

Yonatan Akivis

Advisor(s): Mariana Markell

Vaccination Rates And Relation To Health Beliefs In Inner-city Kidney Transplant Recipients

Purpose: Prophylaxis against viral and bacterial infections as outlined by guidelines issued by the 2013 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for Vaccination of the Immunocompromised Host is especially important in transplant recipients. There is a paucity in the literature regarding vaccination rates, especially in indigent, immigrant populations where health beliefs may play a role in medical decisions.

Results: 31 patients were interviewed. There were 19 (61%) men and 12 (39%) women. Racial breakdown was 26 black, 1 white, 2 Hispanic and 2 other. 13 (56%) had not attending any college courses. 3 pts (10%) were employed with the rest disabled or retired. Mean age was 56+/-2.4 (range 18-79). 17 (55%) pts were born in other countries (mean time in the US 32.6+/-2.7 yrs), mean time since transplant 6.7+/-1.4 yrs. Creatinine was 2.32+0.4 mg/dl. Immunization rates for recommended vaccines were low with 19.51% of patients having received the TDAP vaccine, 19.51% for PPSV23, 17.07% for PCV13, 48.8% for Influenza, 56.1% for Hepatitis B, 2.44% for Meningococcus and 0% for IPV, HIB, Hepatitis A, Zoster, Rotavirus-live and MMR. Patients who had received the TDAP were more likely to have also received PPSV23 ($r=0.379, p=0.015$), PCV13 ($r=0.594, p=0.000$) and Meningococcus ($r=0.321, p=0.041$). Of the 15 patients who did not receive the influenza vaccine, 9 (60%) had refused. All patients who refused believed that the vaccine "made them sick" in the past. Two patients believed it had never been offered to them, although it is clinic policy that all patients are offered the vaccine starting in late September. Older patients were less likely to have received the flu vaccine ($r=-0.32, p<0.05$). There was no relation of any vaccine rate and education, employment status, time in the US or time since transplant.

Michael Danziger

Advisor(s): Kathleen Powderly

Geographical Stratification and Black Maternal Morbidity & Mortality

Maternal mortality is an issue that has received renewed political interest, in large part due to extensive investigative coverage in the popular press. In New York City, black women are more likely to suffer severe maternal morbidity and mortality, regardless of education level, socioeconomic status, or BMI. While the overall maternal mortality rate in NYC has decreased since 2007, the gap between white and black maternal mortality has widened. Recent studies have shown these disparities cannot be accounted for solely by high-risk features of specific populations. The cause of this disparity is complex but is best understood as the legacy of discriminatory policies, such as redlining, that sought to compartmentalize populations into neighborhoods and subsequently deny those neighborhoods adequate support. As a result, such areas have underfunded schools, poor access to food, and less access to healthcare. Such policies create a web of social and environmental issues that cannot be solved singularly and ensure cyclic immiseration. Traditional analyses of maternal morbidity and mortality examine hospital or maternal factors to determine how to improve and account for them. This approach, while invaluable for understanding what occurs in medias res, does not address the deeper causes of these issues. A human geographical approach augments the traditional analyses by unifying the causative factors and examining the contribution of a complex variable (i.e. geographical location). Indeed, when comparing choropleth maps, the geographical relationship to race and maternal morbidity and mortality in New York is apparent. Analyzing maternal morbidity and mortality as a function of geography underscores the fact that these (and other) issues cannot be addressed in isolation. As such, any policy seeking to ameliorate maternal morbidity and mortality must account for the relationship to geography and resources.

