College of Medicine
2019 Research Forum

Friday, November 22, 2019
Student Center West
828 S. Wolcott
2nd Floor Conference Rooms
Thompson Rooms A, B & C
### COM Research Forum 2019
#### List of Abstracts

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<td>Hepatocyte-Specific Ppargamma Contributes To The Development Of Non-Alcoholic Steatohepatitis (Nash) In Male Mice.</td>
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<td>The Age-Dependent Effect of APOE and Sex on Neuroinflammation and A Deposition in Alzheimer’s Disease Transgenic Mouse Model</td>
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<td>Fungal siderophores derived from gut fungi or mouse chow promote Salmonella enterica serovar Typhimurium growth</td>
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<td>Giuseppe</td>
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<td>The role of social determinants of health in Sickle Cell Disease Treatment Center Affiliation Status in a Multi-center Consortium in the United States</td>
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<td>Ugt1a6a, a novel regulator of beta-cell function</td>
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<td>PAK1 preservation of cardiac function for aged females is dependent on RLC phosphorylation</td>
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1. A Role for Notch Signaling in Lymphoid Progenitor Development in the Bone Marrow

Author(s): Kilian Sottoriva, Lijian Shao, Kostandin Pajcini

Department of Pharmacology

ABSTRACT

A major clinical obstacle after treatment of blood disorders with hematopoietic stem cell transplantation (HSCT) is the resultant long-term impairment in T cell mediated adaptive immunity. Though T cell development in the thymus has been extensively characterized, there are significant gaps in our understanding of pre-thymic T cell commitment. The Notch pathway is vital for the development of T cell progenitors in the thymus. We have confirmed a role for Notch signaling in the bone marrow Common Lymphoid Progenitor (CLP) population which suggests that Notch signals may instruct lymphoid progenitors towards the T cell fate even before exiting the bone marrow. Using a genetic Notch1 hypomorhic mouse model, we see decreases in the numbers of T cell progenitors including DN3 and ETP cells in the thymus as well as CLPs in the bone marrow. We have confirmed that these findings are cell autonomous using a bone marrow transplantation model. Furthermore, we see no defect in early B cell or Natural Killer cell progenitor development in the bone marrow, both of which derive from the CLP. Using RNA sequencing, we are compiling a list of genes dependent on Notch signaling within the CLP population. Future work for this project includes validation of candidate genes and modulation of bone marrow lymphoid development towards the T cell fate using pharmacological, genetic and bone marrow transplantation techniques. Our current findings suggest that Notch signaling activates transcription of genes which initiate the T cell developmental pathway within the CLP population in the bone marrow.
2. Preclinical development of small molecule ABCA1 inducers as multifunctional drug candidates

Author(s): Cutler Lewandowski, Md. Wasim Khan, Manel BenAissa, Oleksii Dubrovskyi, Brian Layden, Gregory Thatcher

Department of Medicine

ABSTRACT

The cholesterol transporter ABCA1 is a target of keen therapeutic interest. Increased ABCA1 expression improves lipid transport by raising HDL levels, promotes release of lipid and response to insulin, and reduces inflammatory signaling. Thus, a drug that elevates ABCA1 expression or activity could provide therapeutic benefit against various conditions, including cardiovascular disease, type 2 diabetes, and Alzheimer’s disease. However, transcription factors controlling ABCA1 expression also promote hepatic triglyceride synthesis (via SREBP1c protein), so non-selective activity leads to fatty liver disease. Our objective is to develop novel, selective inducers of ABCA1 that exhibit therapeutic effects without impacting peripheral lipogenesis. To that end, we conducted a luciferase-based high-throughput screen to identify compounds increasing ABCA1, but not SREBP1c, expression. Following validation, structural analogs of one hit were synthesized to identify new compounds with enhanced potency. Through multiple synthetic iterations, we developed a lead compound with sub-micromolar potency toward ABCA1 induction in vitro and minimal SREBP1c effect. This optimized molecule was validated in phenotypic cell-based assays, in which we observed increased cholesterol transport and reduced inflammatory response to LPS stimulation following treatment. Finally, we tested this compound in high-fat diet mice, demonstrating improved insulin sensitivity with treatment. Notably, treatment decreased triglycerides and fatty tissue in these mice, showing the promise of our strategy to develop small molecules with multifactorial ABCA1-mediated therapeutic activity without adverse effects. Additional work is ongoing to continue optimization for potency and pharmacokinetic properties, in preparation for more extensive efficacy and safety characterization in type 2 diabetes and Alzheimer’s disease mouse models.
3. Modulation of Genome Editing Outcomes via Cas9 Regulation

Author(s): Hannah Pennington, Ryan Clarke, Matthew MacDougall, Alex Chavez, Bradley J. Merrill,
Department of Biochemistry and Molecular Genetics

ABSTRACT

Cas9 nuclease enables genome editing through the introduction of double-stranded breaks that are repaired via endogenous DNA repair mechanisms. These mechanisms include non-homologous end joining (NHEJ), an error-prone pathway, and Homology Directed Repair (HDR). Clinical use of genome editing requires precise repair, thus making HDR the outcome of interest; yet, HDR is only available during specific phases of the cell cycle. While current research has focused on the modulation of DNA repair machinery, this work takes advantage of recent breakthroughs in the understanding of CRISPR/Cas9 biology, specifically how ejection of Cas9 from the break is the rate-limiting step during genome editing. Proteasomal motifs, referred to as degrons, were fused to Cas9 proteins in order to speed the kinetics of Cas9 removal from the break. By using a combination of cell-cycle regulated expression and destabilization of active Cas9, editing outcomes can be shifted towards HDR, increasing the frequency of the clinically relevant precise editing outcomes. Use of Cas9 destabilization additionally results in the rescue of activity by guides that previously were unable to mediate genome editing. Furthermore, destabilization enables higher levels of genome editing even with much lower levels of Cas9, potentially reducing the immune burden of the bacterial derived system.
4. Enterobacteriaceae competition in the infant gut

Author(s): Dara Kiani, Kaitlyn Kiernan, William Santus, Judith Behnsen

Department of Microbiology and Immunology

ABSTRACT

Enterobacteriaceae are among the first colonizers of the infant mammalian gut and dominate the early microbiota, frequently reaching colonization levels above 10^9 bacteria per gram of fecal matter. Enterobacteriaceae compete with each other in a multitude of ways. Systems to inhibit or kill competing strains have been described mainly in vitro and include contact dependent inhibition (CDI), Type VI secretion-mediated killing, and colicin or microcin secretion. Roles for these systems for competition in the mammalian gut have been only rarely described. Here we examine one of these systems in a mouse commensal Proteus mirabilis strain. We observed that a strain of Proteus mirabilis effectively eliminated a competing commensal E. coli strain in vivo in neonatal mice. Through co-cultures, we showed that P. mirabilis can not only kill the commensal E. coli but also the human probiotic E. coli Nissle, Salmonella enterica serovar Typhimurium and Citrobacter rodentium. While P. mirabilis has been unsuccessful at eliminating other Proteus strains and the yeast Saccharomyces cerevisiae. We found that this killing requires physical contact with competing cells and occurs when cultures reach a cell density above 10^9 CFU/ml. Contact seemed to be required, as killing did not occur when strains were separated by a membrane. Killing was observed in liquid media as well as on solid media. Understanding how Enterobacteriaceae interact with each other in the gut and what mechanisms specifically determine their success in colonization will help us to rationally design probiotics and interventions.
5. Rat strain differences in operant ethanol self-administration using a paradigm that measures both appetitive and consummatory behavior

Author(s): Ryan Patwell, Hyerim Yang, Margaret Starr, Subhash C. Pandey, Elizabeth J. Glover,

Department of Psychiatry

ABSTRACT

Alcohol researchers often use operant self-administration paradigms to investigate the different facets of alcohol use disorder in a pre-clinical setting. It is common practice in these paradigms to infer consummatory behaviors (e.g., alcohol drinking) based on the number of reinforcers delivered following an appetitive response (e.g., lever pressing). However, recent work suggests that appetitive behaviors alone are not always indicative of consumption. Thus, a paradigm that precisely measures both appetitive and consummatory behaviors is warranted but remains untested in rat models of ethanol drinking. To address this gap, we used a lickometer-equipped spout containing ethanol to discriminate between ethanol seeking and consumption in two rat strains, Long-Evans and Wistar. Interestingly, a significant number of Wistar (~40%), but not Long-Evans rats lever pressed for access to the ethanol-containing spout but never consumed ethanol. Ethanol intake was similar among those rats of both strains that did drink during the operant session. Licks were similarly consistent and were positively correlated with intake. Dependence-induced withdrawal from alcohol produced differential effects on operant responding and alcohol intake in drinkers versus non-drinking responders. Our results show differences in acquisition of operant self-administration across the strains. Furthermore, these data support previous findings in mice and suggest that, in Wistar rats, appetitive behaviors are not robust indicators of consummatory behavior. Overall these findings could impact the way in which new therapeutic compounds aimed at reducing drinking are tested in the pre-clinical setting.
6. Exploring the Role of DNA Methylation in Ethanol Dependent Rats

Author(s): Ryan Patwell, Huaibo Zhang, Elizabeth J. Glover, Subhash C. Pandey

Department of Psychiatry

ABSTRACT

DNA methylation is an epigenetic modification that is associated with the repression of gene transcription and has been implicated in several substance use disorders, including alcohol. The amygdala is a brain region that undergoes epigenetically mediated neural adaptions during chronic alcohol exposure and has been shown to facilitate the anxiety-like behaviors of rodents during acute withdrawal. Here, we have explored the role of DNA methylation mechanisms in the amygdala of ethanol withdrawn rats by examining the mRNA and protein levels of enzymes that regulate DNA methylation. Furthermore, we tested whether 5-azacytidine, an FDA approved DNA hypomethylating agent, could have a positive effect on anxiety-like behaviors and voluntary home cage drinking in these dependent animals. Our results suggest that withdrawal from chronic alcohol exposure can increase the levels of the enzymes that facilitate DNA methylation which in turn may repress the transcription of genes that regulate anxiety-like behaviors. Our results also demonstrate that 5-azacytidine, a drug that reduces DNA methylation, can reverse the anxiety-like behaviors of alcohol withdrawn rats, and reduces home cage drinking regardless of a history of dependence. Overall these studies suggest that compounds capable of reducing the levels of DNA methylation in the brain may have promising therapeutic potential for both reducing alcohol consumption and alleviating the withdrawal induced anxiety that is a hallmark in Alcohol Use Disorder in humans.
7. The Role of Hexokinease 2 in Breast Cancer Metastasis

Author(s): Catherine Blaha, Veronique Noqueira, Hyunsoo Rho, Nissim Hay

Department of Biochemistry and Molecular Genetics

ABSTRACT

One hallmark of cancer cells is accelerated glucose metabolism even in the presence of oxygen. Hexokinase catalyzes the first committed step in glucose metabolism by phosphorylating glucose, thereby trapping it in the cell to be used in various downstream pathways. Previous research in our laboratory showed that while normal mammary gland cells do not express the hexokinase 2 (HK2) isoform, it is highly overexpressed in breast cancer cells, which is responsible for the accelerated glucose utilization. HK2 deletion inhibits the tumorigenicity of cancer cells in vitro and in vivo, making it a good potential therapeutic target. However, metastasis accounts for the high mortality rate in breast cancer, which makes it important to elucidate the role of HK2 in breast cancer metastasis. This study tests the innovative hypothesis that HK2 plays a role in breast cancer’s ability to metastasize. We demonstrate that systemic deletion of HK2 after tumor onset in a mouse model of breast cancer metastasis profoundly inhibited lung metastasis. Single cell RNA sequencing of the mouse primary tumors revealed that the loss of HK2 impaired the expression of genes important for the epithelial-mesenchymal transition (EMT) and metastasis. Mechanistically, HK2 expression appears to drive metastasis through altered gene expression by stabilizing SNAIL, a pro-EMT transcription factor. Additionally, HK2 expression appears to increase glucose availability for flux through the oxidative pentose phosphate pathway in order to maintain a cellular redox state. Overall, this study provides evidence for a new therapeutic target for breast cancer metastasis.
8. Improving Childhood Vaccinations: A Quality Improvement Project Among the Latino Population at PrimeCare Community Health

Author(s): Angelica Cabrera

Department of Medical Education

ABSTRACT

Childhood vaccinations are critical to preventative care. Barriers to vaccination inoculation include financial burdens, insurance status, education and literacy, and general vaccine misconceptions that impact a person’s decision to either delay or deny inoculations for children, with Latino children being one disproportionately impacted. The objective of this quality improvement project is to assist the federally quality health center, PrimeCare Community Health (PCCH), to increase their childhood vaccination rates and vaccination awareness for the Latino patient population.

This project will be completed in three phases with data collection taking place for PCCH’s two resident clinic sites. In phase one, qualitative data was collected via in-person interviews with clinical staff and phone outreach to families with children due for well child visits and vaccines to discuss reasons for missed appointments, social barriers, and reasons for transferring care. Phase two included surveys being distributed at two clinical sites where they were given to parents/guardians of pediatric patients. Using data from the surveys, interviews, and literature review an analysis will be conducted and a list of appropriate and plausible evidence-based approaches will then be provided to PCCH for phase three implementation.

From the results of the qualitative and quantitative data collection in phase one and two, three themes were identified as impacting PCCH’s childhood immunization rates for ages 0-2 among the Latino population. Themes include system/clinical-, individual-, and provider-barriers. With this data, PCCH will be equipped to implement quality improvement initiatives to improve childhood vaccination rates and the health outcomes of their Latino population.
9. Physiological Markers of Depersonalisation / Derealisation Disorder (DPD) in Facial Mirroring

**Author(s): Garrett Williams, Anna Ciaunica, Harry Farmer**

Department of Psychiatry

**ABSTRACT**

Depersonalisation Disorder (DPD) is a common condition characterised by feelings of self-detachment and a reported dullness of emotional and perceptual vivacity. With many patients describing the DPD experience as “living in a dream or a movie”, this surreal and uncanny phenomenological disturbance can be extremely troublesome for affected individuals especially when the condition becomes recurrent and, in some cases, continual. Ultimately, DPD patients fall victim to the same problem that results in the mishandling of many other psychiatric conditions: the subjective nature of the experience limits our ability to diagnose, treat, and study the condition. In this project, we work to bridge this gap by determining the electrophysiological correlates of DPD, thereby presenting a means by which we might be able to quantise the vivacity of dissociative symptoms, diagnose its severity, and provide proper care, counselling and treatment.

In approaching this task, we rely on our understanding of facial mirroring - the reflexive response of facial muscles when presented with an emotionally valanced face in order to gain insight into the mental states of the individual in question. In this experiment of 50 participants, we utilised EMG recordings of the Zygomaticus and Corrugator supercilii muscles in order to measure smile and frown reactions, respectively. While we hypothesised that higher dissociative symptoms would standardise facial mirroring responses between photos of self and others, preliminary data suggests that individuals suffering from DPD/dissociative symptoms actually possess an other-face bias meaning that they maintain a more visceral reflexive reaction to seeing another person’s face. Given our understanding of DPD and its usual catalysts - e.g. traumatic events, emotionally overwhelming situations, stress, and first-time drug use - we can see how this disorder might trigger flight-or-flight mechanisms, thus inducing a stronger reaction when viewing other faces. This research path provides a possible means for more efficacious diagnosis procedures.
10. Cannabinoid Neutral Antagonism Reduces Ethanol Drinking via Epigenetic Regulation of NPY

Author(s): Russell Dulman, Huaibo Zhang, Subhash Pandey

Department of Psychiatry

ABSTRACT

The endocannabinoid system is an intriguing target for developing new treatments for addictive disorders. Cannabinoid antagonists reduce voluntary ethanol consumption in rodents, but brain region-specific mechanisms remain unclear. The amygdala plays a crucial role in both ethanol reinforcement and negative affective states associated with ethanol withdrawal and contains a high density of cannabinoid CB1 receptors. Neutral CB1 antagonists have recently emerged as improved compounds capable of reducing drug consumption without depressive side effects associated with earlier CB1 antagonist rimonabant. We tested neutral cannabinoid CB1 antagonist AM4113 (1mg/kg) for its effects on 24-hour-access home-cage 10% ethanol drinking as well as every other day intermittent access 20% ethanol drinking in male C57 BL/6J mice. We assessed downstream molecular and epigenetic effects in the amygdala of both chronic ethanol drinking and AM4113 treatments. We find AM4113 significantly reduces ethanol drinking compared to vehicle treated mice in both brief and chronic intermittent drinking paradigms without effects on animal mass or water drinking behavior. In addition, we observed that AM4113 treatment increases histone acetylation and CREB-binding protein (CBP) levels in the central and medial nucleus of amygdala. Interestingly, AM4113 treatment enhances NPY expression in the amygdala via increased gene-specific histone acetylation. Overall, these data suggest that CB1 antagonism with AM4113 reduces drinking while epigenetically restoring NPY signaling in the amygdala. These findings suggest the convergence of cannabinoid receptor signaling and epigenetics is an enticing new research avenue for alcohol use disorder pharmacotherapy.
11. Functionally engineered extracellular vesicles derived from mesenchymal stem-cells provide neuroprotection by attenuating microglial activation in retinal ischemia.

Author(s): Raj Patel, Biji Mathew, Mohansrinivas Chinnakesavalu, Lorea Gamboa Acha, Sriram Ravindran, Roth Steven

Department of Anesthesiology

ABSTRACT

Many retinal diseases involve loss or dysfunction of multiple types of retinal neurons, endothelial cells, and pericytes leading to oxidative stress, inflammation, and retinal ischemia. Retinal inflammation with activated retinal microglia (RMG) is major event in diabetic retinopathy. Our previous studies using a rat model of retinal ischemia have demonstrated robust neuroprotective effects of MSCs derived extracellular vesicles (EVs) when injected in the vitreous. MSCs produce extracellular vesicles (EVs) which are specifically involved in intercellular communication and are capable of transferring protein and nucleic acids between cells. The neuroprotective effects of MSCs appear to be largely mediated by EVs in retinal ischemia and are related to anti-apoptosis and anti-inflammatory actions, as shown in recently published studies. Preliminary data suggests that this neuroprotection is in part due to the RMG uptake of MSC-EVs. MSC-EVs appear to suppress the activation of RMG. RMG are the resident macrophages of the neuronal tissue capable of inducing cell proliferation through their activation upon injury; however, RMG exacerbate the situation by releasing toxic and pro-inflammatory compounds, particularly cytokines. RNA Seq analysis indicated miR-424 as one of the primary anti-inflammatory miRNAs in MSC-EVs. Anti-inflammatory effects of MSC-EVs can be enhanced by generating Functionally Engineered EVs (FEEs) containing increased levels of miR-424. In this study we have developed engineered EVs containing increased levels of miR-424. EVs were isolated from MSC conditioned media and characterized by Western Blot (WB), Nanoparticle Tracking Analysis, and Transmission Electron Microscopy. In vitro, the cultured RMGs were pre-incubated for 24h with EVs or FEE miR-424 and subjected to Oxygen Glucose Deprivation (OGD) with experimental groups: OGD, OGD+MSC-EVs/FEE miR-424, and OGD+CM minus EVs/FEE miR-424 as the control. The outcomes were measured by evaluating cell death (LDH), inflammatory cytokines, nitric oxide levels (NO) and ROS measurements. MSC enhanced FEE-miR424 confer significant neuroprotective effects in vitro. This study demonstrates that FEEs miR-424 suppresses RMG activation.
12. Sned1 knockout causes neonatal lethality and craniofacial and skeletal defects

Author(s): Anna Barque, Martin N. Davis, Kyleen Jan, Christina L. Nicholas, Richard O. Hynes, Alexandra Naba

Department of Physiology and Biophysics

ABSTRACT

SNED1 is a novel extracellular matrix protein acting as breast cancer metastasis promoter (Naba et al., eLife, 2014). To study its physiological roles, we generated a Sned1 knockout (KO) mouse which resulted in neonatal lethality (Naba et al., bioRxiv, 2018). The few surviving KO mice were smaller than wild-type mice and exhibited craniofacial malformations. Analysis of Sned1 KO mice by micro-computed tomography revealed upper airway occlusion and under-developed mandibles, potentially complicating the ability of mice to breathe and eat, thus compromising their survival. Interestingly, chromosomal deletion of 2q37.3 in humans, where SNED1 is located, has been associated with dysmorphic facial bones and short stature. Using the lacZ reporter gene expressed under the control of Sned1 promoter, we observed Sned1’s expression in the frontonasal region and pharyngeal arches, structures that will form the facial skeleton. Since cranial neural crest cells (NCCs) will give rise to the craniofacial skeleton, we hypothesize that SNED1 regulates the phenotype of these cells. To test this, we generated a NCC-specific Sned1 KO mouse. Mutant mice survive, but are smaller than control littermates and present craniofacial abnormalities resembling those observed upon global Sned1 KO. We are currently analyzing variations in shape of the skulls by geometric morphometrics. Next, we plan to perform in-vitro assays to determine how SNED1 influences the phenotype of NCCs. Our goal is to understand how SNED1 regulates the formation of the facial skeleton, and determine how the loss of SNED1 contributes to the phenotypes observed in patients with 2q37.3 deletion syndrome.
13. Transthyretin amyloid fibrils deposited in the microenvironment alter cardiac myocyte and fibroblast function and cytoskeletal structure.

Author(s): Kyle Dittloff, Brenda Russell

Department of Physiology and Biophysics

ABSTRACT

Age-related wild type transthyretin amyloidosis (ATTRwt) is a systemic condition that is characterized by deposition of amyloidogenic fibrils of misfolded transthyretin (TTR) in various organ systems. This disease manifests as an infiltrative cardiomyopathy hallmarked by extracellular deposition of misfolded TTR fibrils in the cardiac tissue, leading to cardiac dysfunction and heart failure with preserved ejection fraction (HFpEF); this disease is underdiagnosed and may affect percent of elderly men and women. We hypothesize that deposition of amyloidogenic TTR fibrils alters cardiomyocyte contractility and sarcomere structure via modulation of cell growth due to altered substrate stiffness and nanotopography. Recombinant TTR fibrils were deposited on glass substrates or substrates mimicking the stiffness of the healthy myocardium (10kPa). Neonatal rat ventricular myocytes exhibited decreased rate of linear contractility via line scan kymography and altered cytoskeletal structure when exposed to deposited TTR fibrils, with greater maladaptive effects seen on 10kPa substrates. We also hypothesize that deposited TTR fibrils induce cardiac fibroblast activation and promote progression of fibrosis. Cardiac fibroblasts plated on substrates containing deposited TTR fibrils exhibited increased proliferation rates, potentially indicative of activation to a myofibroblast phenotype. Together, results suggest that amyloidogenic TTR fibrils may affect cardiac myocyte and fibroblast structure and function through both chemical and mechanical pathways.
14. Uncovering the Composition of a Bacterial Peptide Pheromone in Listeria monocytogenes that Facilitates Its Escape from the Hosts Vacuole

Author(s): Omar Niagne, Diandra Vaval, Bobbi Xayarath, Nancy E. Freitag

Department of Microbiology and Immunology

ABSTRACT

Listeria monocytogenes (Lm) is a gram-positive bacterium that once ingested causes gastroenteritis in healthy individuals, and can lead to death in immunocompromised individuals. Even some strains are also known to cause stillbirth. This is based on Listeria’s ability to transition from an extracellular bacterium to a facultative intracellular pathogen in host cells. A lipoprotein produced by Lm encodes a peptide pheromone on its N-terminus and preliminary data suggest that the peptide pheromone(pPplA) enhances the bacterium’s virulence by allowing Lm to spatially sense that it is within the confines of a host cell. Our lab has identified the general region that encodes the pheromone but the exact sequence of the pheromone is not yet known. Therefore, site directed mutagenesis within the N-terminus of the pplA lipoprotein was used to aid in the identification of the peptide pheromone sequence. By Identifying of the pheromone, we will better understand the factors involved in the production of the pheromone. This information can also lead to the development of therapeutic drugs to may delay or inhibit the ability of Lm to sense a change in environment.
15. Overcoming the impact of diabetes induced oxidative stress in diabetic retinopathy

Author(s): Anara Serikbaeva, Yueru Li, Andrius Kazlauskas

Department of Physiology and Biophysics

ABSTRACT

Hyperglycemia, the hallmark of diabetes mellitus, induces oxidative stress, which promotes diabetes complications such as retinopathy. We hypothesize that high glucose induces a durable increase in oxidative stress by altering expression of genes that control redox homeostasis. Indeed, RNAseq analysis revealed that expression of 2,423 genes was significantly different between normal glucose (NG)- and high glucose (HG)- primary human retinal endothelial cells (HRECs). 174 of these genes govern redox homeostasis and are therefore candidate mediators of the increased oxidative stress. Of these 174 genes, the log2(FC) was ≥1 for 7 genes; the greatest difference was for TXNIP. qRT-PCR-based experiments confirmed that HG significantly elevated expression of TXNIP.

Our efforts to test if TXNIP was required for the HG-mediated increase in oxidative stress indicated that it was. Reducing the level of TXNIP mRNA decreased the level of oxidative stress. We also found that attenuating expression of TXNIP in HG cells improved barrier function, which is compromised by HG treatment. These studies demonstrate that HG-induced redox and barrier dysfunction can be mitigated by reversing HG-driven changes in gene expression.

The fact that redox homeostasis involves a host of systems in distinct subcellular compartments raises the question of which of these are compromised by HG. To address this issue, we generated cells that stably expressed subcellular compartment-specific redox sensors. Comparing NG and HG versions of these cells revealed that HG elevated the level of oxidized glutathione in the cytoplasm, whereas the mitochondrial pool was unaffected. The level of hydrogen peroxide in the cytoplasm and mitochondria were also unchanged by HG. We conclude that HG-induced redox dysfunction is both compartment, and system specific. We are currently investigating whether elevation of TXNIP is responsible for the increased level of oxidized glutathione in the cytoplasm.
16. Intestinal Axin1 Regulation of Epithelial Functions and Host-Microbial Interactions in Health and Inflammation

Author(s): Shari Garrett, Yongguo Zhang, Jun Sun

Department of Microbiology and Immunology

ABSTRACT

Background: Axin1 is a scaffold protein in the β-catenin destruction complex which if disrupted can lead to inflammatory bowel disease or colorectal cancer. Our previous study has demonstrated that Axin1 expression was reduced by pathogenic Salmonella colonization. The physical binding between beta-catenin and Axin1 was also decreased during bacterial infection. However, the role of Axin1 in modulating intestinal tissue architecture and microbial homeostasis is unknown.

Methods: To explore the novel mechanism of Axin1 in regulating the functions of intestinal epithelia in health and inflammation, we generated a novel Axin1 conditional knockout model in the intestinal epithelial cells cells (Axin1\textsuperscript{ΔIEC}).

Results: We found that Axin1\textsuperscript{ΔIEC} mice had less PCNA and β-catenin compared to the control Axin1 loxp mice, suggesting the reduction of cell proliferation in intestinal epithelial cells without Axin1. Axin1\textsuperscript{ΔIEC} mice exhibit altered goblet cell spatial distribution as well as disordered Paneth cells in the small intestine. Furthermore, in a Salmonella-colitis model in vivo and cell cultures in vitro, we found bacterial protein AvrA expression modulates the β-catenin/Axin1 interaction.

Conclusion: Lacking intestinal Axin-1 led to reduced proliferation and abnormal goblet cells and Paneth cells, suggesting that intestinal epithelial development and differentiation is regulated in an Axin1 dependent manner. Axin1 is involved in regulating the host-microbial interactions in health and inflammation.
17. Pulmonary vessel casting in rodent models of pulmonary hypertension

Author(s): Yifan Wang, Zhongzhu Kai, Tianyu Feng, Ayako Makino, Wei Huang, Jiwang Chen

Department of Pharmacology

ABSTRACT

Pulmonary hypertension (PH) is a severe cardiovascular disease characterized by sustained elevations of pulmonary artery (PA) pressure and pulmonary vascular remodeling (PVR) with limited treatment options and relatively poor prognosis. Pulmonary vascular network structure and blood flow have been found to be different between patients with PH and healthy controls. Thus, visualization and quantification of vascular changes in the development of PH may aid the detection and understanding of disease pathogenesis. In this study, we have developed a simple reproducible procedure to image the whole pulmonary vasculature and quantify its change in mouse hypoxia mediated PH model, rat monocrotaline (MCT) model, and rat hypoxia sugen mediated PH model. Holistic images of all five pulmonary lobes with the decreased density of the distal pulmonary vessel, the numbers of PA branches and junctions were traced by photoshop and quantified by Image J. Both of branches and junctions significantly decreased in the rats exposed to MCT or hypoxia sugen and mice with hypoxia mediated PH. These numbers are also inversely correlated with the right ventricular systolic pressure (RVSP), suggesting that there is a direct association between PH and the reduction of distal pulmonary structures. To our understanding, this is the first study to demonstrate complete PA branches in five lobes in these rodent models of PH. The innovative protocol and image quantification we presented here are important for the study and understanding of PVR for the evaluation of other vascular disease.
18. Depletion of Caveolin-1 in Type-2 Diabetes Model Induces Alzheimer’s disease Pathology Precursors

Author(s): Aashutosh Shetti, Aashutosh Shetti, Zhenlong Chen, Leon Tai, Richard Minshall, Orly Lazarov

Department of Anatomy and Cell Biology

ABSTRACT

Type 2 Diabetes mellitus (T2DM) is a risk factor for the development of Late Onset Alzheimer’s disease (LOAD). However, the mechanism underlying the development of LOAD is largely unknown. Here we show that levels of the endothelial-enriched protein caveolin-1 (Cav-1) are reduced in the brains of T2DM patients compared to healthy aging, and inversely correlated with levels of beta-amyloid (Abeta). Depletion of Cav-1 is recapitulated in the brains of db/db (Leprdb) diabetic mice and corresponds with recognition memory deficits as well as the upregulation of amyloid precursor protein (APP), BACE-1, a trending increase in beta-amyloid Abeta42/40 ratio and hyperphosphorylated tau (p-tau) species. Importantly, we show that restoration of Cav-1 levels in the brains of male db/db mice using adenovirus overexpressing Cav-1 (AAV-Cav-1) rescues learning and memory deficits and reduces pathology, i.e., APP, BACE-1 and p-tau levels. Knocking down Cav-1 using shRNA in HEK cells expressing the familial Alzheimer’s disease (FAD)-linked APPswe mutant variant upregulates APP, APP carboxyl terminal fragments and Abeta levels. In turn, rescue of Cav-1 levels restores APP metabolism. Taken together, these results suggest that Cav-1 regulates APP metabolism, and that depletion of Cav-1 in T2DM promotes the amyloidogenic processing of APP and hyperphosphorylation of tau. This may imply that depletion of Cav-1 in T2DM underlies, at least in part, the development of AD and imply that restoration of Cav-1 may be a therapeutic target for diabetic-associated sporadic AD.
19. Chemokine-based mRNA-lipid nanoparticle therapy induces acute immune responses

Author(s): Ally Bennett, Kaitlyn Kiernan, Justin Richner

Department of Microbiology and Immunology

ABSTRACT

Advanced age correlates with a decline in immune function that causes reduced vaccine efficacy and increased susceptibility to disease. In a previous publication, we observed a decrease in chemokine accumulation and migration of naive T cells into lymphoid tissue of infected, aged mice. We hypothesize that increasing levels of chemotactic cytokines will increase naive T cell trafficking into lymphoid tissue and enhance magnitude of the immune response. We seek to modulate immune activation through a mRNA-lipid nanoparticle (LNP) gene therapy platform to deliver CCL19 and CCL21 mRNA transcripts. Transfection of HEK293Ts with these LNPs results in robust chemokine production and ability to drive T cell migration. When the CCL19/21-mRNA LNPs were both injected into young C57BL/6 mice, they were able to modulate chemokine production and T cell trafficking into the draining lymph node. Low dose CCL19/21-mRNA LNPs induced equivalent immune responses to those of GFP-mRNA LNPs.
20. Preliminary study on white matter alterations across age in the mouse APP knock-in model of Alzheimer’s Disease

Author(s): Zachery Morrissey, Olusola Ajilore, Orly Lazarov, Alex Leow
Department of Psychiatry

ABSTRACT

Increasing evidence suggests that white matter (WM) damage may precede neuronal loss in Alzheimer’s disease (AD), damaging the network connectivity of the brain, and likely contributing to cognitive impairments. To investigate this further, we hypothesized that impairments of network connectivity across age in AD mouse models are detectable using diffusion tensor imaging (DTI) as a proxy of WM tractography to better characterize these alterations.

Wild-type and APP knock-in (APPKI) female mice were scanned using a 9.4T MRI by applying a T2-weighted and DTI sequence during their fourth and tenth months of age. After preprocessing, for each region of interest the mean fractional anisotropy (FA) was computed for each subject. Results were analyzed using two-way ANOVA and Tukey’s post hoc test.

Our results suggest that the internal capsule and anterior commissure, two prominent WM tracts, had the most divergent FA across age and genotype. The lowest mean FA was observed in the 10-month-old APPKI animals. In addition, we observed the largest divergences in FA across age in the neocortex, hippocampus, and putamen in APPKI animals compared to wild-type.

Together, these results suggest that there are microstructural alterations in both the internal capsule and anterior commissure in APPKI mice that appear to be preserved in wild-type animals. This suggests that deficits in WM take place early in AD and that understanding the mechanism underlying these changes may have therapeutic value. Because these tracts are important for inter-hemispheric and corticothalamic connectivity, these could represent early changes in connectivity that contribute to cognitive impairment.
21. The role of YAP in glucose metabolism changes in proliferating versus quiescent cells

Author(s): Soeun Kang, Nissim Hay
Department of Biochemistry and Molecular Genetics

ABSTRACT

There are two major metabolic pathways following glucose uptake, glycolysis which generates adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NADH) and the pentose phosphate pathway (PPP) producing nicotinamide adenine dinucleotide phosphate (NADPH) and ribose 5-phosphate (R5P). Although rapidly proliferating cells require high levels of ATP and nucleotide pools for DNA synthesis, surprisingly, isotope tracing experiments demonstrate that proliferating cells have significantly lower glucose flux to the PPP than quiescent cells, even though their total glucose consumption and glycolytic flux are significantly higher. Others also have shown that fibroblasts continue to exhibit high metabolic rates such as high PPP flux when they reach the stationary phase. The mechanism by which this metabolic transition occurs and the cellular advantage of the phenomenon are currently unknown.

We hypothesize that rapidly dividing cells reduce their glucose flux to the oxPPP to maintain a certain level of endogenous reactive oxygen species (ROS) and to maintain high glucose flux into glycolysis. We detected higher ROS levels and lower NADPH levels in proliferating cells and N-Acetyl Cysteine (NAC, ROS scavenger) treatment reduced the growth rates of proliferating cells. We also hypothesize that the transcriptional activity of Yes-associated protein (YAP), a coactivator which can be inhibited by Hippo pathway, contributes to the glucose utilization flux transition to glycolysis or to the PPP depending on cell growth status. We detected upregulation of genes associated with glycolysis along with lower PPP/glycolysis flux ratio in constitutively active YAP mutant (YAP 5SA) expressing cells. Future work will focus on the role of ROS in glucose utilization. We will also determine the detailed mechanisms how the phenomenon is regulated by YAP.
22. Study the Gut Microbiome under Antibiotics and Immunosuppressant Treatment

Author(s): Yang Chen, Benjamin Turturice, Ravi Ranjan, Patricia Finn, David Perkins, Department of Medicine

ABSTRACT

Antibiotics (Abx) are commonly used in clinics to defend bacterial infection such as during transplantation. Immunosuppressants (IS) are commonly used to reduce inner immune response during transplantation or to treat allergies. Both Abx and IS are utilized during transplantation and have the similar effect of prolong graft survival. Microbiome, a community of bacteria reside in the gut, is reported to interact with the host immune system. The primary goal is to study how the microbiome are altered by the drugs and how that may relate to the immune system. The secondary goal is to study how the bacteria are enriched against drug selection. In the Abx study, mice were treated with vancomycin (Vanc), metronidazole (Met), gentamicin (Gent), kanamycin (Kan) and colistin (Col). In the IS study, mice were treated using mycophynolate mofeltit (MMF), methylprednisolone (MP), and cyclosporine (CsA). Using whole genome sequencing (WGS) from fecal DNA, we were able to identify the compositional changes of microbiota and the differently altered antibiotic resistance gene (ARG) reside in the bacterial community. These results suggest the different mechanism of the Abx and IM on the gut microbiome.
Synergistic effects of APOE and sex on the gut microbiome of EFAD transgenic mice.

Author(s): Juan Maldonado Weng, Ishita Parikh, Ankur Naqib, Stefan Green, Steven Estus, Mary Jo LaDu

Department of Anatomy and Cell Biology

ABSTRACT

Alzheimer’s disease (AD) is a fatal neurodegenerative disease. APOE4 is the greatest genetic risk factor for AD, increasing risk up to 15-fold compared to the common APOE3. Importantly, female (♀) APOE4 carriers have a greater risk for developing AD and an increased rate of cognitive decline compared to male (♂) APOE4 carriers. While recent evidence demonstrates that AD affects the gut microbiome (GM), the collective genome of microbiota within the gut, how APOE genotype and sex interact to affect the GM in AD remains unknown. This study analyzes the GM of 4-month EFAD mice, a preclinical mouse model that exhibits AD-like pathology and expresses human APOE3+/+ or APOE4+/+. Microbial diversity of the EFAD GM was compared across APOE, sex and stratified by APOE + sex, resulting in 4-cohorts (♂E3FAD, ♀E3FAD, ♂E4FAD and ♀E4FAD). Significant differences in the EFAD GM were associated with APOE genotype and sex. Stratification by APOE + sex revealed that APOE-associated differences were exhibited in ♂EFAD and ♀EFAD mice, and sex-associated differences were exhibited in E3FAD and E4FAD mice. Based on bacterial taxa identified by machine-learning, heatmap analysis revealed clustering of ♀E4FAD separate from other cohorts. The results demonstrate that the GM is modulated by APOE + sex. Importantly, the effect of APOE4 on the EFAD GM is modulated by female sex, a pattern similar to the greater AD pathology associated with ♀E4FAD mice. Therefore, this study demonstrates the importance of studying the interactive effects of APOE + sex on the GM in AD.
24. Role of caveolin-1 in adult hippocampal neurogenesis: Implications for Alzheimer's disease

Author(s): Terilyn Stephen, Terilyn Stephen, Jacqueline Bonds, Aashutosh Shetti, Richard Minshall, Orly Lazarov

Department of Anatomy and Cell Biology

ABSTRACT

Impairments in learning and memory are hallmarks of age-linked cerebrovascular diseases like Alzheimer’s disease (AD) and type-2-diabetes (T2D). Adult hippocampal neurogenesis (ANH), the generation of new neurons from neural stem and progenitor cells (NSC, NPC) in the hippocampus, is thought to play a critical role in learning, memory and cognition. In humans, lower numbers of newly differentiating neurons in the hippocampus are associated with poorer cognitive diagnosis. However, the mechanisms responsible for compromised neurogenesis in AD have yet to be elucidated. Caveolin-1 (Cav-1) is the main component of caveolae and is enriched in the cerebrovascular. We have shown previously that reductions in brain Cav-1 expression is associated with the cognitive deficits seen in T2D. Thus, we tested the hypothesis that depletion of Cav-1 in aging and in aging-linked disorders compromises neurogenesis and plays a role in the development of cognitive deficits. Here we show that global loss of Cav-1 (Cav-1 KO) results in reduced numbers of NSC and NPC in the hippocampus compared to wild-type mice. In addition, NPC isolated from the hippocampus of Cav-1 KO mice exhibit reduced extent of proliferation along with altered expression of key neurogenic factors such as endothelial growth factor receptor (EGFR) and bone morphogenetic protein receptor II (BMPRII). This suggest that Cav-1 is a critical modulator of adult hippocampal neurogenesis, which regulates the checkpoint between NSC quiescence and proliferation. These studies suggest a novel mechanism by which neurogenesis may be compromised in aging-linked disorders, leading to cognitive deficits.
25. The use of formoterol as a potential anti-epileptogenic drug through the induction of DUSP4

Author(s): Allison Kirchner, Shruti Bagla, Fabien Dachet, Jeffrey Loeb

Department of Neurology

ABSTRACT

BACKGROUND: To develop improved epilepsy therapeutics, the pathways that underlie epileptic areas of the neocortex need to be better understood. Using high-throughput genomic studies of human epileptic neocortical tissue, we have identified the mitogen activated protein kinase (MAPK) pathway as highly upregulated in epileptic regions and have further shown that inhibition of MAPK reduces epileptic spiking in an animal model. Clustering of differentially expressed MAPK genes in human epilepsy revealed two gene clusters: one containing known MAPK genes previously linked to epileptic regions and another containing an endogenous MAPK inhibitor, DUSP4. Follow-up studies demonstrated that DUSP4 acts by reducing the transcription of pro-epileptogenic MAPK signaling genes in focal brain regions in epilepsy. Since MAPK activation may be an important driver of epileptogenesis, treatments that augment DUSP4 expression could be novel inhibitors of the epileptogenic process. Recent studies have shown that an FDA approved beta-2 agonist, formoterol, has an effect on DUSP4 in the lung, and therefore could have effects on DUSP4 expression in the brain.

