Joshua J. Joseph, MD

Talk Title: The Role of Modifiable Lifestyle Factors and the Renin-Angiotensin-Aldosterone System in Diabetes Among African Americans

Type 2 diabetes mellitus (diabetes) is more prevalent among African Americans (AAs) compared to non-Hispanic whites (NHWs). Recent trends indicate that diabetes incidence has plateaued among NHWs, but continues to rise among AAs. Thus, examining potential diabetes prevention strategies in AA populations is of paramount importance. The two strategies that will be explored are modifiable lifestyle factors and the renin-angiotensin-aldosterone system. Modifiable lifestyle factors such as physical activity, sedentary behaviors, dietary intake and smoking are well described in NHWs, but evidence on the role of modifiable risk factors in diabetes prevention in AA populations is lacking. In the Multi-Ethnic Study of Atherosclerosis, attainment of ideal cardiovascular health components (total cholesterol, blood pressure, dietary intake, tobacco use, physical activity and body mass index) was associated with a greater magnitude of risk lowering among NHWs compared to AAs. Thus, we performed two further analyses evaluating: 1) the role of modifiable lifestyle factors (exercise, diet, smoking, TV watching, and sleep-disordered breathing burden) and 2) the role of ideal cardiovascular health in the development of diabetes among AAs in the Jackson Heart Study. Our work shows that modifiable lifestyle factors play a role in the development of diabetes in AAs but there are significant racial/ethnic differences. Thus, it is critical to understand novel biological mechanisms underpinning diabetes among AAs. We have been investigating the role of the renin-angiotensin-aldosterone system in diabetes, which may provide a potential targeted strategy for prevention of diabetes among AAs.

Lisa Scarton, PhD

Talk Title: Type 2 Diabetes Prevention and Management: A Multi-Generational Intervention for American Indian and Alaska Native Families

American Indian and Alaska Native (AIAN) populations experience the highest prevalence rate of type 2 diabetes (T2D) in the U.S. and have a disproportionate burden of diabetes complications compared to other racial or ethnic groups. Due to genetic and cultural factors as well as shared environmental factors, T2D is often considered a family disease. Unfortunately, few culturally relevant multi-generational interventions have been developed and tested in the AIAN population. The purpose of my research is to reduce T2D health disparities and improve T2D health outcomes in AIAN populations through the development of a culturally relevant familial multi-generational intervention. The first step involves a two-phase pilot study. Phase 1 of the study will include up to 6 focus groups of AIAN adults with T2D and will seek input on types of intervention components (content and process) that participants may find culturally relevant. Phase 2 will include AIAN families that have at least one adult diagnosed with T2D and one youth who has been diagnosed with prediabetes or is at high risk for T2D. The phase 2 study design will be a RCT to determine feasibility of the intervention. Culturally relevant multi-generational interventions used in the AIAN population, if successful, may highlight the importance of culturally relevant family-centered care in improving health outcomes and increasing health equity while underscoring the need to change the approach used by health care providers when working with ethnic minority populations.
Faustine Williams, PhD, MPH, MS

Talk Title: Using Community-Based System Dynamics and Storytelling to Improve Breast Cancer Outcomes: Overarching Conceptual Framework

Although cancer mortality rates have decreased in the United States (U.S.) over the last two decades, geographic disparities have persisted, with lower decline in the Appalachian region. Between 2003 and 2007, breast cancer (BC) mortality rate among Appalachian women was 24.1 per 100,000, which is significantly higher than non-Appalachian women in the U.S. (23.3 per 100,000). Overall, Central Appalachian states like Kentucky, Tennessee, Virginia, and West Virginia experienced the highest BC mortality. For instance, the incidence rate for BC among white women in Claiborne County in Appalachian Tennessee was 131/100,000 and the mortality rate was 41/100,000, compared to 122.1/100,000 and 24/100,000 for the U.S., respectively. Underlying reasons for this disparity are complex and not well documented. A number of studies have indicated that factors such as cultural perceptions about breast health, screening, and unequal treatment/delay may account for the differences in BC mortality and survival rates. However, no studies have comprehensively assessed the influence of contextual factors in both rural and urban communities, especially poor and remote underserved areas like Central Appalachia. To fill this gap, I propose a novel transdisciplinary mixed-methods research approach. Community-based system dynamics, focus group, and key informant interviews to identify individual and community contextual factors contributing to high breast cancer mortality in Central Appalachia. Spatial analysis to identify hot spot areas for intervention. Additionally, innovative stories will be collected from survivors in the community and used as an intervention to inspire positive health behavior change among women in Central Appalachia to reduce disparities in cancer.

