision to test, factors such as level of education and interactions with children with disability have also been connected with decision to preform prenatal testing (Santalahti 1998; Li 2008; Gottfreodottir 2009). Reasons women refused testing included opposition to abortion, skepticism as to the usefulness of the test, influence of family members, low education level, willingness to keep a malformed fetus, failure to use providers as a useful source of information, and misunderstanding the purpose of the test (Li 2008; Mushen 2010).

Even in some cultures where termination of pregnancy (TOP) is disapproved of, or is unavailable, some couples still perform prenatal testing (Paolini 2009; Gadow 2006). Even in religious communities, prenatal diagnosis is often not pursued for reasons other than religion (Ahmed 2006). Reasons given to perform prenatal testing in an area with no availability for TOP included decreasing parental fears, allowing for better health care during pregnancy and for the newborn; as well as to improve parental disposition to receive a malformed child (Gadow 2006).

Conclusions: Studies suggest that factors apart from religion contribute to the decreased rates found in many traditional societies (Ahmed 2006; Jaber 2000).

Ayomide Babarinde and Natalie Louis

Research Advisor: Mary Valmont

The Impact of Patients' Stage of Renal Disease on Levels of Depression and Adherence

Background: Adherence to treatment for Chronic Kidney Disease (CKD) is critical, including several components (e.g. liquid restrictions, drug therapy). End-Stage Renal Disease (ESRD) patients undergoing hemodialysis require an even higher level of adherence. Depressed patients are less likely to adhere to recommended medical treatments in general. A trial of behavioral interventional psychotherapy with depressed ESRD patients showed improved adherence.

Objective: Determine whether ESRD patients are more depressed and less adherent than CKD patients.

Methods: Dr. Cukor and Dr. Saggi collected data on depression and adherence on CKD at SUNY Downstate Medical Center, and on ESRD at Parkside Dialysis Center. Using the Beck Depression Inventory (BDI), and the Immunosuppressive Therapy Adherence Scale (ITAS), researchers compared average BDI and ITAS scores for 20 CKD and 20 ESRD patients using an independent sample Student's t-test.

Results: The mean BDI score was 11.88 ± 9.22 , with 55% of the population below the mean, and 45% above. ESRD patients had a lower mean BDI score, 11.83, than CKD patients, 11.95 (independent samples t-test: $t=0.047$, $df=38$, $p=0.963$). The mean ITAS score was $10.5\% \pm 1.87\%$ with 45% of the population below the mean, and 55% above. ESRD patients had a mean ITAS score of 10.75% and CKD patients had a mean ITAS score of 10.25% (independent samples t-test: $t=-.844$, $df=38$, $p=.404$).

Conclusion: In this sample, ESRD patients record lower BDI scores than CKD patients. The difference in mean BDI scores between the cohorts was not statistically significant. Given the scores are similar, and that behavioral interventional psychotherapy improved adherence in ESRD patients, CKD patients may benefit from similar treatment. Increasing sample size in prospective CKD studies should be done to evaluate adherence and depression levels, particularly if patients may progress to ESRD.

Ayomide Bamgbose and Jia Min Chen

Research Advisor: Mary Valmont

Hand Hygiene Standards among Health Care Workers at SUNY Downstate Medical Center: A Pilot Study

Background: Hand Hygiene compliance among health care workers is the most effective technique against nosocomial infection, those infections patients acquire in hospitals. According to the CDC, in 2002, 1.7 million cases of nosocomial infections were reported in US hospitals. While antibiotics can reduce mortality due to these infections, proper hand hygiene is the best means of prevention. Proper hand washing is most effective with five elements: water, soap, friction, time (15 seconds), and drying. Wearing gloves is not part of proper hand hygiene.

Objective: To compare hand hygiene compliance among health care workers in SUNY Downstate.

Methods: Healthcare workers were surreptitiously observed at two ICUs. Observations were recorded and a survey was administered after to gauge staff knowledge of proper hand hygiene. Staff professions were recorded. Hand-washing technique was recorded as before patient contact, after, or both. Researchers' calculated proportions from the data.

Results: Of 81 individuals observed, only 17% had full hand hygiene compliance, before and after patient contact; 26% complied before patient contact; and 56% complied after patient contact. In addition, 65% wore gloves. Consistent with the findings of other investigators, doctors had hand-hygiene compliance rates lower than nurses and other health care workers. The survey question with the highest error rate was "Which of the following is NOT part of proper hand hygiene?" The correct answer was "gloves", but most participants thought that gloves were part of correct hand hygiene, a practice which promotes bacterial growth.

Conclusion: The data is statistically insignificant because of limitations of time and sample size. Further studies should increase size and explore other methods that health care workers use to ensure patient safety. Further intervention needs to be done to increase proper hand hygiene compliance among healthcare staff.

Erica Barnett and Briana Renois

Research Advisor: Mary Valmont

The Impact of Non-Adherence on Asthma Control: A Retrospective Study among Minorities over the Age of 40 in the Flatbush Area

Background: Asthma is an inflammatory disease of the lungs characterized by episodic airway obstruction and narrowing of the bronchi. This results in wheezing, coughing, and shortness of breath. Approximately 1 in 20 Flatbush residents currently suffer from asthma (prevalence among African-Americans is 11%). However, overall adherence to chronic-disease treatment (e.g., appropriately using asthma inhalers) is between 48% and 78%. The Adherence Estimator New Prescription Survey (AdEst) measures lack of information, emotional and financial factors as barriers to patients taking asthma medication.

Objective: To determine if non-adherence to asthma medication results in uncontrolled asthma symptoms.

Methods: Since May 2010, clinical staff at SUNY Downstate Medical Center's Adult Asthma and Allergy Clinic administered the AdEst and the Asthma Control Test (ACT). Researchers reviewed responses of 45 minority patients over the age of 40. Non-adherence was defined as having a score of 8 or above on the AdEst, and poor control of asthma symptoms was defined as having a score of 19 or under on the ACT. Researchers evaluated the relationship between non-adherence and control of asthma symptoms using cross-sectional analysis.

Results: Twenty-two percent of sampled population were non-adherent to their asthma medication. Sixty-seven percent of patients had poorly controlled asthma. Patients who do not adhere to their asthma medication have 8.67-fold greater odds of having poorly controlled asthma compared to those who do adhere to their asthma medication. (OR=8.67).

Conclusion: It seemed as if patients taking their medications had less control on their asthma, but our findings were not statistically significant. The main limitation of our study is the small sample size. Nonetheless, these findings highlight a major issue: many asthmatic patients do not have immediate control of their illness and symptoms.

Farzana Nasrin and Vahagn Stepanyan

Research Advisor: Mary Valmont

Prevalence of Comorbidities in Patients with Controlled vs. Resistant Hypertension

Background: Sixty-five million people in the US suffer from hypertension (HTN), and people of African descent are most affected. HTN is exhibited in two forms: controlled and uncontrolled HTN. Patients with controlled HTN maintain normal blood pressure by taking fewer than three antihypertensive medications; patients with resistant HTN exhibit high blood pressure despite being treated by more than three antihypertensive medications. About 35.8 million people in the US are uncontrolled hypertensive. They have higher risks for cardiovascular disease and other medical conditions such as hyperlipidemia and diabetes referred to as comorbidities.

Objective: To determine whether patients with resistant HTN suffer from more comorbidities on average, compared to patients with controlled HTN.

Methods: Researchers reviewed charts of 10 resistant and 10 controlled HTN patients at SUNY Downstate Medical Center Department of Cardiology, noting drugs used and comorbid conditions. All patients in the study were black, mostly non-Hispanic, 70% were women, and 80% were over age 55. Resistant HTN patients were age- and gender-matched with controlled HTN patients. Independent Samples Student's t-test was used to determine which group had more comorbidities.

Results: Average number of comorbidities in the controlled HTN group was significantly higher than in the resistant HTN group, 4 and 2.1, respectively (t-test: $t=2.069$, $df=18$, $p=0.015$) although controlled HTN patients were using significantly less HTN drugs (t-test: $t=3.0969$, $df=18$, $p=0.001$).

Conclusion: Results of this study differ from most clinical findings in patients with HTN. Increasing the study population may support the hypothesis with statistical significance. Overall, SUNY DMC's population is at high risk for HTN, and early screening may slow the development of comorbidities and progression to resistant HTN. Future research should study whether adherence to HTN medication decreases resistant HTN in high-risk groups.

Nasrat Nezia and Asia Wynn

Research Advisor: Mary Valmont

Relationship between engagement in risky behaviors and adherence to primary care visits among HIV+ women

Background: Effective HIV treatment requires regular visits (three or four per year) to a primary care provider. Engagement in risky behaviors such as heavy alcohol use or drug use, may compromise compliance to visits. In addition, if HIV is poorly managed, other health problems may arise. Thus, adherence to scheduled care visits is a key to effective HIV care.

Objective: Assess whether risky behaviors was associated with missed scheduled primary care visits among African American HIV+ women. Participants who engaged in at least one of three risk behaviors were expected to have missed scheduled visits.

Methods: Eligible respondents received primary care at the STAR Health Center at SUNY Downstate Medical Center, and participated in the Women's Interagency HIV Study. Responses to the WIHS interview about alcohol consumption, illicit drug use, and number of sexual partners were collected from 47 participants. Researchers evaluated the relationship between engagement in risk behaviors and number of primary care visits by cross-sectional analysis.

Results: Overall, 48% of the participants consumed alcohol, 28% used illicit drugs, and 0% had 6+ sexual partners. In this sample, women who engaged in risk behaviors showed 1.43- fold greater odds of missing visits in a six-month period (OR=1.43; 95% CI= (.43, 4.75)). Thirty-six percent of participants attended less than two scheduled care visits.

Conclusion: Despite greater odds of missed visits among patients who engaged in risk behaviors, this finding is not statistically significant. Further study using a larger sample size is indicated. Cross-sectional analysis effectively addressed the research question; however, measuring unprotected sex may better demonstrate sexual risk than number of partners. Nonetheless, these findings do matter for they indicate the need to identify and address reasons that limit HIV+ patients from visiting their primary care provider.

Stephen Beasley

Research Advisor: Calpurnia Roberts

A Community-Engaged Approach to Lower Obesity and Diabetes via a Social Marketing Campaign: The Brooklyn Partnership to Drive Down Diabetes (BP3D)

In 2010, the Brooklyn Partnership to Drive Down Diabetes (BP3D), a multi-faceted, public health intervention, was formed to reduce obesity and Type 2 diabetes (T2D) in Central Brooklyn and East New York, Brooklyn, two of the most disenfranchised neighborhoods in New York City (NYC). In 2011, with the support of community members/leaders, local organizations, and researchers, BP3D conducted formative research to create a community-engaged social marketing campaign that would: 1) address the social determinants influencing obesity and T2D in the targeted communities and 2) increase involvement in BP3D. In preparation for the launch, four preliminary advertisements were drafted. Adult residents across the life-course contributed feedback on the concepts/messages, competing factors, and visual quality of the advertisements through either a community survey (n=258) or a formal focus group (n =7). Additional input was provided by 20 of the BP3D Community Coalition members. The final advertisements encouraged healthier eating habits and advocated for better food access. Ads were posted throughout the NYC transit system (e.g. subway cars) as well as Facebook and Twitter on Labor Day in 2011 to correspond with the Brooklyn Labor Day Parade, which has 2+ million attendees annually. Preliminary findings suggest an increased involvement in the diabetes, nutrition, and fitness programs offered by BP3D. Following are the steps taken in successfully implementing the community-engaged social marketing campaign, the evaluation process, the role of our community partners, and the challenges. The community approach taken by BP3D may be informative for other urban settings disproportionately impacted by obesity and T2D.

Constanza Martinez Pinanez

Research Advisor: Ramaswamy Viswanathan

Associations between substance use alcohol use and history of trauma and HIV progression.

Background: CD4 count can be used as a proxy measure to evaluate health status, progression of the illness and adherence to treatment in patients living with HIV/AIDS. Psychosocial and behavioral factors can affect adherence to antiretroviral medications and progression of the illness.

Methods: This is a retrospective chart review study of patients new to the STAR (HIV) Clinic at UHB during the period between 7-1-07 and 6-30-08 (n=167). Data pertinent to social history, substance use and demographics obtained at the beginning of their enrollment and CD4 count during a 2-year period after enrollment were analyzed. The independent variables included were history of emotional or sexual/physical trauma, alcohol use, problematic alcohol use, and substance use. The dependent variables were the difference between the last CD4 count and the first CD4 count. We divided our sample into individuals whose CD4 count increased between the first and last counts and those whose CD4 counts decreased (improving versus worsening CD4 count). We tested relationships between CD4 count progression and substance use, problematic alcohol use and history of trauma using chi-square test, with a significance level of 0.05, and calculating odds ratios (OR). IRB approval was obtained prior to study inception.