OBJECTIVES: To observe the potential induction of DUSP4 expression following formoterol exposure as a potential therapeutic treatment for epilepsy.

METHODS: In vitro studies are performed using the Sh-SY5Y cell line. Animal studies are performed by giving at IP injection of .5mg/kg formoterol to a 2 month Sprague Dawley rats. Expression of DUSP4 is analyzed using standard qPCR, Western Blot to observe mRNA and protein levels respectively.

RESULTS AND CONCLUSION: Formoterol increases the expression of DUSP4 and should be considered for anti-epileptogenic treatment.
Salmonella enterica serovar Typhimurium expresses chitinases that facilitate gastrointestinal infection

Author(s): Jason Devlin, William Santus, Dara Kiani, Xiomarie Navarreto, Kaitlyn Kiernan, Judith Behnsen

Department of Microbiology and Immunology

ABSTRACT

Salmonella enterica serovar Typhimurium (STM) is one of the leading causes of foodborne illnesses worldwide and is responsible for 1.2 million illnesses, 23,000 hospitalizations and 450 deaths a year in the United States. The exacerbation of STM infection requires the efficient invasion of intestinal epithelial cells in order to establish colonization of the gastrointestinal tract. STM expresses a variety of virulence factors that contribute to infection. Our data indicates that two chitinases expressed by STM, STM0018 (ChiA) and STM0233, may be acting as virulence factors. Chitinases show hydrolytic activity towards chitin polymers, but despite chitin being absent in mammals, expression of chiA has been detected during in vitro infection of macrophages and in vivo infection of chickens. Interestingly, chitinases have been recently emerging as virulence factors for various pathogenic bacterial species. ChiA demonstrates catalytic activity towards not only chitin, but also carbohydrate subunits present on surface glycoproteins. We hypothesize that the interactions between STM chitinases and surface glycoproteins facilitate adhesion and invasion of intestinal epithelial cells. Our data shows that chitinases contribute to the invasion of intestinal epithelial cells by STM in vitro. We have also demonstrated that both STM0233 and ChiA promote efficient colonization and invasion of the small intestinal lumen during early infection of mice. Our results indicate that chitinase expression promotes invasion and colonization of STM during intestinal infection and we plan of further exploring their role in more detail.
Contrasting Corneal Nociceptors Functional Alterations to Benign Stimuli and Destruction due to a Common Ophthalmic Preservative

Author(s): Evguenia (Jane) Ivakhnitskaia, Vladislav Souboch, Elizaveta Souboch, Victor Guaiquil, Harumitsu Hirata, Mark Rosenblatt

Department of Ophthalmology and Visual Sciences

ABSTRACT

Corneal nociceptors comprise the densest sensory network in the body, which regulates eye surface protection through trophic support of corneal epithelium and control of blink reflexes and tear production. Injuries of corneal cold fibers have been implicated in a variety of ophthalmic disorders, however, little is known about the functional characteristics of fibers undergoing injury. By using in vivo extracellular electrophysiology of the trigeminal ganglion we have been able to monitor corneal nociceptor functional alterations and destruction in real time. We demonstrate that corneal cold fibers are exquisitely sensitive to ocular surface perturbations that mimic physiological states of the ocular surface, displaying strong sensitization and desensitization responses to stimuli previously considered to be benign to the ocular surface. We contrast these results to a complete collapse of neuronal function seen within 30 minutes of a single, prolonged ocular instillation of a common ophthalmic preservative, Benzalkonium chloride (BAK). Immunohistological analysis parallels electrophysiological findings as nerve density is significantly reduced while nerve fragmentation index is increased in corneas exposed to BAK, indicating structural disintegration of nerve terminals in the BAK condition. The findings in the present study highlight the exquisite sensitivity of corneal nociceptors, provide a time course of functional destruction due to a common ophthalmic preservative, and contrast non-destructive functional alterations to complete functional compromise of corneal cold nociceptors in vivo and in real time.
28. Mechanics and water flux determine extracellular vesicle transport under confinement in extracellular matrix

Author(s): Stephen Lenzini, Ray Bargi, Gina Chung, Jae-Won Shin

Department of Bioengineering

ABSTRACT

Extracellular vesicles (EVs), small cell-derived particles ~50-500nm in diameter, are released by cells for the purpose of intercellular communication. EVs can be found in decellularized extracellular matrix (ECM), and it is likely that in some cases EVs must traverse the ECM to reach target cells. However, the ECM exhibits a range of mechanical properties with features that would lead to a physical confinement of EVs, which is predicted to impede particle transport. Surprisingly, we found that EVs produced from MSCs are capable of transporting within nanoporous decellularized lung tissue. Thus, we hypothesized that mechanisms exist for EVs to become cleared or transported through ECM. Using engineered hydrogels, we show that EVs exhibit anomalous transport under confinement in matrix. EVs are able to transport in this environment and do so much more rapidly than would be expected based on conventional Stokes-Einstein theory. Matrix stress relaxation allows EVs to overcome confinement, and in this context a higher crosslinking density facilitates rapid sliding between consecutive locations, leading to free diffusion and faster transport. Furthermore, water flux through aquaporin-1 (AQP1) on EVs mediates their deformability, causing increased EV transport magnitude in hydrogels and decellularized matrix. Because local fluid gradients exist within the interstitial ECM, these findings are physiologically important as they suggest differential responses in EV transport to the dynamics of fluid gradients in vivo. In sum, this study opens new avenues of investigations into modes of EV transport behaviors occurring in the ECM.
Designing a tetanus toxin-induced model to study the relationship between interictal spikes and seizures in rats

Author(s): Rachael Smith, Jeffrey Loeb

Department of Neurology

ABSTRACT

For the past 50 years, intracerebral microinjections of tetanus toxin (TeNT) have been used to induce epileptiform discharges in various animal models. Low doses of TeNT permit neuronal sparing, which is preferred over alternative epileptogenic substances, such as kainic acid and pilocarpine, that induce status epilepticus followed by profound neuronal death. In addition to neuronal sparing, the TeNT model is preferred because it produces an electroencephalogram (EEG) pattern that looks similar to the recordings from human epilepsy patients, beginning with spikes and occasionally progressing to seizures. In epileptic patients, interictal spikes are generally viewed as a precursor to epileptiform activity, and they can be used to localize areas of focal seizure activity; however, some patients have high levels of interictal spiking that is not associated with seizure activity. Until now, it has been difficult to elucidate the relationship between spikes and seizures, because consistently reproducible animal models of interictal spiking were limited. Recently, our laboratory discovered a method to exploit the mild effects of the TeNT model to induce interictal spiking in rats. In order to elicit a predominantly spiking phenotype, TeNT needs to be injected into the somatosensory cortex; however, this region is over 2 mm away from the motor cortex, where TeNT injections produces a seizure phenotype. The goal of this project was to design a rat model capable of both interictal spike and/or seizure generation with consistent TeNT dosing and electrode placement across all animals.
30. Simultaneous acquisition of magnetic resonance elastography and diffusion tensor imaging of in vivo human brain

Author(s): Shujun Lin, Dieter Klatt

Department of Bioengineering

ABSTRACT

Title: Progress of simultaneous acquisition of Magnetic Resonance Elastography and Diffusion Tensor Imaging of in vivo human brain

Introduction: Magnetic resonance elastography (MRE) is a phase-contrast and non-invasive technique that maps tissue stiffness. Diffusion tensor imaging (DTI) is a diffusion-weighted technique resulting in changes of magnitude images, that maps the intervoxel motion of water in biological system. Both MRE and DTI use motion encoding gradients (MEGs), making it favorable to the simultaneous acquisition of both. Previous study on mice model already proved the possibility to realize this new technique. In this study, we implemented DTI-MRE on in vivo human brain.

Method: The simulation of experiment parameters was conducted with following conditions: b-value within range of [745,750]s/mm^2, encoding efficiency of vibration above 1.5x10^5 rad/m, vibration frequencies within range of [20,70] Hz, separation time between MEGs to be multiple integers of vibration periods, and signal loss due to intravoxel phase dispersion less than 20%. In vivo experiment was performed on a 3T MRI scanner. A SE-EPI-based sequence with trapezoid MEG was used. The experiment parameters were: f = 50Hz, G = , delta/Delta = 10/30 ms, b-value, FOV, matrix size = 100*100, slice thickness = 4mm, TR/TE = 6s/, flip angle = 90 degrees, respectively.

Results: We identified 17 sets of experiment parameters that meet the simulation conditions. The fractional anisotropy and mean diffusivity maps are comparable between DTI-MRE and conventional DTI.

Discussion: The preliminary results is promising from in vivo human DTI-MRE.
31. Piezo1-sAC-IP3R2 axis regulates the adaptive cellular responses of endothelial cells to mechanical cues

Author(s): Dianicha Santana, Dianicha Santana, Ana Santa Cruz-Garcia, Asrar Malik, Dolly Mehta, Yulia Komarova

Department of Pharmacology

ABSTRACT

Mechanosensitive channels expressed by Endothelial Cells (ECs) are responsible for sensing mechanical cues and converting them into chemical signals to elicit specific cellular responses. The mechanosensitive channel Piezo1 plays an important role in vascular homeostasis by sensing hydrostatic pressure and shear stress in ECs. However, specific cellular mechanisms involved in Piezo1-mediated mechanotransduction remains elusive. Here, we investigated the mechanisms of Piezo1-mediated Ca2+ signals in ECs. Using intracellular and endoplasmic reticulum (ER) calcium sensors to respectively monitor the changes in Ca2+I and Ca2+ER concentrations, we have shown that pharmacological activation of Piezo1 induced an increase in Ca2+I that was potentiated by Ca2+ release from ER stores. Ca2+ influx through Piezo1 led to a transient activation of soluble adenylyl cyclase (sAC) which, in turn, activated cAMP-dependent Ca2+ release via Inositol Trisphosphate Receptor 2 (IP3R2), a calcium channel located in the ER. Depletion of either sAC or IP3R2 markedly reduced the Piezo1-mediated increase in cytosolic Ca2+I, indicating that Ca2+ER release represents a mechanochemical positive feedback loop eliciting Ca2+ signals in ECs. Furthermore, depletion of IP3R2 blocked alignment of ECs in the direction of shear flow suggesting that activation of IP3R2 downstream of Piezo1 is an essential element of a mechanotransduction response. Our data, for the first time, establish the role of Piezo1-sAC-IP3R2 axis in regulating the adaptive cellular responses of ECs to mechanical cues.
32. Gemcitabine Resistance Requires the Sustained Uptake of Calcium via L-Type Channels and is Reversed by High Dose Amlodipine

Author(s): Daniel Principe, Ryan Conrardy, Alexandre Aissa, Rui Xiong, Elizaveta Benevolenskaya, Ajay Rana

Department of Biochemistry and Molecular Genetics

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) often presents at late clinical stages, and most patients are managed solely through palliative chemotherapy. With no approved treatment modalities for patients who progress on broad-spectrum chemotherapy, we set to identify druggable targets to prevent or reverse resistance to the first line anti-neoplastic Gemcitabine. We first treated PDAC cells with Gemcitabine in vitro and examined alterations in gene expression via single cell RNA sequencing. This identified Gemcitabine-induced populations with aberrations to several genes in the Calcium (Ca2+) signaling network, including the Calmodulin/Calcineurin target NFAT. We then established in vitro models of Gemcitabine resistance and performed whole proteome analysis via 2D-Gel electrophoresis, revealing significant upregulation of Calmodulin 2. Pharmacologic inhibition of Calmodulin led to the rapid loss of drug resistant phenotypes in vitro, as did depletion of Ca2+ from the culture media or selective blockade of L-Type Ca2+ channels (LTCCs). Subsequent use of the FDA-approved LTCC inhibitor Amlodipine reversed Gemcitabine resistance in orthotopic xenografts, prolonging overall survival and reducing liver metastasis. Similarly, daily Amlodipine enhanced the anti-neoplastic effects of Gemcitabine in an aggressive model of transgenic PDAC, nearly doubling survival time compared to Gemcitabine-treated mice and again reducing liver metastasis. Combined, these results suggest that the acquisition and maintenance of Gemcitabine resistance requires sustained Ca2+ signaling mediated by LTCCs, and that the addition of widely available, well tolerated, low cost agents such as Amlodipine may improve drug responses in the clinical management of PDAC.
33. Single Cell Investigation of Patient Derived Prostate Organoids Reveals 1,25D-regulation over Wnt Pathway

Author(s): Tara McCray, Bethany Baumann, Larisa Nonn

Department of Pathology

ABSTRACT

The prostate is a hormonally-regulated epithelial gland that harbors cancer in 80% of elderly men. Deficiency in the hormone vitamin D (1,25D) is associated with aggressive and less-differentiated prostate cancer, but how 1,25D promotes differentiation in the prostate is not well understood. Using benign human primary prostate epithelial (PrE) organoids as a model, the differentiative properties of vitamin D were examined. Organoids grown in the presence of 1,25D were strikingly larger than those grown in control and showed an earlier luminal population via flow cytometry, indicating increased differentiation. Single cell RNA sequencing was utilized to investigate cell-type specific mechanisms of 1,25D and found differential expression of Wnt pathway members after treatment. Non-canonical Wnt related protein DKK3 emerged as a target and was validated by RT-qPCR, ChIP-sequencing, and western blot. DKK3 was found to be expressed in non-stem cells to restrain proliferation. 1,25D inhibits DKK3 expression, and knockdown of- or treatment with DKK3 enhanced or blocked the effect of vitamin D, respectively. Overall, 1,25D reduces DKK3 in non-stem cells as a means to promote organoid growth and epithelial development, future studies will determine the implications of these findings in the context of disease.
Developmental NMDA receptor dysregulation in the infantile neuronal ceroid lipofuscinosis mouse model

Author(s): Kevin P. Koster, Walter Francesconi, Fulvia Berton, Akira Yoshii

Department of Anatomy and Cell Biology

ABSTRACT

Infantile neuronal ceroid lipofuscinosis (CLN1) is a pediatric neurodegenerative disorder. CLN1 is caused by mutations in CLN1, which encodes the depalmitoylating enzyme palmitoyl-protein thioesterase 1 (PPT1). Palmitoylation entails the post-translational addition of lipid to proteins, which can be depalmitoylated by PPT1. Protein palmitoylation dynamically regulates the function of synaptic proteins, including the N-methyl-D-aspartate receptor (NMDAR) subunits GluN2B, GluN2A, and the scaffold PSD-95. However, how loss of PPT1-mediated depalmitoylation underlies CLN1 is not understood. Here, we studied visual cortex development in the Ppt1-/- mouse model to decipher how lack of protein depalmitoylation drives synaptic dysfunction in CLN1. Visual cortices of wild-type (WT) and Ppt1-/- mice demonstrated decreased levels of GluN2A and PSD-95, which comprise NMDAR complexes at mature synapses. Correspondingly, NMDAR-mediated currents in Ppt1-/- cortical neurons show decreased contribution from GluN2A and enhanced contribution of GluN2B. In dissociated Ppt1-/- neuron cultures, calcium transients were diffuse, extrasynaptic, and sensitive to GluN2B-blockade, whereas WT cells exhibited compartmentalized calcium influx confined to spine heads. Intriguingly, experimentally hindering visual cortical synapse maturation by rearing Ppt1-/- animals in complete darkness exacerbated CLN1 progression. Potentially underlying these disruptions, Fyn kinase, which stabilizes synaptic GluN2B, and GluN2B both demonstrate increased palmitoylation in Ppt1-/- neurons. Indeed, Ppt1-/- neurons demonstrated vulnerability to NMDA-induced excitotoxicity that, together with the overload of palmitoylated GluN2B and Fyn, was reversed by treatment with palmitoylation inhibitors. Thus, loss of PPT1 disrupts NMDAR function and sensitizes neurons to excitotoxicity partly via the palmitoylation of GluN2B and Fyn kinase, revealing these as novel mechanistic targets in CLN1.
PV1 gene deletion in adult mouse endothelial cells decreases caveolae number and promotes the rupture of pulmonary microvessels

Author(s): Joshua Jones, Emily Friedrich, Zhigang Hong, Radu Stan, Richard Minshall, Asrar Malik

Department of Pharmacology

ABSTRACT

Caveolae are responsible for the majority of macromolecule transport through continuous-type endothelium. Caveolae-associated proteins caveolin-1 and cavins 1 and 2 are required for caveolae formation and their depletion results not only in loss of caveolae-mediated transport, but also increased permeability, endothelial dysfunction and vascular remodeling. PV1 (PLVAP) is abundantly expressed in lung endothelial cells as well as fenestrated endothelial cells where it participates in formation of caveolar and fenestral diaphragms. However, its contributions to lung vessel integrity and caveolae function in mature endothelium are unknown. Endothelial PV1 deletion in adult mice via tamoxifen-induced Cdh5.Cre.ERT2 mediated excision of a floxed PV1 allele resulted in vascular hemorrhaging in lungs. Additionally, loss of PV1 in endothelial cells increased permeability to fluid and protein, which was concurrent with loss of serum protein and vascular pressure. Interestingly, endothelial PV1 deletion reduced lung caveolae abundance without altering junctional permeability to protein. Finally, we demonstrate that PV1 is significantly reduced in lungs chronically exposed (96 hrs) to lipopolysaccharide (LPS) endotoxin and this was associated with reduced Cav-1 expression. Taken together, these results suggest PV1 is essential not only for formation of fenestra and caveolar diaphragms, but also maintenance of caveolae number and vascular integrity.
Development of simultaneous diffusion and elastography acquisitions on in vivo human brain

Author(s): Shujun Lin, Brad Sutton, Richard Magin, Dieter Klatt

Department of Bioengineering

ABSTRACT

Magnetic Resonance Elastography (MRE) and Diffusion Tensor Imaging (DTI) are noninvasive motion-encoding MRI techniques that are capable of determining tissue stiffness and diffusivity, respectively. Tissue stiffness and the diffusive behavior of water in tissue represent complementary diagnostic information for a variety of pathologic conditions such as cancer, fibrosis and neurodegeneration to name a few. In MRE, tissue vibrations are encoded into the phase of the complex-valued MRI signal, while DTI uses the magnitude for measuring diffusive information. Both techniques have in common that balanced magnetic field gradients are applied in 3D space for motion encoding. We have previously shown using a mouse brain model that DTI and MRE information can be acquired simultaneously by our developed approach named DTI-MRE. Compared to sequential DTI and MRE acquisitions, DTI-MRE reduces scan time by a factor of ~2 and provides images that are immediately coregistered. However, DTI-MRE requires the identification of experimental parameters with best compromise between maximizing motion encoding efficiency and minimizing intravoxel phase dispersion as the latter may cause interferences of vibration and diffusion measurements. We have recently implemented the DTI-MRE sequence on a 3.0T clinical scanner. In simulations we have already identified valid experimental parameter combinations for DTI-MRE on in vivo human brain. First implementation tests show that DTI-MRE provides similar images of stiffness and diffusion properties as obtained using the conventional methods. Next we will conduct a comparative study of in vivo human brain DTI-MRE and conventional methods using healthy volunteers.
37. Development of A Dengue Virus mRNA Vaccine

Author(s): Clayton Wollner, Mariah Hassert, Michelle Richner, James Brien, Justin Richner,

Department of Microbiology and Immunology

ABSTRACT

Dengue is the most common vector-borne viral disease affecting humans and is endemic across 100 countries in Asia, the Pacific, the Americas, Africa, and Middle East. The virus exists as four, distinct serotypes, dengue 1-4, all of which have experienced steady global spread since their discovery. Disease states range from self-limiting fever to cases involving life-threatening vascular leakage. Antibodies from a previous dengue infection can enhance infection by a heterologous serotype. In this scenario, poorly neutralizing antibodies bind to virus leading to increased uptake by Fc gamma receptor-positive cells. In this way, antibodies produced in response to vaccination are capable of contributing to enhanced disease during a natural infection. As dengue’s endemic region spreads, the need for an effective vaccine that does not induce ADE becomes ever more pressing. This project optimizes and characterizes an mRNA vaccine in order to produce an effective dengue vaccine against each serotype with the ultimate goal of producing a tetravalent vaccine capable of broad neutralizing activity against all four serotypes while avoiding ADE. Lipid nanoparticles containing mRNA represent a vaccine platform that is safe, effective, and can be produced extremely quickly. We have shown that mRNA constructs coding for dengue premembrane and envelope proteins results in protein complex excretion in vitro. Vaccination with this lipid nanoparticle-encapsulated mRNA in mouse models results in neutralizing antibody titer as well as CD8+ and CD4+ T cell activation. Targeted mutations of the coded viral proteins in the vaccine seek to eliminate production of antibodies capable of enhancing disease.
38. Stiffness of aortic arch and carotid artery increases in ApoE-knockout mice: Evidence from echo cardiography

Author(s): Ming Tang

Department of Medicine

ABSTRACT

Atherosclerosis is a chronic inflammatory disorder that is the underlying cause of most cardiovascular disease (CVD). ApoE-knockout (ApoE-/-) mice after deposition of high-fat diet develop phenotypes similar to atherosclerosis. Arterial stiffness, the expression of reduced arterial elasticity, is an effective predictor of atherosclerosis. Measurement of pulse-wave velocity (PWV) is a gold-standard approach to study the arterial stiffness. In this study, we aimed to use high-resolution ultrasound (echo) to measure stiffness of aortic arch and carotid arteries and heart functions in ApoE knockout mice and their WT siblings. Our data shows that, compared with WT group, PWV values in both aorta and carotid arteries of mice were significantly increased in ApoE-/- group, (aorta arch PWV: 469.15±201.51 cm/s vs. 170.67±87.88 cm/s; Carotid artery PWV: 496.87±263.90 cm/s vs. 193.18±103.36 cm/s, respectively; both P < 0.01). In addition, left ventricular diastolic function according to E/A ratios and left ventricular ejection fraction values significantly decreased in ApoE-/- mice. This was consistent with the changes in PWV. The present study indicates that echocardiography could be a potential diagnostic strategy for early detection of atherosclerosis.
39. Salt Inducible Kinases (SIKs) Are Negative Regulators of Follicle Stimulating Hormone (FSH) in Ovarian Granulosa Cells

Author(s): Marah Armouti, Nicola Winston, Elie Hobeika, Jennifer Hirshfeld-Cytron, Juergen Liebermann, Carlos Stocco

Department of Physiology and Biophysics

ABSTRACT

Ovulation is the pinnacle of folliculogenesis, a process requiring granulosa cell (GC) proliferation and differentiation to form preovulatory follicles. In human and rodent GCs, we discovered that pituitary follicle-stimulating hormone (FSH) and insulin-like growth factors (IGFs) have interdependent effects on GC differentiation, converging on the activation of the serine/threonine kinase AKT. However, the AKT-controlled mechanisms involved in GC differentiation remain unclear. Here, we examined the role of salt-inducible kinases (SIKs), a known target of AKT, on the stimulation of GC differentiation by FSH.

We first examined the expression of the three SIK isoforms in ovarian human and rat GCs. Quantitative PCR, immunofluorescence, and immunohistochemical analyses revealed that all SIK isoforms are expressed in the GCs at different levels (SIK3>SIK2>SIK1).

To determine if SIKs play any role in the response of GCs to FSH, we treated rat and human GCs with inhibitors of SIK activity. We observed that SIK inhibition potentiated the stimulatory effect of FSH on aromatase mRNA expression, a marker of GC differentiation. This effect was also seen on aromatase promoter activity, aromatase protein expression, and estradiol production.

In vivo administration of YKL-05-099, a pan-SIK inhibitor, potentiated FSH-induced aromatase expression in wildtype mice. Next, to determine the role of each SIK isoform separately, we utilized a lentivirus carrying small hairpin RNA (shRNA) to target each isoform exclusively. Although each shRNA was successful in significantly knocking down its respective isoform, only the knockdown of SIK2 potentiated FSH stimulation of aromatase, suggesting that SIK2 is the dominant isoform in the ovaries.

These findings demonstrate, for the first time, the involvement of SIKs in the regulation of ovarian GC differentiation and contribute to our understanding of the mechanisms regulated by FSH and IGFs in the control of aromatase expression.
40. Ablating adipose CREB3L3 preserves metabolic health during obesity

Author(s): Maximilian McCann, Guifen Qiang, Victoria Gil, Hyerim Whang Kong, Chong Wee Liew,

Department of Physiology and Biophysics

ABSTRACT

During obesity, adipose tissue becomes supersaturated with lipids, leading to inflammation and release of free fatty acids into the bloodstream. This usually causes metabolic syndrome, but some obese individuals fail to develop metabolic syndrome and have been deemed metabolically healthy obese. Our lab created a mouse model that mimics metabolically healthy obesity, via the adipose-specific ablation of the ER-bound transcription factor, cyclic-AMP Responsive Element Binding Protein 3-like-3 (CREB3L3). We have discovered that CREB3L3 is not only expressed in adipose tissue, but selectively downregulated in the metabolically protective subcutaneous fat in obese mice and human patients. We hypothesized that CREB3L3 downregulation could contribute to the healthier nature of subcutaneous fat during obesity, so we created a CREB3L3 fat-specific knockout (KO) mouse. CREB3L3 KO mice had significantly larger inguinal white adipose tissue (iWAT), epididymal white adipose tissue (eWAT), and body weights compared to wild type controls following 12 weeks of high-fat diet feeding. Unexpectedly, the KO mice did not exhibit the reduced glucose tolerance or insulin sensitivity that would be expected with their more obese phenotype. The KO mice do not exhibit the expected dyslipidemia or hepatic steatosis, suggesting that the larger adipose tissues in the KO mice sequester lipids away from these spaces. The KO iWAT and eWAT have reduced inflammatory marker expression, suggesting that CREB3L3 plays a role in adipose inflammation. Together, these data suggest that adipose ablation of CREB3L3 preserves metabolic health during obesity by allowing the adipose tissue to meet the body’s lipid storage demands via healthy expansion.
Deciphering the role of IFI207 in cytosolic sensing and innate immunity

Author(s): Eileen Moran, Alexya Aguilera, Jingtao Lilue, Susan Ross

Department of Microbiology and Immunology

ABSTRACT

The innate immune response is crucial in controlling infection and reducing pathogenesis. Several receptors and signaling pathways of the mammalian innate immune response such as Toll-like receptors, RIG-I-like receptors, and Aim2-like receptors (ALRs) detect viral and bacterial nucleic acids to initiate type I interferon production or inflammasome assembly. This reduces pathogen spread and activates the adaptive immune system to clear infection. We showed that the Alr locus is highly variable in the number and composition of genes in inbred and wild mouse strains. These differences are thought to be driven by selective pressures of pathogens on these genes. However, the roles of many members of the Alr family remain unknown. We demonstrated that the Alr Ifi207 is highly polymorphic in different mouse strains. IFI207 has a single HIN domain, separated by 10^{26} repeat units of 14 amino acids from the PYD domain. No two wild mouse strains have the same number of repeats, and there is considerable diversity among inbred strains. Using murine primary macrophages and dendritic cells from knockout mice, we determined that Ifi207 is not required for interferon-beta production in response to dsDNA, dsRNA, or certain virus and bacterial infections. However, preliminary data suggest that Ifi207 may play a role in NF-ÎºB signaling during retrovirus infection. Ifi207 knockout dendritic cells expressed lower levels of the cytokine CCL2 upon infection with Murine leukemia virus (MLV). Additionally, Ifi207 knockout mice are more susceptible to MLV infection. Furthermore, we characterized the expression and localization of IFI207 and found that IFI207 interacts with and stabilizes STING expression.
Overlapping and unique neural circuitry underlying temporally unpredictable threat and reward processing

Author(s): Milena Radoman, Lynne Lieberman, Jagan Jimmy, Stephanie Gorka

Department of Psychiatry

ABSTRACT

Mounting evidence suggests that individuals who are intolerant of uncertainty (IU) have a tendency to respond negatively on an emotional, cognitive and behavioral level to uncertain stimuli. Many neuroimaging studies of uncertainty have focused on uncertain threat (U-threat) and have identified a specific frontolimbic circuit that may become engaged during U-threat processing. However, IU is posited to be a broad construct that impacts reactivity to all uncertain contexts, including uncertain rewards (U-reward). To date, it is unclear to what extent the frontolimbic circuit implicated in U-threat is also involved in U-reward and thus, overall individual differences in IU. The present study therefore sought to examine and compare the neural correlates of U-threat and U-reward in a sample of 159 unselected young adults. Participants underwent functional magnetic resonance imaging scan during which they completed two tasks designed to probe neural response to temporally unpredictable threat (i.e., mild electric shock) and reward (i.e., monetary incentive), respectively. Whole-brain family wise error corrected results indicated that both U-threat and U-reward elicited activation in the right anterior insula, right thalamus and right inferior frontal gyrus. U-threat uniquely activated the right posterior insula and dorsal anterior cingulate cortex, relative to U-reward. In contrast, U-reward elicited activation in the right fusiform and left middle occipital gyrus, relative to U-threat. Taken together, these findings support the idea of a shared neural circuitry involved in the processing of uncertainty (as a broadly defined construct), as well as provide evidence that some brain regions may be U-threat and U-reward specific.
43. LUBAC component, HOIL-1, is essential to prevent systemic dissemination, colonic ulceration and lethality from Citrobacter rodentium infection

Author(s): Victoria Hartley, Matthew Wood, Arwa Qaqish, Ta-Chiang Liu, Donna MacDuff,

Department of Microbiology and Immunology

ABSTRACT

Enteropathogenic Escherichia coli (EPEC) and enterohemorrhagic E. coli (EHEC) are gastrointestinal pathogens in humans and are major causes of infantile diarrhea and food-borne illnesses worldwide. Citrobacter rodentium is a mouse intestinal pathogen and model of human attaching and effacing (A/E) EHEC and EPEC strains. HOIL1 is a component of the Linear Ubiquitin Chain Assembly Complex (LUBAC), which generates linear polyubiquitin chains and is involved in regulation of immune signaling pathways. In humans, HOIL1 deficiency causes auto-inflammation, susceptibility to bacterial infections, and IBD-like symptoms. We have shown previously that HOIL1 is essential for survival during C. rodentium infection in mice. Here we show that, while C. rodentium infection causes mild colitis in wild-type mice, infection in Hoil1−/− mice causes severe colitis, ulceration of the distal colon, and death. Hoil1−/− mice shed more C. rodentium in their stool and bacteria spread to systemic sites including the mesenteric lymph nodes, spleen, and liver, although HOIL1 is not required to control bacterial replication at these systemic sites. HOIL1 is not required for induction of inflammatory cytokines, such as IL-22, in the colon during C. rodentium infection. Using bone marrow chimeric mice, we found that HOIL1 expression is important in non-hematopoietic cells to prevent development of severe colitis and weight loss. Our data show that LUBAC is essential in preventing systemic spread and lethality from infection with C. rodentium. Understanding the role LUBAC plays in controlling the pathogenesis of A/E lesion-forming bacteria will yield further insights into the intestinal innate immune response to pathogens.
44. Computing the functional landscape of many-body chromatin interactions in transcriptionally active loci

Author(s): Alan Perez-Rathke, Qiu Sun, Boshen Wang, Valentina Boeva, Zhifeng Shao, Jie Liang

Department of Bioengineering

ABSTRACT

Chromatin interactions are important for gene regulation and cellular specialization. Emerging evidence suggests many-body spatial interactions can play important roles in condensing super-enhancer regions into a cohesive transcriptional apparatus. Chromosome conformation studies using Hi-C are limited to pairwise, population-averaged interactions; therefore, not suitable for direct assessment of many-body interactions. We describe a computational model that reconstructs 3-D structural ensembles based on Hi-C data and identifies significant many-body interactions. For a diverse set of 39 highly-active transcriptional loci with at least 2 super-enhancers, we detail the many-body functional landscape and show DNase-accessibility, POLR2A-binding, and decreased H3K27me3 are predictive of interaction-enriched regions.
ABSTRACT
Metagenomic shotgun sequencing can provide useful information towards characterizing and understanding human microbiomes. Taxonomic classification of the metagenomic shotgun data can generate key insights into the microbial community structure that remains hidden from traditional, culture-dependent methods of analysis. In order to generate a taxonomic structure, the vast amount of data generated in culture-independent methods must be computationally annotated using large genome databases in order to determine the microbial origin of sequenced DNA. Bacterial annotation in particular requires comparing each DNA sequence against tens of thousands of possible genomes, a heavy computational task that requires software to balance resources, speed, and accuracy. Additionally, bacterial annotation must account for uncertainty by annotating DNA sequences at the higher taxonomic ranks such as phylum of genus, but many clinically significant features of bacteria are present at the strain-level. In this work we present an extension to the taxonomic classifier software, WEVOTE that utilizes a novel database structure to allow for strain-level resolution in the gut microbiome.
46. Vascular Insufficiency Behind the Fibrotic Remodeling in Hypertrophic Cardiomyopathy

Author(s): Richard Marszalek, Shamim Chowdhury, Monika HaÅ,as, Ashley Batra, Ross Solaro, Beata Wolska

Department of Physiology and Biophysics

ABSTRACT

Despite the extensive clinical characterization of hypertrophic cardiomyopathy (HCM), the pathobiology remains unclear. We aim at deducing the relevant pathological processes using a transgenic mouse harboring a common human troponin T mutation (R92Q). We hypothesized that altered diastolic function with impairment in perfusion and vascular function precedes and causes fibrotic remodeling in HCM. Echocardiographic data at 7 days of age display mild diastolic dysfunction in TG-R92Q vs. NTG mice (IVRT: 19.9 ± 1.3 vs. 15.2 ± 0.5 ms; DT: 29.2 ± 2.6 vs. 19.5 ± 1.2 ms; E wave: 470 ± 29 vs. 561 ± 19 mm/s; n=8), no changes in atrial size (1.00 ± 0.04 vs. 0.91 ± 0.02 mm) and depressed coronary flow velocities (coronary systolic peak velocity: 107 ± 17 vs. 185 ± 20 mm/s; coronary diastolic peak velocity: 367 ± 32 vs. 561 ± 67 mm/s). These changes coincide with expression of mutant TnT-R92Q protein (about 50% of expression found in older mice) and expression of ssTnI (90 ± 2%; n=8) that is replaced by cTnI at 14 days. At 7 days of age myofilaments from TnT-R92Q mice show increased Ca2+ sensitivity (pCa50: 5.97 ± 0.04 vs. 5.84 ± 0.01 n=4-8). However, no fibrotic remodeling occurs at this age. Our data show that fibrosis is present at 14 days of age at ventricular insertion points, suggesting that changes in coronary function and diastolic function occur early during development and coincide with expression of TnT-R92Q protein. Taken together, the impaired coronary flow may result in the fibrotic remodeling at vulnerable insertion points giving rise to the restrictive physiology apparent later.
47. BINGE DRINKING ALTERS ORTHODENTICLE HOMEBOX 2 GENE AND PROTEIN EXPRESSION IN THE VENTRAL TEGMENTAL AREA

Author(s): Cassandre Coles, Amy Lasek

Department of Anatomy and Cell Biology

ABSTRACT

The ventral tegmental area (VTA) is involved in the development of alcohol use disorder and depression. Depletion of the transcription factor orthodenticle homeobox 2 (OTX2) in the mouse VTA during in juveniles increases susceptibility to depression-like behaviors in adulthood. Since there is comorbidity between alcoholism and depression, we hypothesized that VTA OTX2 may play a role in binge drinking. The purpose of this study was twofold: 1) to measure VTA Otx2 gene and protein expression after binge-like ethanol consumption and, 2) to determine if viral-mediated knockdown of VTA OTX2 during adulthood regulates binge-like drinking. For Aim 1, mice underwent 4 days of binge ethanol (or water, as a control) drinking, and the VTA was dissected immediately or 24 hours after the last drinking session and subjected to qPCR or western blotting. VTA Otx2 mRNA was significantly decreased in both sexes immediately after ethanol drinking. At 24-hours, Otx2 mRNA was increased in the female ethanol-drinking group compared with controls. Interestingly, OTX2 protein levels were higher in females immediately after the ethanol-drinking session and in both sexes 24 hours later. These results demonstrate that binge-like drinking alters VTA Otx2 gene and protein expression. For Aim 2, adult mice were injected in the VTA with lentivirus to reduce Otx2 expression and tested for binge ethanol consumption. There was no difference in ethanol or 2% sucrose consumption in either sex after VTA Otx2 knockdown. Future experiments will determine if manipulating Otx2 expression during the juvenile period plays a role in binge drinking in adulthood.
Coronary Artery Axial Deformation in Native Compared to Stented Arteries

Author(s): Logan Schwarzman

Department of Medicine

ABSTRACT

Background:

Coronary arteries are exposed to complex biomechanical forces during a normal cardiac cycle. These forces potentially contribute to coronary stent failure. Newer stent designs have allowed for transmission of native pulsatile biomechanical forces in the stented vessel. However, there remains a lack of evidence in a human model to measure vessel motion and stent conformability. Thus, we aimed to characterize and define coronary artery axial deformation and the effect of stent implantation on arterial deformation.

Methods:

Intravascular Ultrasound pullback DICOM images were obtained from human coronary arteries using a coronary ultrasound catheter. The DICOM images were uploaded to syngo software and utilized for a novel application to evaluate axial deformation in human coronary arteries. Using 2D speckle tracking, coronary artery axial deformation was defined as the inward and outward displacement (mm) and velocity (cm/s) of the arterial wall during the cardiac cycle. We compared native and third-generation drug eluting stented artery segments.

Results:

A total of 20 coronary artery segments were independently analyzed pre- and post-stent implantation. Stent implantation impacted degree of axial displacement and velocity. Mean axial displacement in native coronary arteries was 0.1230 mm +/- 0.0522 mm compared to 0.0775 mm +/- 0.0376 mm in stented vessels (p=0.0031). Mean axial velocity in native coronary arteries was 0.1194 cm/s +/- 0.0535 cm/s compared to 0.0840 cm/s +/- 0.0399 cm/s in stented vessels (p=0.0228).

Conclusion:

Current stents inhibit the complex biomechanical forces of the normal cardiac cycle. Next generation stent technology strives to provide greater allowance for coronary axial deformation.
ABSTRACT

Objectives: We sought to evaluate the differences in prostate cancer (PCa) characteristics and treatment between Hispanics with different countries of origin using the National Cancer Database (NCDB).

Methods: We performed a retrospective analysis of 54,947 adult Hispanics diagnosed with PCa between 2004-2015. Origin was Mexican (N=7,844; 14.3%), South/Central American (N=4,010; 7.3%), Puerto Rican (N=2,938; 5.4%), Cuban (N=2,549; 4.6%), Dominican (N=1535; 2.8%), Hispanic not specified (NOS, N=36,269; 65.7%). Patient and PCa characteristics were analyzed with chi-square and Kruskal-Wallis tests, and overall survivals analyzed with Kaplan Meier and Cox model adjusting for baseline variables.

Results: Mexicans had overall worse disease at presentation including highest median PSA (7.8 ng/ml), most prevalent T3/T4 stage (6.7%) and high-grade Gleason scores (20.6%) when compared to all other Hispanic groups. Cubans were most likely to receive Hormone therapy and Radiation therapy and least likely to receive surgical treatment. Compared to Mexicans, Cubans (HR=1.30, 95%CI=[1.16-1.44]) had worse overall survival, while Puerto Ricans (HR=1.08 [.95-1.19] had similar overall survival, and Dominicans (HR=0.63 [0.53-0.75]), South/Central Americans (HR=0.75, [0.66-0.84]) and NOS (HR=0.84 [0.79-0.91]) had better survival.