Timiya S. Nolan, PhD, RN, ANP-BC

Talk Title: "Feeding" Young African American Breast Cancer Survivors with a Quality of Life Intervention

There are no published randomized control trials that comprehensively address quality of life (i.e. physical, psychological, social, and spiritual) in breast cancer survivors who are both young (less than age 45) and African American (AA). Yet, young AA women are disproportionately affected with breast cancer and report poorer quality of life (i.e., overall and physical quality of life) throughout survivorship. An existing, effective quality of life intervention adapted for young AA survivors may yield similar effectiveness. My dissertation informed the first iteration of an age- and culturally-targeted quality of life intervention (Y-AMBIENT). Compared to the original intervention, Y-AMBIENT incorporates more spirituality along with content related to finances and insurance, communicating survivorship concerns, dating and relationships, and self-management activities and resources. Over four months, a trained support person delivers via three themed-education sessions with three follow up sessions. Y-AMBIENT content is reinforced with written and video content. The purpose of the current study is to further adapt and pilot test an age- and culturally-targeted quality of life intervention (Y-AMBIENT). Future research will include conduct of a large randomized control trial of the intervention compared to a wait-control group for evaluation of effectiveness.
Zeynep Madak-Erdogan, PhD

Talk Title: Development of multi-scale analysis methods to understand role of extranuclear initiated estrogen receptor in metabolic disease and breast cancer

The importance of kinases in breast cancer and in metabolic disease is well known. In breast cancer increased kinase activity through phosphorylation, mutations or increased expression is often observed in clinical samples and is associated with a poorer prognosis. In addition, kinases play major roles in the regulation of metabolism. However, the mechanisms underlying the interplay between ERalpha and protein kinase pathways in breast cancer and metabolic disease, and the processes by which ERalpha influences these pathways are poorly understood. Our main aim is to elucidate the cross-talk and interrelationships between genomic ERalpha pathways and extranuclear ERalpha-initiated kinase signaling. We will present our recent findings on how these kinase pathways impact ERalpha actions in the nucleus in breast cancer and in metabolic syndrome associated with menopause.
Pranidhi Sood, PhD

Talk Title: Transcriptional Dynamics of Single-Cell Regeneration in Stentor coeruleus

In many multicellular organisms, the ability to regenerate tissue is lost through the course of development. Some organisms, including flatworms, salamanders and zebrafish, retain regenerative potential throughout their lifetimes and are powerful systems for uncovering mechanisms of tissue regeneration. Repair at the single cell scale is also critical for an organism's wound healing response; however, little is known about regeneration at the level of an individual cell. We are developing the ciliate, Stentor coeruleus, as a unicellular model for studying regeneration and wound repair. In addition to its remarkable size (cells can reach up to 1 mm in length) and subcellular complexity, Stentor has incredible regenerative abilities: almost any portion of the cell, when removed through excision, will give rise to a normally proportioned cell with intact subcellular organization. Pioneering studies of Stentor elucidated many morphological principles of its regeneration (Morgan, 1901; Tartar, 1961), but we have much to learn about the molecular basis of Stentor's regenerative and healing abilities. We have recently sequenced and annotated the genome of Stentor coeruleus. With this tool in hand, I am using NGS approaches to describe the molecular details of regeneration of a key organelle in the cell -- the oral apparatus, a complex structure composed of thousands of cilia. A detailed transcriptional time course revealed the involvement of core, conserved genes involved in centriole and cilia production. In combination with RNAi manipulations, these studies will help elucidate the fundamental principles of cell regeneration and healing at the scale of a single cell.

Uduak George, PhD

Talk Title: Computational modeling of embryonic lung branching

Lung branching morphogenesis proceeds in three stereotyped modes (domain, planar, and orthogonal branching). Much is known about the molecular players, including growth factors such as fibroblast growth factor 10 but it is unknown how these signals could actuate the different branching patterns. With the aim of identifying mechanisms that may determine the different branching modes, we developed a computational model of the epithelial lung bud and its surrounding mesenchyme. We studied transport of morphogens and localization of morphogen flux at lobe surfaces and lobe edges. We find that a single simple mechanism is theoretically capable of directing an epithelial tubule to elongate, bend, flatten, or bifurcate, depending solely on geometric ratios of the tissues in the vicinity of a growing tubule tip. Furthermore, the same simple mechanism is capable of generating orthogonal or planar branching, depending only on the same geometric ratios.
Angela Brooks, PhD

Talk Title: High-throughput and full-length characterization of transcript isoforms to investigate cancer-associated mutations

The splicing factor SF3B1 is one of the most frequently mutated genes in chronic lymphocytic leukemia (CLL). Work from our group (Wang, et al. Cancer Cell 2016) and others have identified hundreds of altered 3' splice site changes associated with SF3B1 mutation using Illumina RNA-Seq in primary patient samples. A barrier in understanding how these splicing changes affect gene and pathway function is that we do not know the full-transcript context in which these changes are occurring. Our lab is developing computational methods for full-length isoform-level expression analysis using nanopore sequencing technology to further characterize cancer-associated transcript variants. We have sequenced primary CLL patient samples with and without SF3B1 mutation using Oxford MinION nanopore sequencing and can detect altered isoforms known to be associated with SF3B1 mutation, as well as many novel transcripts. We have benchmarked our computational approaches using spike-in RNA standards. Our preliminary results demonstrate that nanopore sequencing of primary cancer specimens allows us to gain new biological insight into cancer transcript variants.