Results: History of substance use was significantly associated with worsening of the CD4 count during the period of the study (OR: 3.4, X²: 9.5, df: 1, p< 0.002).

Conclusion: This study suggests that history of substance use is related to worse course in HIV patients as measured by CD4 counts. Further research needs to be done to explore if there is a causal relationship, and if so, if it is due to non-adherence to treatment and/or direct biological effects of substance use.

Martin Pendola

Research Advisor: Subrata Saha

Dental Ceramics Using Microwave Sintering

Introduction: Ceramics are frequently used in dentistry because their good mechanical performance and esthetics. However, conventional ceramics sintering is a process that may take up to 12-14 hours. Microwaves for industrial sintering have been used since the 50's. Their advantages are lower energy consumption, faster processing times and better material quality. Microwave sintering of dental ceramics has been describe, but little evidence is available about the mechanical properties of microwave sintered dental ceramics.

Objective: To compare the mechanical properties of microwave sintered dental ceramics with regular furnace sintered dental ceramics.

Methods: Dental ceramic samples of different types were sintered in a microwave furnace, using an Hybrid Sintering process. The microstructure of the samples were analyzed by reflected light microscopy. Density, hardness and bending strength were measured and compared with data published by manufacturers.

Results: The ceramic sintering times were shorter compared to regular sintering. Microwave sintering produced ceramics with densities similar or higher than the theoretical density reported by the manufacturers for all three different types of ceramics tested.

Hardness was also increased compared to the values reported with regular sintering. However, bending strength measured was similar or lower than reported by manufacturers. Problems in the processing of the samples, such as small irregularities on the surface of the samples, may have affected the results of mechanical testing. We are continuing our study by testing additional samples processed under more optimum sintering conditions.

Conclusions: Use of microwaves for sintering of dental ceramics may provide several advantages such as shorter sintering time, lower energy consumption, improved physical properties.

Microwave sintering of dental ceramics can be used for several types of ceramics, not only zirconia as previously reported.

Gavriel Feuer

Research Advisor: Subrata Saha

Shear Properties of Cancellous Bone from Osteoporotic Sheep Treated with Synthetic Bone Mineral

The aim of this study was to determine whether a calcium phosphate-based synthetic bone mineral (SBM) could increase bone strength by preventing bone loss induced by estrogen deficiency and accelerated by a combination of a low mineral diet plus corticosteroid injections in a large animal (ovine) model.

Twenty-eight sheep were randomly allocated to four different groups: sham-operated, ovariectomy, SBM without fluoride (-F), and SBM with fluoride (+F). Osteoporosis was induced into the four different treatment groups using a combination of ovariectomy (OVX), corticosteroid injections, and a diet low in calcium, vitamin D, and trace minerals (magnesium, zinc, and fluoride). After eight months of treatment the sheep were sacrificed. A shear punch test was performed separately on the midpoint of three distal cancellous bone core samples. A load-deflection curve was generated for each slice, and the peak load and the stiffness of the bone samples were derived from the graph. A statistical analysis was performed using analysis of variance (ANOVA) to compare the means for each treatment group with Tukey adjustment for multiple comparisons.

There was a significant difference in the peak load, shear stress, stiffness, and density of the cancellous bone between the four different groups. Specifically, when the SBM with fluoride was compared to the ovariectomy group there was a significant improvement in peak load ($p < 0.05$), shear stress ($p < 0.05$), stiffness ($p < 0.05$), and density ($p < 0.01$) in the cancellous bone.

These results suggest that although there was no significant difference between the SBM (+F) group and the SBM (-F) group, the SBM (+F) tended to be more effective at preventing loss of cancellous bone strength in osteoporosis. However, more research is needed to see if this is an acceptable treatment for osteoporosis in humans.

David McNeil

Research Advisors: Randall Barbour, David Lee and MR Kim

Examination of Necrotizing Enterocolitis in Preterm Infants Using Diffuse Optical Tomography

Necrotizing enterocolitis (NEC) is a common gastrointestinal medical/ surgical emergency in preterm neonates. Despite advances in identifying factors predisposing infants to NEC, noninvasive diagnosis remains challenging. Since diseased bowel in NEC is ischemic, diffuse optical tomography (DOT) can be used to spatially and functionally quantify the oxygenation state of hemoglobin (Hb) in the affected areas. A DOT imaging device, using a dual sixteen-optode illumination/detection array, emitting at 850nm and 760nm, was used to simultaneously measure the dynamic Hb oxygenation state in the abdomen and cranium as control. DOT measurements of local tissue oxygenation were performed on six infants, two of whom presented with clinically confirmed NEC (Bell stage II). Results showed an elevated 850nm/760nm ratio in the abdomens, but not cranium, of NEC positive infants, implying less oxygenated Hb in these regions. DOT reconstructions provided localization of the ischemic bowel as well as other measures of altered dynamics of the Hb signal. DOT measurements taken on infants with confirmed NEC display quantitative findings consistent with the known pathophysiology of NEC.

Mohamed Sherif

Research Advisor: William W Lytton

Investigating effects of NMDA receptor antagonism on theta and gamma oscillations in the hippocampus using computer and animal models

Background: NMDA receptor (NMDAR) antagonists are used in pharmacological animal models related to schizophrenia. Ketamine is a noncompetitive NMDAR antagonist, while CPP is a competitive antagonist. CPP displaces glutamate from NMDAR, so more glutamate is available within the synapse, and can bind to surrounding AMPA receptors (AMPA). The relation between theta oscillations and the firing of cells is thought to play an important role in memory encoding and retrieval. Using a computer model of the CA1 region, we compared between competitive vs noncompetitive NMDAR antagonism. We also compared the modeled competitive antagonism with data obtained from the CA1 in rats injected with CPP.

Methods: Computer simulations were run in the simulation platform NEURON. Model consisted of 800 pyramidal cells (PYR), 200 basket cell interneurons (BAS), and 200 oriens lacunosum-moleculare interneurons (OLM). Antagonists were placed at different cell types to investigate if there is a preferential site of action for the drug. Experimental recordings were made from tetrode arrays in the CA1 region of 6 rats before and after 5 mg /kg of intraperitoneal CPP.

Results: In experiments, CPP reduced theta and increased gamma power. Modeling both competitive and noncompetitive antagonists replicates these changes when the effect of the antagonists are modeled on OLM cells. The amplitude of the changes were more pronounced with noncompetitive antagonism. Also, in the model, there was a reduction in the coupling between the theta phase and the firing of different cell populations.

Conclusions: This work suggests that NMDA receptors on OLM cells are particularly sensitive to the effects of CPP. It suggests basis for differential effect of competitive vs noncompetitive NMDAR antagonism. It also predicts that NMDAR antagonists affect the timing of maximal firing rate of cells in relation to theta phase.

Jordan Iordanou

Research Advisor: Joe Francis

The Effects of ZIP administration in a non human primate

It has been shown that protein kinase m zeta (PKMzeta) is necessary and sufficient for the maintenance of long term potentiation (LTP), and recently a pseudosubstrate for this enzyme, Zeta Inhibitory Peptide (ZIP), has been shown to erase sensorimotor memories induced after learning on a sensorimotor task in rodents. However to our knowledge PKMzeta inhibition has not yet been studied in non-human primates. In order to transition ZIP from a laboratory research tool to a clinical tool, its effects must first be validated in non-human primates. For this study 1 rhesus macaque were implanted with cortical recording electrodes in primary somatosensory cortex, specifically in areas which showed clear response to tactile stimulation of the digits. Additionally cannulas were implanted to allow for direct infusion into the region of cortex being recorded from. Subsequently the rhesus macaque received repeated tactile stimulation on the forepaw and digits using a force-sensitive thwacker and the cortical responses were recorded. After establishing a baseline response level a 1.0ul infusion of ZIP, scrambled ZIP or vehicle was administered through the cannula; a post injection recording was made approximately 2 hours after infusion. The neural recordings were examined for changes in receptive and stimulus field sizes and strengths, as well as mutual information between neurons. Subsequently the macaque was trained to perform 2 different reach for food reward tasks, and performance on those tasks were measured before and after injection of ZIP or vehicle.

John Choi

Research Advisor: Joe Francis

Optimizing multi-channel microstimulation pulse trains with a model-predictive controller

Next-generation limb prosthetics might provide subjects with feedback about external stimuli, perhaps originating from sensors on an artificial limb, by directly stimulating the CNS. Recently, there has been interest in optimizing stimulus encoding schemes that excite sensory neural populations in a way that produces naturalistic sensations. One strategy is to numerically compute multichannel current waveforms that, according to a mathematical model, reproduce a target neural response as closely as possible. We demonstrate the use of this framework for optimizing extracellular stimulation in the thalamocortical system of the anesthetized rat. To model the effects of our stimulus inputs on the affected region, we implanted electrode arrays in VPL thalamus and the analogous area in primary somatosensory (S1) cortex. As a modeling sequence, we stimulated with a known random pulse sequence for 5 minutes in VPL while recording the local field potentials (LFP) in downstream S1. We then trained a linear dynamical model to this input-output data. Using a model-predictive control (MPC) strategy, we computed the stimulation sequences that mimicked (in a squared-error sense) the responses observed in cortex during natural touch stimuli. These electrical pulse sequences successfully recreated naturalistic temporal features e.g. onset/offset amplitude, RMS response power of the cortical response. Interestingly, they also preserved the natural spatial arrangement of response peaks across different touch locations. For any given touch site, the optimization resulted in sequences that, for the most part, injected current through 2-4 electrode configurations with amplitudes below 24 microamperes per phase. For any given “virtual touch,” the strongest burst of pulses occurred 6-8ms following touch onset. Our work represents a preliminary *in-vivo* demonstration of what could be a way of developing stimulation paradigms that achieve biomimetic “write-in” of sensory information.

Stephanie Ishack

Research Advisor: John Ricci

The Use of Three-Dimensionally Printed β -Tricalcium Phosphate/Hydroxyapatite to Further Understand the Regulation of Adenosine Receptors in Osteoclast Formation and Promotion in Bone Regeneration

Using specialized three-dimensional (3-D) printing technology, combined with fillers and bioactive molecules, we can design and characterize custom fabricated 3-D scaffolds for bone repair. Direct-write (DW) fabrication allows for 3-D creation of off the shelf or custom parts with tailored interconnected porosity that other methods lack. The 3D printed scaffolds made of calcium phosphate ceramics (similar to bone mineral) can be made in complicated designs for a series of off the shelf models that can be tailored with a simple dental drill in the operatory to customize them to specific need, or they can be individually built to fit the defect using CT scan data. When the porous space of the scaffold is temporarily filled with Calcium Sulfate, CS, it will block soft tissue from growing in, but goes away just ahead of the bone ingrowth and CS can include a drug carrier such as dipyridamole that will be released over time to stimulate and directionally conduct (and may induce) bone and related vascular formation across large distances, without necrosis, in an accelerated fashion. Recent studies indicated that blockade of adenosine A1 receptors or stimulation of A2A receptors on osteoclast precursors block osteoclast differentiation and function. More recently, there has been the development of novel translational uses for agents that act, directly or indirectly, at these receptors. For instance, A1 antagonist, an A2A agonist or an agent that increases local adenosine levels by blocking cellular uptake of adenosine (dipyridamole) exponentially stimulates bone regeneration in a murine calvarial bone model. The overall goal is to develop these novel topical agents (dipyridamole) and formulations for the promotion of bone regeneration for use in treatment of poorly healing fractures or bone defects. One way to control depot forms of dipyridamole in an *in vivo* model is to develop a well controlled, biocompatible, customized scaffold design for a drug delivery system.

Meghan Walsh

Research Advisor: Mahmood Hussain

Structure-Function Analysis of Microsomal Triglyceride Transfer Protein (MTP)

Hyperlipidemia occurs due to increased production and/or reduced catabolism of apolipoprotein B (apoB)-containing lipoproteins and contributes to atherosclerosis. Microsomal triglyceride transfer protein (MTP) transfers phospholipids (PL) and triglycerides (TG) to apoB and assists in lipoprotein production. In the absence of MTP, apoB is degraded. The current study investigates how MTP structure relates to its function by characterizing missense mutations seen in MTP orthologs and in hypobetalipoproteinemia (HBL). Previous studies revealed that TG transfer activity in MTP progressively increased in vertebrates over the course of evolution. We hypothesize that an increase in amphiphilicity in helix AH1 contributed to the optimization of triglyceride transfer activity in MTP. To test this, we created human MTP with either the frog or zebrafish helix AH1 via site directed mutagenesis. These mutations decreased TG transfer activity, suggesting that changes in helix AH1 over the course of evolution led to increases in TG transfer activity.