Conclusions: Among Hispanics with different countries of origin, disparities in PCa characteristics, treatment choice, and survival do exist. Mexicans had the least favorable PCa characteristics at presentation. Cubans had the worst overall survival while they most likely to receive hormone and/or radiation as first-line treatment. Genetic, environmental and lifestyle differences between Hispanic groups may explain such disparities.
**50. Design and sample characteristics of COordinated Oral health Promotion (CO-OP) Chicago: A cluster-randomized controlled trial**

**Author(s):** Lacey Zimmerman, Molly Martin, Genesis Rosales, Helen Lee, Nattanit Songthangtham, Oksana Pugach

Department of Pediatrics

**ABSTRACT**

Objective: To describe the design of a two-arm cluster-randomized trial with a wait-list control in determining the ability of a community health worker (CHW) intervention to improve young children’s oral health behaviors.

Methods: CHWs delivered family-focused oral health education and support throughout four visits to individual families over one year. Participating families were recruited from community social service centers (Women, Infants, and Children [WIC] Centers) and pediatric primary care medical clinics in Cook County, Illinois. Sites were cluster-randomized to CHW intervention or the wait-list control arm (usual services). Data on brushing frequency, plaque, and other oral health behaviors were collected at baseline, 6-, and 12-months. The primary analysis will assess differences in caregiver-reported child brushing frequency and observed plaque score between the two arms at 12-months.

Results: 420 child/caregiver dyads were enrolled at the 20 participating sites over 11 months. The average child age was 21.5 months (SD 6.9), and families were mainly low-income and Hispanic ethnicity or non-Hispanic Black race. Caregivers reported 5 percent of their children brushed more than twice a day, 40 percent twice a day, 33.8 percent once a day, 15.2 percent sometimes but not every day, and 6 percent did not brush. Mean plaque score values were in the fair to poor range. Demographics varied across the 20 sites, but primary outcomes values at baseline did not.
51. Cell Response to Nerve Transection with Re-approximation in a Murine Model

Author(s): Adam Miller, Bradley Glazier, Awais Hussain, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

It has previously been demonstrated that Wallerian degeneration and microgliosis occur following nerve injury, and differences in response to injury are related to its location along the axon. More proximal lesions are associated with earlier and more extensive cell death, but also more effective axonal regeneration. In contrast, distal lesions are associated with less neuronal death, but also exhibit less axonal regeneration. It is currently unknown what differences occur at the cellular level to account for these variations in regenerative potential, and the consequences of this on neuronal functionality. In this study, adult male rats underwent baseline motor function testing prior to having their sciatic nerve transected and reapproximated via suture at a point either proximal or distal to the trifurcation of the tibial, peroneal, and sural nerves. Testing of motor function continued until time points for sacrifice were reached. Following sacrifice, the muscles were weighed to assess degree of atrophy and the nerves were analyzed for evidence of Wallerian degeneration or regeneration. Both the proximal and distal lesions showed significant reduction in motor function postoperatively, followed by a significant recovery between 7 days and 25 days. There was no significant difference in motor function between groups at each time point. However, those with distal injury returned to baseline motor function more quickly than those with proximal injury. Future work on this project looks to quantify the extent of Wallerian degeneration or regeneration occurring in the injured nerves and its relation to the microglial response in the spinal cord.
52. Height Determines Upper Extremity Long Bone Length, Not Gender

Author(s): Mark Orland, Mark Orland, Dr. Michael Patetta, Nitin Sukumar, Dr. Mark H. Gonzalez,

Department of Orthopaedics

ABSTRACT

Objective: Long bone length in the body is often considered to be a method of differentiation between female and male skeletal remains. This study aimed to examine whether reported gender bone differences were a result of an average height difference between the sexes or whether there was a length difference independent of height.

Methods: The height, distal and proximal ends of the humerus, radius, and ulna of thirteen cadavers were identified and the length of each of the long bones were measured. A mixed error-component model with a repeated measures design and an unstructured covariance matrix were used on both arms of all of the cadavers (n = 26) to examine how left or right sidedness, gender, and height related to upper extremity long bone length.

Results: When comparing the left and right side of the cadavers, there was no significant difference in the length of the humerus, radius or ulna (p > .05). Additionally, when stratifying for height, between females and males, there was no significant difference in the upper extremity long bones. However, there was a significant increase in the length of the radius and the ulna with an increase in the height of the cadaver (p < .01).

Conclusion: There is no significant difference in upper extremity long bone length when comparing between males and females. Therefore, the gender of incomplete anatomical remains cannot be determined solely based on forearm bone length. Rather, the height of the individual to which the remains belong can be estimated.
53. Surgical Duration Implicated in Major Postoperative Complications in Total Hip and Total Knee Arthroplasty

Author(s): Mark Orland, Remy Lee, Edmund Naami, Dr. Michael Patetta, Dr. Awais Hussain, Dr. Mark H. Gonzalez

Department of Orthopaedics

ABSTRACT

Objective: Total hip (THA) and knee arthroplasties (TKA) are two of the most commonly performed orthopedic surgeries and are expected to increase in incidence in the coming decades. We examined whether the duration of these procedures is related to various postoperative complications using data from 2010 to 2017 from the American College of Surgeons National Surgical Quality Improvement Program database (ACS-NSQIP).

Methods: The ACS-NSQIP database was queried for patients undergoing THA and TKA by their respective Current Procedural Terminology codes. Operation time was stratified into 4 quartiles with equal sample sizes in each quartile for THA and TKA separately. The first quartile of operative times was used as the control to which the other three quartiles were compared. Multivariate logistic regression (MLR) analysis was performed on all samples that accounted for possible covariates, totaling 119,076 patients for THA and 189,297 for TKA.

Results: The third and fourth surgical duration quartiles of THA and TKA were significantly associated with higher incidences of wound complications, particularly infections and dehiscence (p < .05, odds ratio > 1). Additionally, prolonged THA was associated with a significantly higher rate of urinary tract infections (UTI) for the third and fourth quartiles, as well as deep vein thrombosis (DVT) in the 4th quartile.

Conclusion: Longer surgical durations in THA and TKA are associated with a significantly higher risk of wound complications. In cases with longer anticipated operative times, appropriate perioperative measures including a comprehensive prophylactic antibiotic regimen should be taken to minimize patient morbidity and reduce hospital costs.
Sarcopenia is Associated with an Increased Risk for Revision of Total Joint Arthroplasty (TJA)

Author(s): Adam Miller, Manpreet Tiwana, Mike Patteta, Anshum Sood, Mark Gonzalez,

Department of Orthopaedics

ABSTRACT

Sarcopenia is defined as an abnormally low muscle mass and has been linked to an increased risk of morbidity and mortality following several surgical procedures. This study is the first aimed at assessing the prevalence of sarcopenia amongst patients seeking total joint arthroplasty (TJA), as well as determining if sarcopenia is associated with an increased risk of complications postoperatively. This was a retrospective, case-control review of 70 patients who underwent either total hip arthroplasty (THA) or total knee arthroplasty (TKA). All patients had a computed tomography (CT) scan of the abdomen/pelvis conducted within a year preoperatively, which was used to evaluate for sarcopenic status. Patients were assigned to the case arm and control arm based upon sex based cutoff criteria for sarcopenia. These two groups were then evaluated for documented presence of all postoperative complications, revision of TJA, and all cause readmission. Eight of the 70 patients were found to be sarcopenic, an incidence similar to that seen in other studies evaluating different populations. Sarcopenic patients were noted to have an increased risk for TJA revision when compared to non-sarcopenic patients (odds ratio [OR] 22.4, 95% confidence interval [CI] 1.7163-292.3568, P = 0.0177). However, sarcopenia was not associated with an increased risk of all postoperative complications (OR 1.1379, 95% [CI] 0.2609-4.9639, P = 0.8635) or readmission (OR 3.5250, 95% [CI] 0.6802-18.2675). Further studies with larger numbers of sarcopenic patients should be conducted to evaluate if sarcopenia should be considered as a screening tool in patients seeking total joint arthroplasty.
55. The interaction of diabetic peripheral neuropathy and carpal tunnel syndrome

Author(s): Ushasi Naha, Adam Hamidi, Michael Patetta, Awais Hussain, Mark Gonzalez, Farid Amirouche

Department of Orthopaedics

ABSTRACT

While diabetes mellitus can lead to diabetic peripheral neuropathy, it also has been established as a contributing factor for carpal tunnel syndrome (CTS). Given the established link between diabetes and CTS, further investigation of how the two diseases affect the other's progression can aid physicians in their treatment of such patients. The objective of the study was to examine the relationship between the severity of DPN and CTS.

Consenting diabetic and control patients (n=292) at University of Illinois Hospital and Health Sciences System (UIH) for a clinic visit were recruited. The Michigan Neuropathy Screening Instrument (MNSI) was used to collect symptomatic and physical exam data.

From the 292 recruited patients, there were 138 (47.3%) Type II diabetics and 154 (52.7%) controls. From our sample, 41 patients had CTS and 46.3% of these patients had both CTS and DM. Of the 138 diabetic patients, 132 (95.7%) fulfilled criteria for peripheral neuropathy. There were similar numbers of patients with CTS between diabetics with and without DPN. The severity of DPN between diabetic and control patients with CTS was also comparable.

Our findings suggest that DPN did not seem to have an interaction with CTS. Surprisingly, the comorbidity of diabetes does not alter the severity of peripheral neuropathy in patients with CTS, given the similar MNSI scores between the groups. Thus, the well-established literature looking at DM and CTS should burrow down to tease out how DPN and CTS differ from one another, in order to tailor patient interventions based on their comorbidities.
ABSTRACT

INTRODUCTION: An estimated 35.7 million U.S. adults have either atherosclerotic cardiovascular disease (ASCVD) or diabetes.1 The American College of Cardiology (ACC) has developed an ASCVD risk estimator and recommends that those with a 10-year ASCVD risk >/=7.5% be initiated on statin therapy.2 The aim of this study was to investigate the percentage of patients presenting to the Emergency Department (ED) with elevated blood pressure (BP) that meet the ACC criteria to initiate statin therapy.

METHODS: This was a retrospective analysis of de-identified patient data collected for the Targeting of Uncontrolled Hypertension in the Emergency Department (TOUCHED) study. All participants were identified as presenting to the ED with an elevated BP (Systolic >140 OR diastolic >90) and were eligible to calculate their 10-year ASCVD risk score (age 40-79). The percentage of patients that would benefit from statin therapy was determined as the number of patients with ASCVD risk >/=7.5% over all participants. The ASCVD risk was estimated using the ACC’s calculator.3

RESULTS: It was determined that 35 of 59 (59.3%) patients that presented to the ED with elevated BP may benefit from initiation of statin therapy. Of those, only 6 individuals (17%) were already on statin therapy.

DISCUSSION: A majority of patients between ages 40-79 presenting in the ED with elevated BP may benefit from statin therapy to reduce the risk of ASCVD. Physicians can use this knowledge to counsel patients to speak to their primary care provider about initiating statin therapy. This study was limited by its small sample size.
Chronic Corticosteroid Use as a Risk Factor for Perioperative Complications in Patients Undergoing Total Joint Arthroplasty

Author(s): Haley Kittle, Andrew Ormseth, Michael Patetta, Anshum Sood, Mark Gonzalez,

Department of Orthopaedics

ABSTRACT

INTRODUCTION: Total Joint Arthroplasties (TJA) are a group of procedures that are commonly used to treat osteoarthritis of large joints. Osteoarthritis may be caused by or be comorbid with diseases that rely on immunosuppressive corticosteroids as a mainstay of treatment. Therefore, there is a sizable population that will undergo TJA while on a regimen of chronic corticosteroids. The aim of this study was to assess corticosteroids as a risk factor for perioperative TJA complications.

METHODS: This was a retrospective analysis of data collected prospectively in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). Patients who underwent primary and revision total knee arthroplasty (TKA) and total hip arthroplasty (THA) were identified. Univariate statistical analysis was performed on baseline characteristics as well as for mortality and perioperative complication measures. Statistical significance was set at P=0.05. Outcome measures were mortality and perioperative complications.

RESULTS: In our cohort, 3.7% (14774/403566) were prescribed corticosteroids for a chronic medical condition. There was no statistically significant difference in the 30-day mortality, bleeding/clotting events, or sepsis between the 2 groups. There was a statistically significant difference in perioperative complications for patients prescribed corticosteroids, including higher rates of all types of infections studied, occurrences of unplanned intubation, and readmission. There was also a statistically significant difference in patient baseline characteristics.

DISCUSSION: Chronic corticosteroid use before TJA is associated with a number of statistically significant perioperative complications, but not an increase in 30-day mortality rate. Many of the complications are due to the immunosuppressive nature of corticosteroids.
58. Do Intra-articular Corticosteroid Injections Prior to Total Knee Arthroplasty Increase Postoperative Complication Rates?

Author(s): David Rhode, Deena Kishawi, Elan Volchenko, Matthew Siegel, Mike Patetta, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Introduction:

There has been controversy surrounding the use of intra-articular corticosteroid injections before total knee arthroplasty (TKA). It has been speculated that these injections may lead to an increase in the rate of postoperative complications, specifically periprosthetic joint infection (PJI). Currently, there is conflicting literature on the topic.

Methods:

This study consisted of retrospective review of over 1,190 patients who received a TKA. The patients were initially separated into two groups: those who received an intra-articular corticosteroid injection and those who did not receive an injection. The injection patients were then further divided into subgroups based on the timing of the most recent injection before surgery: 0-3, 3-6 months, 6-9 months, 9-12 months, and 12+ months. Differences between the groups were analyzed.

Results:

In our patient population, we did not observe a statistically significant increase in rates of PJI (p=.582), the later need for revision (p=.837), the later need for manipulation under anesthesia (MUA) (p=.348), or prolonged postoperative pain (p=.889) in patients who had intra-articular corticosteroid injections compared to patients who did not receive an injection prior to TKA. Dividing the injection patients into subgroups based on timing of last injection also failed to reveal a statistically significant increase in the rates of the above respective complications (p=.409/.985/.732/.582).

Conclusions:

This study revealed no association between preoperative intra-articular corticosteroid injections and postoperative complications after TKA, indicating that these injections may be used safely before surgery.
59. Preoperative Alignment Does Not Impact the Functional Outcomes of Bi-cruciate Stabilized Total Knee Arthroplasty

Author(s): Bradley Glazier, David Rhode, Michael Patetta, MD, Awais Hussain, MD, Mark Gonzalez, MD, PhD

Department of Orthopaedics

ABSTRACT

Background:
Candidates for total knee arthroplasties (TKAs) present with knees of varying alignments. Valgus deformities are encountered less often and present a number of challenges. When cruciate retaining (CR) implants were initially employed in valgus knees, concern arose regarding postoperative instability. This study looks to compare postoperative outcomes between alignment groups in patients receiving a bi-cruciate stabilized (BCS) implant.

Methods:
Using our institutional registry, patients who underwent primary TKA by a single surgeon and received a BCS implant were identified. Patients were categorized as having a varus (<4 degrees), valgus (>8 degrees), or neutral (4-8 degrees) alignment based on their tibiofemoral angles (TFA) calculated from preoperative radiographs. Range of motion (ROM) data and Knee Society Scores (KSS) scores were recorded both preoperatively and postoperatively at 1, 3, 6, and 12 months. Outcomes between the groups were compared using statistical analysis.

Results:
66 patients meeting inclusion criteria were identified. 44 patients (63.6%) had a preoperative varus alignment, 10 (15.2%) had a neutral alignment, and 14 (21.2%) had a valgus alignment. There was no significant difference between groups preoperatively. Kruskal-Wallis tests demonstrated no significant difference between groups at 1 year postoperatively for ROM (P=0.361), or KSS scores (P=0.826). Average KSS score and ROM at 1 year was 84.0 and 105.9 degrees respectively.

Conclusion:
Preoperative alignment does not significantly impact one-year outcomes when using a BCS implant for TKA. Even in the less common and challenging valgus alignment, satisfactory results, similar to those of other alignments, can be achieved.
60. Weighted Gene Co-Network Analysis (WGCNA) Identifies Common Hub Genes Between Cutaneous Sarcoidosis and Discoid Lupus Erythematosus

Author(s): Melissa Nickles, Kai Huang, David Perkins, Patricia Finn

Department of Medicine

ABSTRACT

Sarcoidosis is a granulomatous disease that primarily affects the lungs and skin. The exact pathogenesis of sarcoidosis remains unclear. By studying gene networks of cutaneous sarcoidosis in comparison to other immune-related skin disorders, we can better understand the underlying mechanisms of the disease state. We analyzed microarray expression data from two cohorts of patients with sarcoid, discoid lupus, and psoriasis skin lesions. We used weighted gene co-network analysis (WGCNA) to construct gene-gene similarity networks and cluster genes into modules based on similar expression profiles. We identified a module of interest related to immune activity that was preserved between datasets and correlated with clinical traits. This immune module was significantly upregulated in both sarcoid lesions and lupus lesions versus their respective controls. Protein-protein interaction (PPI) networks were constructed using STRING database and Cytoscape software to look for common hub genes driving this module. We further characterized our hub genes with differential gene expression analysis. We found that the sarcoid group and discoid lupus group had 7 hub genes in common: TLR1, ITGAL, TNFRSF1B, CD86, SPI1, BTK, and IL10RA. There were differences in biologically significant hub genes as well. Our findings suggest that there may be parallel gene dysregulation in the immune processes of cutaneous sarcoidosis and discoid lupus, which could have indications for future therapeutic targets and biomarkers.
Yoga teachers’ perspectives on teaching accessible yoga to people affected by traumatic brain injury through the LoveYourBrain Yoga program?

Author(s): Nirali Chauhan, Shilo Zeller, Kyla Donnelly

Department of Medicine

ABSTRACT

Background
The emerging benefits of yoga for traumatic brain injury (TBI) suggest that broader accessibility to community-based yoga has potential to facilitate ongoing rehabilitation. This study sought to identify best practices for adapting and delivering community-based yoga to people with TBI.

Methods
A cross-sectional, mixed methods study using an online survey among 175 yoga teachers within the LoveYourBrain Yoga program. The survey included questions assessing yoga teachers’ perspectives on the most and least helpful adaptions for asana, meditation, pranayama, and group discussion, and on the helpfulness of the LoveYourBrain Yoga training. Responses were analyzed using descriptive statistics and qualitative content analysis.

Results
86 teachers (n=50%) responded. Best practices for adapting yoga for TBI revealed six themes: simple, slow, and repeated, creating a safe space, position of the head and neck, demonstration, importance of props, and special considerations for yoga studios, and three themes for yoga program delivery: structured yet flexible, acceptability of compensation, and time management. 89% of teachers reported using the manual to guide classes was either very/extremely helpful, yet nearly half (49%) adapted the manual often/always.

Conclusions
To deliver accessible, community-based yoga services to the TBI population, we recommend using a manual that allows for flexibility and an environment that has low light and noise, props, and sufficient space. We also recommend teachers have skills in offering physical modifications for the head and neck; slow, simple, and repeated cueing to facilitate cognitive processing; managing challenging behaviors through redirection techniques; and promoting safety through inclusivity, compassion, and personal agency.
Development of an Artificial Intelligence Program to Autonomously Identify Spinal Anatomy in CT Radiography

Author(s): Michael Foy, Craig Forsthoefel, Kris Siemionow

Department of Orthopaedics

ABSTRACT

Machine learning algorithms are a subset of artificial intelligence that have proven to enhance analytics in medicine across various platforms. Spine surgery has the potential to benefit from improved hardware placement utilizing algorithms that autonomously and accurately measure pedicle and vertebral body anatomy. To assess the accuracy of an autonomous convolutional neural network in measuring vertebral body anatomy utilizing clinical lumbar CT scans and automatically segment vertebral body anatomy. The convolutional neural network was trained utilizing 8,000 manually segmented CT slices from 15 cadaveric specimens and 30 adult diagnostic scans. Anatomic landmarks that were segmented included the pedicle, vertebral body, spinous process, transverse process, facet joint, and lamina. Morphometric measurement of the vertebral body was compared between manual measurements and automatic measurements. Automatic segmentation was found to have a mean accuracy ranging from 96.38% and 98.96%. There was a 3.07% error in measurements that determine screw selection but was not statistically significant between manual and computer methods. Coaxial distance from lamina to anterior cortex was 99.10% with pedicle angulation error of 3.47%. The convolutional neural network algorithm tested in this study provides an accurate means to automatically identify vertebral body anatomy and provide measurements for implants and placement trajectories.
63. Biceps Tenotomy vs. Tenodesis in Patients Younger Than 45: A Matched Cohort Study.

Author(s): Elan Volchenko, David Rhode, Garrett Schwarzman M.D., Benjamin Goldberg M.D.

Department of Orthopaedics

ABSTRACT

Background: Long head of biceps tendon lesions are a major factor in accounting for shoulder pain. These lesions can be addressed intraoperatively with either biceps tenotomy or tenodesis. Tenotomy is a simpler procedure with a much faster recovery. However, it may produce a visible deformity or involve a loss of strength. Tenodesis, on the other hand, is a more complex procedure involving a more arduous recovery but has long been hypothesized to be the better choice for younger, more active patients.

Methods: We retrospectively evaluated patients under 45 years of age who underwent surgery between January 2005 and May 2016 by a single orthopedic surgeon. Matched cohorts were selected from these two groups based on preoperative UCLA shoulder scores, concomitant procedures, and other demographic information. Outcomes between the cohorts were then analyzed.

Results: There was no statistically significant differences between the tenodesis and tenotomy cohorts in terms of postoperative UCLA scores (27.5 and 27.2 respectively, p=.899), range of postoperative forward flexion (172°/174°, p=.678), or rate of postoperative deformity (0%/10%, p=.305). There was a statistically significant increase in the rate of postoperative weakness in the tenotomy group (10%/60%, p=.019).

Conclusion: Both procedures were associated with positive outcomes, as a UCLA score of 27 is considered to be a good to excellent result. Both biceps tenodesis and tenotomy can be considered for young patients, though those undergoing tenotomy should be counseled on the possibility of postoperative weakness.
64. Relationship Between Nicotine Metabolism and Gestational Age of Premature Infants

Author(s): Sophia Bidny, Douglas Weibel, Katie Brenner, Wenxiang Luo, Alan Schwartz, De-Ann Pillers

Department of Pediatrics

ABSTRACT

Purpose:
The many developmental complications effects of cigarette smoke include low birth weight, still birth, placental abruption, and SIDS/SUID. Nicotine is metabolized via CYP2A6 enzyme, first to 3-hydroxycotinine and then to cotinine. Smoking inhibits genetic expression of CYP2A6, causing buildup of unmetabolized nicotine. An increased 3HC/Cot (a measure of nicotine metabolism efficiency) was found in older children, which implies an increase in CYP2A6 activity.

Hypothesis:
We hypothesize that increased nicotine metabolism in premature infants will be positively correlated to gestational age and birth weight.

Methods:
Urine samples were collected from 300 infants born before 37 weeks gestational age at Day 1, Day 2, and Day 3 of life, along with retrospective chart review clinical data on gestational age, birth weight, and maternal smoking status.

Samples were quantitatively analyzed via mass spectroscopy by Metabolon, and nicotine metabolites were identified. Using R (https://www.r-project.org/), the ratio of cotinine to 3-hydroxycotinine was calculated for each sample and we estimated the correlation between gestational age at birth in weeks and (the log of) the ratio.

Results:
Gestational age at birth was positively correlated with log 3HC/Cot controlling for collection day (B=0.273, p < 0.001), and more specifically on the first day of collection (B=0.171, p <0.001).

Discussion:
As gestational age increases, nicotine metabolism increases. This is likely because older neonates have a more advanced hepatic system for nicotine processing and confirms that even as preemies, older children metabolize nicotine faster than younger children.
65. Preoperative Alignment Does Not Impact the Functional Outcomes of Bi-cruciate Stabilized Total Knee Arthroplasty

Author(s): Bradley Glazier, David Rhode, Michael Patetta, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Background:
Candidates for total knee arthroplasties (TKAs) present with knees of varying alignments. Valgus deformities are encountered less often and present a number of challenges. When cruciate retaining (CR) implants were initially employed in valgus knees, concern arose regarding postoperative instability. This study looks to compare postoperative outcomes between alignment groups in patients receiving a bi-cruciate stabilized (BCS) implant.

Methods:
Using our institutional registry, patients who underwent primary TKA by a single surgeon and received a BCS implant were identified. Patients were categorized as having a varus (<4 degrees), valgus (>8 degrees), or neutral (4-8 degrees) alignment based on their tibiofemoral angles (TFA) calculated from preoperative radiographs. Range of motion (ROM) data and Knee Society Scores (KSS) scores were recorded both preoperatively and postoperatively at 1, 3, 6, and 12 months. Outcomes between the groups were compared using statistical analysis.

Results:
69 patients meeting inclusion criteria were identified. 43 patients (62.3%) had a preoperative varus alignment, 11 (15.9%) had a neutral alignment, and 15 (21.7%) had a valgus alignment. There was no significant difference between groups preoperatively. Kruskal-Wallis tests demonstrated no significant difference between groups at 1 year postoperatively for ROM (P=0.361), or KSS scores (P=0.826). Average KSS score and ROM at 1 year was 84.0 and 105.9 degrees respectively.

Conclusion:
Preoperative alignment does not significantly impact one-year outcomes when using a BCS implant for TKA. Even in the less common and challenging valgus alignment, satisfactory results, similar to those of other alignments, can be achieved.
Does the MLB’s Collision at Home Plate Rule Change Prevent Concussion Injuries in Catchers?

Author(s): Elan Volchenko, Hayden Baker M.D., Aravind Athiviraham M.D.

Department of Orthopaedics

ABSTRACT

Background:

In 2013, conduct of catchers and baserunners at home-plate was outlined in new rule 7.13 of MLB Rules. This was mandated to protect athletes from collisions at home-plate. Prior to enactment, no rules were in place governing conduct at home-plate. The aims of this study were to quantify the impact of the Collision at Home Plate rule on concussion rates among MLB catchers, and time spent on the DL after concussions.

Methods:

Data was compiled using public information extracted from MLB transactions. All MLB catchers placed on the DL for concussions from 2012-2013 and 2015-2016 were included. Injury rates were reported per 1000 athletic exposures. Relative risk (with 95% CI) was calculated using injuries per 1,000 athletic exposures for the 2 seasons before and after the rule change (12’-13’ and 15’-16’).

Results:

Among catchers the relative risk of concussion per 1000 athletic exposures was 0.31 (95% CI, 0.11“ 0.85) when comparing the 2 seasons before and after introduction of rule 7.13. Average time catchers spent on the DL secondary to concussion during the 2012-2013 seasons was 11.75 days, reduced to 7 for the 2015 “2016 seasons. There was no significant difference in time on the DL for concussion between 12’-13’ vs. 15’-16’.

Discussion:

The MLB’s rule 7.13 reduced concussions in MLB catchers. This study provides insight regarding injury patterns/rates in catchers and can serve as a benchmark for discussion about injury prevention. To our knowledge, no other study has focused on rule 7.13 and its effect on concussions in MLB catchers.
67. Disparities in Rates of Fusions in Lumbar Disc Pathologies

Author(s): Soobin Kim, James Ryoo, Philip Ostrov, Abhinav Reddy, Mandana Behbahani MD, Ankit Mehta MD

Department of Neurosurgery

ABSTRACT

Background: Surgical management of single-level lumbar disc herniations is achieved by decompression and potentially spinal fusion. Although fusions are routinely performed for disc herniations, current clinical evidence remains inconclusive. This study seeks to identify disparities in surgical decision-making for single-level disc herniations based on patient demographics, hospital characteristics, and temporal characteristics of admission.

Methods: Patients requiring surgical treatment for single-level disc herniation were queried from the National Inpatient Sample datasets spanning 2012-2015. Multivariate logistic regression was performed to assess effects of patient demographics, temporality of admission, and hospital characteristics on rates of lumbar fusion while controlling for patient-level medical comorbidities.

Results: Of 85,403 patients with lumbar disc pathologies, 70,385 patients were treated electively and 15,018 patients were treated non-electively. In elective cases, privately insured and self-paying patients were less likely to receive a fusion compared to Medicare patients (OR 0.83, p<0.001; OR 0.65, p<0.001, respectively), while this effect was limited to self-pay patients in non-elective cases (OR 0.44, p<0.001). Urban teaching and non-teaching hospitals were less likely to perform fusions compared to rural hospitals in non-elective cases (OR 0.57, p<0.001; OR 0.47, p<0.001, respectively). Private for-profit hospitals were associated with higher rates of fusion in both elective and non-elective cases (OR 1.15, p=0.004; OR 1.97, p<0.001).

Conclusions: This study illustrates disparities in the modality of surgical intervention for single-level disc pathologies in terms of demographics, hospital characteristics, and temporal characteristics of admission. The development of evidence-based guidelines is warranted to reduce the variability seen in treatment regimens for this condition.
68. Treatment Options for Mycosis Fungoides: Photodynamic Therapy, Radiation Therapy, Chemotherapy

Author(s): Zobia Chunara, Carolina Puyana, Maria Tsoukas

Department of Dermatology

ABSTRACT

Background: Mycosis fungoides (MF) is an indolent cutaneous T-cell lymphoma. Treatment options include photodynamic therapy (PDT), radiation therapy (RT), and chemotherapy (CT) among others. The purpose of this study is to compare survival rates in MF patients treated with these modalities.

Methods:

Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program database, collected from 1998-2015, was analyzed retrospectively. Patients who had microscopically confirmed MF of the skin and received PDT, beam RT, or CT were included. The effect of treatment categories and their interaction with disease stage on disease specific survival (DSS) probability was evaluated using a Cox proportional hazards model. Graphical analysis was performed using the Kaplan “Meier method. Hazard ratios (HR), 95% confidence intervals, and p-values were calculated (a = 0.05).

Results:

A total of 474 MF cases were considered for analysis: 15% treated with PDT, 32% RT, and 53% CT. DSS was significantly higher for patients in the plaque stage treated with PDT compared to CT (HR 0.099; 0.005-0.619). For patients in the tumor stage, those undergoing RT had significantly increased DSS compared to CT (HR 0.150; 0.018-0.795).

Conclusion:

Our findings suggest that PDT is superior to CT in the treatment of plaque stage, and RT is superior to CT in the treatment of tumor stage MF. These results demonstrate the efficacy of energy-base therapies in treating MF. Additionally, prognostic factors such as age at diagnosis, marital status, and number of lesions indicate high-risk patients who may benefit from additional forms of treatment.
Hepatic Encephalopathy after Viatorr Controlled Expansion Transjugular Intrahepatic Portosystemic Shunt Creation

Author(s): Marie-Louise Kloster, Albert Ren, Ron Gaba, Ketan Shah

Department of Radiology

ABSTRACT

Purpose: To assess incidence and degree of hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic shunt (TIPS) creation using the Viatorr Controlled Expansion (VCX) stent-graft.

Materials and methods: In this single institution retrospective study, 40 consecutive patients who underwent VCX-TIPS creation between 2018-2019 were studied. Patients lacking 30-day clinical follow-up (n=7) were excluded. The final cohort spanned 33 patients (M:F 17:16, mean age 58 years, mean MELD 12). 11/33 (33%) patients had a history of medically controlled pre-TIPS HE. TIPS indications included variceal hemorrhage (n=12) and ascites (n=21). Medical record review was used to collect demographic, procedural and clinical outcome data.

Results: VCX-TIPS were successfully created with hemodynamic success in all cases. Final shunt caliber was 8-mm in 28/33 (85%) and 10-mm in 5/33 (15%). Mean final portosystemic pressure gradient was 6 mmHg. 30-day HE incidence was 27% (9/33), cumulative HE incidence was 64% (21/33; 9/21 recurrent, 12/21 de novo) over median 247-day follow-up; median time-to-HE occurrence was 75 days. HE West Haven grades spanned grade 1 (n=7), 2 (n=8), and 3 (n=6). Medication non-compliance or infection was implicated in HE in 48% of cases. Medical therapy successfully addressed HE in 19/21 (90%) cases, and shunt reduction was necessary in 2/21 (10%) cases. HE still resulted in 39 hospitalizations among 14 patients. Median time to first hospitalization was 75 days.

Conclusions: Though HE symptoms may be medically controlled, hospitalization rates are high, and shunt reduction may be necessary to address refractory HE cases. Further investigation in larger patient cohorts is necessary.
70. Efficacy of histatin peptide treatment in murine model of dry eye disease

Author(s): Megan Helms, Kyung Son, Dhara Shah, Sushma Kalmodia, Vinay Aakalu,
Department of Ophthalmology and Visual Sciences

ABSTRACT

Introduction

Dry eye disease (DED) causes debilitating visual dysfunction in severe cases. Current treatments are primarily palliative and more effective treatment is needed. Previous research has shown the presence of histatins "anti-microbial, histidine-rich peptides normally found in saliva" in lacrimal epithelium, with decreased histatin expression in lacrimal glands of patients with DED. This experiment studied in vivo effects of histatin-5 treatment on the corneal healing process using a murine model of toxic epitheliopathy, simulating dry eye.

Methods

Ten 8-week-old female C57/Bl6 mice were treated OD with 0.1% BAK dissolved in BSS to induce toxic epitheliopathy while untreated OS served as controls. Treatment drops of either histatin-5 or BSS were given OD three times per day for 28 days, while OS were treated with BSS only. Slit lamp images of fluorescein-stained corneas were taken three times per week and scored by modified 15-point NEI scale to evaluate recovery.

Results

Scores from days 0-28 of treatment were averaged for each mouse and experimental group. Data after day 7 showed no clear patterns of improvement in either group, indicating that this method of induction, imaging and analysis primarily detects early re-epithelialization. No time points presented a statistically significant difference; however, analysis revealed H5-treated scores trending lower than controls at each time point.

Conclusions

Although not statistically significant, this data supports our hypothesis that histatin-5 may contribute to faster recovery from an induced dry eye condition. The decreased recovery time seen here could be clinically significant for DED patients and merits continued study.
Diagnostic properties of total and free prostate-specific antigen to predict overall and clinically significant prostate cancer among men with low testosterone and prior negative biopsy.

Author(s): Logan Schwarzman

Department of Urology

ABSTRACT

Objective: To evaluate whether total serum PSA, free-PSA ratio and PSA density have similar diagnostic properties for detecting prostate cancer (PCa) and clinically-significant (cs) PCa in men with normal testosterone compared to men with low testosterone with a prior negative biopsy.

Methods: We conducted a retrospective analysis of 3,295 men undergoing a 2-year prostate biopsy following a negative pre-study biopsy in the placebo arm of the Reduction by Dutasteride of PCa Events (REDUCE) study. Men were divided in two groups based on testosterone level ≤ 300ng/dL. Diagnostic properties of total serum PSA, free-PSA ratio and PSA density to predict PCa and csPCa, defined as Gleason score ≥ 7, were determined for several thresholds and plotted as receiver operator characteristic curves.

Results: A total of 603 men (18.3%) had low testosterone. The prevalence of PCa and csPCa was 92 (15.3%) and 27 (4.5%), respectively, for low testosterone men compared to 458 (17.0%) and 138 (5.1%), correspondingly, for normal testosterone men. Total PSA, free-PSA ratio and PSA density showed similar sensitivity, specificity and accuracy to predict PCa and csPCa among low testosterone men compared to normal testosterone men.

Conclusions: Among subjects in a clinical trial with a prior negative biopsy, total PSA, free-PSA ratio and PSA density have comparable diagnostic characteristics for PCa screening in low and normal testosterone men.
72. Predicting Renal Graft Function with Mid-IR Spectroscopic Imaging and Multivariate Data Analysis

**Author(s):** David Martinez Marin

Department of Pathology

**ABSTRACT**

In the setting of end-stage kidney disease, the renal allograft is the treatment of choice due to reduced mortality and improved patient quality of life post-transplant. The introduction of robust immunosuppressive regiments has aided in markedly reducing the incidence of acute allograft rejection, however, predicting long-term graft survivability has remained elusive and remains an area of great interest. Chronic graft rejection accounts for most renal graft rejections one-year post-transplant, the gold-standard for tracking an allograft’s status is histological evaluation of renal biopsies and serum creatinine and urine protein screening. Unfortunately, by the time creatinine and urine protein levels become elevated, the renal graft has already experienced significant histological damage leading to renal dysfunction and ultimately graft failure. Recent advancements have transformed mid-infrared (MIR) imaging from a research tool into a potentially potent clinical adjunct tool, capable of providing label-free imaging via the extraction of a tissue biopsy’s biochemical information (i.e. carbohydrates, nucleic acids, peptides), while retaining spatial resolution. The biochemical data collected from the tissue can then be probed and analyzed for specific features to assist in disease classification and typing. Here we present our data demonstrating MIR imaging combined with multivariate analysis can be used to predict 1-year post-transplant graft failure. Armed with patient outcome data, our goal here is to probe the kidney allograft’s biochemical heterogeneity for a signature that can help predict a graft’s likelihood of succeeding or failing one-year post-transplant.
73. Cocaine-Induced Pancreatitis: A Case Report

Author(s): Jasmine Arrington, Jessica Strzepka, Frances Tian, Jasmine Arrington, Cemal Yazici, Olga Garcia-Bedoya

Department of Medicine

ABSTRACT

Pancreatitis is the most common gastrointestinal diagnosis resulting in admission, costing 2.6 billion dollars annually. To the best of our knowledge, there are only 5 reported cases of cocaine-induced pancreatitis. A 61-year-old male with cocaine abuse and heart failure with reduced ejection fraction (HFrEF) presented with 3 days of abdominal pain, nausea and vomiting. His last intranasal use of cocaine was a few days prior to onset of symptoms, and he was prescribed metoprolol for his HFrEF. Findings were consistent with acute pancreatitis, yet the abdominal ultrasound was negative for cholelithiasis and other causes of serum lipase elevation were ruled out. We postulate that the patient had decreased cardiac output and thus decreased pancreatic perfusion secondary to concurrent cocaine and beta-blocker use. Cocaine-induced pancreatitis is a rare, and likely under-reported entity, on which no cases have been published involving concomitant beta blocker and cocaine use. Physicians must maintain a high index of suspicion when treating patients with cocaine use who present with abdominal pain.
74. Soft, Wireless Mechano-Acoustic Devices for Sensing Physiological Parameters and Body Motion

Author(s): Manish Patel, Steve Xu, John Rogers

Department of Medicine

ABSTRACT

Advances in soft electronics introduce the potential of developing light-weight wearable devices that conform to the skin. The skin above the suprasternal notch transmits several mechano-acoustic (MA) signals, given the lack of a corresponding bony prominence, that are distinguishable by applying digital frequency filters. These MA signals may provide vital insight into important physiological health information. Examples include vocal fold vibrations (~100 Hz), cardiac activity (~10 Hz), gait and locomotion (~1 Hz), respiration (~0.1 Hz), swallowing and body orientation (~0 Hz). Our flexible, Bluetooth-enabled MA wearable sensor can sense these highly sensitive movements and vibrations and continuously record the output on any smartphone device. Our device captures MA signals with high sensitivity that could be used to monitor and assess health parameters and minimize the use of the current, bulky healthcare technology. Areas of applications of our device include the replacement of polysomnography for sleep studies, monitoring post-operative activity, respiratory health monitoring, physical activity in assisted living environments, and aid in physical therapy to treat aphasia and dysphagia.
75. Assessment of Patient Education on Hydroxyurea Therapy in Sickle Cell Patients

Author(s): Nidhi Suthar

Department of Pediatrics

ABSTRACT

INTRODUCTION: Hydroxyurea prevents vaso-occlusive crises in sickle cell disease (SCD) by increasing fetal hemoglobin levels and in turn reducing hospitalizations and mortality rates. Despite strong evidence for its use, hydroxyurea remains underutilized by patients with SCD, due to fear of side effects, concerns regarding efficacy, or mistrust towards medical professionals. This project aimed to assess the role of patient education in improving patient knowledge and perspective of hydroxyurea, via exposure to the American Society of Hematology (ASH) Hydroxyurea Education Booklet.

METHODS: This study utilized a mixed-methods approach to integrate patient responses via survey and interview following booklet exposure. Twenty participants completed the study, including ten adult patients with SCD and ten parents of pediatric patients with SCD.

RESULTS & DISCUSSION: Booklet exposure resulted in the majority of participants indicating increased interest in continuing hydroxyurea therapy and interest in more patient education. Survey results also indicated that almost half of the respondents incorrectly believed that hydroxyurea works to cure SCD crises rather than prevent them, indicating a gap in knowledge. This perception may contribute to a lack of faith in hydroxyurea and in the medical community that prescribed it, when it ultimately does not cure a patient’s crises. Patients also expressed the importance of including realistic patient experiences in education tools rather than portraying ideal situations. Finally, the theme of medication burden was frequently expressed within patient interviews. Acknowledging and empathizing with this burden through patient education as well as within the physician-patient relationship could positively impact patient confidence in hydroxyurea therapy.
76. 270 Degree Labral Reconstructions Lead to Suction Seal Disruption and Decreased Contact Area As Compared to the Intact Labrum: A Cadaveric Study

Author(s): Laura M Krivicich, Edward C Beck MD MPH, Jorge Chahla MD PhD, Sunikom Suppauksorn MD, Elizabeth Shewman MS, Shane J Nho MD MS

Department of Orthopaedics

ABSTRACT

Purpose: To biomechanically compare the suction seal, contact area, contact pressures, and peak forces of intact native labrum, torn labrum, 90° labral repair, and 270° labral reconstruction.

