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2016 Pathways to Cures:
Clinical Translational Research Day at UCI

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Poster Session Abstracts

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Topic Area: Stem Cell

Topic Area: Translational transcriptomics, proteomics, metabolomics

Reversal of aging phenotype following repopulation of microglial progenitor cells throughout the brain

Elmore, Monica, Ph.D.; Lee, Rafael; Pham, Stephanie; West, Brian; Green, Kim, Ph.D.

Elmore, Lee, Pham, West, Green - Department of Neurobiology and Behavior, UCI MIND, UCI West - Plexxikon, Inc.

Aging is associated with neuroinflammation, reduced neuronal plasticity, and cognitive impairments. Microglia are negatively implicated in many of these phenotypic changes. We hypothesized that the removal of primed/senescent microglia in aged mice using colony-stimulating factor 1 receptor (CSF1R) inhibition, followed by repopulation of the microglial compartment with new progenitor cells, would reverse these deficits. To that end, young (3 months) and aged (22 months) mice were treated with either control chow or PLX5622 (CSF1R inhibitor) to eliminate microglia for 2 weeks. Following elimination, the CSF1R inhibitor was removed and new microglia were allowed to repopulate for 4 weeks. Microglial repopulation has been shown to occur from a microglial progenitor within the brain. Behavioral testing following repopulation revealed a deficit in Morris water maze probe trial performance in aged mice, which was attenuated in aged mice following microglial repopulation. In addition, aged controls showed an increase in the number of microglial cells as well as a higher number of CD68+ microglia, a phagosomal marker, which were reversed with microglial repopulation. Baseline levels of Arc (an immediate early gene) were increased, and induction levels were not inhibited as seen in aged controls, in aged repopulated mice. RNA-Seq analysis revealed a high overlap in the expression of synaptic and neuronal genes between young control and aged repopulated mice compared to aged controls, with pathway analysis highlighting many genes involved in synaptogenesis, microtubule dynamics, and behavior. Finally, there was an increase in dendritic spines in aged repopulated mice compared to aged controls. Together, these data reveal that the elimination of inflammatory resident microglia in the aged brain, and replacement with new microglia from a progenitor cell source, reverses age-related cognitive deficits and alters synaptic plasticity.

Keywords: Microglia; Neurons; Synaptic plasticity; Aging; Hippocampus;

Robotic Retraining of Finger Movements after Stroke

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Robots aid motor rehabilitation, but there has been limited attention to recovery of finger movements. This study evaluated robotic assistance during finger movement training. Functional MRI (fMRI) was acquired at baseline to understand predictors of treatment gains. Patients with chronic stroke underwent a baseline fMRI scan, alternating rest with affected-side finger movements similar to those made during robotic therapy. Next, subjects received therapy 3 hr/wk for 3 weeks using FINGER (Finger Individuating Grasp Exercise Robot), with which subjects moved their paretic index and middle fingers to play a musical game similar to GuitarHero. FINGER provided assistance as needed to facilitate completion of grasping movements, which increased sensory feedback without altering voluntary motor output. Participants were randomized to receive High or Low Assistance (to insure 85% or 55% success, respectively). Thirty subjects (mean age 58 yr; baseline Fugl-Meyer 46 out of 66; 37 mo post-stroke) completed the study. Significant gains were found in the primary outcome measure, change in Box & Blocks (B&B) score (23 to 25.5, $p<0.0001$). There was no difference between High and Low Assistance groups in the primary endpoint, though some secondary outcomes favored High Assistance. The fMRI scans found that greater treatment gains were associated with higher laterality index in primary sensory cortex, indicating greater boost in B&B score over time with higher pretreatment balance of activation towards ipsilesional sensory cortex; laterality index in primary motor cortex lacked predictive value. Sensory factors appear key in regaining finger motor function after therapy with a robotic device: treatment content emphasized augmented sensory feedback, and the hemispheric balance of fMRI activation within sensory but not motor cortex predicted treatment gains. Together these findings suggest Hebbian rules of sensorimotor cortex plasticity during finger robotic therapy after stroke.