HBL is characterized by low levels of apoB containing lipoproteins and normally associated with mutations in apoB or PCSK9. HBL patients have recently presented with missense mutations in MTP. MTP was mutated to create these missense mutations and characterized *in vitro*. Three missense mutations (D169V, D361Y, and D384A) significantly reduce triglyceride transfer activity of MTP and decrease secretion of apoB. Thus, it is likely that these mutations may contribute to the HBL phenotype, suggesting that HBL subjects should also be screened for MTP mutations. These studies provide novel information about the evolutionary changes that led to increases in TG transfer activity in vertebrates and the importance of various residues in the MTP that are critical for apoB secretion.

Christine Ghobrial

Research Advisor: Ming Zhang and MAQ Siddiqui

The Role of Cardiac Lineage Protein (CLP)-1 in Myocardial Infarction

Cardiac disease is one of the leading causes of deaths worldwide. The underlying cause of mortality is due to altered cardiomyocyte function, leading to heart failure. Though the heart has been classified as a terminally differentiated organ with limited regenerative capacity, stem cells have been shown to serve as potential therapeutic agents. Our laboratory has shown that cardiac lineage protein (CLP)-1, a transcriptional regulator of the positive transcriptional elongation factor, P-TEFb, restores proliferation in skeletal myocytes when challenged with low serum. This suggests a role for CLP1 regulating skeletal myogenesis. We are investigating whether CLP1 plays a role in cardiomyogenesis in myocardial infarction.

Based on observed data, there is a greater amount of cardiac remodeling following a 2 week left anterior descending artery (LAD) occlusion ischemic model in both CLP1 haplodeficient hearts and in wildtype hearts, as demonstrated by trichrome staining. Additionally, within the infarct zone, positive stem cell staining is observed, following ischemic damage, as shown by CD117 detection via immunofluorescent staining.

Konstantin Astafurov

Research Advisor: John Danias

Role of Peripheral Inflammation in Glaucoma Pathology

Glaucoma affects more than 60 million people and is the second most common cause of blindness worldwide. The hallmarks of this disease is progressive optic neuropathy and continuous loss of retinal ganglion cell that eventually leads to loss of vision. One of the most important factors implicated in the development and the progression of glaucoma is increased intraocular pressure.

Complement system is a group proteins that serves as an innate immune system. It opsonizes invading pathogens and aids at clearing up apoptotic cells, pruning synapses during development. Complement dysfunction can induce self-attack against healthy cells and give rise or contribute to certain pathologies.

In glaucoma it was reported that several genes of the complement system are upregulated early in the progression of the disease and their expression is correlated with the increase in intraocular pressure.

We examined the effect of short term raise of hydrostatic pressure on the expression of complement genes in the monkey retina. We have previously reported on the effect of pressure on complement gene expression in retinal cell cultures (retinal ganglion cell and Muller cell) and in the murine retinal explants. We employed a model of organotypic retinal cultures; this allowed examination of the response to the elevation of hydrostatic pressure on the primate retina as a whole.

Organotypic retinal cultures from rhesus monkeys were established immediately after the animal sacrifice and after perfusion with ice cold PBS. Cultures were maintained under constant pressure (0, 15, 30, 45mmHg above atmospheric) for periods of up to 72 hours. Complement gene expression and protein levels (C1q, C3, CFH) were compared between groups.

No significant complement upregulation at either the gene or protein level was detected for any of the genes/proteins studied. It appears the complement upregulation observed in glaucoma is not the effect of short term elevation of intraocular pressure.

Mukta Asnani

Research Advisors: Tatyana Pestova and Christopher Hellen

The mechanism of translation initiation on mRNAs of two insect picorna-like I flaviruses: Ectropis obliqua virus (EoPV) and Perina nuda virus (PnPV)

Most eukaryotic mRNAs are translated following cap-dependent initiation, in which ribosomes are first loaded onto the 5'-end of the mRNA and then scan downstream to the initiation codon. An alternative 5'-end-independent initiation mechanism was first found to be used by picornavirus mRNAs, in which ribosomes are recruited to the mRNA by a large structured element in the 5'UTR termed an IRES (Internal Ribosomal Entry Site) through a non-canonical interaction with the canonical initiation factor eIF4G. Viral IRESs are classified into different groups depending on their secondary structure and their different specific interactions with components of the translation apparatus. IRESs usually require only a subset of canonical initiation factors, but many also need one or more specific cellular IRES-trans acting factors (ITAFs), which are thought to maintain the IRES in an active conformation.

Several viral mRNAs, including those of EoPV and PnPV, contain IRESs that are structurally unrelated to existing IRES classes and that may utilize novel mechanisms for initiation. Today, I will report on progress in characterization of the structure and mechanism of initiation on EoPV and PnPV IRESs. Using SHAPE analysis, we verified the predicted secondary structures of these IRESs, and confirmed their structural similarity. Contrary to previous reports, we found that both IRESs are active only in insect cell extracts, but not in mammalian cell-free translation systems. Further analysis done using cell-free and *in vitro* fully reconstituted initiation systems showed that specific recognition of these IRESs in insect cells is not mediated directly by 40S subunits and most likely involves insect initiation factors. Toe-printing analysis revealed a potential specific interaction between a component of the insect translation apparatus and IRES domain VII.

John Odackal

Research Advisor: Sabina Hrabetova

Extracellular Calcium During and After Hyponatremia

[Ca²⁺] regulation is critical for brain function and prevents pathologies such as headache, seizure, and tetany. In 1995, Chebabo et al. (1995) observed that applying a hyponatremic iso-osmotic cerebral spinal fluid (henceforth called low-NaCl) to rodent brain slices causes extracellular [Ca²⁺] ([Ca²⁺]_e) to rapidly decrease. Applying regular artificial cerebral spinal fluid (ACSF) after low-NaCl treatment causes a rapid increase in [Ca²⁺]_e that overshooting baseline. This study examines the amplitude and timing of these surprising Ca²⁺ changes. We also test whether hyponatremia increases Ca²⁺ binding to the negatively charged sites on extracellular matrix (ECM) that may be occupied by Na⁺.

We measure [Ca²⁺]_e using ion-selective microelectrodes inserted into hippocampal brain slices from 10 adult mice. Low-NaCl solutions were made by replacing 40, 60, or 90 mM NaCl from ACSF with fructose. Slices were exposed to each test solution for 30 min and allowed to recover in regular ACSF for 30 min between test solutions. To test if ECM sequesters Ca²⁺ during hyponatremia, treatments were repeated after cleavage of chondroitin sulphate, a negatively charged constituent of ECM.

First we show that [Ca²⁺]_e changes during low-NaCl are similar to changes during hyponatremia without fructose replacement. Second we show that ECM does not contribute to [Ca²⁺]_e changes during low-NaCl. Finally, we show that time to minimum [Ca²⁺]_e during low-NaCl and time to maximum [Ca²⁺]_e in recovery from low-NaCl are significantly different.

Brain Ca²⁺ homeostasis is significantly disturbed by hyponatremia. Our data suggest that Ca²⁺ rapidly enters cells at the onset of low-NaCl treatment and is extruded from cells when low-NaCl is corrected. Differences in timing suggest distinct mechanisms for [Ca²⁺]_e changes during and in recovery from hyponatremia. If defined, these mechanisms might serve as therapeutic targets to regulate [Ca²⁺] during hyponatremia and other pathologies affecting the brain.

Ang Doma Sherpa

Research Advisor: Sabina Hrabetova

Adrenergic signaling mediates plasticity of astrocytic morphology and alters extracellular diffusion in rat visual cortex.

In the hypothalamus, β_2 -adrenergic signaling mediated alteration in morphology of astrocytic processes enhances release of hormones by adjacent neurons. We hypothesize that such morphological plasticity of astrocytes modulates neuronal communication in other brain regions, such as the visual cortex, by altering diffusion properties of brain extracellular space (ECS). Extracellular diffusion is governed by two macroscopic parameters of ECS structure: tortuosity (λ) and volume fraction (α). Tortuosity is the ECS hindrance and volume fraction is the ECS volume relative to the total tissue volume. We tested this hypothesis by measuring ECS parameters and assessing astrocytic morphology in visual cortex of rat brain slices treated with a β_2 -adrenergic agonist DL-isoproterenol (2 μ M). We quantified λ with Integrative Optical Imaging (IOI), and both λ and α with Real Time Iontophoresis (RTI). We expected λ to increase and α to decrease during DL-isoproterenol treatment. Morphological alteration in astrocytic processes was quantified with electron microscopy. With IOI, λ significantly increased (mixed linear model, $p < 0.05$) from a control value 1.65 ± 0.05 (14) [mean \pm SD (n)] to 1.80 ± 0.09 (14) in DL-isoproterenol. Preliminary data from RTI revealed that λ increased from a control value 1.59 ± 0.02 (3) to 1.62 ± 0.03 (4) and α decreased from 0.22 ± 0.02 (3) to 0.18 ± 0.01 (4). Electron microscopy showed significant increases (t-test, $p < 0.05$) in cytoplasmic area (μ m²) [control: 0.05 ± 0.09 (14), DL-isoproterenol: 0.37 ± 0.54 (15)] and plasma membrane length (μ m) [control: 0.81 ± 0.44 (14), DL-isoproterenol: 2.01 ± 0.85] of astrocytic processes. We conclude that adrenergic signaling alters astrocytic morphology, increases λ , and decreases α . These findings suggest that neurotransmitters experience increased hindrance and attain elevated concentration in reduced ECS volume. Hence morphological plasticity of astrocytes modulates neuronal communication in the visual cortex.

Jordan Last

Research Advisor: Richard Kollmar

Analysis of Vocal-Fold Function in the Rat

Unilateral vocal-fold paralysis is commonly caused by injury to the recurrent laryngeal nerve (RLN), which innervates most intrinsic muscles of the larynx. Loss of muscle tone due to nerve damage leads to a bowing of the vocal fold, lack of glottic closure, dysphonia, dyspnea, and a risk of aspiration. Since current repair techniques are unsatisfactory, the goal of this project was to develop ways of assessing new repair techniques. In order to determine whether or not larynx reinnervation has occurred after an RLN lesion, we would measure the function of the vocal cords in a series of tests. Voice parameters and breathing mechanics are the most relevant tests of vocal-fold integrity from a patient's point of view. We, therefore, decided to use ultrasound microphone recordings and head-out plethysmography in rats to assess these functions. To be able to test pre and post-operational vocalization, we monitored rat ultrasound vocalizations. We found that stroking of the neck region in healthy rats induced 50kHz-60kHz vocalizations. The rats also vocalized around 20 kHz when they became agitated. The sound spectra were analyzed with Sound Analysis Pro software to determine parameters such as entropy (signal-to-noise ratio) and pitch. Head-out plethysmography was used to determine breathing flow rates in awake, restrained rats and to construct flow-volume loops, whose shape indicates the presence of obstructions in the airways. These methods can be used to quantitatively measure the high-level functions of vocal cords in rats, and will be used in the future to assess treatments that may accelerate or enhance RLN regeneration.

Olipriya Das

Research Advisor: Richard Kollmar

Otolin-1 and the Ultrastructure of Vertebrate Ear Stones

Otoliths (“ear stones”) in fishes and the homologous otoconia in higher vertebrates are acellular biominerals and essential for the sense of balance. Dislodged otoconia inside the inner ear cause benign paroxysmal positional vertigo, the most common form of vertigo in humans. An important component of both murine and piscine otoliths is the protein otolin-1. It contains both a collagen and a C1q domain, similar to the atypical collagens VIII and X found in Descemet's membrane of the cornea and in developing cartilage, respectively. We propose a model whereby otolin-1 forms a scaffold or “framework” to which other otolith proteins as well as calcium and carbonate ions bind during otolith morphogenesis. The two domains of otolin-1 are critical for the formation of this scaffold: trimers of C1q domains form its hubs and triple-helices of collagen domains form its spokes. To test this model in the zebrafish, *Danio rerio*, we will pursue the following aims: First, we will visualize the ultrastructure of the otolith scaffold by using rotary shadowing combined with electron microscopy or atomic force microscopy. Second, we will investigate the ability of the isolated C1q and collagen domains and of full-length otolin-1 to form multimers. We have expressed and purified the C1q domain as a recombinant protein in bacteria and raised polyclonal antibodies as a first step towards *in vitro* binding experiments and we are currently trying to show that the C1q domain of Otolin-1 forms higher order multimers, *in vitro*. Third, we are identifying the zebrafish ortholog of the trout cerebellin-like protein. We have catalogued the complete family of more than 60 C1q-domain-containing proteins in the zebrafish by using an exhaustive bioinformatics and molecular-cloning approach. We have also begun to characterize the expression of these proteins in the larval and adult ear by *in situ* hybridization and mass spectrometry. Finally, we will test the ability of zebrafish cerebellin-like to modulate otolin-1 scaffold assembly *in vitro* and *in vivo*. Our studies will help to elucidate the molecular basis of the otoliths' ultrastructure, an important step towards understanding how otoliths are formed and maintained in the healthy and the ailing ear.