Daniel Liefwalker, PhD

Talk Title: Codisruption of Epigenetic Drivers in MYC-Addicted T-ALL

c-MYC is a bHLH transcription factor that heterodimerizes with MAX to form an active transcription factor complex that binds to promoter regions across the genome. MYC is a potent oncogene that promotes tumorigenesis in many cell types. Several studies have shown that tumor cells can be dependent on proto-oncogenes such as MYC, a state called oncogene addiction. Recent findings have revealed that c-myc amplifies active gene programs, and our group has previously identified a unique MYC transcriptional signature. In an effort to understand how MYC regulates discrete transcriptional programs across the genome we searched for potential cofactors that coordinate with MYC. Using computational approaches we examined several publicly available human data sets as well as our own conditional MYC murine model for potential co-factor interactions. We have determined that several Jumonji family members coordinate with MYC expression. Currently, we are using CRISPR/Cas9 mediated disruption of target genes in murine cells to investigate whether these genes have a casual role in MYC oncogene addiction.
Talk Title: Uncovering the Genetic Causes of Keloid Formation

Keloids result from an exaggerated response to cutaneous wound healing. They grow beyond the original boundaries of the cutaneous injury, and no known treatment consistently prevents their occurrence or recurrence. Familial inheritance and ethnic differences in prevalence imply that certain genes may predispose people to keloid formation. However, little is known about the genetic factors contributing to keloids in individuals of African or Hispanic ancestry, the two ethnic groups most likely to develop keloids. My research aims to test two hypotheses: that specific genetic variations confer susceptibility to keloid formation in those of African and Hispanic ancestry, and that there exist uncharacterized genes, in keloids as well as in normal skin of those that keloid, critical to keloid pathogenesis. A keloid registry has been established to better characterize subjects and families of African and Hispanic descent with keloids. In participants with a family history of keloids, the other family members (both affected and unaffected individuals) are invited to participate. Linkage analysis and whole exome sequencing are being performed on families with keloids to identify susceptibility loci and rare sequence variations that co-segregate with keloid formation. Whole transcriptome sequencing is being performed on RNA from keloid and normal tissue obtained from the same individual to identify difference in gene expression. Control normal tissue from matched individuals with no personal or family history of keloids will also be studied. The knowledge derived from these inquiries may provide new insights that will guide the development of better treatments for this disease.
Erik Rodriguez, PhD

Talk Title: A far-red fluorescent protein evolved from a cyanobacterial phycobiliprotein

Fluorescent proteins (FPs) are invaluable tools for biology, enabling tracking of gene expression, cell fate, and genetically encoded fusion proteins for precise localization within a cell. Traditional FPs developed from jellyfish and coral are limited in wavelengths, consume oxygen, and produce a stoichiometric amount of hydrogen peroxide upon chromophore formation, thus requiring an aerobic environment tolerant of reactive oxygen species. Far-red and near-infrared FPs are desirable for imaging in living animals because less light is scattered, absorbed, and/or reemitted by endogenous biomolecules. Previously, near-infrared FPs were engineered from nonfluorescent phytochrome precursors, but these suffer from poor quantum yield (QY), are very dim and photobleach rapidly. A new FP was created by evolving an allophycocyanin α-subunit from a cyanobacterium. The new FP, named small Ultra-Red FP (smURFP), was engineered to bind biliverdin, an endogenous heme metabolite ubiquitous to mammals, without an auxiliary lyase. smURFP is a homodimer of 15 kDa subunits and has excitation and emission maxima at 642 and 670 nm and the largest QY (0.18), biliverdin incorporation rate, metabolic stability, and photostability of any current biliverdin binding FP. New methods for increasing chromophore concentration inside cells significantly enhances smURFP fluorescence and is comparable to jellyfish and coral derived FPs. Using smURFP and a phytochrome FP, a far-red and near-infrared fluorescent ubiquitination cell cycle indicator (FUCCI) was created, which should be suitable for monitoring cell cycle progression in intact mammals. New imaging applications using smURFP will be discussed.

Gregory A. Payne, MD, PhD

Talk Title: The Role of Proline-Glycine-Proline in Cardiac Allograft Vasculopathy and Acute Rejection

The extracellular matrix (ECM) is a dynamic, bioactive structure critical to organ development, structure and function. Excessive remodeling of the ECM is a hallmark of a variety of inflammatory conditions including vascular disease. Endothelin-1 (ET1) synthesis is understood to promote cardiovascular diseases including acute cardiac transplant rejection; however, the contribution of ECM-derived chemokines (matrikines) to vascular inflammation remains poorly understood. Herein we demonstrate that the matrikine acetylated Proline-Glycine-Proline (PGP) stimulates vascular inflammation through activation of endothelial CXC Chemokine Receptor 2 (CXCR2) and production of endothelin-1 both in vitro and in vivo. As a proof of hypothesis, we demonstrate that corona PGP levels associate with both circulating endothelin-1 and acute rejection in cardiac transplant patients (sensitivity of 100% and specificity of 86%). These findings establish PGP as a novel mediator in cardiovascular disease, and implicate bioactive matrix fragments as underappreciated agents potentially active in numerous conditions propagated by progressive vascular inflammation.
Jaira Ferreira de Vasconcellos, PhD