Keywords: Stroke; Stroke Recovery; Rehabilitation; Sensorimotor;

Prediction of Treatment Outcome in Infantile Spasms Patients

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Infantile spasms (IS) is a form of epilepsy that is characterized by clinical spasms, severe developmental delay, and a chaotic electroencephalographic (EEG) pattern called hypsarrhythmia. The disease typically develops into other forms of pediatric epilepsy and leaves patients with a bleak developmental outcome, but the prognosis is vastly improved with early diagnosis and treatment intervention. For these reasons, our lab seeks to predict whether infantile spasms patients will ultimately respond to the administered treatment by detecting early biomarkers of success in the patients' EEG. We found that a measure of long-range temporal correlations demonstrates potential to predict treatment efficacy while superseding the chaotic nature of hypsarrhythmia. Long-range temporal correlations (LRTCs) stem from the fractal nature of neural signals and quantify how a given region of the brain modulates its signal amplitude over time. We hypothesize that stronger correlations are a measure of control of neural synchrony and indicate optimal brain network function. We analyzed 31 infantile spasms patient datasets gathered at the Children's Hospital of Orange County (CHOC) before and after treatment with adrenocorticotropic hormone (ACTH). We discovered that the strength of LRTCs increases after treatment and reaches correlation strengths similar to those of age-matched control patients, suggesting that LRTCs are a biomarker of treatment efficacy. We hypothesize that LRTCs may have value in predicting ultimate patient outcome, allowing clinicians to promptly initiate a different drug in the case the patient does not show early signs of treatment success. The cessation of a futile drug and initiation of a new drug spares the patient unnecessary side effects, saves their family thousands of dollars, and maximizes their developmental outcome.

Keywords: infantile spasms; biomarker; long-range temporal correlations; fractal; treatment;

EEG Coherence as a Sensitive Monitor of Coma Recovery after Cardiac Arrest

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Coma is a state of unconsciousness, often occurring in patients following acute brain injury. One of the leading causes of coma is cardiac arrest (CA), which results in survivors emerging in a comatose state for a prolonged period. Standards of coma tracking have not changed in decades, and include hourly neurological exams. Recent studies propose tracking of coma recovery using electroencephalography (EEG). This study sought to monitor neurological recovery with EEG by assessing the coherence (i.e., phase connectivity) among different brain regions following resuscitation after CA. We hypothesized that intersite phase clustering (ISPC)—a measure of coherence—would be a sensitive measure of coma recovery for many days post-CA. Male Wistar rats were implanted with L-R frontal and occipital subdural electrodes, and underwent asphyxial CA and resuscitation while EEG data was recorded. ISPC was calculated between the various electrode pairs (6 total pairs) during the normal baseline and recovery states. In frequencies between 10-40Hz, ISPC among inter-hemispheric, intra- hemispheric, and diagonally connected brain regions significantly increased ($p<0.05$) 24 hours following CA. Other electrode connections at various frequencies (1-150Hz) also demonstrated a prolonged change in ISPC in recordings up to 13 days following CA. During the most accelerated phase of coma recovery (24hrs post-CA), the largest changes in ISPC were seen, with more gradual subsequent changes up until 13 days, when ISPC returned closer to baseline levels. Thus, EEG coherence is highly sensitive in the detection and monitoring of coma recovery in comparison to single-channel EEG monitoring and may have clinical implications for monitoring of comatose patients in the intensive care unit.