Elina Shteyn

Research Advisor: Stacy Blain

Establishing the Role of CDK4 in Pancreatic and Breast Cancer.

Proper regulation of the cell cycle is vital for error-free cell division. The cyclinD-cdk4 complex is responsible for progression of the cell cycle from G1 to S phase. p27Kip1 is a member of the “cdk interacting family” of proteins that transmit extracellular signals to the cell cycle motors: the cyclin-cdk complexes. p27's association with cyclinD-cdk4 can be inhibitory or non-inhibitory and activating. Phosphorylation of a tyrosine residue (Y88) on p27 dictates this differential function. When p27 is phosphorylated, cyclinD-cdk4-p27 complexes are open and active, permitting cdk4 catalytic activity and inactivation of the Rb-dependent G1 checkpoint. When not phosphorylated, cyclinD-cdk4-p27 complexes are inactive, preventing Rb phosphorylation and causing a G1 arrest. Thus, p27 Y phosphorylation functions as a cdk4 on/off “switch”.

Pancreatic ductal adenocarcinoma (PDAC) is the eighth most common cancer and has a low survival rate. It has been suggested that deregulation of cdk4 activity might contribute to the development of PDAC and that inhibition of cdk4 impairs proliferation of some pancreatic cancer cells. Because p27 acts as a cdk4 switch, we hypothesize that increased p27 Y88 phosphorylation is required to increase the activity of cyclinD-cdk4. In support of this, using phospho-specific p27 Y88 antibody, we have detected p27 Y phosphorylation in PDAC tumors, while it is absent in normal or benign tumor regions. Currently, we are testing a panel of pancreatic cell lines from different tumor grades to determine if p27 Y88 phosphorylation correlates with tumor grade and cdk4 dependency. By using a cdk4 specific inhibitor, PD0332991, we are determining the relationship between p27 Y88 phosphorylation and sensitivity to cdk4 inhibition. Our model suggests that cells that are sensitive to cdk4 inhibition (low IC50) will have high cdk4 kinase activity and high p27 phosphorylation. Thus, use of p27 Y88 phosphorylation may serve as a marker for tumors that would respond to cdk4 specific inhibition.

Peiqi Ou

Research Advisor: Chongmin Huan

Identification of Sphingomyelin Synthase 2 as a PKC δ Activator That Mediates B cell Tolerance

B cell tolerance is a self-protective mechanism that prevents the development of B cell-mediated autoimmunity. Protein kinase C δ (PKC δ) has been demonstrated to be required for B cell tolerance through the removal of self-reactive B cells. Nuclear translocation of activated PKC δ induces B cell apoptosis, but the source of diacylglycerol (DAG) that activates PKC δ in B cells is unknown.

Sphingomyelin synthase (SMS) is a lipid enzyme that catalyzes the synthesis of sphingomyelin while generating DAG as a by-product. Neither the physiological targets nor the functional significance of SMS-produced DAG have been determined. However, it has been suggested that DAG derived from SMS might activate PKCs.

Currently, two major SMS isoforms, SMS1 and SMS2, have been identified in mammalian cells. SMS1 is localized in the ER and Golgi membranes while SMS2 is found in the plasma membrane. In this study, we found that the SMS2^{-/-} mice, but not the SMS1^{-/-} mice, had significantly increased peripheral B cells and self-reactive antibodies as well as immune complex type glomerulonephritis, resembling the autoimmune phenotype in PKC δ ^{-/-} mice. More importantly, SMS2^{-/-} B cells had decreased cellular DAG levels and impaired nuclear translocation of PKC δ . The latter could be rescued by the supplement of a DAG analog. In addition, we proved that SMS2 physically interacted with PKC δ , but not with other PKCs in splenic B cells. These results are in line with the current knowledge that PKC δ is activated by DAG in the plasma membrane and strongly suggest that SMS2 regulates B cell tolerance via its interaction with, and its provision of DAG to, PKC δ .

B cell mediated autoimmune diseases remain a major clinical challenge due to the incompletely understood mechanisms of B cell tolerance. Our findings disclose a novel pathogenesis that provides insights for the development of effective therapeutic approaches to these diseases.

Marc LaFonte

Research Advisor: Chongmin Huan

Identification of Reg1 as a Novel Stellate Cell Activator in Regenerating Pancreas

Introduction: Pancreatic stellate cells (PaSCs) are activated in the injured pancreas for their participation in tissue repair. Unchecked PaSC activation, however, leads to disease progression of chronic pancreatitis, pancreatic cancer and cystic fibrosis. Studies of PaSC activators are hampered due to the spontaneous activation of isolated PaSCs and limited *in vivo* systems. We found that PaSCs highly express receptors for Reg1, a mitogenic protein secreted by acinar cells. Others reported increased serum Reg1 in PaSC-involved diseases. To explore the role of Reg1 in PaSC activation, we examined pancreatic regeneration in Reg1^{-/-} mice.

Methods: Exocrine pancreatic regeneration was studied in paired Reg1^{-/-} and Reg1^{+/+} littermates following cerulein-induced pancreatic injury of more than 90% of acini. 3, 7 and 15 days after cerulein administration, pancreata were harvested for weight measurements, biochemical, histological and immunohistochemical studies of tissue injury, inflammatory infiltration and α -SMA-staining for activated PaSC. For PaSC transplantation, activated PaSCs were collected from culture and transplanted under the pancreatic capsule. Collagen production in cultured PaSCs with/without Reg1 incubation was detected by Western blot.

Results: On day 3, Reg1^{+/+} and Reg1^{-/-} mice had comparable pancreas weight, injury and inflammation. On day 7 and 15, Reg1^{-/-} pancreata had more tissue damage and inflammation but significantly lower weights and numbers of activated PaSCs. Transplantation of activated PaSCs restored the weights and reduced tissue injury of the Reg1^{-/-} regenerating pancreas. Reg1 incubation enhanced PaSCs' proliferation and collagen production.

Conclusions: Reg1 is a novel and physiological PaSC activator in regenerating pancreas, suggesting a role of Reg1 in PaSC-associated diseases.

Jeremiah Martino

Research Advisor: William Brunken

Effects of Deletion of Netrin-4 and Laminin beta-2 and gamma-3 Subunits on Corneal Development and Innervation

Purpose: Laminins and netrins are extracellular matrix (ECM) molecules with roles in: basement membrane assembly; cell adhesion, proliferation and migration; and neural guidance. Here we study the role of laminins and netrins in corneal development and its innervation.

Methods: Laminin and netrin expression were studied by immunofluorescence (IF). Corneal organization and innervation were assayed using IF and electron microscopy (EM) in wild-type, Lamb2^{-/-}, Lamc3^{-/-} and Ntn4^{-/-} mice. Innervation was examined and quantified in whole-mounts of P20 corneas.

Results: Netrin-4 IF was present throughout the cornea extending from the limbus to central cornea, including Bowmans membrane, the stroma and Descemet's membrane (DM). Laminin β 2 IF had a similar distribution, whereas γ 3 IF was concentrated in the limbus. Although corneal development was grossly normal in all genotypes, several microscopic alterations were observed. EM revealed keratinization in P15-16 corneas from all three mutant lines. Moreover, the corneal ECM was highly disorganized in the Lamb2^{-/-} mouse; the most important change was an increase in the ratio of the thickness of DM to the endothelium. Cell proliferation was also measured using phospho-histone H3 IF. A 3-fold increase in epithelial proliferation was found in the Ntn4 null animal, with more modest increases observed in the epithelium of the β 2-null animal. We next studied corneal innervation; a developmental series of corneas from each genotype was assayed using the nerve-specific antibody TuJ-1, which targets class III β -tubulin. Results from IF microscopy comparing corneas from P20 wild-type and Lamb2^{-/-}, Lamc3^{-/-} and Ntn4^{-/-} mice demonstrate reorganization of nerve density and patterning in the central cornea and in axon fasciculation in the pericorneal ring.

Conclusions: We show that netrin-4, and the β 2 and γ 3 laminin chains are expressed in corneal ECM. The deletion of these molecules affects not only the proliferation of epithelial cells but also the patterning of innervation. Whether these conditions are linked, or separable, phenotypes is the subject of further investigation.

Hanh Nguyen

Research Advisor: Chris Parks

Identification of novel intracellular neutralization mechanism of HIV-1 2F5 and 4E10 antibodies

Virus-neutralizing antibodies (Abs) are critical component of immune protection against HIV-1 infection. The binding sites for two potent neutralizing monoclonal Abs 2F5 and 4E10 on the HIV-1 Env membrane-proximal external region (MPER) are well characterized; however, the molecular mechanism of neutralization remains unclear. To further investigate the mechanism of neutralization, we used recombinant vesicular stomatitis virus (VSV) in which the 2F5 or 4E10 epitopes functionally replaced sequences in the VSV glycoprotein (G). Because VSV enters cells through endocytosis and subsequent membrane fusion occurs intracellularly in the endosomes, these modified VSV vectors provide an effective model to distinguish between proposed pre-and post-attachment inhibitory mechanisms by HIV-1 MPER Abs. We showed that 2F5 and 4E10 bound to chimeric virus particles but did not prevent attachment to Vero cells. The Abs were able to block infection post-attachment as shown with plaque reduction assays. Most virus-Ab complexes were trapped on cell surface as seen in confocal microscopy, confirming that 2F5 and 4E10 neutralized primarily at a post-attachment step by preventing virus internalization. Interestingly, some Ab-coated viruses entered cells and were trapped inside the endosomes. Presence of Abs was sufficient to prevent fusion in cell-cell fusion assay, suggesting that the 2F5 and 4E10 Abs can neutralize virus through a second intracellular mechanism. Together, these data indicate that binding of virus by 2F5 or 4E10 prior to cell attachment does not prevent cell binding but blocks infection at a post-attachment step. Our study provides a better understanding of the neutralization mechanism of the HIV-1 Abs and is important for HIV-1 vaccine design.

Frank Fabris

Research Advisor: Mohamed Boutjdir

An Assessment of IKr Function in Auto-Immune Associated Long-QT Syndrome: Experimental and Computational Studies

Introduction: The longQT syndrome can be congenital or acquired and is associated with fatal ventricular arrhythmias or even sudden death. A novel autoimmune-associated long QT syndrome has been recently reported in patients with connective tissue diseases (CTD) and is associated with anti-Ro antibodies. QTc (corrected QT) interval prolongation is generally associated with agents that block the Human ether-a-go-go-related gene (HERG) encoding the pore-forming subunits of the rapidly activating delayed K channel conducting (IKr) current. Here, we hypothesize that QTc prolongation is due to inhibition of HERG channel and translates into action potential prolongation and QT interval prolongation on the surface electrocardiogram (ECG).

Methods and Results: HEK293 cells stably expressing HERG channel were used to record IKr via the patch-clamp technique. Anti-Ro antibody positive serum (200 μ l) inhibited both peak and tail of IKr. IKr peak density was inhibited by 39.2% ($P < 0.05$) and IKr tail density by 28.7% ($p < 0.05$). To investigate the consequences of IKr inhibition on the action potential and ECG, a computational model of Human ventricular action potential was used. Simulation of IKr conductance block by serum (39.2%) resulted in the prolongation of action potential and QT interval. Next we simulated conditions of dose dependent inhibition of IKr by anti-Ro antibodies. The results show that APD90 was prolonged by 13.3%, 31.6%, and 56.3%, with an IKr block of 20%, 40%, and 60%, respectively. Similarly, simulations also showed QT interval prolongation with dose-dependent block of IKr.

Conclusions: HERG channel is the target for anti-Ro antibodies from patients with autoimmune diseases. Block of IKr by these antibodies results in action potential and QT interval prolongation. Altogether, the presence of anti-Ro antibodies puts patients with autoimmune disease at risk for developing fatal ventricular arrhythmias and perhaps even sudden cardiac death.