Talk Title: The LIN28-let-7-IGF2BP axis regulates fetal hemoglobin in humans

Sickle cell disease (SCD) is among the most common genetic diseases worldwide. Pharmacologic and genetic regulation of fetal hemoglobin (HbF) remains a major treatment goal for SCD; it is predicted that maintaining HbF at levels above 20% in circulating red cells ameliorates the clinical complications of the disease. In C. elegans, the let-7 miRNA axis regulates larva-to-adult timing and cellular fates. In human reticulocytes, the let-7 miRNAs significantly increase during the fetal-to-adult developmental transition. Therefore, we studied developmental expression and related effects upon HbF levels for the human LIN28-let-7-IGF2BP pathway. In contrast to increased let-7 miRNAs, adult human erythroid tissues demonstrated developmental silencing of LIN28B, IGF2BP1 and IGF2BP3. Lentiviral constructs for the over-expression (OE) of LIN28B, IGF2BP1 and IGF2BP3, and suppression of let-7s in cultured adult CD34(+) cells were compared with donor-matched control transductions. Hemoglobin protein expression patterns measured by HPLC showed variable HbF effects between the constructs compared with 4-6% HbF levels in control transductions. LIN28B-OE increased HbF to 33.6 ± 9.4%, p=0.01. Suppression of the let-7 miRNAs caused a higher HbF of 38.2 ± 3.8%, p=0.00003. Interestingly, while IGF2BP3-OE had only moderate effects on HbF to 18.6 ± 1.0% (p=0.0021), IGF2BP1-OE caused robust effects on HbF with levels rising to 68.6 ± 3.9%, p=0.0004. Post-transcriptional regulation of the HbF-related transcription factor BCL11A was also detected by RNA-binding and a nearly complete absence of BCL11A protein after IGF2BP1-OE in adult cells. Overall, our results support the notion that the LIN28-let-7-IGF2BP pathway may help define the erythroid developmental clock.

Mariana P. Torrente, PhD

Talk Title: Distinct Histone Post-Translational Modifications Are Connected To Neurodegenerative Disease Proteinopathies

Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease (PD) are devastating neurodegenerative diseases involving the progressive degeneration of neurons. No cure is available for patients diagnosed with these diseases. A prominent feature for both ALS and PD is the accumulation of protein inclusions in the cytoplasm of degenerating neurons; however, the particular protein comprising these inclusions varies. The RNA-binding proteins TDP-43 and FUS are most notable in ALS, while alpha-synuclein aggregates into Lewy bodies in PD. In both diseases, genetic causes fail to explain the occurrence of a large proportion of cases and, thus, both are considered mostly sporadic. We aim to understand the role of epigenetics in ALS and PD. In particular, we are interested in delineating histone post-translational modification profiles in both yeast and human ALS and PD models. Histones from yeast cells recapitulating FUS, TDP-43, and alpha-synuclein proteinopathies are probed for different histone modifications. Remarkably, we find distinctive changes in histone modification profiles for each proteinopathy model. We detect the most striking changes in the context of FUS aggregation: changes in several histone marks support a global decrease in gene transcription. We also detect more modest changes in cells overexpressing TDP-43 and alpha-synuclein. Our results highlight a great need for the inclusion of epigenetic mechanisms in the study of neurodegenerative disease. We hope our work will pave the way for discovery of more effective therapies to treat patients suffering from ALS, PD, and other neurodegenerative diseases.
Caitlin Howe, PhD

Talk Title: Methylome changes in sorted cord blood CD4+ cells associated with prenatal tobacco smoke exposure

Prenatal tobacco smoke (PTS) exposure has been associated with altered DNA methylation in newborns. However, most studies utilized methylation arrays, which cover <5% of CpG sites in the human genome, and measured DNA methylation in cord blood, which consists of a mixture of different cell types. Our objective was to evaluate whether PTS exposure alters the methylome of sorted CD4+ cord blood cells from a subset of Hispanic white newborns in the Southern California-based Maternal and Child Health Study (MACHS). 10 PTS-exposed MACHS participants were matched to 10 unexposed newborns based on maternal age, BMI, and diabetes status, and gestational age. Whole genome bisulfite sequencing was performed on CD4+ cells from sorted cord blood at an average CpG depth of 6X. Sequences were mapped to Genome Reference Consortium Human Genome Build 37, using the Wildcard ALignment Tool. Differentially methylated (DM) CpGs and regions (DMRs) were identified using the MethPipe software package, adjusting for baby’s sex and maternal working status. Gene set enrichment tests were conducted using enrichR. We identified >10,000 DM CpG sites and >500 DMRs (PFDR < 0.05), which were significantly enriched within promoter, exon, and 3'ends of genes and within active enhancers. Four PANTHER pathways, which are critical for embryonic development or neuroplasticity, were significantly enriched for genes mapping to DM CpG sites. Using WGBS, we identified >10,000 CpG sites and >500 regions that were DM by PTS exposure, many of which had not previously been identified, in sorted cord blood CD4+ cells.
Adewole Adamson, MD, MPP