Keywords: coma; EEG; cardiac arrest; coherence; resuscitation;

Concurrent assessment of cerebral blood flow, oxygenation, and electrical activity following cardiac arrest and cardiopulmonary resuscitation

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Cardiac arrest (CA) affects over 500,000 people in the USA. Since poor neurological outcome is the leading cause of morbidity in CA survivors, an area of significant unmet clinical need is characterization of longitudinal changes in brain function following CA. We have developed a multimodal platform designed to assess neurovascular coupling in the brain following CA and subsequent cardiopulmonary resuscitation (CPR) in a rat model. The platform includes quantitative electroencephalography (qEEG) to monitor cerebral electrical activity, laser speckle imaging (LSI) to assess cerebral blood flow, and multispectral spatial frequency domain imaging (SFDI) to characterize cerebral hemodynamics. With this unique platform, we can quantify how cerebral blood flow and oxygen saturation are related to the recovery of qEEG signals following CA and CPR. We show that initial cerebral recovery following CA and CPR occurs in two main phases: the first is driven by hyperemic reperfusion of the brain and the second by cerebral oxygen consumption due to increased metabolic demand that coincides with restoration of qEEG activity. The transition point between these two phases is closely linked to the time of the initial burst of the EEG signal, and this initial burst can be predicted by assessing the area under the measured blood-flow curve. Differences in the temporal dynamics of the cerebral blood flow and oxygenation curves suggest decoupling between perfusion and metabolism in the brain during recovery from CA. Our unique, multimodal approach is expected to serve as a valuable translational platform with potential to help understand the dynamic events associated with CA and resuscitation, and ultimately provide knowledge that will improve care for patients suffering cardiac arrest.

Keywords: cardiac arrest; cardiopulmonary resuscitation; optical imaging; electroencephalogram; neurovascular coupling;

A Statistical Method for the Automatic Detection of High Frequency Oscillations in Human Intracranial EEG

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High frequency oscillations (HFOs) are a promising biomarker of epileptic tissue localization, but the detection of these electrographic events remains a challenge. Visual identification, which is the gold standard in present, is highly time consuming and subjective; therefore, automatic detectors show promising results, they typically require optimization of multiple parameters and post-processing steps. We propose a new automatic HFO detection algorithm that uses the amplitude probability distribution of the background activity to identify transient high amplitude events. The optimum threshold is calculated iteratively based on only a single parameter related to the percentage of number of events detected above the threshold. This detector can achieve a sensitivity of 99.31%, false positive rate (FPR) of 0.94%, and false detection rate (FDR) of 58.56% when compared with the visual detection reference and optimized the parameter to each channel individually. Alternatively, if the detection result is optimized to minimize FDR, we can achieve 88.18% sensitivity while decreasing FDR to 18.18%. The performance was superior to four published detectors when tested on the same dataset, demonstrating that the algorithm can automatically detect HFOs with a high degree of accuracy while requiring optimization of only one parameter. This simplicity allows consistent application of automatic detection across research centers and recording modalities.

Keywords: HFO; Epilepsy; Ripple; Fast ripple;

Cisplatin induces mitochondrial damage and hippocampal neurotoxicity: a potential mechanism for chemotherapy-related cognitive impairment

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Chemotherapy-related cognitive impairment is commonly reported following administration of chemotherapeutic agents and comprises a wide variety of neurological problems. Cisplatin is used to treat breast cancer and advanced ovarian cancer among other malignancies. Notably, more than 30% of advanced ovarian cancer patients develop CRCI during and after cisplatin-based chemotherapy. We have identified mitochondrial dysfunction and increased oxidative stress as a mechanism through which cisplatin causes hippocampal cell death, and severe dendritic damage in surviving neurons. The aims of this study were to examine the effect of the antioxidant N-acetylcysteine (NAC) in mitigating cisplatin-induced hippocampal damage and assess the effect of cisplatin on cognitive performance in a rat model. Cisplatin induces caspase-9 activation in cultured hippocampal neurons and non-reversible damage to dendritic spines and branches. Delayed treatment with NAC partially mitigated neuronal apoptosis and ameliorated cisplatin induced dendritic spine loss. When administered to adult Sprague Dawley rats, cisplatin (6 mg/kg) caused ~40% reduction in the number of dendritic spines in CA1 and CA3 hippocampal neurons. Lastly, cognitive testing of rats treated with a chronic cisplatin regimen (4 weeks of weekly injections of 5mg/kg, i.p) revealed significant deficits in hippocampus-dependent tasks. Rats were tested for Cued Context-Fear Conditioning, Novel Object Recognition, and Context Object Discrimination 5 weeks after treatment. Cisplatin-treated rats presented significant impairments in all three tasks. Mitochondrial dysfunction provokes free radical production, with resulting loss of dendritic spines. Our data supports the involvement of mitochondrial toxicity in the mechanisms of cisplatin-induced CRCI. Importantly the data demonstrates that cisplatin-induced hippocampal neurotoxicity and mitochondrial damage can be potentially mitigated with administration of NAC.