Danielle Joseph

Research Advisor: Stacy Blain

Plasticity Potential of the Multiple Myeloma Cancer Stem Cell

Multiple myeloma (MM) is a hematologic cancer characterized by the clonal proliferation of malignant plasma cells. This disease affects approx. 20,000 people in the US and though treatment includes potent chemotherapeutic agents that can prolong life, this disease is fatal. MM relapse in patients receiving high dose chemotherapy and autologous stem cell transplantation indicates that patients have either become resistant to treatment or there exists a cancer stem cell (CSCs) that can reinitiate tumor growth. CSCs and normal stem cells share commonalities in that they are maintained in a quiescent state. The cell cycle profile (CC) of a quiescent cell can be distinguished by its low DNA and RNA content. These CSCs can be characterized by their distinct cell surface markers to investigate expression patterns of CC factors that regulate CC entry and exit. I hypothesize that MM CSCs can be defined by “stemness” parameters: delayed cell cycle entry, and the ability to generate both clonal pluripotent progeny and that of a more differentiated state. Using MM tumor cell lines, I plan to isolate the putative CSC population based on these parameters.

It has been shown that the RPMI-8226 cell line is heterogeneous. Two distinct populations can be isolated based on the expression of cell surface markers CD38 & CD138. The CD38+/CD138- signature however has been described as the putative MM CSC population. Putative CSCs have been isolated from the RPMI-8226 cell line and are being analyzed for their CC status using DNA and RNA stains (7AAD and PY) as well as a live cell permeable stain VybrantDyeCycleGreen; clonogenicity will be measured by colony formation within methylcellulose and tumor formation in NOD/SCID mice; differentiation will be measured by the acquisition of the CD38+/CD138+ signature from the CD138- population post-culture. This project will provide essential new information about CSCs with specific implications for the prognosis and treatment of MM.

Priyank Patel

Research Advisor: Stacy Blain

BRK (Breast Cancer Related Kinase) Regulates G1-S Phase Progression In Breast Cancer

Breast cancer is the leading cause of cancer-related death in women. Benign breast tumors can be diagnosed easily and if treated, patients have a high survival rate. Inhibiting the proliferation of cancer cells to prevent tumor progression would drastically increase the window of opportunity to treat the patient. G1 is the only ‘responsive’ phase of the cell cycle, during which cells can be manipulated to block proliferation. CyclinD-cdk4 regulates G1 phase progression by phosphorylating the G1-gate keeper pRb and its activation is a frequent event in breast cancer. p27kip1 is required to stabilize the cyclinD-cdk4 complex and it can alternatively activate or inhibit the complex. p27 kip1 is phosphorylated on residues Y88 or Y89. This vacates the ATP binding pocket of cdk4, permitting catalytic activation of cyclinD-cdk4. Using phage-ELISA assay, we identified Brk that functions as a high affinity kinase and is able to phosphorylate p27 kip1 *in vitro* and *in vivo*. In contact arrested cells Y phosphorylation of p27 kip1 decreases and cdk4 is inactive. However, we found that Brk levels in these cells were still high. We did detect expression of catalytically inactive alternative splice variant (ALT-Brk) under these conditions. In other cells, ALT-Brk has been shown to bind competitively to Brk’s substrates. Our hypothesis is that ALT-Brk competitively inhibits the phosphorylation of p27 kip1 by Brk, preventing activation of cdk4 activity, and arresting the cell in G1 phase. Thus, ALT-Brk acts as an endogenous inhibitor of Brk that might be manipulated to prevent proliferation of Brk overexpressing breast cancer cells.

Andrew Chang

Research Advisor: Alan R. Gintzler

Sub-Cellular localization of mu-opioid receptor Gs signaling

Long-term opioid administration for pain management leads to a reduction in its effectiveness to treat pain known as tolerance. Many cellular mechanisms have been proposed to explain tolerance such as opioid receptor desensitization and adenylyl cyclase superactivation.

The Gintzler laboratory has previously shown that morphine tolerance results, in part, from an increased association between the stimulatory G protein alpha subunit (G_s) and the μ -opioid receptor (MOR), which would mitigate traditional inhibitory effects of MOR activation.

In the current study, we investigated the membrane microdomains in which these adaptations were taking place. Caveolae, the structurally distinct, flask-shaped invaginations maintained by caveolin proteins, have been known to be platforms for many signal transduction events. Our model system employed Chinese Hamster Ovary (CHO) cells stably transfected with the rat μ -opioidreceptor (MOR-CHO).

In co-immunoprecipitation studies, acute MOR activation with sufentanil increased the association of G_s and adenylyl cyclase (AC) with caveolin-1 in the Triton insoluble membrane fraction. Furthermore, the lesser-phosphorylated form of G_s, which preferentially associates with MOR, was found to be concentrated in caveolae. This emphasizes the relevance of caveolae to MOR-G_s signaling, which increases during tolerance. The trafficking and activity state of other signaling molecules such protein phosphatase 2A into caveolae following chronic morphine is also currently being investigated.

The ability of acute exposure to sufentanil to increase the association of AC and G_s with caveolin, as well as the translocation of signaling molecules into caveolae following chronic morphine treatment suggests that downstream molecules related to acute and chronic opioid sequelae may be localized in the caveolae microdomain of cell membranes.

Arjun Kumar

Research Advisor: Alan R. Gintzler

Sexual Dimorphism in the Regulation of Spinal Endomorphin-2 Release

There is considerable evidence that males and females differentially utilize mu-opioid receptor (MOR) antinociceptive systems. MOR-selective opioids are more effective as analgesics in male rats than female rats (Barrett et al., 2002; Cicero et al., 1997). Furthermore, K⁺-evoked release of spinal cord endomorphin-2 (EM2), the endogenous substrate for MOR, is significantly greater in male rats than female rats (Gupta, von Gizycki, & Gintzler, 2007). The overall hypothesis of the current study is that regulation of the EM2-MOR system in spinal cord shows sexual dimorphism. Specifically, this report aims to examine the regulation of spinal EM2 release by spinal opioid receptors. In this study, I utilized the content of EM2 in intrathecal perfusate to reflect the activity of spinal EM2. First, I validated the method used both to perfuse the intrathecal space *in vivo*, and to intrathecally administer opioid receptor agonists and antagonists. I also validated a plate-based radioimmunoassay (RIA) to measure EM2 release during these pharmacological manipulations. Preliminary data show that this RIA accurately quantifies EM2 in intrathecal perfusate, and that activation of opioid receptors by exogenous opioids may increase endogenous release of EM2. Moreover, spinal MOR regulation of EM2 release appears to be sexually dimorphic. This project will facilitate a better understanding of sex-specific mechanisms for regulating spinal EM2 release, aiding the development of sex-specific medications for the clinical management of pain.

Jian Zhuang

Research Advisor: Frank Barone

Thrombopoietin protect acute brain ischemia by suppressing inflammation through its receptor

Thrombopoietin (TPO), which is initially known to stimulate platelet production, has also been shown to protect heart and brain from ischemia. The specific mechanism(s) of TPO protection of the brain from ischemia requires further investigation. Ischemic brain injury consists of cell loss, axonal injury and brain infarction. Brain inflammatory responses to ischemia can be involved in and contribute to this injury. Erythropoietin (EPO), a hematopoietic growth factor, structurally similar to TPO, also protects the brain and attenuates inflammation in cerebral ischemia. TPO has been shown to reduce myocardial infarction and apoptosis. We show that TPO protect ischemic brain from histological infarction, neurological and cognitive decline not only in rat but also in mice. When administrated in TPO receptor knock out mice, TPO wouldn't protect ischemic brain. And in immunohistochemical studies that we found TPO attenuate TNF-alpha expression, a biomarker for inflammation, compared with PBS treated acute ischemic brain. It suggests that TPO protect ischemic brain acutely by suppressing inflammation, and that protective effect requires TPO receptor's activation.

Carrie Poon

Research Advisor: Frank Barone

Delayed administration of thrombopoietin in ischemic stroke

Stroke is a major cause of death and can result in long-term sensory, motor, and cognitive deficits. Only 5% of stroke patients are able to meet the 4-hour time window for tissue plasminogen activator (tPA), the only current FDA approved treatment for stroke. Our lab has previously shown that thrombopoietin (TPO), a hematopoietic platelet growth factor, has acute protective effects. When administered up to 4 hours after middle cerebral artery occlusion (MCAO), swelling, inflammatory cytokines and blood brain barrier disruption were all significantly decreased. The rats also performed better behaviorally in sensory-motor coordination tasks. We hypothesize that delayed administration of TPO will improve function and cognitive ability post-stroke. Male sprague-dawley rats underwent 2 hours of MCAO and were survived for a total of 4 weeks to look at the long term effects of TPO. They were given 2 doses of either phosphate buffered saline (PBS) or TPO at 0.1ug/kg, intravenously. The first dose was administered 24 hours after MCAO, which is when the infarct is fully developed, and the next dose was on day 4 after MCAO. Neurological deficits at 4 weeks improved significantly ($p < 0.0001$) with the TPO-treated group versus the PBS-treated group. Using the active place avoidance task, the rats' cognitive abilities were tested. The TPO treated group received significantly ($p < 0.05$) less shocks and were able to learn and avoid where the shock zone was whereas the PBS group could not. TPO effects will be analyzed through immunohistochemistry for neurogenesis, angiogenesis, and (re)myelination to further explore the possible mechanisms for such drastic improvement with delayed intervention.

Karen Ta

Research Advisors: Ivan Hand and Frank Barone

Neurobehavioral Testing in A Neonatal Rat Model of Periventricular Leukomalacia

Background: Periventricular leukomalacia (PVL) is a manifestation of neonatal brain injury in preterm infants associated with cognitive, motor and behavioral deficits. PVL models have been developed in rat pups to assess the effects of neuroprotective interventions on brain histology and immunochemistry although behavioral testing in a rat model of PVL has not been extensively studied.

Objective: This study investigates alterations in sensorimotor function and behavior in a modified Rice-Vannucci model of periventricular leukomalacia.

Design/Methods: Sprague-Dawley rat pups at postnatal day 3, corresponding to a gestational age of 24 -32 weeks in preterm infants, were randomly assigned to injury vs. sham groups. Hypoxic ischemic injury was induced by unilateral carotid artery ligation under isoflurane anesthesia followed by 1 hour of 6% hypoxia after a 1 hour recovery period. Rat pups were maintained until maturity with ongoing assessment of growth, developmental reflexes, sensorimotor function, and learning behavior via active placement avoidance (APA) testing. Pups were sacrificed at 8 weeks and brains perfusion-fixed for assessment of specific brain volumes and immunohistochemistry.

Results: There was no significant difference between sham and PVL model groups for growth rate and specific reflexes such as righting, negative geotaxis, eye opening, startle, and grid walking. The PVL model had significantly less limb placing ($p=0.03$) with back limbs more affected than front at 1 week of age. There was a trend towards decreased learning behavior among the PVL vs. sham rat pups ($p=0.17$) as evidenced by APA testing.

Conclusions: Carotid artery ligation with hypoxia in P3 rat pups creates an effective animal model of PVL to study functional deficits in sensorimotor ability as well as cognitive function. Assessment of spatial navigation and learning memory can be a valuable tool in measuring outcomes of therapeutic interventions to provide neuroprotection.

Yogesh Moradiya

Research Advisor: Steven R. Levine

Thrombolytic Utilization in Ischemic Stroke is Significantly Higher in US Hospitals with Neurology Residency Program

Background: Neurology residency programs may influence the frequency of stroke thrombolysis among teaching hospitals.

Objective: To compare thrombolysis utilization for stroke in hospitals with Neurology residency (NR) to non-teaching (NT) and other teaching hospitals (TH).

Design: Population based cross-sectional cohort study. **Methods:** All US ACGME-accredited NR programs and the affiliated hospitals were screened and cross-matched to the hospitals sampled in Nationwide Inpatient Sample (NIS) for years 2000-2010. Stroke thrombolysis rate was calculated using discharge weights to calculate population estimates. Adjusted analysis was controlled for age, gender, ethnicity, comorbidities, hospital stroke case-volume, geographic region, year and the Joint Commission Primary Stroke Center certification status. Sensitivity analysis was conducted using hospitals coding at least one thrombolytic treatment.