Methods: Intraarticular pressure maps were produced for eight fresh-frozen hemipelvises at neutral, 20° extension, and 60° flexion using an electromechanical testing system under the following conditions: 1) intact labrum 2) labral tear, 3) labral repair (12-3 o'clock) and 4) 270° labral reconstruction using iliotibial band allograft. In each condition, contact pressure, contact area, and peak force were obtained. Repeated measures ANOVA was used to identify differences in biomechanical parameters among the four conditions. Qualitative differences in suction seal were compared between labral repair and reconstruction using Fisher’s exact test.

Results: Repeated measures ANOVA for contact area in neutral, extension, and flexion demonstrated statistically significant differences between the normalized study states (p<0.05). Post-hoc analysis demonstrated significantly larger contact areas measured in repair specimens compared to reconstruction in the extension and flexion positions. Region of interest analysis for normalized contact area in extension and flexion positions, as well as normalized contact pressures in neutral position demonstrated statistically significant differences between the conditions (p<0.05). Lastly, 8(100%) labral repairs vs only 1(12.5%) labral reconstruction retained their manually tested suction seal (p<0.001).

Conclusion: 270° labral reconstruction demonstrated decreased intraarticular area and loss of suction seal compared to labral repair. Further, 90° labral repair retained the suction seal in all cases. Clinically, labral reconstruction may not restore the biomechanical characteristics of the native labrum as compared to labral repair.
ABSTRACT

Purpose: To biomechanically compare three conditions: 1) native cam deformity 2) cam deformity with incomplete resection and 3) cam deformity with complete resection.

Methods: A cadaveric study was performed using eight frozen, hemi-pelvises with cam-type deformity (alpha angle >55°) measured on CT scan. Intraarticular pressure maps were produced for each specimen under the following conditions: 1) native cam deformity, 2) cam deformity with incomplete resection and 3) cam deformity with complete resection. Using an open technique, 5.5-mm burr was used to resect the lateral portion of the cam deformity. Contact pressure, contact area, and peak force within a region-of-interest were obtained in each condition using a custom designed jig in the MTS electromechanical test system. Three measurements were performed in each condition; the average value of each parameter was used for statistical analysis.

Results: Repeated measures ANOVA analysis demonstrated that the pressure averages of hips with complete resection of cam lesions were significantly lower when compared to averages of hips with incomplete femoral cam lesion and intact cam deformity (100 vs 93.6+8.3 vs 82.6+16.2, respectively; p-value=<0.0001). Percentage reduction of contact pressure in the complete resection and incomplete resection groups compared to the native cam deformity groups were 17.4% and 6.4%, respectively. Contact area and peak force showed no significant differences across three conditions.

Conclusion: Complete cam resection specimens had significantly lower intraarticular contact pressures compared to specimens with incomplete cam resection or native cam deformity, underscoring the importance of complete cam lesion resection in patients undergoing hip arthroscopy for FAIS.
Disparities in the Symptomatic Presentation of Moyamoya Disease in the United States: A Nationwide All-Payer Analysis.

Author(s): Angelica Fuentes, Ryan Chiu, Ankit Mehta

Department of Neurosurgery

ABSTRACT

Moyamoya disease is a chronic occlusive cerebrovascular disease that presents with hemorrhagic or ischemic symptoms. The objective of this study was to evaluate whether the symptomatology of Moyamoya disease differs according to patient group. We used the Nationwide Inpatient Sample to investigate differences in the presentation of Moyamoya by demographic factors, namely age, gender, ethnicity, and insurance status. The association between these variables and presentation was evaluated using Chi-square tests and multivariate logistic regression analysis for potential baseline confounders. Patients presenting with transient ischemic attack were more likely to be between 45 and 65 years old (p = 0.01) and Caucasian (p = 0.007); those presenting with cerebrovascular accident were more likely to be 65 years and older (p < 0.001), Native American (p < 0.001), and have charity insurance (p < 0.001); patients presenting with intracranial hemorrhage were more likely to be between 45 and 65 years (p < 0.001), Asian (p < 0.001), and have charity insurance (p = 0.002); those presenting with seizure were more likely to be less than 10 years old (p = 0.04), African American (p < 0.001), and have charity insurance (p < 0.001); patients with chorea were more likely to be less than 10 years old (p = 0.003); and those presenting with headache were more likely to be between 10 and 19 years old (p = 0.002) and female (p = 0.003). Our findings demonstrate associations between Moyamoya presentation and patient characteristics, contributing to the collective understanding of this rare condition.
79. Serum Proteins that Enhance Migratory and Invasive Abilities of Breast Cancer Cells

Author(s): Luke Trapp, Ingeun Ryoo, Albert Green, Tapas Das Gupta, Tohru Yamada, Department of Surgery

ABSTRACT

Triple negative breast cancer (TNBC), which does not express ER, PR, or HER2, represents approximately 11% of all breast cancers. 30% of TNBC will cause metastatic recurrent disease, which is associated with poor outcomes. The inhibition of metastasis remains a major challenge of oncology.

Because cancer cell motility is a requirement for metastasis, we hypothesized that upregulating genes found in highly metastatic cancer cells would alter the abilities of other cancer cell lines. Among the genes found to be upregulated in highly metastatic breast cancer cells were fetuin-A and apolipoprotein A-1 (APO A-1). Our objective was to determine whether increased expression of these genes in TNBC MDA-MB-231 would confer increased migratory and invasive abilities. Utilizing a chemical transfection protocol, we introduced plasmids of either fetuin-A or APO A-1 into the MDA-MB-231 cells. Boyden chamber migration and invasion assays were performed to compare the abilities of the parent line with those transfected clones.

We found that the MDA-MB-231 clones that were transfected with fetuin-A (n=3) had significantly greater migratory (p<0.005) and invasive (p<0.05) abilities than the parent line. We also found that the MDA-MB-231 clones transfected with APO A-1 (n=3) had no significant differences in migratory ability but had greater invasive (p<0.005) abilities than the parent line. As fetuin-A and APO A-1 are both serum proteins, these findings suggest that breast cancer cells themselves might be able to modify the host blood, thus creating a more favorable environment for metastasis.
80. The Association of Cancer Specific Anxiety with Disease Aggressiveness in Men on Active Surveillance of Prostate Cancer

Author(s): Ushasi Naha, Michael R. Abern, Daniel M. Moreira

Department of Urology

ABSTRACT

Active surveillance (AS) provides appropriate prostate cancer (PCa)-specific survival while minimizing morbidity, but underlying worry of PCa can generate anxiety. The aim of the study is to evaluate anxiety levels in men on AS and how anxiety relates to disease characteristics and treatment decision-making.

A retrospective analysis was conducted using subjects from the Reduction by Dutasteride of clinical progression Events in Expectant Management (REDEEM) study. Anxiety was measured at baseline and 3, 6, 12, 18- and 36-months post-randomization using the MAX-PC (Memorial general anxiety scale for PCa) questionnaire and analyzed as a continuous and categorical variable. Univariate and multivariate analysis were performed to study the association of disease and anxiety. Cox regression was used to analyze progression time to active treatment as a function of baseline anxiety.

MAX-PC scores decreased from baseline to 18 months. There was a slight increase after receiving PSA results at 18 months, followed by more decline. Percentage of positive cores was associated with baseline anxiety (P<0.05), both as a continuous and categorical variable. When controlling for age, race, number of cores sampled, body mass index, prostate volume and maximum core length, percentage of positive cores remained associated with baseline anxiety (P=0.003). In univariate and multivariate analysis, baseline anxiety was not significantly associated with progression time.

Urologists should recognize how discussing test results with men on AS can worsen underlying anxiety and offer proper support. Clinicians should evaluate patient anxiety when deciding individual management plans and consider the support needed for men with more aggressive disease.
81. Systemic Toxicity and Off-Target Deposition of Magnetic Nanoparticles in a Porcine Kyphoplasty Model

Author(s): Shashank Patil, Shashank Patil, Tania Aguilar, Nikki Barrington, Jack Zakrzewski, Ankit Mehta

Department of Neurosurgery

ABSTRACT

A previous study from Dr. Ankit Mehta’s lab (PMID: 30052650) demonstrated significant localization of iron-core magnetic nanoparticles (MNPs) to a specific site of vertebral kyphoplasty using magnetic cement. To characterize the off-target systemic deposition and toxicity profile of MNPs, thoracic kyphoplasty procedures were performed on two Yorkshire-Landrace pigs using magnetic (Experimental) and non-magnetic (Control) cement. On Day 3, MNPs were injected systemically via ear vein. Blood parameters were assessed on Days 1, 3, 5, 8, and 10. Post-study, organs (liver, right atrium, left ventricle, lungs, kidneys) were harvested, processed to visualize iron deposition (via Prussian Blue and Nuclear Fast Red stains), and quantified using ImageJ. Post-hoc Welch’s unequal variances t-tests were performed to assess significant differences in tissue deposition. Erythrocyte parameters showed minimal fluctuation within normal limits in both conditions, while reticulocyte and thrombocyte counts significantly increased in both conditions (E: +69.1%, C: +264%; E: +29.4% C: +18.6% respectively). CBC revealed significant lymphocytosis in the control (+70.1%) post-MNP administration. Iron studies revealed a decrease in serum iron in both conditions (-20.6%, -21.0%) with no significant changes in TIBC, UIBC, or Ferritin. Significant BUN elevation (+150%) was seen in the experimental animal, while significant AST (+86%) and Creatine Kinase (+44.0%) elevations were observed in the control. No significant changes were recorded in cardiac enzymes (CK-MB, TnI A2, MYO). Histological analysis revealed significantly greater liver iron deposition in the experimental condition compared to control (p=0.018), with no other significant tissue differences. Further histological analysis will be necessary to elucidate differences in toxicity.
82. Weighted Gene Co-Network Analysis (WGCNA) Identifies Common Hub Genes Between Cutaneous Sarcoidosis and Discoid Lupus Erythematosus

Author(s): Melissa Nickles, Kai Huang, Patricia Finn, David Perkins

Department of Medicine

ABSTRACT

Sarcoidosis is a granulomatous disease of unknown etiology that primarily affects the lungs and skin. We propose that investigation of gene networks of cutaneous sarcoidosis in comparison to other immune-related skin disorders may provide insights into underlying disease mechanisms. Microarray expression data from two cohorts of patients with sarcoidosis, discoid lupus, or psoriasis skin lesions was analyzed. We applied weighted gene co-network analysis (WGCNA) to construct gene-gene similarity networks and cluster genes into modules based on similar expression profiles. A module of interest that was preserved between datasets and correlated with clinical traits was identified. This module was related to immune activity and was significantly increased in both sarcoidosis lesions and discoid lupus lesions versus their respective controls. Protein-protein interaction (PPI) networks were constructed using STRING database and visualized with Cytoscape software to detect common hub genes driving this module. We characterized the hub genes with differential gene expression analysis. Sarcoidosis and discoid lupus had 7 hub genes in common: TLR1, ITGAL, TNFRSF1B, CD86, SPI1, BTK, and IL10RA. There may be parallel gene dysregulation in the immune processes of cutaneous sarcoidosis and discoid lupus, which could have indications for future therapeutic targets and biomarkers.
83. One Step in Understanding the Recruitment Frenzy

Author(s): McKenzie Schwarze, Amanda Osta, Stacy Laurent, Michelle Barnes, Alan Schwartz,

Department of Pediatrics

ABSTRACT

Background: Applications to pediatric residency programs have drastically increased as applicants apply to more programs. This has secondary consequences for both applicants and program leadership. USMLE possibly becoming pass/fail has an unknown effect on the programs’ interviewing and ranking strategies.

Objective: Determine interview and ranking strategies of pediatric residency programs. Understand how these strategies might change if USMLE becomes pass/fail.

Design: We created a survey regarding the current inviting and ranking processes for pediatric residency programs and asked how this process might change if USMLE becomes pass/fail. We distributed the survey in spring 2019 through the Association of Pediatric Program Directors.

Results: Of 153 programs surveyed, 60 coordinators and 32 associate program directors participated. Interviewing (-0.38) and ranking (-0.36) more applicants was significantly correlated with the percent down the rank list to match the lowest-matched applicant, but there was no correlation for the top-matched applicant. There were not significant correlations between number of interviews offered and USMLE scores, applicant type, or hospital type. The number of PGY1 positions in a program had the greatest impact on the USMLE scores.

Programs reported USMLE/COMLEX scores as the primary criteria for offering interviews. Many programs stated that if the USMLE becomes pass/fail, they would likely change their selection strategy.

Conclusions: For pediatric residency programs, number of positions determines the strength of the rank list, while interviewing more applicants has no effect. With greater understanding between applicants and programs, the PGY1 application process can become more transparent.
84. Investigation of a Novel Fractional Order Calculus Diffusion Model to Improve the MR Imaging of Clinically Significant Prostate Cancer

Author(s): Zhihua Li, Karen Xie

Department of Radiology

ABSTRACT

Multiparametric MRI (mpMRI) has emerged in recent years as a valuable tool for prostate imaging, combines high resolution anatomical and morphologic visualization of the gland with functional assessment of the biophysiological signatures of tissues. For mpMRI, a key functional component is diffusion weighted imaging (DWI) technique, which measures the capability of water movement or diffusivity in different biological tissues. It has been proven that in normal tissue, water diffusion is relatively free and random; while in cancer, water diffusion is impeded or restricted, due to increased cellularity and decreased extracellular space. An apparent diffusion coefficient (ADC) map is routinely calculated from DWI images for qualitative analysis and quantifications. Research has shown evidence of an inverse relationship between ADC and the underlying prostate cancer aggressiveness defined by Gleason scores. One major limitation of the current ADC analysis is its reliance on an overly simplified, monoexponential model which assumes water diffusion occurs within homogeneous tissue environment. In comparison to the conventional ADC map, FROC analysis of the diffusion dataset is based on a non-Gaussian technique, taking into account of the heterogeneous tissue structures and environment. FROC offers three parameters that have been proven to correlate to tissue microstructures and heterogeneity: a heterogeneity index (B), a spatial scale that is related to the mean free path of water diffusion (u), and a generic diffusion coefficient (D) -- The combination of FROC parameters exhibited greater performance at differentiating different stages of prostate cancer than D alone, which is analogous to ADC.
85. Preliminary Results: Women Centered Care; Investigating the Childbirth Preferences of Women in Benin City Nigeria

Author(s): Debra Eluobaju, Friday Okonofua, Gelila Goba

ABSTRACT

Background: Maternal mortality (MM) remains one of the leading causes of death among Nigerian women; and is on the rise. An increase in the utilization of skilled birth attendants (SBA) has been proven to be an effective method to combat avoidable maternal death. Despite that fact, only 43% of Nigerian women utilize SBAs during childbirth; even though 64% of women utilize SBAs for prenatal-care. A woman-centered obstetric approach should be adopted to allow for a better transition of women from prenatal-care to childbirth with an SBA. Methods: In-depth interviews were conducted with women to explore themes regarding their overall childbirth experience; this included who they prefer to attend their labor, and self-efficacy. Focus groups with husbands, traditional birth attendants (TBAs), and SBAs explored the socio-cultural topics involved with women’s birth preferences such as decision-making, and cultural expectations. Results: Preliminary data indicates that women who choose to deliver with TBAs did so often due to negative experiences with SBAs, or anticipatory mistreatment from SBAs. Women who choose to deliver with SBAs also often reported mistreatment within the clinic setting. Additionally, there is a disconnect between how SBAs report treating women and how women report being treated. Conclusion: Mistreatment of women in labor is a global issue. SBAs need to receive training regarding best practices to meet women’s needs during labor, to encourage their use increasing positive birth outcomes. Also, Nigeria’s healthcare system needs to find ways to productively incorporate TBAs, since their complete elimination is not feasible and undesirable.
86. Systemic Toxicity and Off-Target Deposition of Magnetic Nanoparticles in a Porcine Kyphoplasty Model

Author(s): Shashank Patil, Tania Aguilar, Nikki Barrington, Jack Zakrzewski, Tyler Lung, Ankit Mehta

Department of Neurosurgery

ABSTRACT

A previous study from Dr. Ankit Mehta's laboratory (PMID: 30052650) demonstrated significant localization of iron-core magnetic nanoparticles (MNPs) to a specific site of vertebral kyphoplasty using magnetic cement. To characterize the off-target systemic deposition and toxicity profile of MNPs, thoracic kyphoplasty procedures were performed on two Yorkshire-Landrace pigs using magnetic (Experimental) and non-magnetic (Control) cement. On Day 3, MNPs were injected systemically via ear vein. Blood parameters were assessed on Days 1, 3, 5, 8, and 10. Post-study, organs (liver, right atrium, left ventricle, lungs, kidneys) were harvested, processed to visualize iron deposition (via Prussian Blue and Nuclear Fast Red staining), and quantified using ImageJ. Post-hoc Welch’s unequal variances t-tests were performed to assess significant differences in tissue deposition. Erythrocyte parameters showed minimal fluctuation within normal limits in both conditions, while reticulocyte and thrombocyte counts significantly increased in both conditions (E: +69.1%, C: +264%; E: +29.4% C: +18.6% respectively). CBC revealed significant lymphocytosis in the control (+70.1%) post-MNP administration. Iron studies revealed a decrease in serum iron in both conditions (-20.6%, -21.0%) with no significant changes in TIBC, UIBC, or Ferritin. Significant BUN elevation (+150%) was seen in the experimental animal, while significant AST (+86%) and Creatine Kinase (+44.0%) elevations were observed in the control. No significant changes were recorded in cardiac enzymes (CK-MB, TnI-A2, MYO). Histological analysis revealed significantly greater liver iron deposition in the experimental condition compared to control (p=0.018), with no other significant tissue differences. Further histological analysis will be performed to elucidate differences in toxicity.
87. Comparing Implementation of Youth Health Advocacy Programs: The SHIP Model

Author(s): Collins Mbachu, Natalie Meeder, Ravi Tyagi, Sara Valdivia, Natalia Suarez, Sarah Bunch

Department of Emergency Medicine

ABSTRACT

Chicago experiences major socio-economic disparities which adversely impact health and access to care, and specifically impact youth. Health career pipeline programs which address existing educational gaps and aim to diminish health inequities through workforce development have been an integral way to elevate youth. In order to proactively address educational disparities in underrepresented communities, UIC College of Medicine Hispanic Center of Excellence and UIC Urban Health Program collectively created the Science & Health Immersion Program (SHIP) to contribute to the training of future health professionals. The goals of this study are to evaluate (1) participant engagement in the program and (2) program impact on participant college readiness and career interest. Upon program completion, participants will also be asked to assess the overall quality and content of the program (3). Participants will complete de-identified evaluations at the first session, mid-term, and completion of the program in order to evaluate curriculum delivery and content quality. Participants also complete weekly surveys evaluating satisfaction with the overall session. Data will be entered, coded, and analyzed using mixed methods. Study results will be incorporated in order to improve SHIP infrastructure and curriculum development.
88. The Impact of Learning Culture on Student USMLE Step 1 Preparation: A Qualitative study

Author(s): Natasha Mehta, Shashank N. Patil, Hannah R. Seyller, Zobia S. Chunara, Lander S. McGinn, Kerim B. Kaylan

Department of Medicine

ABSTRACT

Research Question

How do students perceive the learning environment, mental well-being, and administrative/faculty support before and after USMLE Step 1?

Background and Relevance of Study

Previous research has demonstrated the relationship between learning environment, mental well-being and student cohesiveness on exam performance by measuring these relationships quantitatively. While these studies highlight these relationships exist, they do not describe the mechanisms through which they impact students. In contrast, our study aims to explore how the learning environment, well-being, and student cohesiveness impact exam performance using qualitative interviewing methods.

Design and Methods

Using the University of Illinois College of Medicine as the research site, we conducted seven 20-30 minute interviews with five total participants both before and after taking the exam. Interviews were coded by the research team using both a priori and emergent codes. Framework analysis was used to identify common themes among interviews.

Results

Three main themes were identified from these interviews: social isolation as a form of protection from anxiety, common coping strategies to promote mental well-being, and importance of faculty attitudes. Several students described removing themselves from their existing social circles or studying apart from other students to avoid comparison. Consistent with prior literature, students commonly utilized exercise and time for loved ones and hobbies, as coping strategies. Finally, students noted some faculty communicated encouraging messages and realistic expectations, easing anxiety, while others de-emphasized exam importance, leaving some with a false sense of security.

Conclusions

Anxiety is a commonly identified theme among students preparing to take the exam. We discovered that when some students look for mechanisms to cope with anxiety, they may socially isolate themselves to counter the fear of failing to meet expectations. Furthermore, messaging from faculty and advisors can alter the way students process their results after the exam and influence who students look to for support. Advisors may target these areas to improve the exam experience.
The Standardization Of Vitamin D As A Function OF Ethnicity

Author(s): Sresht Iyer, Awais Hussain, Michael Patetta, Anshum Sood, Menachem Meller, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Vitamin D insufficiency is a serious issue that can cause lower bone density, which can increase osteoporosis and fracture risk. African Americans are known to be a demographic with lower levels of vitamin D due to darker skin pigmentation, but existing literature shows that AA also have higher bone mineral density and lower incidence of osteoporotic fractures than Caucasians. The goal of our research was to use pre-operative labs to create a more accurate range of the normal vitamin D levels for African Americans. We collected information from consenting, pre-op patients between age 18-70 at UI Health and at Dr. Meller's clinic that included basic social history and BMI measurements to standardize our data along with 25(OH) vitamin D and FRAX scores (fracture risk) from DEXA scan results. A statistical t-test analysis was done using bootstrapping to increase the sample size from 20 to 200, comparing AA's with FRAX scores below or equal to 3%, to those with FRAX scores above 3%. A mean comparison of their serum 25, OH Vitamin D levels was done, which showed a statistically significant difference at a P-value of .05. with the mean for those in the normal FRAX score range being 22.7273 ng/mL, which compared to the current range of 20-50 ng/mL, is at the lower end. While more data is needed to establish clinical guidelines, this research shows strong indications that the normal Vitamin D levels in African Americans will be much lower than the current standard range without increased fracture risk.
Mohs Micrographic Surgery for the Treatment of External Ear Melanoma; Outcomes Study.

Author(s): Paula Ham, Carolina Puyana, Maria Tsoukas

Department of Dermatology

ABSTRACT

Purpose: To compare survival outcomes in patients treated with Mohs micrographic surgery, narrow margin excision (NME), and wide margin excision (WME) for melanoma on the external ear.

Design: Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program database, was retrospectively analyzed. Patients who received surgical treatment on the external ear and had confirmed diagnosis of cutaneous melanoma were included. The effect of different surgery types: MMS, NME, WME, on melanoma survival was evaluated.

Summary: The external ear is composed of thin skin overlying cartilage making melanoma on the external ear difficult to resect while preserving the intricate anatomy. While surgeons have achieved robust clinical outcomes for nonmelanoma skin cancers treated with MMS, there is lack of research on its application to external ear melanoma treatment.

Findings: A total of 8,212 melanoma cases of the external ear performed during the years 2000-2015 were considered for analysis. Results of the cox proportional hazard models demonstrated that there is no significant difference in survival comparing NME and WME to MMS. Differences in characteristics among surgery groups were as follows: majority of NME (54.7%) and MMS cases (40.5%) were reported in the pacific coast, compared to the majority of WME which were reported in the east (47.2%) (p<.0001). The majority of NME (49.7%) and MMS (70.7%) were performed on in situ tumors, compared to the majority of WME on localized tumors (57.2%) (p<.0001). Our research hints at the strength of MMS and its applicability on tumors beyond non-melanoma skin cancer.
91. Local immune responses in epidermolysis bullosa acquisita

Author(s): Adriana Cordova, Jing Li, Virginia A. Jones, Payal M Patel, M.D., Kyle T. Amber, M.D.

Department of Dermatology

ABSTRACT

Epidermolysis bullosa acquisita (EBA) is an autoimmune subepidermal blistering disease characterized by the development of autoantibodies to collagen VII. Disruption of anchoring fibrils leads to the development of vesicles and bullae on the skin and erosions on the mucous membranes. Due to our limited understanding of the pathomechanisms involved in the induction and development of EBA, management of EBA has primarily been based on non-specific targets and generalized immunosuppression. Generation of a recombinant murine collagen VII (COLVII) peptide and inoculation of rabbits with this results in generation of rabbit anti-COLVII immunoglobulin (Ig). Isolation and repeated administration of this antibody into certain mouse models reliably reproduces the clinical and histological phenotype consistent with the inflammatory variant of EBA. To study the local immune response that results in neutrophil recruitment and cutaneous inflammation, we will utilize a passive transfer model to induce experimental EBA. After generation of disease, we will collect blood and skin to assess differential gene expression. With this approach, we hope to gain significant insight into the direct autoantibodies in inducing an immune response, and the effect of this neutrophil rich response on the skin.
The mechanisms underlying the critical relationship between the gut microbiota and host metabolism are still unclear. Dietary fibers are fermented in the distal colon to short-chain fatty acids (SCFAs). SCFAs have many effects which are partially mediated by the G protein-coupled receptors (GPCRs), including free fatty acid receptor 2 (FFA2). These receptors play an unspecified role in the secretion of incretin hormones as well as in whole-body glucometabolic control. Current literature on the role of FFA2 in the digestive system reveals a growing body of conflicting data.

Previous in vivo studies investigating FFA2 have relied on global knockout mouse models; since these receptors are expressed in many tissues including pancreas, adipocytes, muscles, and macrophages, the isolated effects of receptors in intestinal cells are still unclear. We are studying the effects of intestine-specific FFA2 using a novel tissue-specific knockout mouse model. The role of FFA2 becomes more evident in a metabolically stressed state induced by a western diet. Here, we present the metabolic phenotype of knock-out and wild-type mice fed western diets vs. control diets as measured by NMR of mouse body composition and metabolic calorimetry analysis. Additionally, we present preliminary incretin secretion data as measured by RT-qPCR of mouse intestinal samples.

Understanding the role of SCFA receptors in glucometabolic physiology represents a novel opportunity for pharmacological management of obesity and diabetes "conditions reaching epidemic levels that require more health care resources than any other condition"
93. Chicago Street Medicine: A Retrospective Review of Outreach and Opportunities for Growth

Author(s): Philip Ostrov, Sukhveer Bains

Department of Emergency Medicine

ABSTRACT

Introduction

Recent research indicates that multidisciplinary patient-centered teams can provide continuity of care to the unsheltered homeless, many of whom would otherwise be lost to follow-up. Chicago Street Medicine (CSM), an organization formed by volunteer medical students and residents, utilizes this model in order to bridge unmet health and social needs by reaching these individuals where they reside. This study seeks to identify opportunities for growth and capacity building based on the needs of the unsheltered homeless population of Chicago.

Methods

The CSM program has utilized a shared document of de-identified narrative data to communicate among care teams and describe the events of street runs. Health and Social needs from 61 street run records were categorized into discrete variables and coded into quantitative data for univariate regression analysis.

Results

There was a significant difference in number of patient requests comparing runs with a social worker present (M = 7.8, SD 1.92) and without (M=5.30, SD 2.49); t(59)=-2.18, p=0.034. Results demonstrate a continual need for medical and social resources, in particular wound care, general medicine, and addiction services.

Conclusion

Results establish academic street medicine as a paradigm for patient advocacy through a multidisciplinary approach as well as an opportunity for advanced training of medical students and residents. Additionally, these results corroborate the dearth of continuity-of-care as a significant barrier to better health outcomes for the unsheltered homeless population and indicate a need for streamlined care coordination in Chicago, Illinois. Due to the qualitative nature of this data, further investigation is needed.
Assessing Risk Factors for Voice Disorders among Emergency Call Center Personnel

Author(s): Julia Xie, H. Steven Sims, Jan Potter Reed

Department of Otolaryngology

ABSTRACT

Published data looking at teachers has refined our understanding of occupational voice disorders. Emergency Call Center Personnel (ECP) are a group of voice professionals that have received less attention. Because they are often the primary point of contact for people requesting immediate assistance, a clear, understandable voice is essential.

The purpose of this preliminary study is to assess the potential risks among ECP to reduce consequent voice disorders. Our hypothesis is that ECP have higher risks for voice problems than the general public. Furthermore, we believe education about vocal health and hygiene can be incorporated into their professional training to reduce the rate of voice disorders.

Voice Handicap Index (VHI) and Screening Index for Voice Disorders (SIVD) help patients provide subjective information about their voices and habitual behaviors. In addition, a survey inquiring about average length of shift, number of breaks, and confounding factors were given to two centers. For statistical analysis, the total and partial scores for each VHI section were analyzed as the dependent variables with respect to the results of our survey and the SIVD. Increasing VHI scores indicated a more severe voice handicap.

By results, not using a microphone appears to lower VHI scores. However, this result didn’t account for respondents that didn’t use a microphone being younger and less likely to report a state of altered health. Hoarseness, wet cough, dry cough, and phlegm in throat all correlate with rising VHI scores. Thus, education emphasizing vocal fold hydration and nebulizer therapy may prove effective.
95. Lymph Node Negative Melanoma Survival; Analysis of 51,846 Cases

Author(s): Sara Kim, Claire Wilson, Carolina Puyana, Maria Tsoukas

Department of Dermatology

ABSTRACT

Purpose: The purpose of this study is to examine the predictive factors for survival in lymph node negative melanoma (LNNM).

Design:

Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program database, collected from 1988-2015, was retrospectively analyzed. Patients who had microscopically confirmed malignant cutaneous and negative lymph node status were included. Multivariate stepwise cox proportional hazard models were used to identify significant predictors for disease specific survival (DSS). Hazard ratios (HR) and p-values were calculated (i.e. \( i \mid j = 0.05 \)).

Summary:

Due to melanoma’s high mortality rate and potential to disseminate, understanding predictive factors for survival is essential. Factors commonly used include lesion’s Breslow’s depth, ulceration, mitotic rate, and the status of the sentinel lymph nodes. However, up to 21% of patients with negative sentinel lymph nodes develop metastasis during follow-up. Until now, studies on the prognostic factors for patients with lymph node negative melanoma (LNNM) are scarce.

Findings:

A total of 51,846 cases were considered for analysis. Mean lesion depth was 1.64 mm ± 1.47. After stepwise selection, the cox proportional hazard model included depth, year of diagnosis, age at diagnosis, sex, marital status, primary site, histology, metastases, radiation, chemotherapy, and surgery. Patients who underwent narrow and wide margin excision compared to excisional biopsy alone had increased DSS (HR 0.641, HR 0.743; p<.0001). Alternately, patients who underwent radiotherapy or chemotherapy had decreased DSS compared to those who did not (HR 2.153, HR 2.585; p<.0001). For every 0.01mm increase in lesion depth, DSS decreased by a factor of 1.264 (p<.0001). Similarly, increasing age at diagnosis and scalp lesions were associated with decreased DSS (p<.0001). Conversely increasing year of diagnosis, female sex, being married or in a domestic partnership, or tumors originating in the trunk, upper, or lower limbs were factors associated with increased DSS (p<.0001).
96. Etiologies of Mandibular Fracture: An Epidemiological Analysis

Author(s): Nick Curran, Ryan Chiu, Christopher Micallef

Department of Surgery

ABSTRACT

Introduction: Individual hospital and National Trauma Data Bank (NTDB) data have been analyzed for prevalence of and demographic associations with mandibular fracture etiology, site of fracture, and complications. However, to date no analysis has included National Surgical Quality Improvement Program (NSQIP) data and has utilized this many demographic variables. With this analysis, the authors hope to further inform surgeons about the contexts of mandibular fractures and thus improve outcomes.

Methods: The Nationwide Inpatient Sample (NIS) was queried for years 2015-2016 for patients with a primary diagnosis of Mandibular Fracture. Patients were segregated by age group, sex, race/ethnicity, insurance status, and hometown National Center for Health Statistics (NCHS) urban-rural classification tier. Endpoints of this study included traumatic etiology determined by International Classification of Diseases, Clinical Modification, 10th edition (ICD-10) code. Association with demographic factors was evaluated using Chi-square tests for statistical significance.

Results: Analysis of 2,157 patients revealed that assault, motor vehicle accidents (MVA), and falls were the most common etiologies (P < 0.001). MVA was the most common cause in children, and fall was most common amongst the elderly (and by extension, Medicare) (P < 0.001). Assault was the most common etiology in adolescents, adults, men, and all races/ethnicities (P < 0.001). Fall was more common in women (P < 0.001). Regions with higher populations had relatively higher proportions of mandibular fractures due to assault than due to MVA (P < 0.001).

Conclusions: Significant disparities in etiology of mandibular fracture are present in the United States. Knowledge of these disparities will enable physicians to more effectively treat current fractures and prepare for future ones.
Taking Inventory: Assessing the Roles and Responsibilities of Community Health Workers in the University of Illinois-Chicago System

**Author(s): Kathryn Tabor, Kimberly Orozco, Molly Martin**

Department of Pediatrics

**ABSTRACT**

**Background:**

Community Health Workers (CHWs) serve as crucial liaisons between the healthcare system and under-resourced patient populations. CHWs operate at UIC under a variety of titles, performing essential tasks; however, we do not understand the scope of their service and the unique challenges they face to long-term success. This inventory delineates the roles and responsibilities of UIC CHWs in order to understand the need for a centralized CHW Center to better support this crucial workforce.

**Methods:**

Two surveys were created. The first was designed for administrators, supervisors, and departmental coordinators. The second was for CHWs.

**Results:**

In total, 23 individuals completed the Administrator Survey and 50 completed the CHW Survey.

The surveys reported a total of 182 CHWs operating in 70 different UIC affiliated programs. From our survey population, we identified 39 job titles for CHWs. The most common programmatic purposes reported by administrators included: Education (65%), research (60%), and community service (45%). CHWs most commonly reported a need for greater access to professional development opportunities (58%) and training sessions (50%).

**Conclusions:**

This report demonstrates the existence of a workforce with valuable knowledge of many populations and health conditions; however the lack of standardization in the hiring, training, and oversight of CHWs results in underutilization of their skills. The greatest barriers to CHW program success include inconsistent funding and lacking understanding of this workforce’s contributions. The results of this survey support the assertion that a CHW Center could address existent organizational gaps, enabling CHWs to perform their role more effectively.
98. Salt Inducible Kinases Inhibit CRE Activity in Rat and Human Granulosa Cells

Author(s): Lara Hovsepian-Ruby, Marah Armouti, Nicola Winston, Carlos Stocco

Department of Medicine

ABSTRACT

The production of mature eggs is the most crucial step towards female fertility. Egg maturation relies on the stimulation of follicle growth by follicle-stimulating hormone (FSH). FSH targets follicular granulosa cells (GCs) and causes their differentiation, which is a critical requirement of follicle growth. Although FSH is the primary drug used to stimulate egg production in patients with ovulatory dysfunctions, a subpopulation of women shows inadequate stimulation even in response to higher than usual doses of exogenous FSH. This can be explained by the likelihood that GC differentiation is limited by certain diminishing factors, with recent research pointing to salt-inducible kinase (SIK) as one such factor. It has been shown in mouse and human models that SIK inhibits the translocation of cAMP-regulated transcriptional co-activators (CRTC) into the nucleus. We hypothesize that SIK prevents the FSH signaling by blocking the association of CRTC with FSH-activated pathways, such as cyclic AMP-responsive element-binding protein (CREB). Here, we use in vitro assays to examine the molecular effects of HG-9-91-01 (a SIK inhibitor) in CRTC sub-cellular localization and CREB activity in rat and human GCs. Immunofluorescence staining and western blotting showed an increase in CRTC localization in the nucleus in cells treated with SIK inhibitors prior to the administration of FSH when compared to cells treated with FSH alone. Additionally, in rat GCs transfected with a CRE-luciferase reporter, we observed that CREB activity was higher in cells treated with both FSH and HG-9-91-01 than with FSH alone. These findings suggest that SIKs oppose egg maturation by diminishing transcription of GC differentiation genes controlled by CREB. Clinically, pharmacological modulation of SIK activity could be used to maximize gonadotropin function and ovarian response in women undergoing IVF.
99. Adolescent Attitudes Towards an Internet Based Behavioral Vaccine

Author(s): Calvin Rusiewski, Alex Holtermann, Miae Lee, Benjamin Van Voorhees, Tracy Gladstone, Linda Schiffer

Department of Pediatrics

ABSTRACT

Adolescents develop many long term habits and behaviors related to chronic diseases in later adulthood. Primary care counseling can be time consuming, expensive, and may not reach sufficient numbers of youth. CATCH-IT is a technology-based learning tool that may offer an opportunity to reach the youth population in between primary care visits.

We assessed adolescent attitudes and behaviors related to the CATCH-IT and Health-ED interventions using portions of the Teen Behavior Survey from the PATH study. We measured adolescent beliefs via a combination of scales: trans-theoretical model for intention, theory of planned behavior, sociocultural relevance, and positive relationships in primary care.

At 12 months, CATCH-IT teens scored higher on the Stages of Change scale than HE teens, on average (p=0.02). Among CATCH-IT teens, 21.6% were at the highest stage (decision with plan), compared to 12.5% of HE teens. Conversely, only 10.8% of CATCH-IT teens were in precontemplation, compared to 28.1% of HE teens. CATCH-IT teens rated the intervention more helpful on the sociocultural relevance scale (mean increase of 0.4 compared to no change for HE; p=0.003) and the positive relationship with their primary care provider measure (mean increase of 0.5 compared to a decrease of 0.1 for HE; p=0.02). Measures of planned behavior remained consistent in both groups.

A primary care-based internet intervention appears to be promising in the areas of perceived relevance, behavior, and motivation for depression prevention, as compared with attention control. It did not appear to impact other health behaviors identified as alternate risk factors for depression.
100. Effect of Radiation Therapy (RT) on Bone Quality in Multiple Myeloma (MM) Patients

Author(s): Eitan Katz, Rown Parola, Farid Amrouche, Mark Gonzalez, Jason Koh, Pritesh Patel

Department of Orthopaedics

ABSTRACT

The effects of radiation on bone are not well characterized, as bone is typically less sensitive than soft tissue organs which are frequently the limiting factor for Radiotherapy (RT). The effect of high doses of radiation have been characterized. Fractures of the humeral and femoral head are observed at TD5/5 is 52 Gy and the TD50/5 is 65 Gy. However, the doses received for multiple myeloma (MM) are typically in the range of 20-30 Gy, and these low dose therapies have not been studied. Pre-RT and post-RT computed tomography (CT) scans from a database of MM patients receiving RT to their vertebrae were collected. Using Mimics software, 3D CAD surface and solid renderings were created of the vertebrae treated with RT, and renderings of the vertebrae above and below the area of radiation to be used as a control. Treating each vertebra as a separate subject, meshing was done in 3-matic. At three different levels on each vertebra, we extracted the cross sections and calculated the cortical surface area (CSA). There was a significant decrease in CSA between controls and those sections of vertebrae receiving 30 Gy radiation (138 mm [21.9, 254]). Additionally, those vertebrae with lesions from MM had a decreased CSA compared to control (132 mm [9, 255]), but there was no statistically significant difference between those vertebrae with lesions and those without. Therefore, we believe that there is a cumulative effect on CSA with disease and radiation therapy.
The Relation of Speckle-Tracking Echocardiography-Derived Strain Values to Emergency Department Utilization in Patients with Sickle Cell Disease

Author(s): Hannah Seyller, Hannah Seyller, Dino Guiterrez, Sherin Mahrat, Andrew Harkins MD, Joseph Colla MD

Department of Emergency Medicine

ABSTRACT

Background: Diastolic dysfunction has been shown to be an independent risk factor for increased morbidity for sickle cell disease (SCD) patients. Speckle-tracking echocardiography (STE) can be used to assess diastolic dysfunction by measuring deformation in the endocardium to quantify heart strain.

Objective: To determine whether more positive STE-derived strain values are associated with higher ED utilization, a marker of morbidity.

Methods: Convenience study of SCD patients presenting to the ED with acute pain crises. Limited bedside echocardiograms were performed and retrospectively reviewed for strain values using the three-point method by an EP. Patients were divided into ED utilization groups (super utilizers, high utilizers, and low utilizers) based on previous research and Medicare definitions of utilization. The electronic medical record was reviewed for each patient to determine ED utilization in the two years prior to enrollment. A one-way ANOVA analysis was used to analyze the data.