Sofya Gindina

Advisor(s): John Danias

Tissue Plasminogen Activator: Mechanistic Studies in Steroid Induced Glaucoma

Glaucoma is a group of eye diseases leading to progressive irreversible vision loss via optic nerve damage; the most common form is open-angle glaucoma (OAG). As the second leading cause of blindness worldwide, glaucoma poses a heavy societal burden with 80 million cases projected by 2020. Intraocular pressure (IOP) elevation is a specific risk factor in glaucoma and occurs due to aqueous humor drainage resistance at the trabecular meshwork (TM). The use of an inducible/iatrogenic form of OAG, steroid-induced glaucoma (SIG), provides a controlled model for experimental study. A third of the population can develop IOP elevation and glaucoma following steroid exposure. The mechanism of SIG is also unknown. In previous studies, steroids caused a reduction in tissue plasminogen activator (tPA) at the TM, and administration of tPA prevented steroid-induced IOP elevation in sheep and prevented steroid-induced outflow facility reduction in mice. Our research seeks to determine the mechanism by which tPA regulates aqueous humor outflow and investigate its therapeutic potential. tPA is a serine protease, involved in the fibrinolytic cascade, that is commercially available and used in post-stroke therapy. tPA is comprised of catalytic and non-catalytic regions, allowing it to function as both an enzyme and cytokine. Using a mutant protein form lacking enzymatic activity (NE-tPA) allows us to isolate its cytokine actions and avoid its fibrinolytic actions. The intraocular administration of NE-tPA significantly improved outflow facility in mouse models of SIG. Furthermore, NE-tPA rescued outflow facility reduction in genetically altered mice lacking tPA expression (PlatKO). Experiments are being conducted to determine effects in human tissues and identify the receptor. Therefore, NE-tPA can serve as a potential therapeutic to enhance aqueous humor outflow and prevent IOP elevation following steroid exposure. Its applicability to other forms of OAG remains to be explored.

Bo Lin

Advisor(s): Matthew Pincus

Acetoacetate Enhances the Cytotoxicity of Anti-tumor Agents on Cancer Cells Without Itself Inducing Cell Death

Introduction: Chemotherapeutic drugs are known to cause toxicity to normal cells giving rise to serious side effects. There has therefore been a quest for finding agents that would lower effective doses of these drugs to minimize undesirable side effects.

We have now obtained evidence that the ketogenic agent, acetoacetate (AcAc), lowers the doses of three chemotherapeutic drugs, i.e., rapamycin, methotrexate and the anticancer peptide, PNC-27, needed to kill cancer cells.

Methods: MCF-7 human breast cancer cells were incubated in 10⁻⁶ mM glucose medium with different doses of each anti-cancer agent (range 0-20 nM for rapamycin and methotrexate, 0-400 ug/mL for PNC-27) and different concentrations of AcAc (range 0-40mM) for 48 (PNC-27) or 72 hours (rapamycin and methotrexate). SW480 colon cancer cells were incubated under the same conditions with rapamycin and methotrexate.

Results: AcAc induced a dose-dependent inhibition of cancer cell growth of both MCF-7 and SW480 cells such that growth was totally inhibited at concentration of 20 mM with no evidence of cell death. Furthermore, AcAc induced a dramatic decrease in cancer cell viability for both rapamycin and methotrexate of both cell lines and a major increase in cell killing when MCF-7 cells are treated with PNC-27. For example, for MCF-7 cells, 15 mM AcAc caused a twofold increase of cell killing with 10 nM rapamycin, a three-fold increase of cell killing with 10 nM methotrexate and an almost three-fold increase in cell killing with 200 ug/mL PNC-27.

Conclusions: AcAc significantly reduces the therapeutic concentration of all three chemotherapeutic agents. These findings suggest that ketogenic diets and/or AcAc infusions can reduce the doses of chemotherapeutic agents without sacrificing their efficacies while at the same time preventing undesired side effects.

Carmelo LoMonaco

Advisor(s): Mohammad Faysel

Investigating APOE4 Gene Dose Effect and Risk Factor Prevalence Among Race Groups

Objective: The main objective of this study is to characterize the effects of APOE4 gene dose on cognitive ability and concentrations of pathological protein, along with comparing the prevalence of APOE4 among different race populations.

Methods: The Alzheimer's Disease Neuroimaging Initiative (ADNI) database was accessed. Key variables used to carry out a retrospective statistical analysis include participant race, APOE4 status, their score on MMSE and ADAS-Cog11, and concentrations of ABETA and TAU in their system. Mean scores on MMSE and ADAS-Cog11 were compared across 3 genotype groups (0,1, or 2 APOE4 alleles) using an ANOVA. Similarly, concentrations of ABETA and TAU protein were compared among the same 3 genotype groups using an ANOVA to determine if there was a significant difference in group means. Finally, APOE4 allele frequency among 5 different race groups (Black, Asian, Native American Indian, Hawaiian/Pacific Islander, White) were compared using chi-squared analysis.

Results: Scores on MMSE were significantly different across the genotype groups (mean=26.8, $p<0.0001$) as were scores on ADAS-Cog11 (mean=11.2, $p<0.0001$). Mean ABETA concentrations among the genotype groups varied significantly from each other (mean ABETA=828.8 pg/mL, $p<0.0001$), as did mean concentrations of TAU (mean TAU=260.82 pg/mL, $p<0.0001$). There was no statistically significant difference in APOE4 allele frequency among the races ($p=0.21$).