Results: 712,433 ischemic stroke cases from 6,839 hospitals were included, of which 10.1%, 29.1% and 60.8% were treated at NR, TH, and NT respectively. The thrombolytic rate in NR (3.7%; 95% CI, 3.3%-4.2%) was significantly higher compared to that in TH (2.3%; 95% CI, 2.1%-2.5%) and NT (1.4%; 95% CI, 1.3%-1.6%). From 2000 to 2010, the thrombolytic rates increased in NR from 1.0% to 6.3% (trend $p<0.001$) while the increase in thrombolytic rate was slower in TH (0.8% to 4.9%; trend $p<0.001$) and NT (0.8% to 3.8%; trend $p<0.001$). In multivariate analysis, NR was independently predictive of higher thrombolytic rate [adj. OR:1.50; 95% CI:1.43-1.58 (NR vs. TH), adj. OR:1.84; 95% CI 1.75-1.93 (NR vs. NT)].

Conclusions: Stroke care at NR hospitals is associated with an increased thrombolytic utilization rate. Several unmeasured factors such as experience in thrombolytic treatment and 24/7 availability of general/vascular neurologist may explain the differences.

Benjamin B. Lee

Research Advisor: Andre Fenton

Out-of-Context Activation of Memory Prevents Extinction

Rationale: We previously showed that the stress induced by a forced-swim done one day after learning a left/right (L/R) discrimination task can activate a 1-day-old memory, and that this memory seemed to be strengthened when tested on the third day. We investigated whether stress could activate, and strengthen, memories in an unrestricted environment.

Methods: Rats were trained on an active place avoidance (APA) task upon which a rotating arena had a 60° arc shock zone that was oriented with respect to distal cues located on the walls of the room. On the first day, rats were exposed to the arena on a 10-min habituation trial with the shock turned off. After the habituation trial, the rats were returned to the home cage for 10-min. Following this, the rats were returned to the arena to learn the APA task during eight 10-min in which the shock was turned on with 10-min inter-trials spaced in between. On the second day, we subjected the animals to a 20-min forced-swim. On the third day, recall of the APA task was tested in a single 10-min trial with the shock turned off.

Results: Stress did not strengthen the memory of an APA task as measured by often used metrics including time-to-first entry and number of entrances as there were no differences in these metrics between the forced-swim and non-swim groups. The animals that were subjected to non-swim conditions on the second day extinction behavior during retention test. More interestingly, however, the animals that were subjected to the forced-swim continued to avoid spending any significant time in the shock area even after multiple entries even though the shock was turned off.

Discussion and Significance: These data suggest that a stressful event can modulate and influence subsequent behavior even if the stress was unrelated to the current task at hand. As such, this may have implications for conditions such as post-traumatic stress and other anxiety disorders.

Emma Wallace

Research Advisors: Andre A. Fenton and Juan Marcos Alarcon

Synaptic Organization of Memory Traces within the Hippocampal Circuit

Michael Sangobowale

Research Advisor: Peter J. Bergold

Do PKM ζ changes underlie memory deficits following controlled cortical impact in rats?

Memory deficits frequently accompany mild traumatic brain injury. In the United States there are approximately 1.7 million people each year who have a traumatic brain injury. Eighty percent of these are classified as mild TBI. Currently there are no drugs to treat TBI. Recent research has shown that the drug combination of minocycline (MINO) plus N-acetylcysteine (NAC) work synergistically to improve cognition and memory in adult rats after mild controlled cortical impact (mCCI), a model of mTBI. This was shown on an active place avoidance task (APA). MINO was sufficient to improve acquisition of APA, but the combination with NAC was needed for long-term memory (LTM). Protein kinase M zeta (PKM ζ) is an isoform of protein kinase C whose activity mediates long-term retention of hippocampal-dependent tasks. Levels of PKM ζ undergo long-term increases in the stratum radiatum of the hippocampal CA1 region after a rat acquires and retains the APA task. These observations lead to the hypothesis that MINO plus NAC improves LTM through modulation of PKM ζ levels. To test this hypothesis, adult rats will be subjected to sham-mCCI or mCCI. The sham and injured group will be subdivided into two groups; untrained control rats that stay in their home cage or rats trained on the APA task. The following day rats will be sacrificed, and their hippocampi stained for PKM ζ . Trained sham injured rats are anticipated to have increased PKM ζ as compared to untrained controls. In contrast, trained injured rats are anticipated to have similar PKM ζ levels as untrained rats. These data will suggest that the behavioral deficits induced by mCCI are accompanied by impaired regulation of PKM ζ . We will then test whether the restoration of task acquisition and memory by MINO plus NAC is accompanied by increases in hippocampal PKM ζ .

Margalit Haber

Research Advisor: Peter J. Bergold

Minocycline plus N-acetylcysteine induces remyelination and reformat microglia response in a rat model of mild traumatic brain injury

There is currently no treatment for traumatic brain injury (TBI) that promotes repair of the brain. Mildly injured rats show improved cognition and memory after treatment with the FDA-approved drugs minocycline and N-acetylcysteine (MINO plus NAC). The mechanisms underlying this improvement in cognition and memory are unknown. Mild injury selectively demyelinate white matter and impairs communication between distant brain regions leading to disruption of cognition and memory. Myelination of selected white matter regions were examined using luxol fast blue (LFB) in mildly injured rats following saline or drug treatment. LFB density following saline treatment decreased at 4 days and was unchanged at 14 days. LFB density also decreased in injured rats following MINO plus NAC treatment at 4 days, yet LFB density increased at 14 days. These data suggest that MINO plus NAC induced remyelination. Neuroinflammation coordinates both demyelination and remyelination through activation of pro-inflammatory M1 microglia and anti-inflammatory M2 microglia. Microglial activation was assayed using Iba-1 that is expressed by both M1 and M2 microglia. Even though MINO suppresses microglial activation, MINO plus NAC increased Iba-1 immunoreactive cells in the corpus callosum at 2 days post-injury. This increase by MINO plus NAC was further seen with markers for M1 (CD68, iNOS) or M2 (FIZZ-1, Arginase-1) markers. This increase in both M1 and M2 microglia suggest that the drugs rapidly reformat the microglial response to brain injury. Prolonged changes in microglial activation were also seen up to two weeks after mild injury (R. Izarry, Research Day, SUNY Downstate, 2013). We are testing whether this change in microglial activity correlates with attenuation of oligodendrocyte loss and remyelination of demyelinated axons. MINO plus NAC may improve cognition and memory by repairing the brain through remyelination.

Rachel Irizarry

Research Advisor: Peter J. Bergold

Long-term Modulation of Microglial Activation in a Rat Model of Mild Traumatic Brain Injury by Minocycline plus N-acetylcysteine

The combination of FDA-approved anti-inflammatory drugs Minocycline and N-acetylcysteine (MINO plus NAC) demonstrates a synergistic effect improving both cognition and memory and attenuates white matter damage in rats in the controlled cortical impact (CCI) model of traumatic brain injury (TBI) (Abdel Baki et al., 2010). TBI can induce long-lasting neuroinflammation after injury. Upon activation, microglia can differentiate into pro-inflammatory M1 microglia or anti-inflammatory M2 microglia. Microglial expression was investigated by staining for the antigenic marker Iba-1 which is expressed by both M1 and M2 microglia. M1 and M2 microglial subset markers and phagocytic marker CD68 were also investigated. In a previous study, MINO plus NAC increased the number of Iba-1 immunoreactive cells and selectively increased M1 (iNOS) and M2 (FIZZ-1, Arginase) immunoreactivity at times when the drugs are present (M. Haber, Research Day, SUNY Downstate, 2013). This study focused on alternation of microglia activity at 4, 7, and 14 days post injury, when the drugs were no longer present. At seven days post-injury there was a strong trend to increase the number of M2 microglia having high Arginase expression as compared to saline-treated injured rats. At 14 days there was high expression of iNOS and the phagocytic marker CD68. These data suggest that the drug combination of MINO plus NAC continues to influence neuroinflammation after dosing has ended. Modulation of earlier microglia activation by MINO plus NAC can therefore have a long lasting effect and may underlie repair of white matter tracts after injury.

Sergio Angulo

Research Advisor: Herman Moreno

Calcium buffer capacity in subicular neurons in an old AD mouse model

The subiculum function is related to memory retrieval and is affected in early stages of Alzheimer's Disease (AD). Because calcium dysfunction is also present in early and late phases of AD, we studied the calcium dynamics of the apical dendrite of subicular pyramidal neurons (SPNs). Our hypothesis is that calcium-binding proteins, specifically calbindin (CB), are affected in AD and produce alterations in calcium homeostasis throughout the disease worsening during late phases. We used fluorescence calcium imaging combined with patch-clamp whole-cell recordings in acute mice brain slices. The calcium buffer capacity and the dynamics of depolarization-evoked calcium transients from old mice (14-18 months old) were analyzed in wild-type, CB knockout (CBKO) and AD mouse model (J20). For those phenotypes, our previous work in SPNs from young mice shows that calcium buffer capacity and resting calcium are similar to those obtained in CA1 pyramidal neurons. In old mice, we find no statistical significant differences in the resting calcium concentration between groups, with values ranging from 67 to 80 nM. Data from wild-type and CBKO were well approximated by the predictions of a homogeneous compartment and yielded estimates for the buffer capacity of 91 and 40 respectively, in accord with a substantial reduction of buffer capacity upon CB deletion. The relation between the decay time constant and added calcium buffer from J20 mice deviated from linear function, rendering the estimation of the buffer capacity difficult and suggesting a global dysregulation of internal calcium buffers.

Usman Khan

Research Advisor: Herman Moreno

Imaging Preclinical Alzheimer's Disease and Mouse Models Pinpoint Dysfunction in the Medial Temporal Lobe and Suggest a Pattern of Spread

The entorhinal cortex (EC), a gateway of the hippocampal formation, is subdivided into the medial EC (MEC) and the lateral EC (LEC), and each interconnects with functional distinct pathways within the medial temporal lobe (MTL). While the MEC interconnects with the parahippocampal cortex (PHC) to form the posterior pathway, the LEC interconnects with the perirhinal cortex (PRC) forming the anterior pathway. Although studies suggest that dysfunction in Alzheimer's disease (AD) begins in the EC, patterns of vulnerability within, and patterns of spread out of, the EC remain unknown. Here we address these questions by using a high-resolution fMRI variant that can map metabolic defects in patients and mouse models. The variant uses the exogenous contrast gadolinium to generate brain maps of cerebral blood volume (CBV), a proven correlate of oxygen metabolism, with submillimeter resolution.

In mice, we studied regionally-selective mutations in amyloid-precursor protein (APP), tau, or both APP and tau isolated to the entorhinal cortex. The human study pinpointed the lateral division of the entorhinal cortex as the earliest site of dysfunction, while the mouse study showed that this division is sensitive to a combined effect of APP and tau. Moreover, findings from human and mice suggest a pattern of spread out of the lateral entorhinal cortex.

Sally Dricks

Research Advisor: Katherine Perkins

Effects of Neonatal Stress on Gamma Oscillations in Hippocampus

Separation of rat pups from dams for three hours per day from postnatal days 2 thru 14 – though preceded and followed by normal rearing procedures – is sufficient to induce lifelong impairment of the stress response. This protocol is used as a model for early life trauma, neglect and abuse. Effects of early life trauma, neglect and abuse in both rats and humans include impairment of the negative-feedback signal that restores the release of cortisol (corticosterone in the rat) to basal levels. The result is excessive exposure to cort which has been shown to reduce the number of parvalbumin-expressing basket cells (PVBCs) in hippocampus. PVBCs' rapid, synchronous firing induces the rhythmic inhibitory postsynaptic potentials observed as gamma oscillations.

The number of PVBCs was also shown to be reduced in postmortem studies of schizophrenia and bipolar disorder, illnesses thought to involve neurodevelopmental events. Gamma oscillations are intrinsic to cognition, perception and memory; aberrant gamma oscillations are hallmarks of schizophrenia and bipolar disorder, illnesses in which many gamma-linked functions are impaired.

We asked whether gamma oscillations in neonates would be affected by lengthy separations from the dam; and if so, whether that effect would be mediated by compromised development of the PVBC network. Litters of pups were separated from their dams for either 15 or 180 min/day from postnatal days 2 thru 14. On postnatal days 15 thru 21 we used *in vitro* slice electrophysiology to record local field potentials of cholinergically-induced gamma in hippocampus. Gamma power increased with – and was strongly correlated to – weight, age and gamma frequency in the 15-minute group, but not in the 180-minute group. Differences between the groups became greater with age and were consistent with developmental disruption of the PVBC network.