Results: 19 SCD patients were included in the analysis. There were 5 patients who fell into the category of super utilizers, 11 high utilizers, and 3 low utilizers. The mean strain for the super utilizers, high utilizers, and average utilizers was -15.76%, -20.47%, and -21.31%, respectively (p=0.01105).

Conclusion: SCD patients with more positive strain values were more likely to be higher ED utilizers. If these findings can be replicated in larger studies, strain values may serve as a marker of morbidity in SCD patients presenting to the ED.
ABSTRACT

Purpose: Skin cancer has the highest incidence of all cancers in the United States, developing in approximately one in five Americans during their lifetime. The purpose of this study was to examine utilization patterns of conventional surgical excision (CSE) and Mohs Micrographic surgery (MMS) in the United States for non-basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) skin cancers.

Design: Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program database was retrospectively analyzed. Patients who received MMS or CSE and had microscopically confirmed diagnosis were included in the study. Of the total procedures performed during the years 1988-2015, 12,654 MMS cases and 267,291 CSE were analyzed.

Findings: Results from the multivariate regression model yielded significant predictors for the utilization of MMS compared to CSE. Increasing age categories increased the likelihood of undergoing MMS compared to CSE (p<.0001). Black and Hispanic patients were less likely to undergo MMS compared to white and non-Hispanic patients (OR 0.72, p=0.0041; OR 0.82, p=0.0012). Females were more likely to undergo MMS compared to males (OR 1.08, p=0.0002). Patients diagnosed after 2010 were more likely to undergo MMS compared to the prior years (p<.0001). Cases diagnosed in the pacific coast, east, and southwest regions were more likely to undergo MMS compared to those in the northern plains (p<.0001). Lastly, cases localized in the face and staged as in situ had the highest likelihood of being treated with MMS compared to other sites and stages (p<.0001).
Investigation of Risk Factors for Congenital Syphilis and Syphilis Infection Among Pregnant Women at a Large Chicago Hospital

Author(s): Corinne Thornton, Susan Bleasdale

Department of Medicine

ABSTRACT

Early syphilis cases rose from 11.4 to 30.2 per 100,000 in Chicago between 2007-2016, presenting a public health concern as syphilis can be transmitted mother-to-child during pregnancy leading to multi-system birth defects if untreated. Illinois mandates universal screening at first and third trimesters, and at delivery for high-risk populations. The University of Illinois Hospital (UIH) also serves a vulnerable patient population carrying more demographic risk factors for syphilis, including lower socioeconomic status, racial minorities, and LGBT-identifying. The aim of this retrospective review is to describe the risk factors for congenital syphilis and syphilis infections among pregnant women delivering at UIH.

Syphilis diagnoses are collected by the UIH infection prevention department. Through this established database, 110 possible cases were identified between 2015-2018 (33 congenital syphilis and 77 syphilis in pregnant women). Electronic medical records were reviewed for medical and sociodemographic information for final syphilis diagnoses and potential risk factors.

Based on preliminary review of 33 identified cases, there were 4 proven or highly probable and 3 possible congenital syphilis diagnoses. Of the women who gave birth to these 7 infants, 6 were black (1 black-Hispanic), 5 received late or scant prenatal care, 4 had comorbid psychiatric history, and none were HIV-positive. Furthermore, none reported recent incarceration, intravenous drug use, homelessness, having sex for money, or having sex with men-who-have-sex-with-men.

Preliminary data suggest that congenital syphilis may also impact women with a psychiatric history. Our study hopes to provide further insight into specific risk factors and behaviors for urban patient populations.
104. Cooperative Properties of VEGFR2 & R3 in Injury-Induced Corneal Lymphangiogenesis & Angiogenesis

Author(s): Neeraj Chawla, Jin-Hong (Robert) Chang

Department of Ophthalmology and Visual Sciences

ABSTRACT

Introduction: Innate corneal avascularity is pivotal to the physiologic maintenance of visual clarity. Injury and inflammation may lead to the unwanted emergence of lymphatic and blood vessels that ultimately compromise vision. However, knowledge of the underlying mechanisms and possible interactions of lymphangiogenesis (LA) and angiogenesis (HA) are currently lacking. Research Question: To what extent does the knockout of lymphatic endothelial (LEC) VEGFR2 and/or R3 affect injury-induced corneal angiogenesis and lymphangiogenesis in a dual fluorescent transgenic mouse model? Methods: Prox1-GFP and Flt-dsRed mice were bred to generate a dual PGFD fluorescent transgene model that enables the simultaneous visualization of lymphatic (green) and blood (red) vessels. Conditional knockout (KO) of LEC VEGFR2 and/or R3 was induced by IP tamoxifen and confirmed by PCR genotyping. Changes in the corneal vascular profile following whole corneal epithelium (WC) debridement were determined using a AxioZoom V16 microscope over 14 days. Results: WC debridement without receptor KO led to neovascularization in the form of LA and HA. Normal blood vessel growth occurred in all groups, regardless of receptor KO. However, tamoxifen-induced receptor KO consistently halted lymphatic vessel growth. KO of VEGFR3 impaired growth more than R2, but combined R2/R3 KO had the greatest inhibitory effect on lymphatic proliferation overall. Conclusion: PGFD mice are a suitable model for in vivo visualization of corneal LA and HA. Lymphatic receptor knockout halted lymphatic growth, albeit with no effects on blood vessels. The significant effects of combined receptor deletion in corneal LA indicate a likely cooperative role of VEGFR2 and R3.
Peripheral Nerve Fusion Using Polyethylene Glycol Following A Crush Injury

Author(s): Joyce Chung, Abhishek Deshpande, Justin DesLaurier, James Walter, James Kerns, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Introduction

Traumatic peripheral nerve injuries (PNI) induce downstream Wallerian degeneration (WD) and often result in functional deficits. Studies on polyethylene glycol (PEG) application following PNI have demonstrated distal nerve sparing, but more work must be done to optimize and simplify PEG application. This study explored the efficacy of 600 mW PEG in a tibial nerve crush lesion model. A novel histological classification method was used to quantify nerve sparing/degeneration.

Methods

Male Fischer 344 WT rats were anesthetized via intraperitoneal injections. The left tibial nerve was isolated mid-thigh then crushed with forceps for 30 seconds. The nerve was given no treatment (N=2) or injected with PEG-600 (N=5), 50% diluted PEG-600 (N=3), or Dulbecco saline (N=4). Animals were sacrificed 5 days later via cardio-perfusion. Tibial nerves were harvested, stained, sectioned, and imaged with light and electron microscopy. Axons were categorized based on the extent of WD: (A) spared, (B) partial WD, (C) advanced WD. Five counters were each given four 0.01 square-mm fields per injured nerve and counted A/B/C fibers.

Results

The average ratio of A fibers to total fibers was compared across groups: uninjured control (96.7%), no treatment (9.5%), Dulbecco (6.8%), PEG (5.5%), dilute PEG (2.5%). There was no statistical difference between treatments.

Discussion

The results have several possible indications: low molecular weight PEG may not be therapeutically effective; PEG concentration and protocol were not optimized; physical injection causes more damage than no intervention; or a crush lesion model is not replicable/appropriate for testing PEG. Future studies are needed to evaluate these factors.
106. Decreasing Restraints Using the Model for Improvement and Implementation Science

Author(s): Younglak Hong, Amy Abramowitz, Alana Peters, Rachel Goldstein, Priyanka Nasa, Melissa Wagner-Schuman

Department of Psychiatry

ABSTRACT

BACKGROUND: Restraint and seclusion events are a challenge for inpatient psychiatric care teams. Using seclusion and restraints impairs staff-patient rapport building, can cause trauma, and frequently creates barriers to recovery and treatment. We sought to use implementation science methodology to reduce the use of mechanical restraints on the adult psychiatric unit at UI Health by 50% and to sustain reduction.

METHODS: We employed the model for improvement framework to assess the effectiveness of interventions developed to reduce mechanical restraint use on the Adult inpatient psychiatric unit. Multiple Plan-Do-Study-Act cycles were completed on interventions. Intervention success was determined by assessing for special cause variation on a control chart tracking the rate of mechanical restraint use.

RESULTS: Safety huddles were started in March 2019, initially twice weekly, and were expanded to every shift. This huddle intervention resulted in a greater than 50% reduction in the use of mechanical restraints. Further, huddles being spread to every shift resulted in a sustained reduction in mechanical restraints for more than 5 months.

CONCLUSIONS: Acute inpatient psychiatric units frequently care for patients who place themselves and staff at risk of harm due to the severity of their illness. Due to the potential adverse effects of mechanical restraints, there is a call to reduce the use of mechanical restraints across psychiatric hospitals. Here we demonstrated the successful use of huddles, studied and implemented using the model for improvement, to sustainably reduce the rate of mechanical restraints on an adult inpatient psychiatric unit at UI Health.
ABSTRACT

Background: Pediatric physicians must utilize effective communication skills to establish a relationship with not only their patients, but also their patients' families. We modified the Erikson Institute Fussy Baby Network’s FAN (Facilitating Attuned Interactions) communication tool to teach pediatric residents to communicate with families using an empathy-driven process.

Objective: Improve pediatric residents’ empathy, communication skills, and self-awareness in their interactions with families.

Design: Nine pediatric residents were trained to use the FAN Family Communication Tool to guide their clinical encounters for six months. Residents completed weekly self-reflections and faculty mentors provided monthly reflective supervision. After six months, we interviewed nine residents and two mentors to assess changes in communication practices. Interview transcripts were coded using NVivo software to identify major themes through open and focused coding.

Results: The semi-structured interviews and subsequent analysis demonstrated perceived improvement in residents’ empathy, mindfulness, and ability to develop a comprehensive view of family concerns. Additional themes found were improved adaptability, better relationship building, and stress reduction during clinical encounters.

Conclusions: Family-centered communication training can improve physician empathy in response to patient signals. Trainees who used the FAN developed a comprehensive view of a family’s concerns by understanding their emotions. Improved self-awareness also abled trainees to act mindfully and process their own emotions to reduce stress during encounters. Given emerging literature on a protective effect of mindfulness against resident burnout, utilization of the FAN may mitigate burnout among pediatric residency programs. Future studies will examine broader use of the FAN in supporting communication skills training.
108. HR-HPV Prevalence Rates by Zip Codes in Chicago, Illinois- A Preliminary Look

Author(s): Divya Singh, Gelila Goba, MD, MPH, Sienna Moriarty

Department of Obstetrics and Gynecology

ABSTRACT

Background: The National Health and Nutrition Examination Survey (NHANES) indicates that 20.4% of adult women have High-Risk Human Papilloma Virus (HR-HPV). This indicator has been used as the basis for national guidelines for HR-HPV care. However, new research in New York City and the Midwest shows higher rates of HR-HPV as well as neighborhood level variation of HR-HPV types compared to national samples.

Methods: As part of a larger study to correlate the effects of structural violence on prevalence of HR-HPV and higher rates of cervical cancer among African American (AA) and Hispanic populations, we identified 13,466 patients residing within the University of Illinois Health Network’s 24 Chicago neighborhood service areas that received Pap smears between January 2014 and December 2018. A retrospective chart review is ongoing, with 9,055 completed.

Results: A preliminary look of the data reveals that 6,555 patients received both Paps and HR-HPV testing. Of these patients, 1,317 had a positive HR-HPV test within our 5-year study period. The overall prevalence in adult women within UI Health Network is 20.09%, comparable to NHANES data. However, some zip codes have HR-HPV rates as high as 27%.

Conclusion: Areas within UI Health Network have higher percentages of African American and Hispanic residents, poverty, and structural violence. By further studying indicators like rates of homicide and sexually transmitted infections as potential contributors to HR-HPV prevalence, we aim to improve care across the city and lower the rate of HR-HPV and cervical cancer incidence and mortality in specific geospatial locations.
109. Combined Transjugular Intrahepatic Portosystemic Shunt (TIPS) plus Variceal Obliteration versus TIPS Alone for Management of Gastric Varices: Comparative Single Center Clinical Outcomes

Author(s): Albert Ren, Albert Ren, Ketan Y. Shah

Department of Radiology

ABSTRACT

Purpose: Gastric varices (GV) result in significant morbidity in liver cirrhosis patients. Though transjugular intrahepatic portosystemic shunt (TIPS) creation and variceal obliteration both effectively treat GVs, few studies have evaluated the clinical outcomes of combined TIPS-obliteration. This study assessed the efficacy and safety of combined TIPS-obliteration for treatment of GVs compared to TIPS alone.

Materials and Methods: In this IRB-approved single-center, retrospective study, patients treated with TIPS-obliteration or TIPS alone for GV bleeding or high-risk GVs between 2010-2019 were identified. The study cohort spanned 34 patients treated with TIPS-obliteration (n=18) or TIPS alone (n=16). Combination therapy was performed in a single session (n=7) or planned, staged manner (n=11), with mean 19 days between procedures. There was no significant difference in age, sex, MELD score, or type of GVs between the two groups (P>0.05). Measured outcomes included rate of technical success, hemodynamic success, GV persistence, rebleeding, ascites, hepatic encephalopathy (HE), and adverse events.

Results: TIPS-obliteration and TIPS procedures were successfully performed in all cases. Hemodynamic success rate was 97%. Patients were followed for a mean of 404 days. The rate of persistently patent GVs was significantly lower in the TIPS-obliteration group (8% vs 50%; P=0.036). Cumulative rebleeding rates favored the combined therapy group (0% vs 19%; P=0.094). While median time-to-rebleeding was not reached in either group, estimated rebleeding rates at 1, 12, and 36 months in the TIPS-obliteration and TIPS alone groups were 0%, 0%, and 0% vs 7%, 7%, and 44%, respectively. Rates of post-procedure ascites (7% vs 19%; P=0.648) and HE (56% vs 56%; P=1) were similar. Adverse events occurred in 3 combined therapy cases (liver infarct and biliary dilation related to TIPS, and probable retroperitoneal hemorrhage after obliteration).

Conclusions: Clinical outcomes of combined TIPS-obliteration compare favorably to TIPS alone. TIPS-obliteration offers a higher rate of GV eradication, which may translate into lower rebleeding incidence. Larger comparative cohort and prospective data may further determine optimal management of GVs.
110. Retrospective Review of Single Incision Robotic Cholecystectomy

Author(s): Natalia Jelen, Stephan Gruessner, Yevhen Pavelko, Francesco Maria Bianco

Department of Surgery

ABSTRACT

Background: Single Incision (SI) robotic surgery was first introduced in 2011, using one small incision generally hidden in the umbilicus. This technology represents a significant improvement over standard Laparoscopic SI surgery, which is currently almost abandoned due to the technical and ergonomic challenges. We present our initial experience of SI robotic cholecystectomy and perioperative results.

Methods: Retrospective cohort study from June 2012 to June 2018, in which 248 patients underwent SI. Operative times (OT), conversions, postoperative complications, and re-operations were evaluated.

Results: 248 SI were performed, 33 with associated procedures. Patients were predominantly females (81%), mean age 40±14 years, and body mass index (BMI) 32±7.1kg/m2. Overall, mean OT from incision to closure was 85min (95 % CI: 81.2-88.7), and without associated procedures was 84min (n=215; 95 % CI: 80.05-87.95). OT in obese patients (BMI ≥30) was 87min (95 % CI: 81.06-92.94); non-obese: 83min (95 % CI: 78.25-87.75). 3 SI were converted to robotic multiport and 1 patient had an accessory port placed. A total of 8 patients developed an incisional hernia after the procedure (3.2%), of note the incidence of hernias in the last 150 patients went down to 0.6%. 2 patients required ERCP for retained stone. 7 additional patients required admission to the hospital: 5 for pain control and 2 for urinary retention.

Conclusions: 248 SI were completed with minimal complications and showed minimal increase in OT in high BMI patients. The only conversions were to the multiport system, or where an accessory port was placed. SI is a safe and viable technique for cholecystectomy.
111. Chicago Homeless Preferences in Accessing Contraceptive Care

Author(s): Jennifer Grage, Stephanie Frazin, Corey Elizabeth, Morgan Dillard, Fleisher Jonah,

Department of Obstetrics and Gynecology

ABSTRACT

Homeless people are significantly more likely to have unintended pregnancy. Unpublished data from our institution has revealed significant barriers to care in Chicago homeless people's access to care. Prior to developing an intervention in response, we planned to investigate how homeless persons at risk for unintended pregnancy would like to access contraceptive education and methods.

Our hypothesis were: (1) Homeless persons at risk for unintended pregnancy would prefer to have contraception education and administration via an on-site clinic at the shelter and (2) After receiving comprehensive contraception education, that preference would shift to receive care in a formal clinical setting.

Homeless people of reproductive potential in Chicago underwent a two-part survey and educational intervention. The initial survey included questions regarding demographic information, barriers to healthcare access as well as their insight on how they would like to receive contraceptive education and contraceptive medical care. Participants then underwent a 30-minute shared decision-making educational intervention with a trained health care professional. Following the intervention, they were surveyed to assess potential change in how participants would like to receive contraceptive education and medical care.

The majority of the participants desired to access contraceptive care in a formal clinical setting. Most of the participants highlighted their desire for assistance with transport and appointments.
Do Clinical Outcomes and Sagittal Parameters Differ Between Transforaminal Lumbar Interbody Fusion and Posterolateral Lumbar Fusion for Degenerative Spondylolisthesis?

Author(s): Landan Banks, Clayton Maschhoff, Kyle Kunze, Jannat Khan, MD, Howard An, MD,
Department of Orthopaedics

ABSTRACT

BACKGROUND: Both transforaminal interbody (TLIF) and posterolateral lumbar (PLF) fusions have been demonstrated to be efficacious techniques for treating degenerative lumbar spondylolisthesis; however, the degree to which they affect spinal sagittal alignment is poorly understood.

METHODS: Patients who underwent TLIF or PLF for degenerative lumbar spondylolisthesis between January 2011 and March 2018 by one of three fellowship-trained spine surgeons were analyzed. Exclusion criteria were patients under 18 years of age, history of lumbar fusion, revision lumbar fusion procedures, and less than three-month follow-up. Outcomes included the Oswestry Disability Index, Visual Analog Scale scores for back and leg pain, and radiographic spinopelvic parameters.

RESULTS: 456 patients with a mean age of 64.5 +/- 10.5 years and body mass index of 31.5 +/- 6.4 kg/m2 were included. 407 (89.3%) patients underwent PLF while 49 (10.8%) underwent TLIF. TLIF patients had significantly greater VAS back pain scores at final follow-up (4.3 +/- 3.1 vs. 3.6 +/- 3.07;p=0.031) than PLF patients. Interbody placement was associated with increased operative time (beta+40.8 minutes,p=0.003), greater preoperative-postoperative disc height change (beta+2mm,p<0.001) and greater preoperative-postoperative foraminal height change (beta+2.2mm,p=0.012). TLIF was associated with 4 degrees more kyphosis at final follow-up compared to PLF (beta-4.3 degrees,p=0.008). There were no differences in complication or re-operation rates.

DISCUSSION: TLIF and PLF had similar clinical and radiographic outcomes; however, TLIF was more kyphogenic and caused greater back pain at latest follow-up. Given the increased cost, longer operative times, and similarity in outcomes, TLIF may be an unnecessary approach to the surgical correction of grade I degenerative spondylolisthesis.
113. Identification and Quantification of Key Mitophagy-Regulating Gene Expression in Sickle Cell Disease Patients

Author(s): Kareem Al-Qadi, Vinzon Ibanez, Ramasamy Jagadeeswaran, Angela Rivers

Department of Medicine

ABSTRACT

Sickle cell disease (SCD) is a blood disorder that affects millions of people and causes hemolytic anemia, painful crises, and multisystem organ damage. The disease results from a beta-globin gene mutation that forms sickle hemoglobin (HbS). HbS polymerization and accumulation of reactive oxygen species (ROS) are major mediators of hemolysis in SCD. Recently, Dr. Rivers’ lab discovered that mitochondria are abnormally retained in erythrocytes in SCD. This is associated with elevated levels of ROS and hemolytic markers such as LDH and bilirubin. To investigate the role of mitochondrial autophagy in SCD, we identified key regulators of the autophagy pathway in SCD patients (SS and SC phenotype) and healthy patients. PCR analysis revealed a general downregulatory trend of mitophagy genes in SC patients compared to healthy individuals. Preliminary data showed 55/88 genes were downregulated in SS and SC patients, with 11 being statistically significant (p<0.05) in SS and 8 in SC. In SS patients, 6 genes were upregulated with 2 being statistically significant. In SC patients, 7 genes were upregulated with 4 being statistically significant. These dysregulated genes have functions that may help explain the mitochondrial retention seen in SCD. One downregulated gene in SS patients mediates membrane proteins in autophagosomal vesicles, so downregulation can cause mitophagy interference. An upregulated gene in SC patients maintains the mitochondrial membrane and masks changes in mitochondrial membrane composition that may serve as mitophagy catalysts. By identifying these genes, new therapeutics can be developed to induce mitophagy in SCD patients and reduce vaso-occlusive events/pain crises.
114. ENGAGE-2: Engaging Self-Regulation Targets to Understand the Mechanism of Behavior Change and Improve Mood and Weight outcomes

Author(s): Sushanth Dosala, Sushanth Dosala, Rohit Shrestha, Tessa Eckley

Department of Medicine

ABSTRACT

Background: Despite new evidence for effective integrated behavior therapy for treating comorbid obesity and depression, the underlying mechanisms remain unknown. Building on our team’s prior work, the ENGAGE trial focuses on methodological enhancements to examine the mediating effects of changes in large-scale brain circuits, gut microbiome, and proinflammatory cytokines on changes in health behaviors and outcomes to elucidate potential mechanisms along the microbiome-gut-brain axis underlying integrated behavior therapy for obesity and depression (I-CARE2).

Aim: Test the degree to which engaging neural circuits produces desired changes in health behaviors and outcomes for mood and weight management. Investigate the role of the gut microbiome and proinflammatory cytokines in neurobiological mechanism complexes.

Methods: 105 UI-Health outpatients are randomized in a 2:1 ratio to receive I-CARE2 intervention or usual care. Study assessments occur at baseline (0), 2, and 6 months. Neural targets are measured by fMRI, and stool and blood samples are collected for microbiome and cytokine assays.

Hypothesis: Changes in the activity and/or connectivity of a priori target neural circuits in response to I-CARE2 vs. usual care at 2 months mediate changes in health behaviors (problem-solving ability, dietary change, physical activity) and outcomes (weight-loss, depression) at 6 months. Gut-microbiome and proinflammatory cytokines are associated with activity and/or connectivity of the target neural-circuits, and together these central and peripheral mechanisms may have synergistic effects on the behavioral and clinical outcomes.
A Novel Classification Method for Analysis and Quantification of Wallerian Degeneration following Peripheral Nerve Injury

Author(s): Abhishek Deshpande, Justin DesLaurier, Joyce Chung, James Kerns, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Wallerian degeneration is a biological process that occurs when a nerve fiber is injured due to a cut or crush injury, resulting in degeneration of the axon distal to the injury. However, full functional recovery rarely occurs clinically following PNS injury, as the lack of nervous innervation for an extended period has been shown to irreversibly destabilize the neuromuscular junction. As a result, therapies that slow and/or prevent the process of Wallerian degeneration are critical for restoring muscle function and improving quality of life. In our study, we tested the effect of applying 600 MW Polyethylene glycol (PEG 600) on slowing the process of Wallerian degeneration in rats after inducing a peripheral nerve injury (PNI) in the tibial nerve. We measured the effect of PEG 600 on the rats after three different types of PNI in the rat tibial nerve: a crush lesion, a partial lesion, and a full transection. In addition, in order to characterize and quantify the extent of Wallerian degeneration on light microscopy, we developed a novel counting method, termed the ABC method, in order to compare the level of Wallerian degeneration between different groups. We found that our counting method was internally consistent and could differentiate between normal, healthy nerve fibers (A), those exhibiting moderate Wallerian degeneration (B), and completely degenerated fibers (C) on light microscopy. We believe that this novel categorization method could be useful in the future to quantitatively measure the effects of different therapeutics on the Wallerian degeneration process.
116. Retrospective Review of Open Lysis of Adhesions (LOA) for Treatment of Stiffness After Primary Knee Arthroplasty.

Author(s): Edmund Naami, Edmond Awah, Awais Hussain, Anshum Sood, Michael Patetta, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Introduction: Stiffness is a common complication preventing patients from meeting the goals of total knee arthroplasty (TKA). A case series of 1000 patients reported the prevalence of stiffness to be 1.3%. Although stiffness is uncommon, the limitations to activities of daily living can be significant. Most patients with stiffness after primary TKA benefit from open lysis of adhesions (LOA).

Methods: We retrospectively reviewed 23 patients who underwent open LOA for stiffness at a single institution. The primary outcome was ROM at six months or later after open LOA. Characteristics analyzed included age, gender, ROM, medical history, and intraoperative variables. Two sample t-tests were used for side by side comparison of means of different variables.

Results: Overall, the average ROM prior to open LOA was 50.9°. The average gain of ROM post open LOA was 25.6° increasing the average ROM to 76.5° (p<0.001). Seven patients with stiffness prior to TKA on average gained 26.8° (p=0.017) in ROM from 51.4° to 80.0°, compared to the six patients without stiffness prior to TKA who on average gained 2.5° (p=0.863) in ROM from 50.8° to 53.3°.

Discussion: Patients had improvements in ROM and flexion contractures after open LOA. The patient subset without stiffness prior to primary TKA gained less ROM than the other groups. Our results suggest that ROM prior to primary TKA should be considered when deciding to perform open LOA.

Conclusion: Patients without stiffness prior to primary TKA have less improvement in ROM after open LOA compared to other patients groups.
117. Surgical Duration Implicated in Major Postoperative Complications in Total Hip and Total Knee Arthroplasty

Author(s): Edmund Naami, Mark Orland, Remy Lee, Anshum Sood, Michael Patetta, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Objective: Total hip and knee arthroplasties are two of the most commonly performed orthopedic surgeries and are expected to increase in incidence in the coming decades. We sought to examine whether the duration of these procedures is related to various postoperative complications using data from 2010 to 2017 from the American College of Surgeons National Surgical Quality Improvement Program database (ACS-NSQIP).

Methods:
The ACS-NSQIP database was queried for patients undergoing total hip and knee arthroplasty by their respective Current Procedural Terminology codes. Operation time was stratified into 4 quartiles with equal sample sizes in each quartile for total hip and knee arthroplasty separately. The first quartile of operative times was used as the control to which the other three quartiles were compared. Multivariate logistic regression analysis was performed on all samples that accounted for possible covariates, totaling 119,076 patients for total hip and 189,297 for total knee arthroplasty.

Results: The third and fourth quartiles of total hip and total knee arthroplasty were significantly associated with higher incidences of wound complications, particularly infection and dehiscence. Additionally, prolonged total hip arthroplasty was associated with a significantly higher rate of urinary tract infections for the third and fourth quartiles, as well as deep vein thrombosis in the 4th quartile.

Conclusion: The surgical duration of total hip and knee arthroplasties is an independent risk factor for wound complications and several other important postoperative complications. Therefore, extensive preoperative planning and postoperative prophylactic measures should be performed to minimize patient morbidity and reduce hospital costs.
Trends in Modality of Injury in Closed Traumatic Subdural and Subarachnoid Hemorrhage

Author(s): Abhinav Reddy, James Ryoo, Abdel Metwally, Ankit Mehta

Department of Neurosurgery

ABSTRACT

Introduction:
Neurosurgical trauma is a leading cause of death and disability in people under 40 years old, highlighting the need to prevent such events from occurring in the first place. This study attempts to identify trends in the most common etiologies of subdural and subarachnoid hemorrhages with closed head injuries and observe the effect of modality of injury on mortality.

Methods:
Patients presenting in the inpatient setting with closed traumatic subdural/subarachnoid hemorrhage were queried from the National Inpatient Sample spanning 2012-2015. Multivariate logistic regression was performed to assess association of patient demographics, geography, and temporality of admission with prevalence of various common external causes of closed traumatic subdural and subarachnoid hemorrhages as well as the association of modality of injury with mortality.

Results:
76,380 patients were admitted for closed traumatic subdural/subarachnoid hemorrhage during the study period for which accidental falls (66.3%) and MVAs (11.9%) were the most prevalent causes. Multivariate analysis of cases due to accidental falls showed an increased incidence with age, female sex, with a decreasing prevalence further from metropolitan areas (OR 1.04, OR 1.28, OR 0.61, respectively; p<0.001 for all). Cases due to MVAs had increased incidence in younger patients (OR 1.04, p<0.001) and farther away from metropolitan areas (OR 1.41, p<0.001), but no association was seen with sex. Cases caused by surgical/medical complications and non-motor vehicle road accidents were associated with significant changes in mortality (OR 1.38, p=0.01; OR 0.36, p<0.001, respectively).

Conclusion:
This study illustrates the association of patient demographics and location with modality warranting further investigation, which may provide insight into targeted prevention strategies that addresses the greatest drivers of injury in each specific region. Patient demographic associations also provide a better baseline, that largely confirms previous work regarding vulnerable populations, upon which counseling for particular patient populations can be provided.

Author(s): Gina Qin, Stephen Brown

Department of Emergency Medicine

ABSTRACT

Introduction: Frequent users (FUs) use emergency departments (EDs) as an important source of health care. Homeless FUs often exhibit particularly high usage and worse health. This retrospective study examined correlations in characteristics, morbidity, and healthcare utilization of homeless and non-homeless FUs to understand the factors that contribute to frequent use and best approaches to improve health outcomes in these unique populations.

Methods: All adult (≥18 years) patients who met the definition of FU between January 1, 2016 and November 30, 2018 were included. Data were extracted from the UIC/UIHHSS electronic medical record. Homeless and non-homeless FUs were compared using Chi-squared tests, t-tests, and multivariable linear and logistic regression.

Results: Of the 4412 ED FUs that met full inclusion criteria, 447 (10.1%) were homeless and 3965 (89.9%) were non-homeless. Sex, race/ethnicity, and insurance status were strongly associated with homeless status (p<0.0001). Psychiatric illness (71.6%) and substance abuse (75.6%) were the most common diagnoses among homeless FUs, while hypertension (63.8%) and psychiatric illness (50.3%) were most common among non-homeless FUs. The number of comorbidities was higher among homeless compared to non-homeless FUs (p=0.0004). The number of ED visits (p<0.0001) was higher among homeless FUs, while outpatient visits (p<0.0001) and Mile Square encounters (p<0.0001) were higher among non-homeless FUs. The number of inpatient admissions did not differ between the two groups.

Discussion: Characteristics, morbidity, and healthcare utilization of homeless and non-homeless FUs differ in many ways that require distinct approaches to better serve the needs of both homeless and non-homeless FUs.
Exosome Derived Bone Marrow Mesenchymal Stem Cells in Corneal Trigeminal Nerve Regeneration

Author(s): John Hickernell, Ilham Putra, Yasmin Rassouli, Ali Djalilian MD

Department of Ophthalmology and Visual Sciences

ABSTRACT

Mesenchymal stromal cells (MSCs) have been shown to modulate inflammation and promote repair, with their exosomes as one of the important mediators. These factors are of particular interest in corneal repair, with corneal opacity diseases being the second leading cause of blindness. While corneal injury treatments have greatly advanced, little work has focused on corneal nerve regeneration. We now examine the efficacy of exosome derived from bone marrow MSCs (BM-MSCs) in promoting corneal nerve regeneration in vitro and in vivo.

Conditioned media BM-MSCs was collected after 48 hours and exosomes were isolated using ultracentrifugation. Exosome sizes were characterized with dynamic light scattering. For in vivo experimentation, murine trigeminal nerve cells were treated with exo BM-MSC media. After 48 hours, cells were imaged for axon length using confocal microscopy. In in vivo experimentation, murine subbasal corneal nerves were wounded with a 2mm biopsy. The mice were then treated topically with exo BM-MSCs for 10 days. Corneal sensitivity tests were conducted on Day 7 and 14 of treatment.

Trigeminal neuron cells treated with exo BM-MSC, showed 3.4 ± 1.2 mm total dendrite lengths vs. control treatment’s 0.9 ± 0.6 mm total dendrite lengths. In vivo, bmMSC exosome-treated corneas showed sub-basal neuron regeneration and increased corneal sensitivity performance versus control.

Our results show the positive effect ex BM-MSCs have on trigeminal nerve growth in vitro and in vivo. Further analysis on in vivo studies will be done to show anatomical nerve regeneration patterns in the subbasal layer of the cornea.
Exploring Factors Contributing to High Blood Pressure in the Emergency Department

Author(s): Drew Hollender, Brenda Lara, Sara Heinert, Maya Jackson, Heather Prendergast,

Department of Emergency Medicine

ABSTRACT

Background: Uncontrolled and undiagnosed hypertension is common in the United States, and is a large risk factor for cardiovascular morbidity and mortality. Being that hypertension is primarily asymptomatic, healthcare-system based strategies to identify individuals in the community with hypertension are essential. The Emergency Department (ED) is well situated to screen for hypertension, creating a novel opportunity for intervention. Blood pressure (BP) can be heightened by a myriad of factors unique to each patient’s lifestyle. In this study, the ED was used as a nidus for investigating factors contributing to high blood pressure in the UI Health population.

Methods: As a part of the Targeting of Uncontrolled Hypertension in the ED (TOUCHED) study, hypertensive (>140/90mmHg and <180/110mmHg) individuals were identified upon discharge from the ED. Participants enrolled in the study completed a number of baseline assessments including the Modified Morisky Medication Adherence Scale (MMS) and a hypertension knowledge assessment.

Results: We find that low scores on neither the MMS nor the hypertension knowledge questionnaire were associated with higher BP values in the ED. However, within the MMS, participants who report that they stop taking their medications when their symptoms improved had higher diastolic BP values (p=0.0129; n=28).

Conclusion: These findings suggest that medication adherence and knowledge of hypertension are not sufficient to account for the variation in blood pressures amongst hypertensive individuals in the ED. However, the finding of elevated diastolic BP in those who halt their medications when their symptoms improve may provide insight for further investigation.
122. Inflammasome Caspase-1 Activity in the Cerebrospinal Fluid of Subarachnoid Hemorrhage Patients as a Predictive Biomarker for Functional Outcome

Author(s): Yonatan Hirsch, Joseph Geraghty, Cory Reiter, Eitan Katz, Jeffrey Loeb, Fernando Testai

Department of Neurology

ABSTRACT

Introduction: The proteolytic enzyme, caspase-1, activated by the inflammasome complex, is known to contribute to numerous downstream pro-inflammatory effects. We investigated caspase-1 activity in the cerebrospinal fluid (CSF) of subarachnoid hemorrhage (SAH) patients and its association to outcome.

Methods: CSF samples from 18 SAH subjects were collected via an external ventricular drain and obtained within 72 hours of the onset of symptoms. For controls, we collected the CSF from 9 patients undergoing lumbar puncture with normal CSF and normal brain MRI. Caspase-1 activity was measured using luminescence assays. SAH subjects were categorized at hospital discharge into those with good outcomes (Glasgow Outcome Scale, GOS, of 4-5) and poor outcomes (GOS of 1-3).

Results: Caspase-1 levels from SAH patients were significantly higher than those in the control group (p = 0.0002). Within the SAH group, 10 (55.6%) had good outcomes and 8 (44.4%) had poor outcomes. Caspase-1 activity was significantly higher in the poor outcome group (p = 0.0012). Additionally, caspase-1 activity had a significant correlation with GOS score (r = -0.60; p = 0.01). Our regression model yielded significant results (p = 0.011) and our ROC curve for caspase-1’s predictive ability showed an area under curve (AUC) of 0.936, which was higher than that of Hunt & Hess score (0.679) currently used to determine patient prognosis..

Conclusions: Caspase-1 is elevated in CSF early after SAH and higher in those with poor functional outcome. Analyses suggest that caspase-1 activity levels in CSF may be a novel biomarker for predicting patient outcome.
123. Testing Polyethylene Glycol (PEG) 600 as a Novel Fusogen for Peripheral Nerve Injury (PNI): Partial Transection Model

Author(s): Justin DesLaurier, Joyce Chung, Abhishek Deshpande, James Kerns, James Walter, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

PNI regularly presents a challenge for the orthopedic clinician to achieve appropriate and timely rehabilitation following traumatic injuries. This is due to the slow (~1 mm/day) natural regenerative process of peripheral nerves. Wallerian Degeneration (WD) describes the degenerative process that occurs distal to a nerve lesion and continues to the neuromuscular junction (NMJ). There is a developing focus on pharmacologically halting and reversing the process of WD rather than enhancing regeneration to expedite the post-PNI rehabilitation process and improve functional recovery. While the mechanism has not been firmly established, it has been hypothesized that PEG's osmotic properties increase the energy of activation required for the initiation of WD. PEG has been histologically demonstrated to be effective in promoting distal sparing of nerve fibers in the literature. However, the use of PEG with varying conditions and molecular weights have yet to be explored, and there has been a lack of data establishing that parameters utilized in the literature have been optimized. We tested the application of PEG MW:600 without the use of a low-calcium wash in a partial transection injury model performed on the tibial nerve of rats. A novel method for quantitative analysis of WD was applied to establish our results. PEG 600 showed a slight trend of fiber sparing, but overall did not demonstrate the tremendous effectiveness of PEG shown by previous protocols. The novel quantitative analysis method did demonstrate reproducibility and further sensitivity for the analysis and optimization of future PNI treatment modalities.
ABSTRACT

Introduction:

In patients undergoing surgery for degenerative lumbar pathologies, depression has been associated with worse outcomes including postoperative pain and disability. Despite association with poor outcomes, information regarding spine surgery among depressed patients is limited.

Methods:

Patients requiring surgery for degenerative lumbar spine pathologies were queried from the National Inpatient Sample 2012-2015 datasets. Propensity score matching on patient demographics, medical comorbidities, temporality of admission, and hospital demographics was performed comparing patients with and without depression on rates of lumbar spinal fusion. Subsequent propensity score matching was performed separately in patients who underwent fusion and those who did not to assess effects of depression on length of stay, discharge disposition, and hospitalization cost.

Results:

Patients with depression had significantly higher rates of fusion procedures compared to patients without depression (OR=1.12, p<0.001). Among patients undergoing LSF, diagnosis of depression was significantly associated with increased LOS (difference=0.10 days, p=0.002) and decreased likelihood of home discharge (OR=0.91, p=0.010). Similarly, among patients who did not undergo LSF (lumbar decompression patients), depression was significantly associated with longer length of stay (difference=0.24 days, p<0.001), decreased likelihood of home discharge (OR=0.77, p<0.001), and increased hospitalization cost (difference=$5313.2, p<0.001).

Conclusions:

Our results demonstrate that depressed patients undergo higher rates of fusion, and are associated with worse outcomes in degenerative lumbar pathologies, regardless of whether they undergo fusion. Considering non-fusion management options and postoperative measures may improve outcomes in depressed patients.
125. Optimizing immunohistochemical staining of layer-specific epileptic biomarkers in bovine neocortical brain tissue

Author(s): Ajit Augustin, Allison Kirchner, Jeffrey Loeb, Jesica Herrick

Department of Neurology

ABSTRACT

Background and Significance: Previous studies in the Loeb lab have demonstrated that the MAPK pathway is significantly upregulated in the human epileptic neocortex, specifically in layer 2/3. In a parallel animal model of epilepsy using tetanus toxin injection in the rat neocortex, the same layer-specific upregulation of the MAPK pathway was observed. This finding indicates that the layer 2/3 activation of the MAPK pathway may be used as an epileptic biomarker. Neurocysticercosis is an infectious disease, prevalent in developing countries that commonly leads to seizures. However, the role and location of the epileptic activity in regard to neurocysticercosis is unknown.

Objective: To optimize the immunohistochemical (IHC) staining of human and bovine neocortical brain tissue in hopes to observe the layer-specific activation of epileptic biomarkers to better understand the epileptic activity involved in neurocysticercosis.

Methods: Human epileptic neocortical tissue was obtained following a 2-step procedure. The first step involves recording the epileptic activity and the second involves removing the epileptic focus. The human epileptic neocortical tissue was then fixed in 4% PFA and embedded in OCT. Bovine tissue with neurocysticercosis was received from the Cysticercosis Working Group in Peru, following formalin fixation and paraffin embedding. Typical IHC protocol was performed with staining for total ERK, total CREB, pERK, pCREB, and EGR1 in both human epileptic neocortical tissue and bovine samples.