Talk Title: Surgical delays in melanoma associated with insurance type

Health insurance can affect quality of care for cancer patients. We analyzed factors associated with surgical treatment delays of melanoma patients with Medicare, Medicaid, or private insurance. Patient population and Methods: Patients diagnosis with melanoma (2004 to 2011) were identified through the North Carolina Central Cancer Registry and linked with claims from Medicare, Medicaid, and private insurance. For study inclusion, patients had a first or only diagnosis of melanoma and continuous enrollment for at least one month prior to diagnosis to 12 months after diagnosis. The primary outcome was surgical delay, defined as surgical excision of more than 6 weeks after diagnosis. Generalized linear models with log link, Poisson distributions, and robust standard errors were used to estimate adjusted risk ratios (RR) to model risk of delay. A total of 7,629 patients were included, 48% (n=3,631) Medicare, 48% (n=3,667) privately insured and 4% (n=331) Medicaid. After adjustment, the risk of surgical delay was increased in patients with Medicaid compared to private insurance (RR 1.36 [95% CI, 1.09-1.70]). Delays were more likely in non-whites (RR 1.38 [95% CI, 1.02, 1.87]). Surgical delays were less likely if the physician performing the surgery (RR 0.82 [95% CI, 0.72-0.93]) or the diagnosing provider (RR 0.81 [95% CI, 0.71-0.93]) was a dermatologist compared to a non-dermatologist. Surgical treatment delays were common, but decreased in patients diagnosed or treated by a dermatologist. Medicaid patients experienced the most delays. A reduction in delays could be achieved through better access to specialty-care and cross-disciplinary co-ordination.

Dana Prince, PhD, MPH

Talk Title: Impact of Cumulative Risk on Homelessness for Youth Exiting Foster Care: Finding from the National Youth in Transitions Database

Annually approximately 28,000 youth "age out" of the US foster care system. Securing stable housing is critical for the successful navigation of other normative transitions in young adulthood. Housing instability is associated with a range of adverse outcomes. However, studies to date have not examined the impact of state-level factors, such as child welfare funds allocated to housing supports for these youth, or variation in state housing market factors, on reducing homelessness. This study used two waves of longitudinal data from the National Youth in Transition survey, a national sample of older foster youth transitioning from care (N=7,449). Multilevel modeling was employed to simultaneously examine the relationships of individual risk and protective factors, child welfare case characteristics, state child welfare spending on housing supports and proportion of renter housing burden on youth homelessness at age 19. Lifetime experience of homelessness, substance abuse problem, and incarceration before age 17 significantly predicted greater risk of being homeless at age 19. Removal from home for child behavioral problem, placement instability and history of runaway increased risk. Conversely, connection to an adult, kinship care placement and remaining in foster care to age 19 reduced risk of homelessness. State-level variation in spending on housing supports for transition-age youth and the proportion of renters who are housing cost burdened did not impact homelessness. Further research is warranted to explicate the relationship of substance use problems and incarceration on later homelessness and to identify state-level factors that may reduce homelessness among this high risk group.
LaTrice Montgomery, PhD

Talk Title: Marijuana and Tobacco Co-Use among African American Young Adults

Marijuana and tobacco co-use is associated with several negative health consequences, such as an increased risk of developing cannabis and tobacco use disorders and exacerbation of mental health symptoms. Although studies have identified an increased likelihood of co-use among African Americans relative to other racial/ethnic groups, very few studies have assessed the reasons for co-use or the prevention and treatment needs of African Americans who use marijuana and tobacco. My line of research aims to address these significant gaps in the literature, including a special focus on blunts (i.e., partially or fully-hollowed out cigars that are filled with marijuana). The societal/historical context of blunts in the African American community is one significant, yet understudied, contributor to the high rates of co-use in this population. This presentation will highlight recent national survey and social media (e.g., Twitter) studies on marijuana and tobacco co-use, especially through blunts, among African American young adults.

Mercedes M. Morales-Aleman, PhD

Talk Title: Sexual Healthcare Access among Adolescent Latinas in Alabama: Challenges and Opportunities for Health Promotion

Alabama (AL) experienced a 145% increase in its Latino population between 2000 and 2010, making it the state with the second fastest growing Latino population in the United States (US) during that time. Adolescent Latinas in the US and in AL are disproportionately affected by sexual health disparities compared to their non-Hispanic, white counterparts. This work examined adolescent Latinas' sexual healthcare needs through qualitative semi-structured interviews (phase 1 of 3-phase study). Community based participatory research (CBPR) and the socioecological model of health provided the philosophical and theoretical frameworks. In early 2017, we conducted 20 qualitative interviews with adolescents who: self-identified as Latina, were between 15 and 20 years, had been in the US for over five years, and lived West AL. A multi-coder, iterative process (between independent coding and consensus building) was used to code and analyze the interviews in NVivo 11. Three types of barriers were identified: (1) parental disapproval and embarrassment (peña); (2) structural barriers (e.g., lack of transportation); and (3) negative experiences with providers (e.g., perceived discrimination based on immigrant status). When asked what they would like in a sexual health promotion program, themes included: (1) "parents should be involved in programming"; and (2) "the program should be delivered by young Latinas who understand our experience". The next steps in this work will include developing community driven, theory based, culturally-relevant, multilevel intervention strategies through a community-engaged intervention mapping process. Our long-term goal is to implement intervention strategies that reduce sexual health disparities among this group in Alabama.
Tamanna Tiwari, MPH, MDS, BDS