Discussion and Conclusion: Our study revealed that having one or more copies of the APOE4 risk factor would lead to worse performance on MMSE and ADAS-Cog11, which is consistent with previous studies. Also, participants who had one or both copies of APOE4 were shown to have lower mean levels of ABETA, but higher levels TAU, which contrasts many previous studies. Finally, the APOE4 allele frequency is not significantly different among the different races, although previous studies show it to be more prevalent in the Black population.

Sridesh Nath

Advisor(s): Patrick Geraghty

Protein Phosphatase 2A Prevents Cigarette Smoke-Induced Cathepsin S and Loss of Lung Function

Introduction: Cathepsin S (CTSS) is a cysteine protease that is observed at higher concentrations in bronchoalveolar lavage fluid and plasma of chronic obstructive pulmonary disease (COPD) subjects. The objective of this study was to investigate whether CTSS is involved in the pathogenesis of cigarette smoke-induced COPD and determine whether targeting upstream signalling could prevent smoke induced disease.

Methods: Cathepsin S expression was investigated in animal and cell models of COPD. Ctss^{-/-} mice were exposed to long-term cigarette smoke and forced oscillation and expiratory measurements were recorded. Animals were administered chemical activators of protein phosphatase 2A (PP2A).

Results: Here we observed enhanced CTSS expression and activity in mouse lungs following exposure to cigarette smoke. Ctss^{-/-} mice were resistant to cigarette smoke-induced inflammation, airway hyperresponsiveness, airspace enlargements and loss of lung function. CTSS expression was negatively regulated by PP2A in human bronchial epithelial cells isolated from healthy non-smokers and COPD donors. Modulating PP2A activity, with a chemical inhibitor or activator or PP2A specific shRNA, during acute smoke exposure in mice altered inflammatory responses and CTSS expression and activity in the lung. Enhancement of PP2A activity prevented chronic smoke induced COPD in mice.

Conclusion: Our study indicates that the decrease in PP2A activity that occurs in COPD contributes to elevated CTSS

expression in the lungs and results in impaired lung function. Enhancing PP2A activity represents a feasible therapeutic approach to reduce CTSS activity and counter smoke-induced lung disease.

Joel Rosiene

Advisor(s): Marcin Imielinski

Emerging Landscapes of Structural Variation in Cancer

Analysis of structural genomic variants and their specificity of association with altered transcriptional states and driver events remains an open realm of investigation in cancer biology. At present, clinical exome and targeted sequencing panels, such as WCMC EXaCT-1 and MSK-IMPACT, represent the standard of care in clinical cancer genomics. Notably, emerging analytical techniques coupled to the developing wealth of deep sequenced cancer whole genomes have enabled the characterization of novel, highly complex genomic states focal to regions of the genome not covered by exome based tests. In this work we describe multiple complex event types which have been identified within a pan-cancer analysis cohort via the application of graph based genomic modeling and subsequent topic modeling upon generated graph features. The diversity of complex event types discovered includes frank tandem duplication, local chromothripsis/chromoplexy, and a number of novel event types as yet undescribed in the literature. Additionally, we are able to demonstrate that, using features defined within the structural genomic space, particular patterns of rearrangement are enriched in different genotypic contexts. In one example, we are able to demonstrate an association between Homologous Recombination Deficiency (HRD) status, the previously defined Catalogue of Somatic Mutations In Cancer (COSMIC) signature 3, and our topic model defined structural variant signature 11. The implications of these analyses describing diverse alterations derived from the non-coding genome are such that the implementation of clinical whole genome sequencing can be expected to expand rapidly in the coming years.

Niki Sheth

Advisor(s): David Schwartz

Burnout in Radiation Oncology: A Pilot Residency Wellness Program

Objective: Residency burnout has been of increasing concern in recent years and radiation oncology residents are no exception. As there has been no formal residency wellness curricula published within the field, we set about to report upon the process of formation of a pilot wellness program developed within the SUNY Downstate Radiation Oncology Residency program.

Methods: First, a wellness committee was established with the residency program with an attending advisor. Prior to initiation of the curriculum, a questionnaire was distributed to the residents to gauge interest in wellness activities and to determine presence of any major concerns preliminarily relating to wellness. When it came to development of the specific curriculum, an informal survey of other residency programs within the hospital was also conducted. In order to target the needs of our radiation oncology department specifically, we focused on the most popular options from the initial questionnaire as well as our unique stressors. The questionnaire was then again distributed approximately 1 year later.