Results and Conclusions: We observed positive staining for MAPK signaling in the infected bovine tissue, which will provide later insight into the relationship between epileptic activity and neurocysticercosis.
Correlation of pathologic tumor necrosis and disease recurrence rates in liver resection patients

Author(s): Hwa-Pyung Lim, Alexander Kim, MD

Department of Medicine

ABSTRACT

PURPOSE

To assess if tumor necrosis affects disease recurrence rates after hepatectomy in patients undergoing portal vein embolization (PVE) +/- locoregional therapy (LRT).

MATERIALS

This is a retrospective, single-center study of patients who underwent PVE +/- LRT before surgical resection from July 2009 to July 2019. 73 patients were stratified into 2 groups: those who did or did not receive LRT. Tumor resection rates, recurrence rates, overall survival and tumor necrosis on pathologic specimens were assessed.

RESULT

Of the 73 patients who underwent PVE during this period, 43 received PVE alone and 30 received PVE+LRT. 13 patients who received LRT >60 days from PVE were excluded from analysis. The resection rate was 33/43 (77%) in the PVE group and 9/17 (53%) in the LRT group (p=0.12). No patients in either group demonstrated complete tumor necrosis, but partial necrosis was demonstrated in 12/33 in the PVE group vs. 8/9 in the LRT group (p=0.008). Recurrence occurred in 3/12 PVE and 4/8 LRT patients with partial necrosis, compared to 5/19 and 0/1 patients with no necrosis noted. The rate of recurrence after resection was 8/33 (24%) in the PVE group vs. 4/9 (44%) in the LRT group (p=0.41).

CONCLUSIONS

We found no correlation between tumor necrosis and recurrence rates in post-resection patients. Although there was a statistically higher rate of tumor necrosis in patients undergoing PVE+LRT, this did not lead to a decreased rate of tumor recurrence. Further studies are needed to assess if complete pathologic response leads to improved post-resection outcomes.
127. Cardiovascular Disease Associated with Higher Incidence of Major Postoperative Complications in Total Hip and Knee Arthroplasty

Author(s): Remy Lee, Edmund Naami, Mark Orland, Anshum Sood, Awais Hussain, Mark Gonzalez

Department of Orthopaedics

ABSTRACT

Objective: Cardiovascular disease affects over 28 million Americans and has been attributed to 1 in every 4 deaths in the United States. The demand for total joint replacement is expected to increase due to an aging population and advances in technology. Given the prevalence of cardiovascular disease and the expected increase in total joint replacement procedures, we sought to examine whether cardiovascular disease was associated with increased postoperative complications in patients undergoing total hip and knee arthroplasty.

Methods:

Current Procedural Terminology (CPT) codes were used to search the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database for patients who underwent total hip or knee arthroplasty from 2010 to 2017. Cardiovascular disease status was classified according to the American Health Association guidelines. Patient demographics and non-cardiovascular comorbidities were included as covariates for the multivariate logistic regression analysis. A sample size of 119,076 for total hip and 189,297 for total knee arthroplasty were analyzed.

Results: Patients with a history of cardiovascular disease were found to have a statistically significant increased risk of the following postoperative complications: sepsis (p<0.001), wound complication (p<0.001), pneumonia (p<0.001), urinary tract infection (p<0.001), myocardial infarction (p<0.001), unplanned intubation (p<0.001), and cardiac arrest (p=0.003).

Conclusion: A history of cardiovascular disease prior to a total hip or knee arthroplasty is a major risk factor for many postoperative complications. Stringent preoperative evaluation, prophylactic use of antimicrobial medication, and antithrombotic management may help lower the risk of postoperative complications in this population.
Training and infrastructure needs identified through an assessment of emergency care capacity in Kisumu, Kenya

Author(s): Mahi Singh, Kristin Auge-Bronerski, Vinay Mikkilineni, Nneka Ukegbu, Kevin Rombosia, Janet Lin

Department of Emergency Medicine

ABSTRACT

Background: The disease burden from emergencies in Kenya (DALYs of 42,779 per 100,000) is among the highest in low and middle income countries. Kenya’s healthcare system of public and private care has not been able to meet the increasing burden of trauma and acute conditions. The Ministry of Health of Kisumu County, which houses the 3rd largest city in Kenya, has identified an urgent need to assess and build emergency care capacity.

Methods: A county-wide needs assessment was conducted in Kisumu at 22 facilities representative of the six-tiered health system. For each site, quantitative data on medical resources and infrastructure was collected through interviews of key medical personnel and focus groups. Facility assessments were used to evaluate current emergency medicine capabilities and qualitative analyses of interviews were performed to understand priorities in the region.

Findings: Gaps exist in general infrastructure, with only 3 facilities having surgical capabilities and many lacking the necessary supplies. However, formal emergency medicine training is one major gap observed in all facilities. Only one-third of personnel in Casualty areas have basic emergency medicine training, and less than a third of facilities have an adequate triage system in place.

Interpretation: To optimize limited resources, a hub-and-spoke model of emergency care has been proposed. Establishing effective communication channels between facilities and improving patient flow can lead to efficient provision of emergency care. More immediately, triage training for effective recognition of acutely ill patients and development of clinical modules will enhance emergency care by current healthcare workers.
129. Chicago Street Medicine: A Retrospective Review of Outreach and Opportunities for Growth

Author(s): Philip Ostrov, Sukhveer Bains
Department of Emergency Medicine

ABSTRACT

Introduction

Recent research indicates that multidisciplinary patient-centered teams can provide continuity of care to the unsheltered homeless, many of whom would otherwise be lost to follow-up. Chicago Street Medicine (CSM), an organization formed by volunteer medical students and residents, utilizes this model in order to bridge unmet health and social needs by reaching these individuals where they reside. This study seeks to identify opportunities for growth and capacity building based on the needs of the unsheltered homeless population of Chicago.

Methods

The CSM program has utilized a shared document of de-identified narrative data to communicate among care teams and describe the events of street runs. Health and Social needs from 61 street run records were categorized into discrete variables and coded into quantitative data for univariate regression analysis.

Results

There was a significant difference in number of patient requests comparing runs with a social worker present (M = 7.8, SD 1.92) and without (M=5.30, SD 2.49); p=0.034. Results demonstrate a continual need for medical and social resources, in particular wound care, general medicine, and addiction services.

Conclusion

Results establish academic street medicine as a paradigm for patient advocacy through a multidisciplinary approach as well as an opportunity for advanced training of medical students and residents. Additionally, these results corroborate the dearth of continuity-of-care as a significant barrier to better health outcomes for the unsheltered homeless population and indicate a need for streamlined care coordination in Chicago, Illinois. Due to the qualitative nature of this data, further investigation is needed.
130. A Rapid Tear Recovery Device for Diagnostic and Investigative Purposes

Author(s): Zobia Chunara, Abdul Zakkar, Ameera Lodhi, Farhin Patel, Sandeep Jain

Department of Medicine

ABSTRACT

Introduction:

Tears, which are composed of water, electrolytes, mucins, lipids, and proteins, can be analyzed for early diagnosis and monitoring of numerous diseases, including cancer. However, there is no standard method to collect tears, and current methods are tedious and risky. At our institution, only one physician, a dry eye specialist, analyzes tears. His collection process requires a highly trained ophthalmologist, a slit lamp, two research assistants, and eight glass capillary tubes.

Device Description:

Our proposed solution is a rapid tear recovery device that samples tears after buffer fluid has been administered to the eye. The device has two components. The handheld, pen-shaped component has two disposable parts: 1) a soft medical grade silicone tip which is held to the eye during collection and 2) a sample collection tube. The vacuum pump component creates negative pressure inside the pen, causing the sample to be sucked directly into the collection tube. There is a duplicate pen component to avoid cross contamination between eyes. After collection is complete, samples are sent for analysis, and the used disposable parts are discarded.

Evaluation:

Using our device, one trained personnel can collect tears in three minutes as compared to the current process which requires three personnel and seven minutes. Most importantly, our device poses a reduced risk of scratching the ocular surface.

Conclusion:

Further development of this class II device will allow for consistent, rapid, and safe tear sampling by a single minimally-trained practitioner, leading to diagnostic and investigative use amongst various specialties.
Comparison of PROMIS Computerized Adaptive Testing-Administered Item Banks versus Fixed Short Forms in Juvenile Myositis

Author(s): Valeria G. Esparza BS, Ruchi N. Patel BS, Jin-Shei Lai PhD, Elizabeth L. Gray MS, Rowland W. Chang MD, MPH, Kaveh Ardalan MD, MS, David Cella PhD

Department of Medicine

ABSTRACT

Background
In comparison with healthy youth, those with juvenile myositis (JM) often report poorer health-related quality of life (HRQoL). Legacy HRQoL measures may underestimate impact of JM due to floor/ceiling effects. Patient-Reported-Outcomes-Measurement-Information-SystemÂ® (PROMIS) HRQoL measures have undergone initial validation, however relative benefits of Computer-Adaptive-Testing (CAT) vs Fixed-Short-Forms (FSF) are unknown. The purpose of this study was to compare CAT and FSF.

Methods
JM-patients (5-17 y/o) and parents were recruited at clinic visits. Demographic/clinical assessments were collected: Physician Global Assessment of Disease Activity/Disease Activity Score/muscle enzymes/Childhood Myositis Assessment Scale. Patients (8-17 y/o) completed self-report versions and parents (of patients 5-17 y/o) completed parent proxy-versions of the following PROMIS domains in both CAT and FSF: Fatigue/Pain Interference/Upper Extremity Function/Mobility/Anxiety/Depressive Symptoms. Pearson correlations, paired t-tests, & Cohen’s d were used to compare PROMIS CAT and FSF for entire cohort and three T-score groupings (<45, 45-55, >55).

Results
Data from 67 patient/parent dyads were analyzed. PROMIS CAT and FSF were highly correlated (Pearson’s 0.79-0.92). Mean scorers between CAT and FSF were not significantly different except in parent proxy anxiety & fatigue. Correlations between CAT & FSF varied based on domains, patient vs parent report, & T-score groupings. Scatterplots showed floor/ceiling effect at less symptomatic extreme in all FSF domains.

Conclusion
PROMIS CAT is feasible in clinical settings and is comparable to FSF. CAT had less pronounced floor/ceiling effects than FSF allowing detection of individual differences in low symptom/disability scorers. CAT is recommended for long-term follow-up of JM patients given deconditioning often persists in remission.
132. Biomechanical Consequences of Progressive Full Thickness Focal Osteochondral Defects involving the Medial and Lateral Femoral Condyle in Goat Model

Author(s): Kevin Jacob, Farid Amirouche, Rohan Kulkarni

Department of Orthopaedics

ABSTRACT

Introduction: Study aims to assess the effect of full thickness osteochondral defects on biomechanical properties of lateral and medial femoral condyle at defect rim

Methods:

8 fresh-frozen goat (mean 1 yr old) knees were obtained. Full thickness osteochondral defects of progressively increasing diameter size (3mm, 5mm, 7.5 mm) were created at the weight bearing contact area for flexion/extension in either the Medial Femoral Condyle (MFC) or Lateral Femoral Condyle (LFC) on each knee. Specimens were loaded onto custom testing frame with TekScan force sensors inserted intrasrticularly. At each testing condition, knee was loaded at 100 N, and underwent ROM from 90° flexion to 15° extension. Contact area, force, pressure, and peak pressure [PP] were collected.

Results: For Group 2, PP on MFC at full extension increased by 18.9 % as defect size increased from 3mm (1.976 MPa) to 7.5 mm (2.349 Mpa) [p < .001], whereas in group 3, PP on LFC at full extension increased by 78.6 % as defect size increased from 3 mm (1.725 MPa) to 7.5 mm (3.08 MPa) [p < .001]. For equivalent dual defects of 3mm diameter on both condyles, peak pressure on MFC was significantly higher than peak pressure on LFC in both group 4 and group 5.

Clinical Significance: Isolated Osteochondral lateral defects experience greater rate of increase and greater variation in Peak pressure when compared to medial counterparts. Clinically, this may suggest that lateral defects progress more rapidly.
ABSTRACT

Introduction

Subependymal giant cell astrocytoma (SEGA) is a rare brain neoplasm that commonly arises with tuberous sclerosis complex. Although neurosurgical resection has been the mainstay of treatment, alternative modalities have been explored such as everolimus, an mTORC1 inhibitor, which was published as a prospective study in 2010. This study seeks to provide an analysis of epidemiological risk factors in this tumor while comparing trends in surgical management before and after 2011.

Methods

Patients with a diagnosis of SEGA were queried from the National Cancer Database (NCDB) spanning 2004-2015. Multivariate regressions were performed to assess the association of several variables with odds of performing surgery and odds of survival.

Results

A total of 460 patients were diagnosed with SEGA. Multivariate analysis of survival demonstrated that increased age was associated with decreased survival (HR=1.05; 95%CI 1.02-1.07; p<0.0001). Multivariate analysis of surgery showed increased age (OR=1.02; 95%CI, 1.00-1.03, p=0.04) and tumor size >20mm (OR=9.52-16.75, p<0.0001 for all) were associated with higher odds of surgery. Radiotherapy (OR=0.12; 95%CI, 0.02-0.57; p=0.008) and chemotherapy (OR=0.21; 95%CI, 0.06-0.66; p=0.008) were associated with lower odds of surgery. A comparison of surgery rates between 2004-2010 and 2011-2015 showed a decreased rate after 2011 (60.63% vs 48.06%, p=0.007).

Conclusion

Our analysis of SEGAs demonstrated that age was the only variable that affected survival. Additionally, surgery was performed in older patients with larger tumors >20mm, usually as a primary treatment without multimodal chemoradiotherapy. Rates of performing surgery were found to have decreased since 2011, which suggests everolimus has modified treatment approach to reducing surgery.
134. Integrating Hand-Hygiene Education into Medical Student Clinical Responsibilities “ A Pilot Program and Study Involving Students as Active Observers

Author(s): Ajit Augustin*, Shashank Patil*, Joseph Geraghty, Matthew Orlando, Michelle Barnes, Asra Khan

Department of Medical Education

ABSTRACT

In 2015, the University of Illinois at Chicago College of Medicine (UICOM) was selected to be one of ten institutions in the AAMC Core Entrustable Professional Activities (EPA) Pilot. At that time, UICOM formed a committee focused on EPA 13: Identify system failures and contribute to a culture of safety and improvement and developed a project centered on medical student observation of hand hygiene among preceptor physicians. 31 medical students documented patient encounters with physicians, recording hand hygiene behavior performed before and/or after each patient encounter. Data on physician gender, specialty, level (attending/resident), setting (inpatient/outpatient), and time of year (fall, winter, or spring) were collected representing a total of 274 patient encounters with 43 supervising physicians. Qualitative analysis of students’ perceptions was reported. Hand hygiene before an encounter was observed to be performed at a significantly higher rate (91.8%) compared to after a patient encounter (83.7%), p<0.0001. Multivariate logistic regression revealed that male gender (OR 3.698, p=0.049) and resident level (OR 6.451, p=0.005) significantly predicted those who failed to perform hand hygiene before and after a patient encounter. The pilot was received favorably in that 72% of students recommended a full expansion to the entire medical student class. Our pilot project successfully incorporated hand-hygiene education into medical students’ early clinical responsibilities and helped identify several factors that could predict failure to perform hand hygiene. Future research is needed to determine if observing preceptor hand-hygiene behaviors contributes to student habits that are sustainable throughout training.
135. Value added from a family centric perspective in patients transferred to regional ICUs

Author(s): Margaret Mass, Clifton Callaway, Jonathan Elmer, Francis Guyette
Department of Emergency Medicine

ABSTRACT

Background:
Many medical systems operate through a tiered system where medical centers transfer higher intensity patients to regional centers for greater levels of care. There is a question of transfer value from a family centered perspective where there is not patient centric benefits: in negative outcomes despite transfer, or if there is no care greater than referring hospital could provide.

Purpose: To identify family perspectives on the value of interfacility transfers as a means of identifying value from a family centric care perspective.

Method: Data was gathered through structured interviews with family members in an opportunity sampling from ICUs in a single site University of Pittsburgh Medical Center regional hospital. Field notes and post hoc reflections formed the text for framework analysis to identify themes, then analyzed for saturation, frequency, and trends.

Findings: Key elements of value gain include the family members confidence in care: incorporating hospital capacity, expert opinion, and receiving the best possible care. Elements of value lost through the interfacility transfer include physical and financial burdens to family members and the cognitive emotional burden of weighing patient vs visitor needs. Analysis demonstrated predominantly elements of value gained in the patient interfacility from a family perspective.

Conclusion: This study identified family perspectives on elements of value gained and lost in interfacility transfers at the time of the transfer. More work is needed to evaluate family centric value long term especially in the context of negative or positive outcomes.
136. Efficacy Assessment of a Fibrin Hydrogel-based Exosome Delivery Platform in a Traumatic Brain Injury Model

Author(s): James Ryoo, Anisse Chaker, Clay Rosinski, Saavan Patel, Nikki Barrington, Tania Aguilar

Department of Neurosurgery

ABSTRACT

Introduction

Traumatic brain injury (TBI) is a critical condition that remains the leading cause of death and disability in young adults. Current standard of care is devoid of therapy to mitigate the secondary inflammatory cascade caused by TBI; however, recent studies have shown the efficacy of intravenous mesenchymal stem cell-derived exosomes in rat TBI models. Based on these studies, we hypothesize that exosome treatment through a previously developed fibrin hydrogel delivery vehicle will better mitigate inflammation in a TBI model compared to systemic delivery.

Methods

Exosomes were isolated from the media of bone marrow stem cells through serial ultracentrifugation and characterized through NanoSight analysis. A modified Dixon contusion model will be used to administer a cortical injury will be delivered to the left motor cortex. A pilot study was performed on 8 rats that were contused and followed up through the modified Neurological Severity Score to gauge replicability of injury. 6 treatment groups of Wistar rats were administered the injury and monitored until sacrifice at 6 days post injury (6DPI).

Results

The isolated exosomes were a mean size of 116.9nm±51.5nm at a mean concentration of 2.72*10^7±6.34*10^6particles/mL. The 8 rats in the pilot study had comparable mNSS scores, which indicated adequate replicability of the cortical contusion model.

Conclusions/Future Directions

The current results demonstrate the development of replicable methods of TBI and exosome production. Histopathological and immunohistochemical analyses will be performed on the brain tissue harvested from the sacrificed rats to observe the effects of different exosome delivery platforms on neuroinflammation.
137. Targeted Treatment of Spinal Cord Injuries Using Fibrin Containing Exosomes

Author(s): Amy Zhu, Tania Aguilar, Nikki Barrington, James Ryoo, Eddy Aguilar,
Department of Neurosurgery

ABSTRACT

Each year in the United States, there are approximately 17,000 new cases of spinal cord injuries (SCI). Previous literature has shown bone mesenchymal stem cell (BMSC) transplantation to be effective in treating spinal cord injuries, but this method is complicated by low cell survival rates, dedifferentiation, and tumors formation. Recent studies have proposed that exosomes produced by BMSCs were able to help repair SCI in rats. The purpose of this study was to further investigate the effect of exosomes on inflammatory cells such as macrophages that significantly impact secondary injury, a time period in which it would be most feasible to treat SCI. It also proposed that delivery of these exosomes could be optimized by using a fibrin glue vehicle for localized delivery.

The first phase of this experiment analyzed the genotypic profiles of THP-1 monocytes following treatment with exosomes during differentiation. qPCR was used to quantify M1 inflammatory and M2 anti-inflammatory gene expression. In M1 differentiated THP-1 macrophages, exosome treatment during differentiation yielded higher expression of pro-inflammatory M1 markers CB80, HLA-DR, IL-18, IL-6, and TNF-alpha. Similarly, in M2 differentiated THP-1 macrophages, exosome treatment resulted in higher expression of pro-inflammatory markers CD80, CXCL10, HLA-DR, IL-18, and TNF-a. However, the fold inductions seemed to be slightly higher for the M2 markers in comparison to the M1 markers with the exception of HLA-DR meaning the anti-inflammatory properties could be more substantial. This experiment will be repeated to better understand the effect of these exosomes before moving on to in vivo experiments.
138. Predictors of Mortality Following Penetrating Upper Gastro-Intestinal Injuries

Author(s): Samara Albazzaz, Eduardo Fernandes, Kevin Chow, Francesca Kimelman, Maria Ramirez, Jennifer Pan

Department of Surgery

ABSTRACT

Introduction
Penetrating injuries to the upper gastro-intestinal tract (esophagus, stomach and duodenum), represent a surgical challenge for the trauma surgeon. There is currently no consensus on how to best manage patients with such injuries or what are the predictors of mortality.

Methods
We conducted a retrospective analysis on 281 patients who suffered a penetrating injury to the upper gastro-intestinal tract at a level 1 trauma center over 10 years. A logistic regression was utilized to determine how a series of predictive factors on patient’s presentation impacted the 30-day mortality.

Results
Injury location (thoracic esophagus, Gastro-esophageal junction, stomach and duodenum), associated intrabdominal injury (liver, pancreas, spleen, kidney/urether, diaphragm, cardiac, pulmonary, colon, small bowel) presence of a major vascular injury, hemodynamic status and peritonitis on presentation were computed in the logistic regression. An associated liver injury (p&lt;0.05, OR 2.9, 95% C.I. 1.0-8.3) and the presence of hemodynamic instability (P&lt;0.05, OR 5.3, 95% C.I. 1.9-14.9) were independent risk factors of peri-operative mortality.

Conclusion
Associated liver injury and hemodynamic instability are independent risk factors of peri-operative 30-day mortality in penetrating upper gastro-intestinal injuries. Adequate management of the liver injury and prompt correction of the patient’s hemodynamics should be offered to potentially improve patients’ outcomes.
139. Accuracy of AI Algorithm Characterization of Incidental Pulmonary Nodules on DCE-CT

Author(s): Elise DeBruyn

Department of Medicine

ABSTRACT

Dynamic contrast enhanced computed tomography (DCE-CT) is widely used for imaging of pulmonary nodules. There is no standardized non-invasive imaging technique used to characterize pulmonary nodules but several imaging modalities, such as DCE-CT and positron emission tomography (PET-CT), are currently being investigated for their utility. Several studies have demonstrated that the maximal mean nodule enhancement measured in Hounsfield Units (HU) has a sensitivity of 93% and specificity of 76% when classifying pulmonary nodules as benign or malignant. In this study, an AI algorithm was implemented in a set of pulmonary nodules identified through incidental finding on DCE-CT to determine their risk of malignancy. A region of interest (ROI) tool was used to identify the area and volume of the pulmonary nodule on narrow and wide field of view (FOV) and a risk score was generated for each nodule pre-contrast and at 60 seconds, 120 seconds, 180 seconds, and 240 seconds post-contrast. Pulmonary nodules were included if they measured at least 8mm when viewed on mediastinal window and DCE-CT was used. A one-way repeated measures ANOVA and descriptive analysis was performed for each nodule. Effects of nearby vasculature, change in ROI, and narrow vs. wide FOV on the generated risk score were also investigated. One-way repeated measures ANOVA for narrow FOV reveal that $\text{FDF}_n,\text{DF}_d = 12.36, p < 0.05, \hat{\eta}^2 = 0.77$, using a Huynh-Feldt correction for sphericity on $p$. Comparison of narrow FOV with wide FOV with a paired samples t-test reveal that the data are not normally distributed.
The Efficacy of Simulated Patient Models in Improving Physician Attitudes Toward Patients with Disabilities

Author(s): Zoie Sheets

Department of Medical Education

ABSTRACT

People with disabilities (PWD) encounter more barriers to primary care than their non-disabled counterparts (47% vs. 29%), and physician attitudes are one of these barriers. Negative physician attitudes may stem from the lack of training physicians receive on interacting with and treating PWD. Various government and academic entities have recommended disability curriculum be mandated for physicians, and several medical colleges in the US have developed disability curriculum for their students. Simulated patients, however, have not often been used. This study aimed to assess whether simulated patient models can fill gaps in medical disability curriculum to both center the voices of PWD in their care and ensure physicians understand how to treat PWD in a culturally-relevant manner. Using two theories' Miller's Pyramid and Kingdon's Policy Model" to guide the development, this study's methods included three main components: developing simulated patient models, piloting the models, and assessing the attitudes of the medical students who participated using pre- and post-surveys. Both attitudes and confidence levels improved overall. Some students reported regressions in 1-2 questions; however, the conversations that occurred during the colloquium may explain potential causes for these transitions in attitudes and/or confidence levels.

Author(s): Abhinav Komandur, Heather Weinreich, Thanyani Magwaba, Barry Wenig

Department of Otolaryngology

ABSTRACT

Cancer of the head and neck afflicts over 650,000 new patients and kills over 330,000 patients annually. Patients with cancers of the head and neck can have painful and debilitating morbidity associated with their illness. In patients with advanced cancers of the head and neck (ACHN), this morbidity has long been noted to have an adverse effect on both self-image and ability to participate in normal activities. The impetus to treat such patients aggressively can therefore be strong. However, the decision as to how and when to treat such patients is not always an easy one.

The standard of care for ACHN in many settings worldwide is set by academic organisations such as the National Comprehensive Cancer Network (NCCN). Some variability may occur with guideline source or patient preference, but the standard of care in advanced cases will involve surgical treatment coupled with non-surgical treatment such as chemotherapy or radiotherapy. However, some patients may only have access to (or time for) surgical intervention.

For such patients, guidelines are few, and anecdotal accounts indicate that management can be difficult. To elucidate the clinical decision-making context surrounding such patients, we evaluated surgical texts dating from 1873 to the present day to investigate why such patients lack access to life-saving treatment, and how past surgeons have described their management. Our review revealed many opportunities to perform new research, to clarify current practice, and potentially to re-evaluate the care models used to treat such patients.
142. A Devastating Journey: A Comparative Practice Analysis of Optic Neuritis Evaluation and Treatment Between Johannesburg and Chicago State-Sector Hospitals

Author(s): Abhinav Komanur, Michael Giovingo, Peter MacIntosh

Department of Ophthalmology and Visual Sciences

ABSTRACT

Optic neuritis, especially when un-treated, can be a devastating illness across the globe. Currently, the landmark Optic Neuritis Treatment Trial (ONTT), first published in 1992--and with 15 years of follow-up since--has established the premier care model for the evaluation and treatment of acutely-presenting optic neuritis. The resources required to properly follow the care guidelines established by the ONTT can be beyond the reach of many healthcare systems however. Within the context of a literature review, we evaluate the policies and procedures in place at Leratong Hospital in Krugersdorp, Republic of South Africa, The University of Illinois Hospital, in Chicago, and the John H. Stroger Jr Hospital of Cook County, also in Chicago. We also propose a study design to test the hypothesis that resource limitations will not affect an individual facility's de jure care models in the case of acutely-presenting optic neuritis.
143. My Luck Has Run Out: A Comparative Practice Analysis of Uveal Melanoma Evaluation and Treatment Between Johannesburg and Chicago State-Sector Hospitals

Author(s): Abhinav Komandur, Michael Giovingo, William Mieler

Department of Ophthalmology and Visual Sciences

ABSTRACT

Uveal melanoma can be treated effectively and with minimal intervention when presenting as a purely local disease. Advanced, or metastatic uveal melanoma in contrast can be a devastating and lethal illness. Currently, there is no FDA-approved care model for the treatment of advanced uveal melanoma. Multiple academic organisations and individual research studies have established rival care models for the evaluation and treatment of first-presentation advanced uveal melanoma. Within the context of a literature review, we evaluate the policies and procedures regarding the evaluation and treatment of advanced uveal melanoma in place at Leratong Hospital in Krugersdorp, Republic of South Africa, The University of Illinois Hospital, in Chicago, and the John H. Stroger Jr Hospital of Cook County, also in Chicago. We also propose a study design to test the hypothesis that resource limitations will not affect an individual facility’s de jure care models in the case of first-presentation advanced uveal melanoma.
144. Global Child Mental Health Research: Time for the Children

Author(s): Mahi Singh, Andrea Marques, Steven Weine

Department of Psychiatry

ABSTRACT

Goal: To advance global child mental health research, a satellite of leading researchers was convened at the Consortium of Universities for Global Health (CUGH) by the University of Illinois at Chicago Center for Global Health and the National Institute of Mental Health.

Method: Leading researchers discussed 1) current mental health interventions to be scaled-up in low- and middle income countries (LMICs) to promote prevention and treatment of psychiatric conditions in children, 2) techniques to increase global awareness and dissemination of these interventions, and 3) knowledge gaps necessitating further inquiry.

Results: We identified multiple child mental health interventions that address children exposed to extreme adversity (i.e., armed conflict, HIV/AIDS in parents, extreme poverty) in LMICs. To scale-up these interventions, researchers should reduce reliance on specialists by training community members, using one treatment for multiple problems, forgoing diagnostic assessment, and building skills for self-management. Researchers should work with policymakers to create and advance bills that include child mental health, use the media to increase public awareness, and work with economists/financers to demonstrate the return on investment for child mental health services. To create sustainability, researchers should build the administrative and research capacities of academic, government, and NGO institutions in LMICs. Key areas for further research include: social drivers of child mental health, implementation quality, and equity of access to child mental health resources.

Conclusion: Child mental health research in LMICs should prioritize developing scalable and sustainable interventions to address child mental health problems amidst social adversity.
**Characteristics of Voluntary Blood Donors in Mekelle, Ethiopia**

**Author(s): Meha Desai, Yibrah Zelelow, Gelila Goba, Erin Cavanaugh**

Department of Obstetrics and Gynecology

**ABSTRACT**

In 2017, the voluntary nonremunerated blood donation (VNRBD) rate in Ethiopia was 1.64 units/1000 people, far below the WHO recommendation of 10 units/1000 people. Little information exists about current donors in Ethiopia and their motivations for donating. The aim of this study was to examine new and repeat voluntary donor characteristics in Mekelle, an urban city in northern Ethiopia, with the hope of identifying ways to increase the active donor pool. A retrospective review of voluntary donor data logged in Mekelle from November 2017 to April 2018 was performed. For each characteristic “age, sex, occupation, and collection site” the proportion of new and repeat donors was determined. Examination of 4738 donations found 68.8% new and 30.9% repeat donors. Most donors were aged 19-24, with 48.6% between 20-24 (33.5% of those being repeat donors). Male donors comprised 66% of donations (28.9% repeat). Students provided 60.2% (32.7% repeat), while civil servants provided 15.4% (39.4% repeat). 93.6% of donations were at a mobile site (28.5% repeat). Of the 6.4% donations at the central blood bank, 67.2% were from repeat donors. Our data suggests great response of students and civil servants to known targeted mobile campaigns. However, this may be unintentionally limiting recruitment of other eligible cohorts. Additionally, the central blood bank having a majority of repeat donors suggests limited access and/or public knowledge about its purpose and location. Future recruitment efforts should therefore focus on expansion of mobile campaigns and exploration of awareness and education about the central blood bank.
146. Core decompression of the femoral head (CDFH) extends the lifetime of joint replacements in Avascular Necrosis of the Femoral Head (AVNFH)

Author(s): Diego Barragan Echenique, Anshum Sood, Michael Patteta, Awais Hussain, Mark Gonzales,

Department of Orthopaedics

ABSTRACT

INTRODUCTION: Total hip arthroplasty (THA) is the definite treatment of AVNFH, however the disease presents in young patients who outlive the life of their prosthesis. Consequently, CDFH was developed as a conservative treatment to relieve symptoms and extend native joint lifespan. In this study we investigate the efficacy of CDFH at native joint lifespan prolongation.

METHODS: We performed a retrospective study looking at 57 hips in a total of 45 patients who underwent CDFH, after clinical diagnosis of AVNFH. We recorded Steinburg Classification, sickle cell disease, rheumatologic disease, ongoing alcohol use, or chronic corticosteroid use as possible risk factors of reduced joint lifespan after CDFH. Statistical analysis using Kaplan Meyer survival curves and cox proportional hazards ratios were utilized to estimate the median survival age of joints until conversion to THA and to establish the hazard ratio of the respective risk factors.

RESULTS: In total, 25 of the original 57 hips needed to be converted to THA over the entire course of the study (43.7%). The estimated median survival of the native hip following core decompression was 5.54 years (95% CI: 3.45 - 7.62) Steinburg classification and age were the only factors that reduced joint lifespan after CDFH (p<0.001 and p<0.003 respectively).

DISCUSSION: The study was limited by a small sample size and early loss of f/u. However, the study matches with previous studies that state that CDFH for AVNFH significantly prolongs native joint lifespan. Additionally, it illustrates that early intervention in younger patients is more successful.
147. TARGETED EPGENOME EDITING PREVENTS BEHAVIORAL AND MOLECULAR CHANGES INDUCED BY ADOLESCENT ALCOHOL EXPOSURE IN ADULTHOOD

Author(s): Peyton Bohnsack, Huaibo Zhang, Donna He, Amy Lasek, Subhash Pandey

Department of Psychiatry

ABSTRACT

Consumption of alcohol during adolescence increases the likelihood 5-7 times to develop an alcohol use disorder (AUD) later in life and having a comorbid psychiatric disorder (e.g. depression and anxiety). Adolescent alcohol exposure causes epigenetic changes that persist until adulthood, including decreases in histone acetylation which drive decreased gene expression. CRISPR Cas9 technology has revolutionized the ability to make targeted changes to the epigenome. Here, we utilized a Cas9 that has been mutated to be catalytically inactive, so it doesn’t cut DNA and attached the histone acetylation transferase domain of P300 to it (dCas9-P300) as a method to make targeted epigenetic changes at the Arc SARE site. We hypothesize that by restoring H3K27Ac to this important locus we will be able to reverse the decreased Arc expression and anxiety-like behavior in adulthood caused by adolescent alcohol exposure. Our results indicate that infusion of dCas9-P300 and sgRNAs that target the ARC SARE into the central nucleus of the amygdala prevents decreased Arc expression, decreased H3K27Ac associated with the Arc SARE site, and anxiety-like behavior in a light dark box assay. Our results demonstrate the role of Arc SARE as a key epigenetic location that is dysregulated after adolescent alcohol exposure in adulthood which supports our previous studies in humans who began drinking before the age of 25. Further, these studies indicate the utility of using dCas9 platforms to both modulate and probe different epigenetic modifications in order to determine their role on higher level functions, including gene expression and behavior.
148. A Lifespan Approach to Examining Differences in Amygdala Volume Among Individuals with and without Social and Generalized Anxiety Disorders

Author(s): Jennifer Suor, Jagan Jimmy, Christopher Monk, K. Luan Phan, Katie Burkhouse,

Department of Psychiatry

ABSTRACT

Background. Structural differences in the amygdala (AMG) are implicated in anxiety and observed among individuals with generalized (GAD) and social anxiety (SAD) disorders. Findings are mixed, perhaps because studies rarely examine differences between GAD and SAD, test comorbidity, or age-related effects. We tested AMG volume differences among a sample of adults and youth with/without SAD and GAD. Method. 242 participants (ages 7-60) underwent an MRI scan, and completed diagnostic and anxiety symptom assessments. Groups were formed from diagnostic interviews: Typically developing (TD; n = 91); GAD (n = 54); SAD (n = 35); and comorbid SAD/GAD (n = 62). We used ANOCA to test group and age x group interaction effects in relation to AMG size. Regression was performed to examine associations between anxiety symptoms and AMG volume. Results. SAD and comorbid SAD/GAD groups exhibited increased AMG volume compared to the TD group. GAD and TD groups did not exhibit differences in AMG size. SAD group, but not the comorbid SAD/GAD group, displayed greater right AMG size relative to the GAD group. SAD and comorbid SAD/GAD groups did not differ from the GAD group in left AMG volume. SAD and SAD/GAD groups did not demonstrate differences in AMG size. The age x group interaction was not significant. Greater social anxiety symptom severity predicted enlarged AMG volume. Conclusions. Enlarged AMG volume could be a specific biomarker for SAD risk across the lifespan, even when GAD co-occurs. We will discuss the implications for earlier risk identification and neural treatment targets for SAD.
149. Anti-VEGF-mediated closure of a chronically breached endothelial cell barrier involves antagonism of the RAAS pathway

Author(s): Yueru Li

Department of Ophthalmology and Visual Sciences

ABSTRACT

The goal of this project is to elucidate the mechanism by which anti-VEGF overcomes chronic, VEGF-driven leakage, which is quintessential to diabetic retinopathy (DR). We used electric cell-substrate impedance sensing (ECIS) to quantify the barrier function of cultured, primary human retinal endothelial cells (HRECs). While VEGF maximally opened the barrier within 40 min, increasing the subsequent duration of exposure to VEGF resulted in a corresponding increase in the time it took anti-VEGF to re-close the barrier. Furthermore, anti-VEGF-mediated closure of the barrier to much longer than needed to reverse post-translational modifications (such as phosphorylation of VEGFR2). These results suggested that posttranscriptional changes do not fully account for how VEGF/anti-VEGF govern the barrier in a chronic setting.

Pre-clinical and clinical studies demonstrate that the renin angiotensin aldosterone system (RAAS) pathway contributes to leakage of retinal vessels and progression of DR. Thus, we hypothesized anti-VEGF curbs leakage of retinal vessels by antagonizing the VEGF-activated RAAS pathway. Our in vitro findings with HRECs strongly support this hypothesis. VEGF increased expression of ACE and AGTR1 (RAAS components), and anti-VEGF reversed these changes in gene expression. Furthermore, either ACE or AGTR1 antagonists attenuated VEGF-induced permeability. Finally, adding purified ACE or angiotensin II significantly reduced the ability of anti-VEGF to re-close the barrier that was opened with VEGF. We conclude that suppression of the RAAS pathway is part of the mechanism by which anti-VEGF closes the endothelial barrier that has been chronically breached with VEGF.
HEPATOCYTE-SPECIFIC PPARgamma CONTRIBUTES TO THE DEVELOPMENT OF NON-ALCOHOLIC STEATOHEPATITIS (NASH) IN MALE MICE.