Talk Title: Maternal Factors Associated with Dental caries in Urban Latino Children

The objective of this study was to describe maternal psychosocial and behavioral factors associated with early childhood caries in urban Latino mother-child dyads. A cross-sectional survey was conducted with 100 mothers whose children were patients at the Dental Center at Children's Hospital Colorado in Aurora, Colorado. All children participating in the study received an oral examination to measure decayed, missing, filled, surfaces (dmfs). Participating mothers were given the option to sign the consent form and complete the survey in English or Spanish, according to their convenience. The survey used demographic, behavior, knowledge and several psychosocial variables. Bivariate analysis was conducted with dmfs as a dependent variable. The associations between independent variables and dmfs were modeled using negative binomial regression. Mean dmfs for the entire sample was about 11 (SD =16.85). The mothers who spoke Spanish had children with higher dmfs 15.2 (P=0.046) compared to English speaking mothers (7.56). Preference of Spanish language was significantly associated with self-efficacy (P=0.0043), oral health knowledge, (P=0.0024), and three subscales of the Health Belief Model, Perceived Severity (P=0.057), Perceived Barriers (P=0.0002) and Perceived Susceptibility (P=0.008). Moreover, in the multivariate model, oral health behaviors and preferential use of Spanish remained a predictor of higher dmfs. Results of this study demonstrate that maternal oral health behaviors and preferred language are significant factors associated with early childhood caries in urban Latino children.
Dennis Jones, PhD

Talk Title: Methicillin-resistant Staphylococcus aureus pathogenicity causes sustained lymphatic dysfunction

Methicillin-Resistant Staphylococcus aureus (MRSA) is a major cause of morbidity and mortality worldwide and is a frequent cause of skin and soft tissue infections (SSTIs). Associated with SSTIs is a decline of lymphatic vessel function, increasing the likelihood for recurring bacterial infections and lymphedema. However, the mechanism of infection-induced lymphatic dysfunction remains unclear. To interrogate this, we utilized a model of localized MRSA infection. Intravital imaging revealed both an acute reduction in lymphatic contractility and lymph flow after infection as well as chronic lymphatic impairment long after the MRSA is cleared and inflammation is resolved. Attempts to inhibit host inflammation were not able to rescue lymphatic function during and after MRSA infection. Thus we are focusing our attention on MRSA produced products, including MRSA virulence factors. Using proteomic approaches we are identifying and testing candidate virulence factors in order to determine the mechanism of the long term inhibition of lymphatic pumping following MRSA infection.

Felipe H. Santiago, PhD

Talk Title: How Cryptococcus neoformans crosses cellular barriers

The fungal pathogen Cryptococcus neoformans infects the brain, killing hundreds of thousands of people yearly. However, it gains access to its host through inhalation, establishing first an infection in the lungs, away from the brain, the site of its fatal pathology. In order to reach the brain it has to overcome several obstacles, including surviving the onslaught of phagocytes and breaching cellular barriers formed by epithelial and endothelial cells. Experimental evidence suggests that host phagocytes play a role in this dissemination from lungs to brain, but this role remains ill defined. Using in vitro models of these barriers, I compared the different proposed mechanisms of crossing and tested whether host immune factors normally produced during infection affect the transmigration efficiency of the different pathways. I focused first on traversal of the blood-brain barrier (BBB), where I directly showed that Trojan horse transit contributes significantly to fungal BBB crossing. I am currently testing crossing of the lung epithelia, finding significant differences between the mechanisms used by the fungus when compared with the BBB. Understanding how Cryptococcus crosses cellular barriers has implications not only for development of new antifungal treatments but for others diseases involving pathogens acquired by inhalation and non-infectious diseases such as asthma or atherosclerosis. Here I present a general model for phagocyte assisted infection of the brain by Cryptococcus, and discuss possible roles for Trojan horses in dissemination out of the lungs.
Milena Gianfrancesco, PhD, MPH

Talk Title: Performance of machine-learning methods using electronic medical records to detect and predict a clinical infection

Varicella zoster virus infections (VZV) can be associated with significant morbidity in immunosuppressed hosts. However, methods do not exist to systematically identify which patients with rheumatic diseases are at highest risk for VZV, information critical for implementing preventive strategies such as vaccination or antiviral prophylaxis. Machine learning methods that can combine large amounts of information from across the electronic health record (EHR) are increasingly being explored in healthcare. In this study, we derived and compared machine learning algorithms to classify the development of VZV using health system wide EHR data. We used data from an EHR with over 800,000 patients from a university-based health system from 2012-2016. Both structured (immunizations, vitals, allergies, medications, laboratories, insurance, encounters, providers, demographics) and unstructured data (i.e. text from clinical notes) were used. A sample of 201 patients was selected and chart reviewed to validate case status. We used a supervised approach to identify predictors of VZV and compared performance metrics of 6 machine learning algorithms, including: logistic regression, elastic net, random forests, support vector machine, generalized boosted models, and Naïve Bayes. Preliminary results indicate that generalized boosted models based on 3 months of data prior to VZV outperformed all other algorithms (AUC 0.85; accuracy 0.80; Kappa 0.60) Top variables associated with VZV included sociodemographics (age, sex, race), clinical (blood pressure, BMI, medications), and health care utilization (number of encounters). Generalized boosted models outperformed other algorithms in identifying VZV in a large university health system. Further refinement of algorithms with a larger sample size and incorporating more data will assist in developing a highly accurate classification algorithm for VZV that can be used to inform clinical decision making in real-time. This proof-of-concept study highlights the promise of leveraging all the data available through EHR to flag patients who may be at risk for adverse drug events or medical complications before they occur.