Isaac Naggar

Research Advisor: Mark Stewart

Optimal Efferent Vagus Nerve Stimulation in Large Animals and its Effect on Wall Motion during Ventricular Fibrillation

The vagus nerve modulates electrical activity of the cardiac ventricles. In large animals, vagus nerve stimulation (VNS) decreases the current necessary to defibrillate a period of VF. In rats, it can even defibrillate periods of ventricular fibrillation (VF). While the mechanism of the anti-arrhythmic properties of VNS is a source of debate, the action of the vagus nerve during VF has not been shown. We studied VNS during sinus rhythm and VF in pigs and sheep. We sought to determine: 1) what is the most potent frequency of VNS for its cardiac effect and 2) whether VNS has any physical effect on the ventricles during disrupted conduction, as in VF.

We studied 8 pigs and 10 sheep anesthetized with urethane 1 g/kg intravenously and ventilated. Platinum electrodes were wrapped around the vagus nerves. Electrocardiogram and blood pressure recordings were made. VNS was performed in animals at 1, 2, 5, 10, 20, 50, and 100 Hz. Potency of VNS was evaluated by counting the number of beats during stimulation. VF was produced by opening the thorax and applying direct current to the ventricles. Epicardial echocardiography was performed during sinus rhythm, VNS, and during VF for three periods—before, during, and after VNS. Left ventricular wall motion data was extracted from all four cardiac walls from 2D echo data.

In both sheep and pigs, 50 Hz was found to be the optimal frequency required to produce cardiac standstill. This was true for both nerves stimulated separately and bilaterally. VNS produced a motionless state for the cardiac walls in sinus rhythm and decreased wall motion significantly during VF, to a state similar to that of VNS during sinus rhythm.

We conclude that 50 Hz is the optimal frequency for VNS to exert its cardiac effects. The ability of VNS to produce changes to wall motion in VF serves as physiologic evidence for a growing body of evidence that the vagus nerve has direct effects on the ventricles, even when the entire conducting system is disrupted.

Lindsay Silva

Research Advisor: Diana Dow-Edwards

Early life experience affects behavioral responses to adolescent delta-9-tetrahydrocannabinol exposure in the rat

Marijuana is the most commonly abused illicit substance in the United States. Additionally, almost 60% of all first time marijuana users were under the age of 18 in 2010. Adolescents who use marijuana are more likely to exhibit anxiety, depression and other mood disorders including psychotic-like symptoms. However, our study on the effects of early adolescent (P29-38) D-9-tetrahydrocannabinol (THC) exposure in rats shipped on P14 showed no effect on a measure known to be altered in clinical and pre-clinical models of psychosis, the pre-pulse inhibition (PPI) task. PPI is a measure of sensorimotor gating and reduced response to the pre-pulse can indicate abnormal sensory information and motor integration and processing. Since early postnatal stress is known to alter the function of the endocannabinoid system (ECS), we repeated the study in rats born in our vivarium and exposed to our standard rearing/handling protocol (weigh weekly starting at P1). Preliminary data suggest that THC dampens the PPI response in animals raised in our vivarium, with a stronger effect in males than females. In contrast, our study examining early adolescent THC effects on elevated plus maze (EPM) behavior (a measure of anxiety) showed no effects in male animals born in our vivarium, but significant effects in males shipped at P14. Similar effects were found in males in the forced swim test (FST) (a measure of depressive-like behavior). Males shipped at P14 showed less anxiety and less depressive-like behavior in the EPM and FST, respectively, following THC administration. Therefore, early life stress increases responsiveness to THC in some behavioral modalities (EPM and FST) and decreases responsiveness to THC in others (PPI). These data indicate that early life experience can alter the effects of adolescent THC exposure on aspects of rodent emotional and psychotic-like behavior which could be due to unique alterations in ECS function in brain regions mediating these different behaviors.

Yekaterina Merkulova

Research Advisors: Nicholas Penington and Keith Williams

Intracellular ATP Has Opposing Regulatory Effects on TRPC4 and TRPC5 Channel Activity

The TRPC4 and TRPC5 members of the canonical subfamily of the transient receptor potential channels are non-selective, Ca²⁺-permeable ion channels expressed in the CNS and in the peripheral vasculature. Several studies have suggested a role for these channels in the development of hyper-excitability and synchronous neuronal networks, and in regulation of vascular tone and cardiac function. Currently there are no known differences in their function and regulation, except for the finding from our laboratory that intracellular ATP inhibits TRPC5 and potentiates TRPC4 activity. Given the properties of ATP, this finding suggests that changes in the metabolic state of the cell may affect TRPC4 and 5 channels. The differential effect of ATP on these channels can be studied to identify the role of TRPC4 and TRPC5 in events that alter intracellular ATP levels and distribution. Preliminary single channel data demonstrate channel activity and a conductance of 40 pS at -50 mV for murine TRPC4 β in the presence of 4 mM ATP. These studies also show activation of the channels by muscarinic ACh receptors, with an increase in channel activity upon application of carbachol, and suggest a possible ten-fold increase in nPo for murine TRPC4 β . The activation of TRPC4 β is further confirmed by the absence of channel activity in the -20 to +20 mV voltage range, due to a block of the channel pore by extracellular Mg²⁺. Whole-cell voltage clamp recordings of murine TRPC5 and TRPC4 β channels demonstrate channel inhibition and potentiation, respectively, by the same concentration of ATP. Additionally our whole-cell and single-channel recordings demonstrate persistent channel activity in the presence of GTP- γ -S, a non-hydrolyzable form of GTP that is used to simulate G-protein activation. Site directed mutagenesis, along with electrophysiological studies will be performed to elucidate the site and mechanism by which ATP interacts with TRPC4 and TRPC5. In the long-term, we plan to investigate the potential role of TRPC4 and TRPC5 in hypoxia-induced epileptogenesis.

Sonia Afroz

Research Advisor: Sheryl Smith

A Role for GABA-mediated Inhibition in Adolescent Development: α 4-containing GABA-A Receptors Modulate Synaptic Pruning and Post-pubertal Cognitive Flexibility

Neuroplastic modifications, like synaptic pruning, underlie the transition from childhood to adulthood through refinements of neuronal circuits that are poorly understood although signaling cascades triggered by NMDA receptors (NMDARs) are implicated. Activation of these receptors is impaired at puberty due to the emergence of extrasynaptic α 4 β δ GABA_A receptors (GABAAR) on the spines of CA1 pyramidal cells, which generate a shunting inhibition. For the present study, we tested the hypothesis that α 4 β δ GABAARs play a role in synaptic pruning during adolescence. We found 50% reductions in spine density on CA1 pyramidal cells in post-pubertal (post-pub) wild-type (WT) female mice but not in post-pub α 4^{-/-} mice, implicating the increase in α 4 β δ expression as the mediating factor. We recorded spontaneous excitatory postsynaptic currents which are NMDAR- and AMPAR-mediated events indicative of information transmission from CA1 pyramidal cells and found lower frequency and amplitude of these events in the in WT post-pub mice compared to post-pub α 4^{-/-} mice. Furthermore, behavioral flexibility, an index of information signaling and processing was found impaired in hippocampus-dependent tasks in post-pub α 4^{-/-} mice. This corresponded with impaired NMDA-dependent LTD induction in these mice. Selective enhancement of α 4 β δ GABAAR function with GBX (gaboxadal) resulted in significant post-pub reductions in spine density in CA1 pyramidal cells. GABAAR blockade with picrotoxin (PTX) resulted in increases in spine density compared to post-pub vehicle mice. Additionally, LTD induction was impaired after pubertal PTX treatment but was enhanced after GBX treatment. Behavioral flexibility, however, was compromised in all cases suggesting an optimal level of synaptic pruning regulated by α 4 β δ GABAARs. These findings suggest that α 4 β δ GABAARs may act beyond the normal functions of inhibitory synaptic transmission to regulate synaptic pruning in the transition to adulthood.

Oksana Mihnuik

Research Advisor: Miriam Caboral

Obesity as a Risk Factor in the Development of Atrial Fibrillation: A, Epidemiologic Study

Purpose: The purpose of this study is to determine the prevalence of developing new onset AF among obese individuals compared to normal weight individuals.

Background: Atrial Fibrillation (AF) is the most common cardiac arrhythmia in the United States (US). Recent studies have identified that advanced age, presence of diabetes, hypertension, and cardiovascular disease can increase a person's the risk of developing AF. Nevertheless, the one factor of most concern is the link between obesity and developing of AF. Obesity plays an important role in the evolution of cardiovascular disease. Although obesity is associated with several conditions however it is unclear whether obesity in itself predisposes someone to AF.

Method: This is a quantitative, descriptive, epidemiologic and case-controlled research design. The sample will consist of the new onset AF group and a control group. Ninety medical charts of patients discharged with a diagnosis of new onset AF within the past three years from SUNY Downstate Medical Center will be reviewed. One-hundred eighty medical charts of patients discharged from the same institution will be randomly pulled. A diagnosis of new onset AF will be based on the ICD-9 code assigned at discharge. Both cohorts will be separated into obese and normal weight group after review. Obese sample will be defined as having a BMI of >30.

Conclusion: At the present time, there is certainly knowledge deficit due to the limitation of studies that relate obesity to AF. With the increasing prevalence of AF, it is important to draw attention to obesity as a correlative factor to this prevalence. Findings from this study may provide further explanation as to whether obesity, occurring independent of other risk factors, contributes to the increased incidence of new onset AF.

Maria Rosario-Sim

Correlates of Depression among Asian American Adolescents in NYC

Background: A high rate of depressive symptoms was discovered in both smokers and nonsmokers for a study of smoking behavior among Asian American adolescents in New York City, which prompted the investigators to explore the correlates of depression among this sample. Therefore, the purpose of this study is to explore correlates of depression among Asian American adolescents.

Method: This is a cross-sectional study design of a convenience sample of 328 Asian American adolescents, ages 16 to 19, and who lived in New York City. Participants were recruited from members, friends, and affiliates of six organizational sources. Demographic, depression (CES-D scale), English language acculturation, and smoking opportunity survey questionnaires were used.

Results: Three-hundred sixteen participants were included in the final analyses. Twelve participants who reported taking antidepressant medications and/or receiving psychological counseling were excluded. Results indicated that English language acculturation, ethnicity, current enrollment in school and smoking status were found to be significant predictors of depression among Asian-Americans, as well as the interaction between smoking status and ethnicity.

Conclusions: Depressive symptoms are prevalent among Asian American adolescents and it is critical to focus attention on this significant health problem. It is essential that smoking prevention programs are culturally and ethnically sensitive to the needs of Asian American adolescents.

Emily (Emmet) Phipps and Jeannine O’Hagan Murphy

Research Advisor: Maria Rosario-Sim

Nurse Practitioner students’ knowledge of DSD (disorders of sex development)

Background: The Consortium on the Management of Disorders of Sex Development (2008) define DSD as “conditions involving congenital development of ambiguous genitalia, congenital disjunction of internal and external sex anatomy, incomplete development of sex anatomy, sex chromosome anomalies, and disorders of gonadal development.” DSD have a controversial relationship to medicine both historically and clinically. There has been a very small surge of research guided by the desire to improve the medical experience of people affected by DSD, considering that as many as 2% of people are born with sex differences.

Purpose: The purpose of this study is to assess the knowledge NP students have at the end of their schooling regarding DSD and to increase NP students’ awareness of DSD as a means to de-stigmatize diversity of sex and provide better care for their patients.

Method: A 5-item multiple-choice test was created by the researchers on the definition, prevalence and treatment of DSD that will be given to graduating FNP and WHNP students.

Results: There are no results considering the research has not been performed.

Conclusion: The significance of this study is two-fold. The researchers both draw attention to an often-forgotten aspect of patients’ experiences - differences of sex and gender - while obtaining information about the level of knowledge that NPs have about these differences. Lack of basic knowledge of DSD will impinge on an NP’s ability to support their patients, and calls for increased NP education about the diversity of sex development. The researchers expect that conducting this study might increase NPs awareness of DSD.

Meriam Caboral

Effectiveness of Patient Activation Interventions (PAI) in Adults with Cardiovascular Disease: A Review of Literature

Background: Patient activation (PA) describes a person’s ability and willingness to take on the role and responsibility of managing their health and health care. It is a reflection of the degree to which a person feels “in charge” of their own health. Patient activation interventions (PAI) are designed to increase a patient’s involvement in their health care through education and skill-building techniques. The purpose of this research is to conduct a systematic review of literature to determine the effectiveness of PAIs in older adults with cardiovascular disease.

Methods: A search of the literature published from January, 1985 to May 2012 was conducted. The inclusion criteria included in this review were studies conducted in older adults with cardiovascular disease that were published in English. Two authors independently obtained quality scores of each study.