Author(s): Samuel Lee, Carolina Pusec, Gregory Norris, Grace Guzman, Brian Layden, Jose Cordoba-Chacon

Department of Medicine

ABSTRACT

The PPARg agonists, thiazolidinediones (TZD), are insulin sensitizers that could reverse NASH. However, given that hepatic PPARg promotes steatosis in mice and its expression is increased in murine and human NASH, we hypothesize that hepatocyte-specific PPARg contributes to the progression of NASH. Control and adult-onset hepatocyte-specific PPAR knockout (Pparg Hep) mice were fed a high-fat, -cholesterol, and “fructose (HFCF) diet for 24 weeks to induce NASH. Also, control and Pparg”Hep mice were generated in mice that had been fed a HFCF diet for 24 weeks. A subset of these mice was switched to a HFCF diet supplemented with TZD for 8 weeks to reverse NASH. Pparg”Hep mice showed reduced liver weight, steatosis, ALT, NAS score, and bridging fibrosis. The analysis of RNAseq data indicated that the HFCF diet upregulated pathways associated with fibrosis and inflammation and downregulated those associated with mitochondria metabolism. Interestingly, Pparg”Hep mice had reduced expression of pro-inflammatory and pro-fibrogenic genes, and markers associated with mitophagy, but had increased mitochondrial DNA as compared with HFCF-fed controls. TZD treatment improved insulin sensitivity in the HFCF-fed control and Pparg”Hep mice; however, the TZD-treated Pparg”Hep mice had impaired glucose tolerance compared to controls. Interestingly, TZD-treated Pparg”Hep showed significantly reduced liver weight, steatosis, ALT, and expression of profibrogenic genes compared with the TZD-treated control mice. In sum, hepatocyte-specific PPARg contributes to the progression of NASH and its activation reduces the therapeutic effect of TZD in NASH in mice.
151. Smooth muscle cell specific Caveolin-1 deficiency enhances the progression of pulmonary hypertension

Author(s): Haibin Li

Department of Medicine

ABSTRACT

Pulmonary hypertension (PH) is a chronic pulmonary vascular disease characterized by pulmonary arterial remodeling (PVR) and elevated pulmonary vascular resistance that eventually leads to right heart failure and death. Caveolin-1 (Cav-1) has been reported to play a role in the development of PH, however the role of smooth muscle specific Cav-1 in PH is still controversial. To address this question, we generated smooth muscle cell specific Cav-1 deficient (Cav-1flox/flox MHC Cre+) mice. In three weeks after tamoxifen injections, the mice were exposed to normoxia or 10% FiO2 for four weeks. Right ventricular systolic pressure (RVSP), right ventricle: left ventricle + septum (RV/LV+S) weight ratio and pulmonary artery remodeling via Aperio image software were measured. Pulmonary artery smooth muscle cells (PASMCs) isolated from Cav-1-/- and WT siblings were used to study cell proliferation via BrdU assays. Strategies of silencing or overexpressing Cav-1 via adenovirus system were employed to examine their effect on hPASMC proliferation. Under normoxic exposure, RVSP and RVH did not differ in Cav-1flox/flox MHC Cre+ mice between tamoxifen-induced and vehicle groups. After hypoxic exposure, the mice with tamoxifen induction developed significantly elevated RVSP, RVH and pulmonary vascular remodeling, compared to their vehicle group. The PASMCs isolated from Cav-1-/- mice are more proliferative compared to wild type (WT) mice. In vitro silencing of Cav-1 in hPASMC promoted cell proliferation and overexpressing of Cav-1 inhibited cell proliferation. Taken together, our study shows that smooth muscle cell specific Cav-1 plays a significant role in the progression of PH.
Sarcomere disassembly after unloading is regulated by ubiquitination and acetylation of CapZ and alpha-actinin

Author(s): Christopher Solis, Brenda Russell

Department of Physiology and Biophysics

ABSTRACT

Assembly and disassembly of sarcomeres occurs to adjust muscle mass to altered mechanical demand. In the heart, hypertrophic cardiomyopathy results from myofibrillar assembly controlled by post-translational modification of proteins directed by signaling pathways. More is known about assembly on loading than disassembly on unloading. Here, the hypothesis tested is that unloading of mechanical forces affects acetylation (Ac) and ubiquitination (Ub) of the actin-binding proteins, CapZ and alpha-actinin. Blebbistatin (1 micromolar) decreased myocyte contractility in rat ventricular myocytes (NRVMs) and caused significant sarcomere disassembly by 6 h and ~70% atrophy by 24 h. Ac and Ub levels in alpha-actinin over the 24h unloading time period were determined by α-actinin immunoprecipitation (IP) western blots using K48 oligo-Ub and acetyl-lysine antibodies, respectively. Ac decreased by 24 h blebbistatin treatment compared to untreated NRVMs. Ac and Ub in the Z-discs were quantified on immunofluorescent images. The Z-discs colocalized oligo-Ub (K-48 oligo-Ub linkage) and Ac in untreated samples; this Z-disc localization of Ub and Ac was diminished with blebbistatin. Fluorescence Recovery after Photobleaching (FRAP) measured the dynamics of alpha-actinin after reduced cell tension. FRAP assays showed that the dynamics of alpha-actinin-YFP localized in the Z-discs decreased with blebbistatin. Similar findings with CapZ FRAP were found with unloading, and IP experiments are ongoing. Overall, results suggest sarcomere assembly is regulated by mechanical forces and signaling pathways involving Ac and Ub of myofibrillar proteins. It is likely that Ac is responsible for reducing the rate of Ub and subsequent degradation in atrophy. These findings could have consequences for cardiac heart disease with abnormal sarcomeric proteostasis. Funded by NIH HL62426.
153. tRNA queuosine modification enzyme modulates the growth and microbiome recruitment to breast tumors

Author(s): Jilei Zhang, Rong Lu, Yongguo Zhang, Żaneta Matuszek, Yinglin Xia, Tao Pan, Jun Sun

Department of Medicine

ABSTRACT

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Background: Transfer RNA (tRNA) queuosine (Q)-modifications occur specifically in 4 cellular tRNAs at the wobble anticodon position. tRNA Q-modification in human cells depends on the gut microbiome because the microbiome product queuine is required for its installation by the enzyme QTRT1 encoded in the human genome. Although tRNA Q-modification has been studied a long time regarding its properties in decoding and tRNA fragment generation, how QTRT1 affects tumorigenesis is still poorly understood.

Methods: We generated single clones of QTRT1-knockout breast cancer MCF7 cells using Double Nickase Plasmid. The impacts of QTRT1-deletion on cell proliferation and migration in vitro were evaluated using cell culture, while the regulations on tumor growth in vivo were evaluated using xenograft BALB/c nude mouse model.

Results: We found that QTRT1 completely deleted from human breast cancer MCF7 cells could change the functions of regulation genes which are critical in cell proliferation, tight junction formation, and migration in human breast cancer cells in vitro and a breast tumor mouse model in vivo. We also found evidence that microbiome was involved in the breast cancer development in vivo.

Conclusions: Our results demonstrate that microbiome-dependent tRNA Q modifications likely play a critical role in breast cancer development.
154. Development of Genetically-tailored Porcine Models of Hepatocellular Carcinoma

Author(s): Lobna Elkhadragy, Kyle Schachtschneider, Ron Gaba, Lawrence Schook, Hanna Chen

Department of Radiology

ABSTRACT

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is an aggressive disease with low rates of response to treatment at advanced stages. Animal models that recapitulate human HCC are necessary for preclinical assessment of novel therapeutic strategies. Here we aim to generate clinically-relevant porcine models of HCC by using the Oncopig, a transgenic pig that encodes Cre recombinase-inducible TP53-R167H and KRAS-G12D oncogenic proteins. Porcine HCC cells were developed by in vitro transformation of hepatocytes isolated from 15 Oncopigs. HCC cells were autologously injected into 6 subcutaneous (SQ) sites in each Oncopig. SQ tumors measuring 1-2 cm developed within 2 weeks at a success rate of about 80%. Two weeks later, the SQ tumors were excised and engrafted autologously in the liver. Intrahepatic masses were detected by ultrasound and CT scan in two Oncopigs. The SQ and intrahepatic tumors were histologically characterized as HCC. Next, we developed genetically modified HCC lines that can be implanted in Oncopigs to form HCC tumors with different mutational profiles. CRISPR-Cas9 was used to knockout genes in Oncopig HCC cells including ARID1A, KRAS-G12D, and TP53-R167H. Single cell clones with gene knockout were successfully isolated and functionally characterized. Knockout of TP53-R167H decreased cell proliferation, whereas knockout of ARID1A increased Oncopig HCC cell proliferation. Furthermore, Oncopig HCC cells with 97% ARID1A disruption formed a tumor upon autologous SQ injection. To conclude, we have developed intrahepatic HCC tumors in pigs, and demonstrated the feasibility of utilizing the Oncopig as a platform for generating genetically-tailored HCC tumors.
155. Sedentary Behavior and Longitudinal Changes in Kidney Function in US Hispanics/Latinos: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

Author(s): Mary Hannan, Ana Ricardo, Jianwen Cai, Nora Franceschini, Robert Kaplan, James Lash

Department of Medicine

ABSTRACT

Introduction: Sedentary behavior increases cardiovascular risk due to detrimental effects on blood pressure, vascular function, and glucose metabolism. U.S. Hispanics/Latinos have a high prevalence of sedentary behavior and a large burden of chronic kidney disease (CKD). Therefore, we evaluated the association between sedentary behavior and changes in kidney function over time.

Methods: We used data from the HCHS/SOL, a community-based cohort of self-identified Hispanic/Latino adults from diverse backgrounds in the U.S. This study includes 11181 adults who underwent one-week accelerometry at Visit 1 and completed Visit 2. Linear regression was used to assess the association of sedentary time with change in eGFR and urine albumin-to-creatinine ratio (ACR), and Poisson regression with robust variance was used to estimate the association with rate of incident CKD (composite of either development of eGFR <60ml/min/1.73m2 with decline in eGFR 1 ml/min/year, or ACR 30 mg/g), adjusted for covariates and time elapsed between visits.

Results: At baseline, mean age was 42.2 years, 51.4% women, mean sedentary time was 11.8 hours, mean eGFR was 106.1mL/min, and median ACR 6.7mg/g. After median follow-up of 5.9 years, the average decline in eGFR was 0.8ml/min/year and the average change in ACR was 0.3mg/g/year. In fully adjusted models, individuals with higher sedentary time experienced a greater eGFR decline. Sedentary time was not significantly associated with change in ACR or incident CKD.

Conclusion: Sedentary behavior may be associated with a decline in kidney function in U.S. Hispanics/Latinos, which may have important implications for prevention of kidney disease in this population.
ABSTRACT

Background: Although adolescent depression carries a high burden of disease worldwide, few scalable depression interventions target adolescents in primary care. We explore the long-term effects of CATCH-IT (Competent Adulthood Transition with Cognitive Behavioral Humanistic and Interpersonal Training) compared to a general health education (HE) program in a multicenter randomized clinical trial with 24 month follow-up.

Methods: We randomized 369 adolescents (Mean [SD] age= 15.4 [1.5] with subsyndromal and/or history of depression with a prior DSR3 (62%) and DSR4 (40%). Participants were assessed up to 24 months.

Results: In intention to treat (ITT) analyses, the hazard ratio favoring CATCH-IT for first depressive episode was not statistically significant at 24 months (HR=0.87, 95% CI, 0.52, 1.47, p=0.61). Per protocol 2 (2 modules completed) analysis favored CATCH-IT over HE at 6 months (HR=0.41; 95% CI, 0.17, 0.99, p=0.47), but results attenuated at 12 months (HR=0.65, 95% CI, 0.34, 1.21, p-value=0.17) and similarly at 24 months (HR=0.71, 95% CI, 0.41, 1.23, p=0.22). At 6 months, adolescents with higher baseline CES-D10 scores showed a stronger effect of CATCH-IT on time to event, but this effect was not seen at 24 months. Moderated analyses showed preventive benefits from CATCH-IT in adolescents with lower baseline levels of hopelessness (p=0.04) and higher baseline levels of paternal monitoring (p=0.046).

Conclusion: The incidence of depressive episodes was lower than expected for a high risk sample in CATCH-IT and HE, suggesting protective elements common to both interventions. These findings suggest several benefits to investing in internet based telehealth systems for at-risk adolescents.
157. Enhancing Neurogenesis may Rescue Cognitive Impairments in Alzheimer's disease

Author(s): Rachana Mishra, Muskan Gupta, Kyra Lauren Lopez, Orly Lazarov,
Department of Anatomy and Cell Biology

ABSTRACT

Alzheimer’s disease (AD) is characterized by progressive loss of memory and cognitive function. However, the mechanism underlying memory loss is not fully understood. The entorhinal-hippocampal circuitry is particularly vulnerable in AD. The dentate gyrus of the hippocampus plays a unique role as a neurogenic niche, where new neurons born and get incorporated in its granular cell layer. We have shown previously that hippocampal-neurogenesis is impaired in mouse models and AD patients. Thus, we hypothesized that impaired neurogenesis compromises learning and memory in AD and that enhancing neurogenesis can improve cognitive function. To address this, we bred the 5XFAD mouse model with an inducible Bax knockout and Nestin-driven CreER mice (NestinCreERT2; Baxfl/fl; 5XFAD). We show that following tamoxifen-induced recombination, NestinCreERT2; Baxfl/fl; 5XFAD mice have significantly more new neurons compared to corn-treated NestinCreERT2; Baxfl/fl; 5XFAD mice. Importantly, tamoxifen-treated NestinCreERT2; Baxfl/fl; 5XFAD mice exhibited significantly better spatial recognition in contextual fear conditioning test, compared to the impaired corn-treated NestinCreERT2; Baxfl/fl; 5XFAD mice. Using virus-mediated engram labelling strategy, a cocktail of AAV9-cFos-tTA and AAV9-TRE-ChR2-eYFP, we show that the number of new neurons that get recruited into the memory circuit is significantly increased in tamoxifen-treated NestinCreERT2; Baxfl/fl; 5XFAD. Importantly, the relative proportion of new neurons in the engram is also increased in these animals, suggesting a direct role of new neurons in the spatial recognition-memory formation. This is the first report showing that new neurons play a central role in memory formation in AD and that enhanced neurogenesis can ameliorate cognitive deficits in AD.
158. The role of HOIL1 in type 2 intestinal inflammation

Author(s): Matt Wood, Donna MacDuff

Department of Microbiology and Immunology

ABSTRACT

Genetic mutations in the HOIL1 gene result in a lethal condition consisting of autoinflammation, immunodeficiency and inflammatory bowel disease-like symptoms in humans. We observed that HOIL1 is essential for intestinal homeostasis in mice, even in the absence of infection. The ileum of Hoil1−/− mice showed cellular abnormalities and cytokine production characteristic of type 2 inflammation. We identified the lamina propria as the major source of type 2 cytokines, and flow cytometry analysis revealed excessive IL-13 production by T cells in Hoil1−/− mice. However, Rag1−/−;Hoi1−/− mice, lacking T cells, also exhibited type 2 inflammation, suggesting a complementary role for type 2 innate lymphoid cells. We detected elevated mRNA expression of type 2 inducing cytokine, IL25, which will aid us in identifying the cell types that require HOIL1 to regulate type 2 inflammation. Furthermore, antibiotic treatment partially relieved this inflammation indicating commensal microbes as an initiating factor. Further characterization of the mechanism by which HOIL1 regulates type 2 inflammation will advance our understanding of intestinal homeostasis and inflammatory disorders, and may lead to the identification of new targets for treatment.
159. The Age-Dependent Effect of APOE and Sex on Neuroinflammation and Aβ Deposition in Alzheimer's Disease Transgenic Mouse Model

Author(s): Deebika Balu, Allison Hansen, Austin Nguyen, Efstathia Loukenas, Jason York, Mary Jo LaDu

Department of Anatomy and Cell Biology

ABSTRACT

While age is the greatest risk factor for Alzheimer's disease (AD), APOE4 is the greatest genetic risk factor, increasing risk up to 15-fold compared to the common APOE3 and the rare but protective APOE2. APOE4 is associated with the accelerated accumulation of amyloid-beta (A-beta) peptide, which aggregate to form both amyloid plaques and soluble oligomers of A-beta. Recently, studies have shown that female APOE4 carriers have a higher risk for developing AD than male APOE4 carriers. In our novel EFAD transgenic mice, expressing human APOE and overexpressing human A-beta42, we have demonstrated that male 6-month old (M) E4FAD mice exhibit an increase in neuroinflammation and A-beta deposition. However, the effects of both age and sex, two important AD risk factors that modulate pathology with age in EFAD mice, have not yet been characterized. Thus, male and female EFAD mice aged 4M to 18M were compared for measures of AD pathology that included neuroinflammation and A-beta pathology. The Kaplan-Meier curves from our EFAD mice include sex and APOE genotype, demonstrate that female sex is dominant compared to APOE4. With age, the regional progression of pathology begins in the hippocampus, specifically the subiculum, spreading to the cortex and then the thalamus. Both neuroinflammation and A-beta pathology increase in E4FAD > E3FAD and are consistently greater in females compared to males in both E3FAD and E4FAD mice. Because EFAD mice develop pathology dependent on age, sex, and APOE genotype, they are a novel preclinical AD mouse model that mirror risk factor-induced pathology in humans.
Fungal siderophores derived from gut fungi or mouse chow promote Salmonella enterica serovar Typhimurium growth

Author(s): William Santus, Kaitlyn Kiernan, Jason Devlin, Judith Behnsen

Department of Microbiology and Immunology

ABSTRACT

Salmonella enterica serovar Typhimurium (Salmonella) is a leading cause of gastrointestinal infection worldwide. During Salmonella infection, the host restricts microbial access to vital micronutrients, such as iron. Bacteria and fungi have overcome this host response by evolving siderophores, secreted small molecules able to chelate iron. Salmonella produces two siderophores and their cognate receptors, but expresses three additional receptors for a variety of other siderophores. Fungal siderophores are acquired through the receptors FhuA and FhuE. We demonstrate that Salmonella can use purified fungal siderophores as a sole source of iron. We also grew Salmonella in the presence of siderophore-producing fungi commonly found as part of the commensal fungal gut microbiota. Salmonella strains able to use fungal siderophores showed competitive advantage over strains unable to use fungal siderophores. We hypothesize that Salmonella can use fungal siderophores during pathogenesis and identified two potential sources: fungi residing in the gut, and fungal siderophores present in food. We demonstrated in vitro that regular mouse chow confers a competitive advantage to Salmonella strains expressing the genes fhuA and fhuE. Regular mouse chow likely contains siderophores from agricultural fungal pathogens. The competitive advantage was lost when a non-plant-based purified diet was used. We are currently testing the relative contribution of siderophores produced by the mycobiota and food-derived fungal siderophores to Salmonella pathogenesis. In summary, our results show that inter-kingdom siderophore piracy helps Salmonella to grow in iron limited conditions that mimic conditions found in an inflamed gut.
161. EPIGENETIC REGULATION OF GABAAR RECEPTOR SUBUNITS AND NEUROSTEROID BIOSYNTHESIS IN SUBJECTS WITH ALCOHOL USE DISORDER (AUD)

Author(s): Eleonora Gatta, Alessandro Guidotti, Dennis R. Grayson, Dario Aspesi, Subhash C. Pandey, Graziano Pinns

Department of Psychiatry

ABSTRACT

The extrasynaptic GABAAR-mediated inhibition is enhanced by allopregnanolone and its equipotent GABAergic isomer, pregnanolone. The biosynthesis of these neurosteroids is initiated by cholesterol translocation into the mitochondria by the 18 kDa translocator protein (TSPO). Ultimately, 5alpha-reductase type 1 (5alpha-R1) and 3alpha-HSD convert progesterone into allopregnanolone. Previous work from our group showed reduced mRNA and protein levels of delta subunit in the cerebellum of AUD subjects suggesting an impaired sensitivity of GABAAR to neurosteroids. However, the long-term effects of alcohol exposure on neurosteroid biosynthesis and its consequences on GABAergic neurotransmission in the cerebellum of individuals with AUD remain underinvestigated.

In a cohort of postmortem brains from 20 male controls and AUD subjects, we determined the mRNA levels of GABAAR subunits and neurosteroid biosynthetic enzymes. DNA methylation levels were assessed by MeDIP. Protein levels were determined by Western blot and neurosteroid concentrations were quantified by GC-MS.

GABAAR alpha2 mRNA and protein expression were reduced in the cerebellum of AUD subjects. These changes were associated with increased DNA methylation levels at the alpha2 and delta promoter region. Neurosteroid biosynthesis was also altered with reduced mRNA expression of TSPO, 5alpha-R1 and 3alpha-HSD. Increased DNA methylation levels were observed at the promoter region of 3alpha-HSD. As expected, this resulted in marked reduced levels of allopregnanolone and pregnanolone in the cerebellum.

Given the key role of allopregnanolone and pregnanolone in the fine-tuning of extrasynaptic GABAAR-mediated inhibition, our data suggest that alcohol-induced impairments in GABAergic neurotransmission might be profoundly impacted by reduced neurosteroidogenesis.

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162. Δ⁹-Tetrahydrocannabinol Enhances Fronto-Striatal Resting State Functional Connectivity

Author(s): Natania Crane, K. Luan Phan

Department of Psychiatry

ABSTRACT

Background: Preliminary evidence indicates the main psychoactive component of cannabis, Delta-9-Tetrahydrocannabinol (THC), activates brain reward circuitry, especially the nucleus accumbens (NAcc) and medial prefrontal cortex (mPFC). However, few studies have examined this in humans. In this study, we examined if an acute dose of THC altered functional connectivity (FC) between the NAcc and the mPFC among healthy young adults.

Methods: Participants received THC (n=24) or placebo (n=22) in a double-blind, randomized, between-subject design. Participants completed self-report measures of euphoria and drug-liking throughout the visit. Approximately 120 minutes after drug administration, participants completed resting state functional MRI (rs-fMRI) scan. We utilized seed-based FC of the NAcc to the whole brain.

Results: THC increased FC between the right NAcc and the right mPFC, the right dorsomedial prefrontal cortex (dmPFC), and the right angular gyrus compared to placebo. THC increased FC between the left NAcc and the left lingual gyrus. THC also increased subjective euphoria ratings, but not subjective drug liking compared to placebo. Higher ratings of euphoria were related to greater right NAcc-dmPFC connectivity for the THC group, but not for the placebo group.

Conclusion: This is one of the first studies to examine how THC alters rs-fMRI in healthy young adults. We found that THC increases NAcc-mPFC FC, regions implicated in reward, compared to placebo. In addition, THC increased subjective euphoria ratings, which were positively associated with NAcc-dmPFC FC. Overall, our findings suggest that THC produces subjective and neural reward responses that may contribute to the rewarding, reinforcing properties of cannabis.
OLIGOMERIC Aβ in Human Plasma as a Mechanistic Biomarker for Alzheimer's Disease

Author(s): Giuseppe Scesa, Giuseppe Scesa, Ana Valencia-Olvera, Linda Van Eldik, Craig Atwood, Mary Jo LaDu

Department of Anatomy and Cell Biology

ABSTRACT

Alzheimer's disease (AD) is a fatal neurodegenerative disease that is the 6th leading cause of death in the United States with no cure and few palliative treatments. Currently, there is no preventative treatment, and even if such a therapeutic could be identified, without a predictive biomarker, a target population for treatment cannot be determined. Although the mechanism remains unclear, AD is caused by increased levels of the amyloid-beta peptide (A-beta), which aggregates to form both amyloid plaques and soluble oligomeric Aβ (oA-beta), the latter considered a proximal neurotoxin. We believe that levels of oA-beta in human plasma are a prognostic biomarker, and have developed and licensed a method for their detection (LOD<100pMol). While age is the greatest risk factor for AD, APOE4 is the greatest genetic risk factor, increasing risk up to 15-fold compared to the more common APOE3. Importantly, female APOE4 carriers have an increased risk for AD compared to male APOE4 carriers. The goal of this study is to validate oA-beta in human plasma as a mechanistic and predictive biomarker for AD. Key to the success of this project is the stratification of both control and AD patients by sex within APOE genotype, with the results that plasma oA-beta levels are: Female APOE4 > Male APOE4 > Female APOE3 > Male APOE3. This response is observed in two human post-mortem cohorts and mirrors AD risk in the human population. We now seek to threshold oA-beta levels using longitudinal and human AD trial data to further establish prognostic potential.
164. Using scRNA-seq to target drug resistance in Non-Small Cell Lung Cancer (NSCLC)

Author(s): Alexandre F. Aissa, Majd M. Ariss, Abul B.M.M.K. Islam, Cammille Go, Alexandra E. Rader1, Ryan D. Conrardy, Alexa Gaida, Odile David, Klara Valyi-Nagi, Mary M. Pasquinelli, Lawrence E. Feldman, Maxim Frolov, Elizaveta Benevolenskaya

Department of Biochemistry and Molecular Genetics

ABSTRACT

Cancer therapies that target oncogenic driver mutations nearly eradicates tumors, but the diversity of malignant and microenvironmental populations within a single tumor can mitigate the success of the treatment. Thus, efforts to dissect intratumoral heterogeneity is crucial to the rational application of targeted therapies. We performed single cell RNA-sequencing (scRNA-seq) to identify differences in individual cells underlying drug resistance. We analyzed the Non-Small Cell Lung Cancer (NSCLC) cell lines PC9 and HCC827, both with a mutation in the epidermal growth factor receptor (EGFR), and three patient NSCLC tumors obtained from the UIC hospital. The scRNA-seq analysis showed that both PC9 and HCC827 erlotinib resistant cells are highly heterogeneous and represent several distinct clusters, suggesting that one should look for additional inhibitors to impair the growth of all cell populations. Based on the scRNA-seq data, we designed drugs that inhibit large sets of cluster-specific genes and were effective in inhibiting survival of erlotinib resistant cells. Using the two cell line models, we have also identified regulatory network of transcription factors, biological process and molecular pathways. This informed us about processes which would be potentially involved in emerging drug resistance in the NSCLC patient who is currently undergoing treatment at the UIC hospital. In conclusion, scRNA-seq is a powerful tool to identify molecular changes in cells coping with drug perturbation. Our preliminary analysis showed that NSCLC tumors contain different populations of cancer cells. scRNA-seq offers unprecedented opportunity for identification of cancer cell vulnerabilities in patient tumor samples. The results of this project may guide personalized management in improving design and selection of specific drug combinations in cancer therapies.
165. The Role of Social Determinants of Health in Sickle Cell Disease Treatment Center Affiliation Status in a Multi-center Consortium in the United States

Author(s): Gustavo Mendez, Judith Nocek, Michael Berbaum, Lewis L Hsu, Victor Gordeuk,

Department of Medicine

ABSTRACT

Background: The NIH Sickle Cell Disease Implementation Consortium (SCDIC) of 8 comprehensive sickle cell centers, developed a multi-center patient registry. To explore treatment center affiliation status of the registry patients, the working definition for an unaffiliated patient developed by the SCDIC is: having had no appointments with a SCD expert in the non-acute setting in 2 years. The socioeconomic distress of SCD patients was examined with the distressed communities index (DCI), which is publicly available from the Economic Innovation Group, Washington, DC (EIG.org). DCI ranges from 0 to 100, and the fifth quintile (80-100), is most distressed.

Hypothesis: Unaffiliated SCD patients are more likely than affiliated patients to live in zip codes with high DCI.

Methods: The registry cohort includes patients 15-45 years old. A retrospective review of the patient’s medical chart was used to find zip codes, patient demographics, insurance status, SCD complications and co-morbidities and specialty care services utilization to determine affiliation. EIG provided zip codes with DCI for the year 2018.

Results: Of 2389 patients in the SCDIC Registry who met the inclusion criteria (56.6% female), 287 (12.0%) met the definition for unaffiliated (57.6% female). Unaffiliated patients were older than affiliated patients (mean age at enrollment 30.4 years vs 27.7 years, p<.0001) and had significantly fewer complications and co-morbidities than affiliated patients (p<.0001). The 8 SCDIC sites included urban and suburban populations and had mean DCI of 47 to 75. There was no significant difference in DCI between affiliated and unaffiliated 39% and 38%, respectively, residing in DCI quintile (80-100).
A Correlative Lightsheet and Electron Microscopy (CLEM) approach to define the adult hematopoietic stem cell niche

Author(s): Sobhika Agarwala, Keun-Young Kim, Sebastien Phan, Saeyeon Ju, Mark Ellisman, Owen Tamplin

Department of Pharmacology

ABSTRACT

Hematopoietic stem and progenitor cells (HSPCs) that originate from the hemogenic endothelium in the dorsal aorta finally home and engraft within the fetal bone marrow (BM) and remain quiescent until they expand and differentiate to supplement the blood system. While it is known that HSPCs receive signal from surrounding niche cells, the ultrastructure of this complex microenvironment is not well defined, as current imaging technology does not allow direct visualization of the fetal BM niche. Zebrafish have a similar hematopoietic ontogeny to mammals, and because the embryos are transparent, intrinsic HSPC interactions with the niche can be directly visualized. To track HSPCs during colonization of the presumptive adult niche, the kidney marrow (KM), we used our previously validated HSPC-specific transgenic reporter lines (Runx:GFP and Runx:mCherry). In 5 days post fertilization fixed larvae, we detected ~100 HSPCs/larva. To precisely locate these rare HSPCs within the larger dense KM, we genetically tagged endogenous HSPCs to track them live using lightsheet microscopy, followed by high resolution serial block-face scanning electron microscopy (SBEM) (XY=10.8 nm/pixel, Z=70 nm/pixel). Using this technique, we could visually track single mCherry+ HSPCs, then confirm their exact location in a SBEM dataset with high contrast APEX2 peroxidase label. We found proliferating HSPC clusters within vessel lumens, as well as a novel perivascular niche with quiescent HSPC in a defined cellular assembly. In this perivascular site, a single HSPC was seen to simultaneously contact one mesenchymal stromal cell, multiple endothelial cells, a glial-like cell, and other hematopoietic cells. Our technique can be used as a general approach to identify the ultrastructure of single rare cells within dense tissues by using multiple imaging modalities. Further, we can now identify novel intercellular structures that form between an unperturbed HSPC in its endogenous perivascular niche.
167. Endothelin-1-mediated Drug Resistance in EGFR-mutant NSCLC

Author(s): Ines Pulido, Jeffrey Becker, Agustin Lahoz, Julian Carretero, Takeshi Shimamura,

Department of Surgery

ABSTRACT

EGFR mutant NSCLC tumors are exquisitely sensitive to tyrosine kinase inhibitors, but a mesenchymal phenotype is prevalent in NSCLC cells with transient tolerance or acquired resistance to drug treatments. As EMT consists of multifaceted cellular processes, the exact mechanisms providing the drug resistance remain elusive, underscoring the need for patients with EGFR TKI resistance associated with a mesenchymal phenotype.

Our results demonstrate that EGFR TKI tolerant and resistant NSCLC cells with a mesenchymal phenotype secrete endothelin-1 (EDN1), a potent vasoconstrictor. EDN1 has been implicated in cancer progression and EDN-receptor inhibitors have been evaluated in several clinical trials with disappointing results. The trials were designed to interrupt the EDN1-EDNR axis that contributes to tumor growth. However, EDN1 is a potent vasoconstrictor acting on vascular smooth muscle cells and the impact of EDN1 in modifying tumor microenvironment or contributing to drug resistance has not been evaluated yet.

Here we find that NSCLC tumor cells, after the exposure to TKIs or under hypoxic conditions promote secretion of EDN1. These changes in tumor-associated vasculature affects the efficiency of drug delivery, protecting tumor cells from therapy. Additionally, the ectopic overexpression of EDN1 confers drug resistance and retarded growth in vivo but not in vitro. Furthermore, the depletion of EDN1 or the use of dual-endothelin receptor inhibitor, bosentan, improved drug penetration to the tumors and restored the blood flow. These results suggest a simplistic endogenous, yet previously unrealized, resistant mechanism inherent to a subset of EGFR-positive NSCLC to limit the delivery of therapeutic drugs.
168. Maturation of prefrontal cortical responses to basolateral amygdala inputs during adolescence: regulation by local NMDAR transmission

Author(s): Meagan Auger, Kuei Tseng

Department of Anatomy and Cell Biology

ABSTRACT

Basolateral amygdala (BLA) inputs to the prefrontal cortex (PFC) are involved in the regulation of decision-making, impulse control and affective processing. Past research has suggested that BLA innervation of the PFC is remodeled during adolescence, which may contribute to the adolescent maturation of these cognitive faculties. If so, functional refinement of how the PFC processes inputs from the BLA is likely to occur during adolescence. To test this hypothesis, we conducted local field potential recordings in the PFC and changes in the pattern of responses elicited from the BLA using different frequencies of train stimulation were compared across 4 age groups of rats (postnatal day): P30-37, P40-47, P50-57, and P65-85. Reduced facilitation of PFC responses to 15 Hz BLA stimulation was observed during adolescence in comparison to adults, an effect that was most prevalent before P50. In contrast, adolescents showed blunted suppression of responses to 40 Hz BLA stimulation before P40. We also found that the facilitation of PFC responses to 15 Hz BLA stimulation observed in adult animals was no longer apparent after local NMDAR antagonism, while a GluN2A-specific NMDAR antagonist reduced the level of suppression of PFC responses to 40 Hz stimulation. These results suggest BLA recruitment of excitatory and inhibitory components in the PFC matures over adolescence, with both components being modulated by PFC NMDA receptors. Collectively, these findings point to a novel feature of PFC development during adolescence that may support the dynamic cognitive and emotional changes that occur during this time.
169. N-terminal truncation of cardiac troponin I modifies Ca2+ response in hypertrophic cardiomyopathy sarcomeres and induces alterations in signaling pathways

Author(s): Monika Halas, Chad M. Warren, Jian-Ping Jin, Beata M. Wolska, Pieter P. de Tombe, R. John Solaro

Department of Physiology and Biophysics

ABSTRACT

N-terminal truncated cardiac TnI (cTnI-ND) is a unique form of the inhibitory subunit of troponin complex. Specific restrictive proteolysis removes the N-terminus (aa 1-29) from cardiac troponin I (cTnI), mimicking the effect of PKA phosphorylation sites, and resulting in decreased sarcomere Ca2+-sensitivity. It has been shown that cTnI-ND expressed in hearts is upregulated in pathophysiologic adaptations. In hypertrophic cardiomyopathy (HCM) sarcomere Ca2+-sensitivity is enhanced inducing diastolic abnormalities and remodeling. We tested whether the presence of cTnI-ND in sarcomeres regulated by an HCM mutant could reduce enhanced Ca2+-sensitivity and if phosphorylation affects signaling pathways involved in cardiac function. We investigated an HCM mouse model with a mutation in α-tropomyosin (Tm E180K) compared to the wild type (WT). Fiber bundles were dissected from ventricular papillary muscles. The skinned fibers were incubated in exchange buffer, containing purified troponin complex with either WT cTnI or cTnI-ND. Following exchange, force-pCa measurements were performed. Results showed a significant difference in pCa50 between WT- and cTnI-ND-exchanged fibers in the TM180 transgenic mice model. We also compared transgenic mouse hearts over-expressing cTnI-ND with wild type (WT) controls. In transgenic mice we found 73 proteins with significantly different phosphorylation levels. The 3 top canonical pathways were integrin, protein kinase A, and RhoA. Together our results indicated this modification of cTnI results in not only changes in the Ca2+ response and restoration of sensitivity to WT levels, but also modulation of signaling pathways associated with global cardiac function and adaptation.
Robotic Single Port (SP) TAPP Inguinal Hernia Repair, a Preliminary Report of a Novel Approach

Author(s): Stephan Gruessner, Yevhen Pavelko, Ahmad Nourallah, Roberto Bustos, Alberto Mangano, Francesco Bianco

Department of Surgery

ABSTRACT

Introduction:
Robotic inguinal hernia repairs are the fastest growing robotic surgeries nationwide. The multiport approach has been widely adopted in the surgical community, whereas the robotic single incision approach has encountered limited adoption. This may be due to the extremely flexible and non-endowristed instruments, which can limit the ability to reduce the hernia sac and suture. Due to the reduced triangulation and work space in inguinal hernia repair, the new robotic DaVinci SP platform could allow the application of single access surgery to the treatment of inguinal hernias.

Material and Methods:
Given that this novel technique is not an FDA approved procedure, we operated under IRB protocol 2011-1104. Seven consecutive patients underwent SP transabdominal preperitoneal (TAPP) inguinal hernia repair: 3 bilateral, 1 left, and 3 right. Demographics were collected, and analysis was focused on estimated blood loss (EBL), operative time (OT), length of stay (LOS), peri-, and post-operative complications.

Results:
Sample consisted of 7 men, with an average age of 47.2± 18.4 years (range 19-64). Average BMI was 24.4± 2.6 kg/m2 (range 22.8-28.8). Average OT was 92.9± 5.50 min (range 80-119 min), with console time of 44.7± 11.7 min (range 31-58 min). The EBL was minimal in all patients at 5 mL. There were no transfusions, conversions, additional ports placed, or peri/post-operative complications. All patients were discharged home from recovery after 98.1± 30.6 min (range 54-152 min).

Conclusions:
The application of SP hernia repair is safe/feasible. The new platform allows for optimal exposure, adequate suturing and dissection of the preperitoneal space as well as the hernia sac.
171. Blockade of CCR10-eNOS Interaction Improves Diabetic Wound Healing

Author(s): Zhenlong Chen

Department of Anesthesiology

ABSTRACT

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder and a leading cause of death in the US. Chronic skin wounds, such as diabetic foot ulcers (DFUs), are a common complication of T2DM. Diabetic foot ulcers (DFUs) take longer to heal due to reduction of endothelial nitric oxide synthase (eNOS)-NO which induces the inadequate blood flow to tissues resulting in decreased angiogenesis. However, the molecular mechanisms associated with endothelial dysfunction and pathological angiogenesis remain unclear in DFUs. Here we observed increased expression of chemokine CCL28 and its receptor CCR10 and reduced eNOS expression NO bioavailability in skin punch biopsies from human subjects with T2DM and dermal skin of diabetic mice. In human endothelial cells (ECs), CCR10 showed a great co-localization with eNOS suggesting these two proteins may have direct interaction. Thus, we engineered a myristoylated 7 amino acid CCR10 binding domain (CBD7) peptide and showed that it can block eNOS interaction with CCR10 in ECs, resulting in upregulation of eNOS activity. Importantly, topical administration of CBD7 peptide improved dermal wound healing by rescuing eNOS expression and NO production, enhancing microvessel density in diabetic mice. Our data reveal novel insights into the role of CCL28/CCR10 signaling in regulation of eNOS/NO in delayed skin wound healing associated with T2DM and highlight novel potential therapeutic strategies for DFUs.
172. Experimental models of cardiac remodeling through myocardial infarction and transverse aortic constriction

**Author(s): Ayman Isbatan, Ming Tang, Maricela Castellon, Zhigang Hong, Leo Chen, Jiwang Chen**

Department of Medicine

**ABSTRACT**

Cardiac remodeling is characterized as changes to the shape, size, and anatomy of the heart and is most commonly induced by myocardial infarction or increased pressure overload. Myocardial Infarction (MI) involves heart muscle damage resulting from the decrease or cessation of blood flow to part of the heart, whereas pressure overload leads to concentric hypertrophy of the cardiac muscle caused by excessive afterload during systole. To better understand cardiac remodeling and its consequences, our Core has established MI and transverse aortic constriction (TAC) in mice. Here the main procedures, echocardiography, PET imaging and hemodynamic characterization for these two models have been provided. Our data shows that mean resting blood pressure values of the experimental groups are lower than their control groups. Cardiac output (CO), as well as ejection fraction (EF) and fractional shorting (FS) values are significantly decreased in two mouse models compared to their controls. PET with 18FDG labeling clearly demonstrates left ventricular heart failure in mouse models of MI. In the TAC mouse model, color/PW Doppler Imaging of the aortic arch view demonstrates that transverse aorta blood peak pressure and pressure gradient significantly increased in the mice with TAC surgery. Both MI and TAC models are well established characterized and highly reproducible in our Core to examine heart failure and cardiac remodeling.
LOSS OF HEPATOCYTE PPAR\(\gamma\) EXPRESSION IN ADULT MICE AMELIORATES DIET-INDUCED NON-ALCOHOLIC STEATOHEPATITIS

Author(s): Jose Muratalla, Gregory Norris, Danielle Pins, Grace Guzman, Jose Cordoba-Chacon,

Department of Medicine

ABSTRACT

NASH is positively associated with insulin resistance. The PPAR\(\gamma\) agonists, thiazolidinediones (TZD), are insulin sensitzizers that could reverse NASH. However, given that hepatic PPAR\(\gamma\) promotes steatosis in mice and its expression is increased in murine and human NASH, we hypothesize that hepatocyte-specific PPAR\(\gamma\) contributes to the progression of NASH. Adult male PPARg-floxed mice were injected with an adeno-associated virus serotype 8 (AAV8) expressing hepatocyte-specific Cre recombinase, driven by a thyroxine-binding globulin (hepatocyte-specific) promoter, to generate aHepPPARgKO mice, or with an AAV8 bearing a null vector to generate controls. Two weeks later, mice were fed a high-fat, -cholesterol and -fructose (HFCF) diet for 8 or 24 weeks to induce steatosis and NASH, respectively. Control mice fed a HFCF diet showed increased expression of hepatic PPARg as compared to mice fed a low-fat diet. aHepPPARgKO dramatically reduced hepatic PPARg expression (by 85-98%). aHepPPARgKO mice fed the HFCF diet for 24 weeks had larger adipose tissue, higher plasma insulin, and impaired glucose tolerance compared with the HFCF-fed control mice. However, aHepPPARgKO mice showed reduced liver weight, steatosis, and ALT. Of note, aHepPPARgKO mice had reduced expression of pro-inflammatory (Tnf\(\alpha\), and Mcp1), and pro-fibrogenic (Tgf\(\beta\)1, Col1a1, Mmp13 and Timp1). In addition, aHepPPARgKO mice had reduced NAS score, and bridging fibrosis as compared to control mice fed a HFCF diet. These data suggest that hepatocyte-specific PPAR\(\gamma\) contributes to the progression of NASH independently of the development of insulin resistance. Outgoing studies are assessing the impact of TZD-mediated activation of hepatocyte-PPAR\(\gamma\) in the treatment of NASH.
Effect of JAK-STAT Pathway Inhibition on Expression of Inflammatory and Epithelial-Mesenchymal Transition (EMT) Genes in Hyperoxia-Exposed Mouse Lung Alveolar Epithelial Cells (AEC)

Author(s): Wenxiang Luo, Isabel Kwan, De-Ann Pillers

Department of Pediatrics

ABSTRACT

Bronchopulmonary dysplasia (BPD) is a major complication affecting preterm infants. Hyperoxia is an important contributor to BPD. In previous studies, we reported that hyperoxia altered expression of genes for inflammatory cytokines, EMT (epithelial-mesenchymal transition), and fibrosis in alveolar epithelial cells (AEC). Cytokines including IL6 function in fibrosis. JAK-STAT is a key pathway transducing cytokine effects, leading us to hypothesize that the JAK-STAT pathway may function in mediating the effects of hyperoxia on inflammatory and EMT gene expression in AEC. A non-tumorigenic C10 mouse AEC line was treated in room air or hyperoxia condition. PCR was used to measure mRNA expression in response to hyperoxia and the JAK-STAT inhibitor (Tofacitinib or Ruxolitinib) in C10 cells. Tofacitinib reduced induction of IL6 by hyperoxia, and it reversed the hyperoxia-suppressed expression of occludin, an epithelial marker. Furthermore, Tofacitinib decreased hyperoxia-induced expression of serpin peptidase inhibitor clade E member 1, an EMT and fibrosis marker gene. However, unexpectedly, Tofacitinib treatment led to a significantly enhanced increase in transcription of alpha-smooth muscle actin (alpha-SMA), a gene marker of fibrosis, compared with cells exposed only to hyperoxia. Ruxolitinib also slightly increased expression of alpha-SMA. Thus, blockade of the JAK-STAT pathway both enhances and counteracts effects of hyperoxia on inflammation, EMT and fibrosis. This suggests that there is a complex regulatory signaling network in disorders where hyperoxia-induced lung inflammation and fibrosis play a prominent role. It is also a reminder that altered expression of genes involved in normal development may have unanticipated consequences.
175. Ugt1a6a, a novel regulator of beta-cell function

Author(s): Christopher Carmean, Michael Landeche, Robert Sargis

Department of Medicine

ABSTRACT

Arsenic exposure correlates with diabetes mellitus. Animal models of inorganic arsenic (iAs, As3+) exposure have suggested that iAs-induced glucose intolerance manifests as a result of dysfunctional insulin secretion from beta-cells. To define the mechanisms responsible for this beta-cell defect, the MIN6-K8 mouse insulinoma cell line was exposed to environmentally-relevant doses of iAs. Exposure to 0.1—1 µM iAs for 3 days significantly decreased glucose-induced insulin secretion (GIIS). Metabolomics screening revealed that serotonin and its precursor, 5-hydroxytryptophan (5-HTP), were both decreased. Supplementation with 5-HTP, which loads the system with bioavailable 5-HTP and serotonin, rescued GIIS, suggesting that recovery of this pathway was sufficient to restore function. Exposure to iAs was accompanied by an increase in mRNA expression of UDP-glucuronosyltransferase 1 family, polypeptide a6a (Ugt1a6a), a phase-II detoxification enzyme that facilitates the disposal of cyclic amines, including serotonin, via glucuronidation. Elevated Ugt1a6a expression was also observed in mouse and human islets following 3 days of iAs exposure. Knockdown by siRNA of Ugt1a6a during iAs exposure restored GIIS in MIN6-K8 cells. This effect was prevented by blockade of serotonin biosynthesis, suggesting that the observed iAs-induced increase in Ugt1a6a is responsible for decreased GIIS by targeting serotonin or serotonin-related metabolites. This study provides evidence that Ugt1a6a, acting on the serotonin pathway, regulates GIIS under both normal and pathological conditions.
176. The intersection of structural violence, environmental inequalities and family history: study design and methodology

Author(s): Molly Scannell Bryan, Jyotsna Jagai, Susan Hong, Maria Argos, Sage Kim, Kent Hostkins

Department of Medicine

ABSTRACT

Introduction

Breast cancer is the most commonly diagnosed cancer in American women, and women of color bear a disproportionate burden of breast cancer morbidity and mortality. Breast cancer risk is influenced by harmful social forces (structural violence), environmental inequality, and familial history, but the independent effects of each of these factors explain less than half of breast cancer diagnoses.