Mohamed Abdel-Mohsen, PhD

Talk Title: Breaking the Sugar Code of HIV Persistence

All living cells assemble a diverse repertoire of glycan structures on their surface via their glycosylation machinery. With recent advances in the glycobiology field, host glycosylation and glycan-lectin signaling have been shown to play critical roles in immune responses and in cell-cell and cell-pathogen interactions. Glycan structure alterations have been identified as biomarkers for cancer and multiple cellular processes. Activated, HIV-infected cells have altered cell-surface glycosylation patterns with respect to resting, uninfected cells. While the association between hyposialylation and chronic HIV infection was suggested over two decades ago, the relevance of host glycosylation to HIV persistence has never been characterized. However, recent development in glycobiological technologies provides an opportunity to revisit this critical issue. In a recent publication, we demonstrated that the human carbohydrate-binding protein galectin-9 regulates HIV transcription and potently reactivates latent HIV in vitro, as well as ex vivo using CD4+ T cells from the blood of HIV+ individuals on suppressive antiretroviral therapy, in an N-glycan-dependent manner. This suggests that host glycan-lectin interactions likely mediate signals that define, in part, the transcriptional state of HIV and that host glycosylation machinery may be exploited to develop novel HIV therapeutic strategies. Furthermore, we recently used cutting-edge glycomics technologies to demonstrate that host glycan-lectin interactions and altered host glycosylation are associated with deficits in immune function that in turn contribute to HIV persistence. The cell-surface sugar-coating may hold the key to new therapeutics that can be harnessed to cure HIV and possibly a range of other infectious diseases.
Norberto Gonzalez-Juarbe, PhD

Talk Title: Caspase activation simultaneous to non-canonical necroptosis promotes inflammation during bacterial pneumonia

Necroptosis is an inflammatory cell death program traditionally understood to occur in exclusion of caspase activity. Caspases are cysteine-aspartic proteases that regulate inflammation and cell death programs. Only recently has RIPK3, a component of the necroptosis signaling pathway, been shown to activate parallel caspase-8 mediated apoptosis during Influenza infection. Here we show that respiratory epithelial cells (RECs) undergoing pore-forming toxin (PFT)-induced necroptosis simultaneously experienced caspase-2, -4, and -10 activation independently of RIPK3 activity (i.e. caspase-associated necroptosis, CAN). This impacted alarmin release and subsequent inflammation. RECs deficient on the effector molecule of necroptosis the mixed lineage kinase domain like pseudokinase (MLKL), treated with a pan-caspase inhibitor were protected in an additive manner against PFT-induced death. Subsequently, cleaved versions of these caspases were detected within RECs undergoing necroptosis. Caspase activation was observed in lung samples from mice and non-human primates experiencing Gram-negative and Gram-positive bacterial pneumonia, respectively. During apoptosis, caspase activation normally leads to cell shrinkage, condensation, and death in an immunouiescent manner. In contrast, caspase activity during PFT-induced necroptosis altered the morphological characteristics of RECs death and increased the release of alarmins and subsequent macrophage activation. Deletion of caspases -2 and -11, the mouse orthologue of caspase-4, reduced pulmonary inflammation and damage in a Serratia marcescens (Sma) model of pneumonia. Thus, caspase activity modified the morphological properties of PFT-induced necrototic death and plays a critical pro-inflammatory role during bacterial pneumonia. Together these results provide new roles for these non-canonical caspases and suggest they can be targeted for therapeutic purposes in addition to antimicrobials.
Kim-Lien Nguyen, MD

Talk Title: Ferumoxytol Enhanced Magnetic Resonance Imaging for Patient-Specific Cardiovascular Applications