Results: One hundred ten articles were identified and 48 abstracts were reviewed. Twenty-five articles were retrieved for full text review. Twelve articles met the inclusion criteria and were included in this review. The 12 articles identified consisted of six articles on diabetes, one article each on hypertension and heart failure, and four articles on chronic conditions that included heart disease, diabetes, hypertension, obesity, and dyslipidemia. One of the studies evaluated a web-based intervention and another examined the effects of an intervention on patients from the perspectives of their primary care providers. The results were mixed on the effect of PAI on physiologic measures and health behaviors. One major limitation of this review was the lack of PAI studies focusing specifically on heart disease or coronary artery disease.

Conclusion: Studies have suggested the potential benefit of interventions that may increase patient activation. This finding should not be taken as a report on the failure of the activation interventions rather a congregate of information for future research design.

Susan Holman

Research Advisor: Tracey Wilson

Awareness and Acceptability of Vaginal Microbicides and Oral Pre-Exposure Prophylaxis for Prevention of HIV Acquisition Among at-Risk HIV-Negative Women

Rationale: Recent studies show that a vaginal microbicide (VM) and oral pre-exposure prophylaxis (PrEP) with antiretroviral agents can be effective in preventing sexual transmission of HIV to women. We undertook a study to explore what US women know about these new agents, acceptability and likelihood of use, and possible facilitators or barriers to use.

Methods: This study was conducted as part of a multi-center prospective cohort study of HIV in women, the Women's Interagency HIV Study, that currently follows 1,360 HIV positive women and 615 at-risk HIV negative women every 6 months in 5 cities across the US. Survey questions about awareness, acceptability and preference of use of VM and/or oral PrEP agents were administered to all HIV negative women as part of their standard study interview at one study visit.

Results: Among the 466 HIV negative women who completed the survey between 10/1/2011 and 3/31/2012 and reported at least 1 male partner within the past 12 months, 88% were African American or Hispanic. Mean age was 44.4 (SD + 9.4). 61% reported recent unprotected vaginal or anal sex (UVAS) and 17% had >2 partners. Only 5% of women had ever heard of VM or PrEP although about 60% reported they would probably or definitely try them, if available. Reported likelihood of using VM/PrEP did not differ by UVAS status. If these options were available, 19% would choose to use VM, 29% to use PrEP, 20% to continue using condoms, 11% to sometimes use condoms and sometimes VM and 21% would use something else, weren't sure or didn't have enough information.

Discussion/Significance: Very low rates of awareness of either vaginal microbicide or PrEP as agents that can be effective in preventing sexual transmission of HIV to women were shown in this sample, although a majority reported they would be willing to try them. Our findings can help inform education programs to promote awareness and acceptability of VM/PrEP when these agents become approved for use.

Mark Hoglund

Research Advisor: Rebecca M. Schwartz

Mental Health in Deployed and Non-deployed Veteran Men and Women in Comparison with their Civilian Counterparts

Studies of male and female military personnel have found associations between combat exposure and adverse mental health. This study's purpose was to investigate the mental health status of deployed veterans and non-deployed veterans in comparison with civilians, and, specifically, to explore gender differences.

The sample for this study came from the Behavioral Risk Factor Surveillance System survey, specifically from states using the optional module "Veteran's Health" in the survey. Our study sample included 22,587 respondents (14,384 women and 8,203 men; 1,395 individuals had military experience). Using multivariate logistic regression to control for demographic factors, we estimated the effects of gender on the mental health status of deployed veterans, non-deployed veterans, and civilians, and we estimated the effects of deployed military service and non-deployed military service separately for men and women.

Results: Compared to male counterparts, odds of adverse mental health were 76% greater for civilian women, 200% greater for non-deployed women veterans, but only 47% greater (non-significant) for deployed women veterans. Compared to civilian counterparts, deployed males had 44% greater odds of adverse mental health and deployed women had 39% greater odds (non-significant) of adverse mental health. Compared to civilian counterparts, male non-deployed veterans had non-significantly greater odds (17%) of adverse mental health; female non-deployed veterans had almost 60% greater odds of adverse mental health.

Conclusions: Among deployed veterans, both men and women have increased odds of adverse mental health in comparison to the civilian population. However, among non-deployed veterans, adverse mental health consequences appear to fall exclusively upon women. Our findings suggest that policymakers should closely monitor the mental health status of both men and women, not only among combat forces, but in all military occupations.

George Chadderdon

Research Advisor: William W. Lytton

A dual-circuit neocortical model explored in a spiking model of primary motor cortex

Layer 5 pyramidal cells form two distinct groups: corticostriatal (STR) cells that project to striatum and to other cortical areas, and corticospinal (SPI) cells that project downwards to brainstem and spinal cord. These cell types anchor partially separable subcircuits involved in intercortical processing and information export, respectively. These subcircuits receive lamina-specific activations from targeted long-range axons from different cortical and thalamic sources. We hypothesize that the one-way projection (corticostriatal to corticospinal) between subcircuits effects a code transformation: dominant corticocortical temporal coding (corticostriatal subcircuit) to dominant rate coding (corticospinal subcircuit).

We simulated primary motor cortex (775 spiking neurons with 10 cell types) based on connection topology, synaptic weights, and intrinsic properties determined experimentally. We examined network responses to brief single stimulation of individual layers. The pattern of interlayer propagation depended both on location and amplitude of stimulation. Low stimulation produced transient activation of multiple layers, while higher amplitudes produced sustained oscillatory firing. Amplitude threshold for sustained responses varied by layer: 13% in L2/3, 54% in L5A, 25% in L5B, 17% in L6. Sustained activation produced oscillations in the gamma range with frequencies, phase relations, and interlayer interaction differing depending on the initial source of the activation. Strong connections from L2/3 spread activity to L5. Corticostriatal cells in L5 then acted as a network hub distributing activity more widely. Phase and strength of oscillation in STR and SPI cells depended on the location of stimulation. Our results suggest that lamina-specific inputs from different upstream cortical and thalamic areas will activate these distinct cortical subcircuits that will then partition activity for further cortical processing and for export to physical effectors.

Yosef Skolnick

Research Advisor: William W. Lytton

Ih-dependent tuning of theta and gamma oscillations in a multiscale computer model of CA3

Theta (4-12 Hz) and gamma (> 25 Hz) brain oscillations are hypothesized to have many functions including involvement in working memory and in sensory integration. The ubiquitous HCN (Ih) channels are a major influence on the dynamics of individual neurons, suggesting that they are involved in the emergence of these waves in the network. HCNs contribute to neuronal membrane resonance, have multiple isoforms (HCN 1-4), are hyperpolarization-activated, are differentially expressed in cell-types, are found in appreciable quantities almost all cell types, and are modulated by second messengers such as cAMP.

We investigated the role of HCN in the generation of theta and gamma rhythms, using a multiscale computer model of hippocampal CA3, where cell classes contained type-appropriate isoforms of Ih. The network consisted of 800 pyramidal cells, 200 basket cell interneurons, and 200 oriens lacunosum-moleculare (O-LM) interneurons interconnected probabilistically with AMPA/NMDA, and GABAA synapses.

Testing Ih modulation across different cell types within the full network demonstrated consistent but dramatically different effects depending on which cell type was targeted. At the dendritic and cellular level, Ih generally increased both EPSP and IPSP magnitude and duration with some variation by cell type. At the cell level, excitability increased due to cell depolarization. At the network level, Ih modulation altered both theta and gamma, with effects depending on where in the circuit the modulation occurred. Increasing Ih in pyramidal cells increased theta amplitude and frequency, while more Ih in the basket cells increased gamma amplitude but decreased gamma frequency. In addition, Ih allowed setting the cross-frequency coupling (CFC) and phase relations between theta and gamma oscillations. These are hypothesized to allow for the dynamic encoding of information. Our model suggests that Ih may allow for setting the CFC level *in vivo*.

Robert McDougal

Research Advisor: William W. Lytton

Computational study of neuronal calcium waves

Calcium (Ca^{2+}) waves provide a complement to electrical signaling in the neuron, forming a key part of a neuron's second messenger system. This chemical phenomenon interacts bidirectionally with electrical activity. Ca^{2+} is normally sequestered into the endoplasmic reticulum (ER) via pumping of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA). Inositol triphosphate (IP3) is a ligand that regulates admittance of Ca^{2+} from ER into the cytosol when it binds to IP3 receptors (IP3R) on the ER. ER IP3Rs are also co-regulated by Ca^{2+} . Therefore, when Ca^{2+} binds to IP3Rs, it can induce its own release into the cytosol (calcium-induced calcium release: CICR). These phenomena have clinical relevance: dysregulation of Ca^{2+} channels of the smooth endoplasmic reticulum (SER) has been implicated in Alzheimer's and Huntington's disease. We developed a reaction-diffusion model of a neuron which contained separate cytosolic and ER volumes, each containing their own local Ca^{2+} concentrations. Our model included diffusible IP3 and Ca^{2+} and replicates Ca^{2+} wave initiation and spread, as observed *in vivo* [2]. We tested different distributions and densities of IP3 receptors in the dendrite, assessing the effects on speed and strength of Ca^{2+} wave boosting. Lowered SERCA pump expression, elevated global IP3R, or reduced spacing between IP3R clusters increased wave spread and speed, altering neuronal excitability. We also assessed propagation efficacy of Ca^{2+} waves in complex neuronal geometries. Ca^{2+} wave entry into the soma is impeded due to an impedance-mismatch-like effect. This has implications for Ca^{2+} dysregulation leading to neurotoxicity: if Ca^{2+} is more likely to be elevated in dendrites, this would suggest that dendrites may have more susceptibility to apoptotic and ischemic damage.

Kamala Anumukonda

Research Advisor: Christopher A. J. Roman

Role of TFEB in Macrophage Autophagy

Autophagy is a process of self-degradation of cellular components in response to various kinds of environmental stress, in which double-membrane autophagosomes sequester intracellular material such as defective organelles or pathogens and fuse with lysosomes for breakdown by resident hydrolases. Autophagy is particularly important for macrophage development and function. First, monocytes must up regulate autophagy in order to differentiate into macrophages. Once mature, macrophages also need autophagy for efficient phagocytosis of intracellular bacteria, antigen presentation via MHC II to CD4 T cells, host antiviral defense, anti fungal responses and activation of defense against gram-negative bacteria via TLR signaling.

Recently, TFEB has been implicated by others to regulate genes involved in autophagy and lysosomal biogenesis. Given the importance of autophagy to macrophage function, I aim to study the role of TFEB in autophagy in macrophages. One approach is using transformed RAW 264.7 macrophages in which autophagy and lysosome biogenesis can be activated, and the other is using primary bone marrow derived macrophages from mice conditionally deficient in TFEB. TFEB null mice are embryonic lethal, so I plan to use the macrophage-restricted Lyz2CRE transgene to express Cre in mice containing the flox allele of TFEB.

My preliminary studies show that in RAW cells, TFEB abundance and nuclear localization is responsive to immunological stimuli that activate autophagy such as pathogen associated molecules like LPS from *E.coli*, cytokines involved in antiviral defense like IFN- γ , and the mTOR inhibitor Rapamycin. Interestingly, I show that TFEB is dispensable for differentiation of monocytes into macrophages *in vivo*. However, in an *in vivo* model for sterile peritonitis, TFEB deleted macrophages appear impaired in their maturation response. Follow up studies include functional assays on phagocytosis, and immune-dependent activation of autophagy.

Jonathan Davila

Research Advisor: Christopher A. J. Roman

Ectopic VpreB Expression Drives T-cell Independent Expansion of Splenic B-1-like cells

A distinguishing feature of the synovia of many patients with Rheumatoid Arthritis is that they are abnormally enriched for autoreactive B cells that express VpreB , a molecule normally produced only by B cell progenitors. VpreB is a component of the surrogate light chain (SLC), which has a critical role during early B cell development by vetting the functionality of newly synthesized immunoglobulin heavy-chains (HCs) with which it must pair to form the precursor B Cell Receptor (preBCR), a receptor required for pre-B cell differentiation. Typically, SLC expression is restricted to early development and is extinguished as LC rearrangement commences. To better understand the relationship of VpreB to B cell development and autoimmunity, here we report a novel transgenic mouse model for ectopic VpreB expression in mature B cells, in which transgenic VpreB expression is variegated and as a result drives the selective emergence of novel B220 lo B cells including a splenic B-1-like B220 lo IgM hi CD9 + population in an expanded splenic marginal zone. B220 lo B lineage cells were found in the fetal liver and bone marrow, and emerged in the presence of two different HC transgenes and without T cells. Moreover, VpreB transgenic mice expressed elevated circulating autoantibodies. Thus, VpreB itself can selectively alter B cell fate and break self tolerance.

Mizanur Ahmed

Research Advisor: Christopher A. J. Roman

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