Study Description

A secondary data analysis women who underwent mammography screening and answered questionnaires about family history of cancer (N=600 women consented). We aim to assess the relationships between ecological indicators of structural violence, environmental exposures, and clusters of high familial risk of cancer.

Further, we aim to characterize whether breast density, an early risk factor for later breast cancer that will be extracted from mammography notes using Natural Language Processing, is associated with the broad matrix of exposures.

The project goals will be revised over quarterly meetings with our partner organization Sisters Working It Out (SWIO), and SWIO will facilitate dissemination of research results to neighborhoods with traditionally low mammogram rates. A full conceptual model and details on the analytical approaches will be presented.

Discussion and Expected Findings

Our study will provide a more detailed understanding of how knowledge of how neighborhood-level characteristics can complement known risk factors to identify women who may be at increased risk for breast cancer. Additionally, it may suggest possible routes of intervention that could occur before breast cancer develops invasive potential.
177. I-CARE2: An Adapted Intervention with Integrated CoAching foR BEtter Mood and Lifestyle

Author(s): Amruta Barve, Amruta Barve, Corina Ronneberg, Justine Kessler, Lindsey Stewart,

Department of Medicine

ABSTRACT

BACKGROUND: Obesity and depression are two highly prevalent chronic conditions that often co-occur and can lead to worsened patient outcomes. Therefore, effective interventions targeting both coexisting conditions are critical. The I-CARE2 intervention synergistically integrates two evidence-based programs (for weight loss and depression) and is being delivered to eligible UI Health patients with comorbid obesity and depression enrolled in the ENGAGE-2 study, a 2-arm RCT (n=105). Participants are randomized in a 2:1 ratio to receive either the I-CARE2 intervention (n=70) or usual care (n=35).

AIMS: I-CARE2 is an integrated intervention that innovatively combines two behavioral interventions: Group Lifestyle Balance (GLB) and the Program to Encourage Active and Rewarding Lives (PEARLS). The GLB program focuses on improving weight through diet and lifestyle changes and the PEARLS program employs Problem Solving Treatment (PST) and behavior activation, combined with as-needed antidepressant medications, to improve mood.

METHODS: I-CARE2 is designed to help people improve mood (depression symptom reduction ≥50%), lose weight (5-10% body weight), and become more physically active (≥8,000 steps/day and 150+ minutes of higher-intensity physical activity/week). A certified health coach delivers I-CARE2 across six months, through nine one-on-one coaching sessions, complemented by self-study materials between sessions. The first four sessions help build problem-solving skills and encourage behavioral activation. Starting with session five, participants are also expected to self-monitor (via Fitbit) to increase physical activity and make healthy dietary changes leading to clinically significant (≥5%) weight loss.

HYPOTHESES: Participants enrolled in I-CARE2 will experience clinically significant improvements in mood and greater weight loss compared to usual care controls.
178. X40L-Jagged-1 co-treatment expands follicular regulatory T-cells and alleviates experimental lupus

Author(s): Prabhakaran Kumar, Swarali Surendra Lele, Bellur Prabhakar

Department of Microbiology and Immunology

ABSTRACT

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease in which T-follicular helper (TFH) and B-cell mediated self-reactive immune responses lead to autoantibody production and deposition into multiple organs including kidneys. Current treatment modalities such as anti-inflammatory corticosteroids (prednisolone) and immunosuppressant are associated with a higher risk of infections, cancer, and osteoporosis. T-regulatory (Treg) cells suppress auto-reactive T- and B-cells, and thereby maintain self-tolerance. While defective Treg homeostasis implicated in SLE pathogenesis, augmenting Tregs can ameliorate the disease. T-follicular regulatory (TFR) cells, a specialized subset of Tregs, has recently been shown to effectively suppress TFH and B-cell responses in lupus. Adoptive transfer of Tregs into lupus-prone NZBWF1/j mice alleviated experimental lupus nephritis. Although adoptive Treg therapy is promising, it requires sorting of Tregs from peripheral blood, in vitro expansion and repeated transfusion to patients and thus, rendering it unsuitable routine clinical use. Moreover, this cannot supplement TFR cells as they are not abundant in peripheral blood. Hence, an alternative approach that can cause selective expansion of Tregs and TFR cells in vivo could be more effective in treating SLE. Here, we show that Tregs and TFR cells can be expanded in NZBWF1 mice with weekly injections of soluble OX40L and Jagged-1 proteins. This resulted in reduced TFH/TFR ratio and B-cells in the spleen and draining renal lymph nodes. Compared to vehicle-treated mice, OX40L-Jagged1 treated mice showed reduced proteinuria and attenuated lupus nephritis, and improved survival. Thus, OX40L-Jagged-1 induced Treg and TFR cell expansion could be beneficial in treating lupus.
179. Extracellular vesicles as novel targeted therapy for retinal damage and repair in MS

Author(s): Sophie Tran, Lorea Acha, Leianne Torres, Sergey Kalinin, Steven Roth, Biji Mathew

Department of Anesthesiology

ABSTRACT

Optic Neuritis, characterized by optic nerve fiber and retinal ganglion cell degeneration, is responsible for impaired, and often irreversible vision loss in about 20% of MS patients. Current treatment therapies focus only on minimizing MS disease symptoms. However, none of these offer a cure for RGC and axonal loss. It is therefore imperative that the treatment focus be shifted to developing neuroprotection and regeneration of RGCs and axons. Stem cell-based RGC replacement is an encouraging approach. Recently it has been shown that stem cells release extracellular vesicles (EVs). MSCs-EVs decrease neuronal cell death after hypoxia in vitro and in vivo and attenuate oxidative stress. They can be administered cross-species, do not proliferate, and their stability and low toxicity make them attractive therapeutic delivery vehicles. Our previous research using in vitro and in vivo retinal ischemia models demonstrated sustained EV uptake into retinal neurons and microglia and amelioration of functional impairment of retina, reduction in RGC loss and apoptosis after prolonged acute retinal damage. We aimed to modify EVs to specifically target RGCs. EVs isolated, labelled and modified using carrier peptide to enable RGC targeting. Our data demonstrates remarkably enhanced neuroprotection and uptake by retinal neurons when treated with EVs.
180. Effects of THC on Schizophrenia-Related Gene DNA Methylation and Expression in Mouse Primary Neuron Culture and Adolescent Mice

Author(s): Gian Paolo Vallerini, Maheen Kazmi, Shumila Kazmi, David Gavin

Department of Psychiatry

ABSTRACT

THC is the main psychoactive component of marijuana and exerts its pharmacological actions through activation of specific receptors highly expressed in the brain, namely cannabinoid receptors 1 (CB1) and 2 (CB2). Increasing evidence suggests a link between cannabis use during adolescence and a higher risk of psychosis. Increased expression of DNA-methylating enzymes, such as DNMT1 and DNMT3A, and increased BDNF promoter methylation associated with reduced BDNF expression has been reported in postmortem brain samples in schizophrenia. A decrease in Bdnf levels is reported in rodent studies following THC treatment. In the current study, we examined whether THC affects Dnmt expression and genes associated with schizophrenia using mouse primary neuron culture and in vivo. We tested the effects of CB1 and CB2 agonists, and THC with and without CB1 and CB2 antagonists on mouse E18 primary cortical neuron cultures. Using mice, we examined the effects of adolescent chronic THC exposure on gene expression changes in the prefrontal cortex and hippocampus. In mouse primary cortical neuron cultures we found concentration-dependent increased levels of Dnmt1 and Dnmt3a following THC or cannabinoid agonists application. In adolescent mice treated with IP injections of THC twice a day for 10 days Dnmt3a mRNA expression was significantly increased. In the adolescent mice there was also a significant reduction in Gad1, Reln, and Bdnf mRNA expression. These early studies suggest that THC produces robust changes in expression of epigenetic pathways that may contribute to gene expression changes observed in schizophrenia.
181. berrant enteric neuromuscular system and dysbiosis in mice with amyotrophic lateral sclerosis

Author(s): Yongguo Zhang, Rong Lu, Shari Garrett, Yinglin Xia, Jun Sun,

Department of Medicine

ABSTRACT

Background: Amyotrophic Lateral Sclerosis (ALS) is a neuromuscular disease characterized by the progressive death of motor neurons and muscle atrophy. We reported elevated intestinal inflammation and dysbiosis in ALS patients and ALS mice (expressing human mutation SOD1G93A, G93A). However, the relationship between intestinal mobility and microbiome in ALS progression is still unknown. Methods: Age-matched WT mice and G93A mice were subjected to studies of ALS progression. Data on rotarod, grip-strength and motility and microbiome have been recorded. ENS marker (GFAP) and smooth muscle marker (SMMHC) have been examined. To study the microbiome in ALS, we used butyrate and antibiotic treatments. Results: G93A mice 1 month-old showed no significant changes of ENS and motility but altered gut microbiome compared with WT mice. At the before ALS onset (2 month-old) and ALS onset period (3 months), G93A mice had significant lower intestinal motility, decreased grip strength, and reduced time in the rotarod test. GFAP expression was increased and SMMHC were decreased. Human-G93A-SOD1 mutated protein showed severe aggregation in colon and small intestine. Compared with G93A control mice, G93A mice with butyrate and antibiotic treatment showed a significantly longer latency to fall in the rotarod test. Butyrate and antibiotics treatment led to enhanced ENS function and reduced SOD1G93A aggregation in intestine. Conclusions: We have demonstrated a novel link of microbiome, SOD1 aggregation, and intestinal mobility. Manipulating the microbiome improves the muscle performance of G93A mice. Our study provides insights into fundamentals of intestinal neuromuscular structure/function and microbiome in ALS.
182. The Enrichment Analysis of Differential Gene Expression between the Bronchoalveloar Lavage and PBMCs of Pulmonary Sarcoidosis

Author(s): Yue Huang, Christian Ascoli, Ben Turturice, Cody Schott, David Perkins, Patricia Finn

Department of Medicine

ABSTRACT

Rationale: Our preliminary data identified signature circulating microRNAs as diagnostic and prognostic indicator of Sarcoidosis. Six transcripts might be responsible for the racial disparity, which proposed the possible difference from PBMCs between Caucasians and African Americans. The overexpressed miRNAs in sarcoidosis were found significantly associated with cell proliferation pathways from the post transcriptomic profile of the BAL fluid cells. We postulated that biomarkers from both PBMCs and BAL cells will be more precise to predict the disease’ onset and indicate the outcome of intervention. Therefore, we design to analyze the differential gene expression of PBMCs and BAL, from the same time point pulmonary sarcoidosis subjects.

Methods: BAL fluid and PBMCs samples were collected and processed from the same subjects(n=2) at the time point of diagnosed. RNAs were extracted (RINs > 9). mRNASeq libraries were sequenced by the Illumina MiSeq system. RNASeq data was annotated through Salmon. Enrichment analysis was based on the normalized reads, and was performed by uploading the significant overexpressed genes, respectively in BAL cells and PBMCs, to Metascape online platform.

Results: We identified 12676 genes, 2645 of them were significantly differentially expressed(P<0.05). The enrichment outcome of top 20 overexpressed genes in PBMCs are more associated with the adaptive immune by enriched GO biological process, while more with the innate immune related in BAL by KEGG pathway.

Conclusions: The enriched terms networks of both PBMCs and BAL cells signified the upregulation of fibroblast proliferation in BAL cells may indicate how the disease initialized.
183. Alternative Cre Recombinase Delivery Systems for Transformation of Oncopig Primary Cell Lines

Author(s): Shovik Patel, Byoungsoo Kim, Ron Gaba, Lawrence Schook, Joon Kong, Kyle Schachtschneider

Department of Radiology

ABSTRACT

Biomedical research of cancer requires effective animal models and cell lines in order to translate diagnostic and treatment strategies into clinical practice. Transgenic pig models represent ideal cancer models due to similarities between pigs and humans in terms of anatomy, physiology, drug metabolism, and genetics. This study utilized the oncopig cancer model, a transgenic pig model that develops site and cell specific tumors through Cre recombinase induced expression of KRAS^G12D and TP53^R167H transgenes. Previous studies have shown that adenoviral vectors encoding cre recombinase (AdCre) can successfully transfect and transform Oncopig primary cell lines. However, in vivo Oncopig tumors through AdCre administration results in significant inflammation and tumor regression, therefore limiting the applicability of this model for drug discovery and development. Here, we tested additional cre recombinase protein delivery systems, including nanoparticles and lipofectamine, to transfect and transform Oncopig primary cell lines. Growth rates were measured and compared between primary cell lines (hepatocytes and fibroblasts) transfected with AdCre, nanoparticles, and lipofectamine. Phenotypic characterization of the transformed cell lines was performed several passages post-transfection. RT-PCR was performed to confirm KRASG12D and TP53R167H gene expression and wound healing assays were performed to characterize cell migration between non-transformed and transformed cell lines. The results indicate that nanoparticles and lipofectamine represent possible alternatives for in vivo cre recombinase delivery.
ACAT inhibition in the CNS as a therapeutic target for APOE4-induced Alzheimer’s disease risk

Author(s): Efstathia Loukenas, Ana Valencia-Olvera, Deebika Balu, Sandra Coronel, Jason York, Mary Jo LaDu

Department of Anatomy and Cell Biology

ABSTRACT

APOE4, the gene encoding apolipoprotein E4 (apoE4), is the greatest genetic risk factor for Alzheimer’s disease (AD), compared to common APOE3, and APOE2, which is protective but rare. While the mechanism underlying APOE-modulated AD risk remains unclear, APOE4 is associated with accelerated amyloid-beta (A-beta) accumulation, both as amyloid plaques and soluble oligomeric forms of A-beta, the latter considered a proximal neurotoxin. In addition, apoE4 levels in the brains of humans and transgenic mice expressing human APOE are lower compared to apoE3, suggesting that the poorly lipidated apoE4 particles are unstable. Thus, one possible therapeutic target for APOE4 carriers is increasing the intracellular free cholesterol pool in neurons and glial cells to allow greater lipidation of apoE4 particles. This was tested using an Acyl-CoA: cholesterol-acyltransferase (ACAT) inhibitor avasimibe (AVAS). ACAT esterifies intracellular free cholesterol to produce cholesteryl ester droplets and reduce the free cholesterol pool. Therefore, our therapeutic target for APOE4 carriers is increasing intracellular cholesterol for transport to lipidate the intercellular apoE4 particles via inhibition of ACAT. In this study, we treated male E4FAD mice, which specifically overexpress A-beta42 and express human APOE4, with AVAS in a prevention paradigm (6-8M). AVAS treatment prevented memory loss, reduced soluble and insoluble Ab levels, APP processing, A-beta deposition, amyloid deposition, and neuroinflammation. However, there was no evidence of indirect target engagement as measured by an increase in apoE4 lipidation. Thus, AVAS demonstrates efficacy with significant changes in mechanistic pharmacodynamics readouts for both neuroinflammation and A-beta solubility/deposition, two critical components of APOE4-induced AD-related pathology.
185. THE EFFECT OF AGE, SEX, AND APOE GENOTYPE ON ABETA PATHOLOGY IN AN ALZHEIMER’S DISEASE TRANSGENIC MOUSE MODEL

Author(s): Rebecca Ainis, Ana Valencia-Olvera, Bingtao Xiang, Jason York, Mary Jo LaDu,

Department of Anatomy and Cell Biology

ABSTRACT

While age is the greatest risk factor for Alzheimer’s disease (AD), APOE4 is the greatest genetic risk factor, increasing risk up to 15-fold compared to the common APOE3, while APOE2, though rare, reduces risk. APOE4 is associated with the accelerated accumulation of amyloid-beta (Abeta) peptide, which aggregates to form both amyloid plaques and soluble oligomers of Abeta (oAbeta). Recently, studies have shown that female APOE4 carriers have a higher risk for developing AD than male APOE4 carriers. Using our novel EFAD transgenic mice, expressing the human APOE genotypes and overexpressing human Abeta42, we demonstrate an increase in soluble oAbeta in 6M male and female E4FAD compared to male and female E3FAD mice. We hypothesize that the effects of age, APOE genotype, and sex will act synergistically to increase Abeta pathology in female E4FAD. To generate biochemical extraction profiles for Abeta and apoE, the cortices of 4-18M male and female E3FAD and E4FAD mice were extracted via a 3-step sequential method, producing soluble, detergent and insoluble fractions. Total levels of Abeta42 increase with age, with E4FAD>E3FAD and female>male. Importantly, soluble oAbeta levels increased with age in all genotypes (maleE3FAD<maleE4FAD<femaleE3FAD<femaleE4FAD), while soluble Abeta42 levels plateaued in the following temporal order: maleE3FAD, femaleE3FAD, maleE4FAD, femaleE4FAD. This is critical as even in EFAD brain tissue, soluble oAbeta tracks disease progression. Biochemical analysis of the EFAD mice reveals an age-induced increase in Abeta pathology that mirrors the increased AD risk in humans (maleE3FAD<maleE4FAD<femaleE3FAD<femaleE4FAD). Thus, the EFAD mice serve as a tractable therapeutic preclinical mouse model.
186. Optimized tissue clarification for blood-brain barrier reconstruction in neuroinflammatory disease

Author(s): Andrea Ochoa-Ray, Harrison Fredrick

Department of Anatomy and Cell Biology

ABSTRACT

In multiple sclerosis, the blood-brain barrier (BBB) becomes compromised and effector T cells are able to cross into the central nervous system (CNS) and cause demyelination. The BBB is a selectively permeable physical barrier formed by CNS blood vessel endothelial cells. It becomes increasingly penetrable during neuroinflammatory diseases. Currently there are several ways of identifying the proteins involved in neuroinflammation, such as immunohistochemistry. Whole organ clearing is the ideal method for imaging entire structures to build a series of 3D images. The current method for doing this is expensive, difficult to implement, and requires a degasser. We sought to optimize a published mPACT organ clearing protocol to visualize BBB proteins in mice with the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis. We optimized antibody combination and incubation times as well as fashioned a home-made apparatus for electrophoretic clearing of opaque proteins and then utilized epifluorescence microscopy to identify protein distribution in neuroinflammatory disease. We were able to construct a 3D image of neurovascular segments using widefield microscopy. Future studies will utilize this technique to assess regional anatomic distribution of BBB damage and T cell infiltration in disease. This will further our research and allow us to make relevant discoveries regarding neurodegenerative disease.
187. Studies on the Effects of Hepatic HKDC1 Ablation on Maternal Glucose Metabolism and Newborn Outcomes

Author(s): Isaac Jose, Wasim Khan, Brian Layden

Department of Medicine

ABSTRACT

Gestational diabetes mellitus (GDM) affects nearly 10% of pregnancies in the United States. In a recent study among pregnant women, hexokinase domain containing-1 (HKDC1), a novel 5th hexokinase, was shown to have a significant association with GDM. Furthermore, hepatic HKDC1 has been hypothesized to play a major role in gestational glucose and lipid metabolism, and pathophysiological conditions such as NASH. Our earlier work has shown that hepatic HKDC1 overexpression improves whole-body glucose homeostasis and insulin sensitivity. Therefore, we hypothesize that liver-specific ablation of HKDC1 would lead to impaired maternal glucose and insulin homeostasis leading to adverse outcomes in the offspring. In this study, a novel mouse model was developed with in-utero ablation of liver HKDC1 (HKDC1-LKO) by crossing HKDC1 floxed mice with the Albumin-Cre mice. These mice were subjected to metabolic testing before pregnancy and during days 18-19 of gestation. Additionally, we followed the weights of the offspring and put them to metabolism testing at weeks 4 and 10 after birth. Our results indicate that both male and female offspring from HKDC1-LKO mice had significantly less bodyweight at four weeks with impaired glucose tolerance. However, both glucose tolerance and bodyweights progressively returned to control levels by the tenth week which suggests a compensatory mechanism and/or an adaptive response. Overall, our data suggests that maternal hepatic HKDC1 ablation negatively affects glucose homeostasis in the offspring.
188. Chemokine receptor CXCR7 reactivates ERK signaling to promote resistance to EGFR kinase inhibitors in NSCLC

Author(s): Jeffrey Becker, Ines Pulido

Department of Surgery

ABSTRACT

Activating EGFR mutations in NSCLC confer sensitivity to reversible EGFR TKIs, including gefitinib and erlotinib. Despite promising initial responses, acquired resistance develops mediated by the emergence of the secondary T790M mutation or by focal amplification of MET. An epithelial mesenchymal transition (EMT) is clinically linked to NSCLCs with acquired EGFR TKI resistance. The exact mechanisms of EGFR TKI resistance with an EMT phenotype remain elusive.

We discovered that an atypical GPCR, chemokine receptor type 7 (CXCR7), is commonly overexpressed in the cell line models of EGFR TKI resistance with a mesenchymal phenotype. 50% of NSCLC patients harboring an EGFR kinase domain mutation who progressed on EGFR inhibitors showed an increase in CXCR7 expression. Using cell line models, we find that CXCR7 activates the MAPK-ERK pathway via arrestin. Depletion of CXCR7 abrogates the MAPK pathway and significantly attenuated EGFR TKI resistance. In the long term, the depletion of CXCR7 resulted in a mesenchymal to epithelial transition. Ectopic overexpression of CXCR7 was sufficient to activate ERK1/2 for the generation of EGFR TKI resistant cells. Furthermore, CXCL12 stimulation resulted in an increase in ERK phosphorylation while EGFR was inhibited in TKI-resistant mesenchymal cells. Similarly, we found CXCL12 expression is elevated in patient samples with an increased CXCR7 expression.

Taken together, we discovered that the CXCR7-CXCL12 signaling axis is necessary and sufficient for the maintenance of EGFR TKI resistance with a mesenchymal phenotype and CXCR7 inhibition could significantly delay and prevent the emergence of acquired EGFR TKI resistance in EGFR mutant NSCLC.
Whole genome approaches reveal novel epigenetically regulated signaling molecules in the amygdala during alcohol dependence

Author(s): Harish Krishnan, John Bohnsack, Huaibo Zhang, Ying Chen, Dennis Grayson, Subhash Pandey

Department of Psychiatry

ABSTRACT

Anxiety during withdrawal from chronic ethanol exposure predisposes to alcohol use disorders (AUD). Epigenetic mechanisms responsible for transcriptomic changes in the amygdala may lead to these phenotypes. We used RNA-sequencing and ChIP-sequencing (H3K9/14ac) to identify epigenetically regulated gene networks in the amygdala to better understand the neuroadaptive mechanisms of alcohol dependence. Adult Sprague-Dawley male rats received control (C) or ethanol (E) (9% v/v) Lieber-DeCarli diets for 15 days. A third group of ethanol-fed rats were withdrawn (W) for 24h. Amygdala was collected for RNA-sequencing (paired-end) and ChIP-sequencing (single-end) using the Illumina platform. Following bioinformatic analysis, we merged the datasets by comparing H3K9/14ac peaks present around transcription start sites (TSS) (+/-2kb) to RNA-seq data. We identified 725 unique genes that were differentially expressed (FDR<0.1; W vs C) and contained an associated acetylation peak. Ingenuity Pathway Analysis (IPA) helped identify candidates from mitogen-activated protein kinase (MAPK) signaling pathway - Spry4 (Sprouty RTK Signaling Antagonist 4), Spry2 (Sprouty RTK Signaling Antagonist 2) and Dusp6 (Dual specificity phosphatase 6). All three had increased mRNA levels and histone acetylation at the TSS (W vs C). These genes may be responsible for synaptic changes in the amygdala and development of anxiety-like behaviors in rats undergoing withdrawal, which will be determined using functional approaches. Our results also demonstrate the use of integrating large data sets for the discovery of novel gene targets that are involved in alcohol dependence.
190. Accessibility of healthcare for people living with HIV who are out of care in Chicago

Author(s): Celina Garza, Amber Hathcock, Mary Kate Mannion, Sara Heinert Wieseneck, Janet Lin,

Department of Emergency Medicine

ABSTRACT

Background: Almost half of people living with HIV (PLWH) are out of care and are more likely to be victims of institutional barriers that lead to inequities in health. Lack of transportation options and absence of healthcare services are two factors that can particularly impede engagement in the HIV care continuum.

Objectives: To evaluate and characterize institutional barriers to care for PLWH who are out of care (PLWH-OOC) in Chicago utilizing geographic information system (GIS) mapping.

Methods: Using pre-existing data from a prior research project, we mapped residences of PLWH-OOC by zip code and hospital and HIV medical and support service locations. We also explored hospital accessibility by utilizing the percent of hospitals in Chicago located within an hour from the PLWH-OCC’s home zip code.

Results: Out of 31 PLWH-OOC, 12 (38.7%) were located in zip codes with limited public train access (1 or fewer train stations). Almost half (42%) of PLWH-OOC lived in zip codes where the percent of hospitals available via public transport within an hour was less than the median for Chicago, which is 47.1%. Nine (29%) lived in zip codes with no hospitals. Ten (32%) lived in zip codes with no designated HIV care clinics.

Conclusion: PLWH-OOC in our dataset tended to be clustered in areas with limited health care access and limited transportation options. This may contribute to a lack of retention in care. A medical care model, such as a mobile clinic, with the ability to provide medical services where PLWH reside is needed.
191. Optimized tissue clarification for blood-brain barrier reconstruction in neuroinflammatory disease.

Author(s): Andrea Ochoa-Raya, Elizabeth Pietruczyk, Harrison Fredrick, Anais Mancini, Sarah Lutz,

Department of Anatomy and Cell Biology

ABSTRACT

In multiple sclerosis, the blood-brain barrier (BBB) becomes compromised and effector T cells are able to cross into the central nervous system (CNS) and cause demyelination. The BBB is a selectively permeable physical barrier formed by CNS blood vessel endothelial cells. It becomes increasingly penetrable during neuroinflammatory diseases. Currently there are several ways of identifying the proteins involved in neuroinflammation, such as immunohistochemistry. Whole organ clearing is the ideal method for imaging entire structures to build a series of 3D images. The current method for doing this is expensive, difficult to implement, and requires a degasser. We sought to optimize a published mPACT organ clearing protocol to visualize BBB proteins in mice with the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis. We optimized antibody combination and incubation times as well as fashioned a home-made apparatus for electrophoretic clearing of opaque proteins and then utilized epifluorescence microscopy to identify protein distribution in neuroinflammatory disease. We were able to construct a 3D image of neurovascular segments using widefield microscopy. Future studies will utilize this technique to assess regional anatomic distribution of BBB damage and T cell infiltration in disease. This will further our research and allow us to make relevant discoveries regarding neurodegenerative disease.
Improvement in Epilepsy Self-Management Practice and Behaviors following 12 weeks of Personalized Epilepsy Self-Management Education: Preliminary Results from PAUSE to Learn Your Epilepsy

Author(s): Jessica Levy, Dilip Pandey, Katharine Ozenberger, Anna Serafini, Mitra Habibi, Jeffrey Loeb

Department of Neurosurgery

ABSTRACT

Almost 40% of people with epilepsy (PWE) report recurring seizures despite being on anti-epileptic drugs. Recurring seizures increase the risk of hospitalizations, depression, and death. Uncontrolled or frequent seizures and generalized tonic-clonic seizures (GTCS) have been reported as risk factors for Sudden Unexpected Death in Epilepsy (SUDEP). We compared SM skills in poorly and uncontrolled GTCS patients to those with well-controlled epilepsy.

The PAUSE study evaluates the effectiveness of personalized SM education using mobile technology to improve the lives of adult PWE from underserved populations. Data includes 86 participants who completed self-reported study questionnaires. SM skills were assessed using epilepsy SM practice questionnaire. PWE with poorly controlled epilepsy included those with partial seizures within 3 months. The well-controlled seizure group included PWE reporting no seizures or 1 partial seizure in past 3 months. Uncontrolled GTCS was examined as a separate group. Descriptive statistics included chi-square statistics or t-test.

Overall, mean age was 37.7 years, 62.8% were female, and 46.5% were non-Hispanic black. The mean AESMMI score was significantly lower in the poorly controlled epilepsy group and in the uncontrolled GTCS, indicating PWE with poorly controlled epilepsy or uncontrolled GTCS are poorer self-managers of their epilepsy. PWE with poorly controlled epilepsy had the lowest skills in managing their seizures and had significantly lower self-efficacy in self-managing epilepsy.

Our findings are highly significant and identify sub-groups of PWE who have poorer epilepsy SM behaviors. It underscores the need for additional resources and support for targeted self-management education tailored for these sub-groups.
A Novel Internet-Based Intervention for Preventing Adolescent Depression: Perspectives from Healthcare Providers

Author(s): Alex Holterman, Benjamin Van Voorhees, Tracy Gladstone, Linda Schiffer, Miae Lee, Calvin Rusiewski

Department of Pediatrics

ABSTRACT

Primary healthcare providers are uniquely positioned to identify, screen, and initiate management of possible depression in adolescents. CATCH-IT is a web-based depression prevention intervention with the potential to be effective and cost-effective in primary care settings. To assess readiness for implementation we surveyed primary care providers who participated in the PATH study.

We assessed provider (MD/NP N= 41, and nurse/MA N= 121) attitudes pre- and post-intervention using surveys which measured opinions regarding responsibilities caring for adolescent depression, personal abilities to treat adolescent depression, and perceived barriers to intervention implementation. We have organized these broad areas into appropriate Consolidated Framework for Implementation Research (CFIR) constructs.

Both MD/NP and Nurse/MA groups showed an increase in willingness to implement CATCH-IT (15.6% and 1.7%, respectively). MD/NP showed a 6.5% decrease in readiness to prescribe medication to treat depressive symptoms. MD/NP also showed a decrease in confidence in own knowledge of depression (13.3%) and recognition of depression (5.2%) while Nurse/MAs showed an increase in both measures (14% and 5.9%). Additionally, MD/NPs reported a lower confidence in being able to provide brief interventions to reduce depressive symptoms (13.5%) while nurse/MAs reported higher confidence (1.6%). Both groups showed an increase in confidence regarding discussing major depression with patients post-intervention (MD/NP = 7.5%, nurse/MA = 11.3%).

Health care providers were generally supportive of implementing the CATCH-IT intervention in primary care. Placing these attitudes in the context of the CFIR framework allows us to prepare this data for a larger implementation study.
194. Targeting of Uncontrolled Hypertension in the Emergency Department (TOUCHED): Preliminary Findings of a Hypertension Screening and Education Intervention in an Urban, Academic Emergency Department

Author(s): Maya Jackson, Brenda Lara, Priscilla Aluko, Alexia Kovlari, Heather Prendergast,

Department of Emergency Medicine

ABSTRACT

Background: Uncontrolled hypertension (HTN) is frequently encountered among Emergency Department (ED) patients as many utilize the ED as a source of primary care. The TOUCHED study is an ongoing randomized control trial that identifies individuals with HTN, provides educational interventions, and establishes care with a primary care physician (PCP). We analyzed demographic and baseline data from ongoing participant enrollment to present with HTN at an urban academic ED.

Methods: Eligible ED patients are fluent in English or Spanish, living in the Chicagoland area, not in moderate to severe pain, and have a minimum of two blood pressure readings that were >140/90 mmHg and <180/110 mmHg. Participants were randomized to one of two arms: usual care or intervention. Participants completed baseline assessments post-randomization.

Results: Baseline demographics of study participants (n=72) include an average age of 50.1 years with 76.4% of participants identifying as African American, 18.0% Hispanic, and 5.6% other. Out of the 72, 53% are female. Average blood pressure reading at time of enrollment was 156.1/96.9 mmHg for African Americans, 156.0/96.4 mmHg for Hispanics, and 155.3/94.1 mmHg for others. 31.9% expressed the need to establish follow-up care with a PCP.

Conclusions: Preliminary baseline results reflect that minorities are unproportionately impacted by HTN. This suggests that the ED is a unique opportunity to reach HTN patients likely missed by PCPs, and ED-initiated HTN interventions are a means of reducing health disparities in high risk populations.
ABSTRACT

Maternal Newborn and Child Health Guidelines and Tobacco Control in Low and Middle Income Countries

M. Chibber,1 B. Sthapit,1 E. Twentyman, 2 S. Naseer, E. Resnick, 1 I. Ahluwalia, 2 J. Klein, 1

1. UIC College of Medicine
2. Centers for Disease Control, Office on Smoking and Health

Objective:

Low and low middle income countries (LMIC) have prioritized maternal and newborn survival. Tobacco use and secondhand smoke (SHS) exposure are leading causes of preventable morbidity and mortality, affecting maternal mortality, miscarriage, low birth weight, and prematurity. Little is known about whether or to what degree MNCH guidelines in LMICs include tobacco control interventions.

Methods:

We searched for online maternal newborn and child health (MNCH) documents for the 80 countries designated as LMICs by the World Bank in 2018. Search terms included country name along with MNCH, Maternal and/or Child Health, Guidelines, and various related terms. We categorized identified documents as MNCH Care Guidelines, Health Plans, Health Policies, Health Programs, Health System Reviews, Health Strategies, Investment Cases, and Charting Handbooks. Each document was reviewed and coded for tobacco content and for other newborn survival priorities.

Results:

Documents were found for 67 countries. Of these, 55 were available in English and coded. Ten countries mentioned tobacco in the context of MNCH; among these, 6 addressed prenatal cessation and avoidance, 3 addressed prenatal SHS, and 7 addressed children’s SHS exposure, respectively. Two of seven MNCH guidelines addressed tobacco use. Of the four charting handbooks, three addressed tobacco use. In contrast, 37 countries mentioned breastfeeding in one or more of their documents.

Conclusion:

Few countries incorporate tobacco-related guidance into their MNCH documents. This is a missed opportunity for LMICs aiming to decrease smoking-related outcomes. To address maternal and newborn survival, tobacco control and SHS should be incorporated into MNCH guidelines and care.
196. Wagner Cone Mid-term Survivorship and Outcomes

Author(s): Alejandro Gonzalez, J. Joseph Gholson, Faisal Akram, Kyle N. Kunze, Sara S. Wallace, Brett R. Levine

Department of Orthopaedics

ABSTRACT

BACKGROUND: Total hip arthroplasty in patients with abnormal proximal femoral anatomy requires an individualized treatment to prevent complications. Metaphyseal engaging stems in this population risk fracture, size mismatch, and aseptic loosening. The Wagner conical femoral implant is a short diaphyseal engaging femoral stem which could improve treatment in this patient population. A large series of patients with mid-term outcomes of the Wagner femoral prosthesis has not been published.

METHODS: We identified 302 patients having THA using the Wagner cone femoral prosthesis between January 2010 and January 2017. Clinical, radiographic, and patient reported outcomes were obtained through chart review and radiographic measurements of post-operative x-rays. We utilized multivariate analysis to determine predictors of poor outcomes. Furthermore, a Kaplan-Meir curve was created to demonstrate implant survivorship. The average follow-up was 3.2 years, with a minimum follow-up of 2 years.

RESULTS: The implant retention survival rate during the 3.2 year study period was 98.7%. Overall reoperation rate was 4.2%, with infection post fracture being the most common reasons for reoperation. No patients were revised for aseptic loosening and no patients were revised for subsidence. The average subsidence was 1.1mm. The Harris Hip Score improved from 48.6 ±7.3 (range 28-64) preoperatively to 86.1 ±8.5 (range 66-100) at latest follow-up. The patient reported satisfaction rate was 98.3%.

CONCLUSION: The Wagner cone femoral prosthesis demonstrated excellent clinical, radiographic, and patient-reported functional outcomes at mid-term follow-up. We recommend the Wagner cone in THA patients with difficult proximal femoral anatomy, small femoral diameter, or poor metaphyseal bone quality.
197. **PAK1 preservation of cardiac function for aged females is dependent on RLC phosphorylation**

**Author(s): Ashley Batra, Chad M. Warren, R. John Solaro, Paola C. Rosas**

Department of Physiology and Biophysics

**ABSTRACT**

p21 activated kinase (PAK1) is a serine/threonine kinase, activated by Rac and CDC42 by phosphorylation. It promotes a signaling cascade that modulates post-translational modifications of downstream proteins, such as myofilament and calcium regulatory proteins. We hypothesize that gender and aging stress alters PAK1 activity affecting cardiac function. We used male and female global Pak1 knock-out mice (PAK1+/−) and wild type (WT) controls at 3 months (young) and 13 months of age (old) for a total of 8 groups. We found that PAK1 phosphorylation in WT old females is trending lower than WT young males. Even though, we did not find statistically significant differences in the total expression of Pak1, due to high sample variability, there was a trend for increased PAK1 expression in old females as a potential compensatory mechanism of decreased phosphorylation. Echocardiographic studies show that aged PAK1−/− females exhibit slower peak myocardial relaxation velocity, (19.2±2.8 mm/s) than their WT counterparts (30.9±1.4 mm/s), indicative of diastolic dysfunction. Moreover, aged PAK1−/− females show slower peak myocardial contraction velocity, Sa, (18.1±0.6 mm/s) when compared to aged female WT (25.5±1.6 mm/s). All echocardiographic data is presented as mean ± standard error. All groups maintained an ejection fraction (EF) >50%. Western blot analysis indicates that Pak knockouts have reduced phosphorylation levels of regulatory light chain (RLC). Alterations in RLC phosphorylation via Pak1 may contribute to the modulation of cardiac function.