Recent controversies about gadolinium use have led to rising interest in ferumoxytol as a contrast agent for magnetic resonance imaging (MRI). Gadolinium is associated with nephrogenic systemic fibrosis in patients with severe kidney disease and deposition in brain tissues of patients undergoing repeated gadolinium MRI. In contrast, ferumoxytol is an ultrasmall iron nanoparticle that is FDA-approved for the treatment of anemia in patients with kidney disease. Once taken up by macrophages, the iron core is metabolized by the reticuloendothelial system and incorporated into the body for vital biologic processes. As an agent with a long intravascular half-life and potent T1/T2 relaxivity, ferumoxytol can be leveraged for many applications beyond those available with gadolinium-based contrast agents. We aim to develop and validate a toolbox of ferumoxytol-enhanced MRI techniques for cardiovascular MRI applications. We demonstrate its value and effectiveness for cardiac phase-resolved MRI in small pediatric patients with congenital heart disease and patients with severe aortic stenosis and renal impairment who require vascular mapping prior to transcatheter interventions. We provide preliminary data for ongoing investigations using ferumoxytol-enhanced myocardial mapping techniques to establish a myocardial blood volume (MBV) index. The MBV index can be used to assess microvascular function and ischemic disease. Lastly, we summarize our safety experience and introduce the FeraSafe MRI Registry. Overall, ferumoxytol-enhanced MRI has high potential to offer a patient-specific approach to cardiovascular MRI applications and may serve as a safe and powerful alternative to gadolinium-enhanced MRI. The implications are substantial. Its footprint and research applications merit further investigations.

Wenndy Hernandez, MS, PhD

Talk Title: Using pharmacogenomic genotyping data to define genetic ancestry in patients and enable population-specific pharmacogenomic implementation

The allele frequencies of a number of clinically important pharmacogenomic variants vary between populations and clinical pharmacogenomic guidelines are now being published that include population-specific recommendations. Utilizing a development cohort of 1,572 individuals from 1000 Genomes, and two additional independent cohorts of Caucasians and African Americans (AA) plus a real-world validation population of patients undergoing pharmacogenomic genotyping, we demonstrated that clinical pharmacogenomic panels can estimate individual genetic ancestry (IGA) with excellent precision when compared to genome-wide genotyping (sensitivity >82%, specificity >80%, positive predictive value >95%, negative predictive value >47%). Integration of IGA into an institutional clinical decision support tool was accomplished to enable population-specific pharmacogenomic guidance at the point-of-care. These capabilities are immediately applicable to the need for implementing population-specific pharmacogenomic guidance for warfarin dosing in AA versus Caucasian patients and provide a real-world solution which will increasingly be extended to other populations and drugs as actionable pharmacogenomic evidence accumulates.
Clare Harrop, PhD

Talk Title: Understanding Social Motivation and Attention in Females with Autism Spectrum Disorder

Research suggests that females with Autism Spectrum Disorder (ASD) differ in subtle yet important ways. Two areas of distinction include fewer and/or different restricted and repetitive behaviors, particularly the content of circumscribed interests, and greater social motivation. These differences may contribute to later diagnoses and a greater ability to camouflage their difficulties. Eye tracking has been used to examine these areas in ASD, however has not examined sex differences. In a series of eye tracking studies, we examined sex differences in social and nonsocial attention in school-aged children with and without ASD. In a paired-preference paradigm with a face paired with an object, a sex effect was observed; females attended to faces first and spent longer looking at faces. In a social scene paradigm, typically developing (TD) children and ASD females attended to similar aspects of the scene, particularly those depicting triadic social interaction. ASD males focused more on objects and actions with objects. In the final paradigm, children were displayed an array of images. Results suggest that ASD females were more detail orientated than all other groups. This effect was found across stimuli types. Our data suggest that ASD females have more “typical” patterns of attention, replicating some sex effects observed in TD. Our paradigms highlight the importance of considering biological sex not just ASD diagnosis. These attention patterns may serve as protective mechanisms by promoting higher social motivation and reduced perseveration to nonsocial stimuli. Future research will extend this work to examine neural signatures of social motivation.

Ellen Terry, PhD

Talk Title: The effect of experimental reduction of pain catastrophizing on pain perception, nociceptive flexion reflex, and temporal summation of the nociceptive flexion reflex as verified by mediation analyses

Pain catastrophizing (the cognitive-emotional tendency to ruminate about pain, magnify pain, and feel helplessness in response to pain) contributes to increased pain and poorer pain-related outcomes. However, the mechanisms by which catastrophizing modulates pain are poorly understood. Evidence suggests that catastrophizing modulates supraspinal processing of pain, but does not modulate spinal nociception (as assessed by nociceptive flexion reflex [NFR]). Unfortunately, these previous studies have been cross-sectional and relied on correlations, which limits conclusions about causation. To address this limitation, the present study experimentally reduced catastrophizing to determine whether it modulates spinal nociception. Healthy pain-free participants (N=113) were randomly assigned to a brief 30-minute catastrophizing reduction manipulation or a pain education control condition. Before and after manipulations, painful electrocutaneous stimuli were delivered to elicit: (1) NFR (single trains of stimuli) and (2) temporal summation of NFR (3 stimulations at <3s inter-stimulus-intervals). After each set of stimuli, participants were asked to report their pain intensity and unpleasantness, as well as their situation-specific catastrophizing. Manipulation checks confirmed that catastrophizing was effectively reduced. Furthermore, pain intensity and unpleasantness to both stimulation types were reduced by the catastrophizing manipulation, effects that were mediated by reductions in catastrophizing. Although NFRs were not affected by the catastrophizing manipulation, temporal summation of NFR was reduced. However, this effect was not mediated by catastrophizing. These results indicate that reductions in pain catastrophizing lead to reductions in pain perception but do not modulate spinal nociception and provide further evidence that catastrophizing modulates pain at the supraspinal, but not spinal level.