Results: The wellness committee conducted meetings, mostly via conference call, a total of 13 times during the period reported, 3/24/17-7/13/18. The ultimate curriculum design included a variety of events: a formal retreat for the incoming residents, a lecture on burnout, less formal weekend and after-work gatherings, as well as a guided meditation session. A list of wellness and/or mental health resources was also compiled and made available to residents. Lists of resources were compiled and distributed to the residents along with encouraging supplementary content in the form of a wellness newsletter.

Conclusion: The activities of this pilot wellness program represent the first such curriculum to be reported in our field. We encourage other departments to pursue wellness efforts and hope that they will be aided by the individual and organizational support to help maximize its impact.

Stacey Subbie-Saenz de Viteri

Advisor(s): Jacquelyn Meyers

The Role of Trauma, Familial and Polygenic Risk for Alcohol Dependence on Post-Traumatic Stress Disorder and Executive Functioning in Adolescence and Young Adulthood

Those with a family history of alcohol dependence (AD) are more likely to experience traumatic events, post-traumatic stress disorder (PTSD), and AD, all of which have independently been shown to adversely affect planning and problem-solving aspects of executive function. Despite higher incidence of comorbid AD found in individuals with PTSD, few studies have examined these risk factors together. Using data from the Collaborative Study on the Genetics of Alcoholism (COGA) prospective cohort (N=3910), we investigated associations of (1) trauma exposure (assaultive, nonassaultive, and sexual assaultive), (2) family history density of AD (FHD), and (3) polygenic risk scores (PRS) derived from a recent Psychiatric Genomics Consortium (PGC) GWAS of DSMIV AD on (1) PTSD, AD, and comorbid PTSD/AD, and (2) planning and problem-solving ability assessed using the Tower of London test. The PGC AD PRS (p -threshold <0.05) provided genomic support for the associations observed among FHD and PTSD, AD, and PTSD/AD ($p<0.001$). Assaultive trauma moderated the association of the AD PRS (p -threshold $<10^{-4}$) with PTSD and PTSD/AD ($p<0.05$) and not with AD. Assaultive trauma was associated with poor planning and problem solving ($p<0.01$). The AD PRS (p -threshold <0.05) was associated with poor problem solving ($p<0.05$), which was moderated by assaultive ($p<0.05$) and non-assaultive ($p<0.01$) trauma. These findings suggest that familial and genetic risk for AD and exposure to trauma influence both risk for PTSD and AD, as well as planning and problem solving.

Kristen Whitney

Advisor(s): Peter Bergold

Delayed dosing of minocycline plus N-acetylcysteine limits gray matter injury and restores function after experimental TBI

There are currently no approved drug treatments for traumatic brain injury (TBI). After TBI, treatment may be delayed hours to days after injury due to lack of medical access or perceived symptom resolution. Therefore, a clinically useful drug to treat TBI must retain potency with delayed dosing. We examined the potency of the drug combination minocycline plus N-acetylcysteine first dosed 72 hours after injury (MN72) in a unilateral closed head injury (CHI) mouse model. CHI produces long-term and, likely permanent, impairments on Barnes maze, a spatial navigation task that requires one intact hippocampus. CHI also decreases synaptic density and impairs long term potentiation (LTP) in the hippocampus ipsilateral and contralateral to the impact site. MN72 improves acquisition of Barnes maze, increases synaptic density and restores LTP only in the contralateral hippocampus. In contrast, a first dose of drugs at 12 hours (MN12) post-injury bilaterally restores behavior and LTP. At 14 days post-injury, hippocampal regions CA3 and CA1 have bilateral neuronal loss. Golgi stain analysis of the surviving neurons reveals fewer dendrites with shorter branches and reduced complexity and synaptic fields. In CA1, MN72 bilaterally prevents neuronal loss and prevents dendritic degeneration. MN72 does not prevent CA3 neuronal loss, but protects spared neurons from further dendritic degeneration. These data suggest that (1) CHI produces a diffuse gray matter injury that spreads beyond the initial impact site and (2) MN72 is less potent than MN12, yet MN72 retains potency since there are multiple cellular and synaptic functions that can be targeted with drugs 3 days after injury. Minocycline plus N-acetylcysteine limits gray matter injury and improves cognition and memory when dosed at a clinically relevant therapeutic window, and is an excellent candidate to treat clinical TBI.