Keywords: cisplatin; n-acetylcysteine; chemotherapy related cognitive impairments; mitochondrial damage; hippocampus;

Microglial homeostasis dynamics in response to CSF1R inhibition and withdrawal

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Microglia are critically dependent on signaling through the colony stimulating factor 1 receptor (CSF1R) for their survival, and are depleted with CSF1R inhibition. Upon removal of CSF1R inhibitors, microglia repopulate the brain both through proliferation and differentiation of a microglial progenitor cell in the adult brain as well as proliferation of surviving microglia (Elmore et al. 2014). We further investigated the dynamics of this microglial repopulation using two different doses (600- and 290mg/kg chow) of CSF1R inhibitors, and found that the rate of repopulation is directly proportional to the extent of depletion; 95% elimination resulted in rapid repopulation and an overshoot past control levels within 7 days, whilst a 50% elimination resulted in slow repopulation, not achieving control levels within 7 days. Additionally, we sought to determine the regenerative capacity of microglia by exploring proliferative cycles via CSF1R inhibitor administration and withdrawal. Mice were treated with 3 cycles of 7-day CSF1R inhibition followed by 7 or 28 days of withdrawal. Repopulated microglia were fully dependent on CSF1R signaling, but microglia do not return a second or third time with 7-day recovery periods. However, given 28-day recovery cycles, microglia continue to repopulate, indicating that the microglial progenitors are able to regenerate themselves and contribute to multiple cycles of repopulation. Elmore, M.R.P. et al., 2014. Colony-Stimulating Factor 1 Receptor Signaling Is Necessary for Microglia Viability, Unmasking a Microglia Progenitor Cell in the Adult Brain. Neuron, 82(2), pp.380–397. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0896627314001718 [Accessed April 16, 2014]. NIH 1R01NS083801 Neurobiology of Aging Training Grant, NIH AG00096 ARCS Foundation Scholar Award

Keywords: microglia; progenitor; CSF1R; depletion; repopulation;

Microglial Elimination in 5xfAD Mice Prevents Neuronal Loss Without Modulating Amyloid Pathology

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In addition to beta-amyloid (Ab) plaque and tau neurofibrillary tangle deposition, neuroinflammation is considered a key feature of Alzheimer's disease pathology. Inflammation in Alzheimer's disease is characterized by the presence of reactive astrocytes and activated microglia surrounding amyloid plaques, implicating their role in disease pathogenesis. Microglia in the healthy adult mouse depend on colony-stimulating factor 1 receptor (CSF1R) signaling for survival, and pharmacological inhibition of this receptor results in rapid elimination of nearly all of the microglia in the CNS. In this study, we set out to determine if chronically activated microglia in the Alzheimer's disease brain are also dependent on CSF1R signaling, and if so, how these cells contribute to disease pathogenesis. Ten-month-old 5xfAD mice were treated with a selective CSF1R inhibitor for one month, resulting in the elimination of ~80% of microglia. Chronic microglial elimination does not alter A? levels nor plaque load; however, it does rescue dendritic spine loss and prevent neuronal loss in 5xfAD mice, as well as reduce overall neuroinflammation. Importantly, behavioral testing revealed improvements in contextual memory. Collectively, these results demonstrate that microglia contribute to neuronal loss, as well as memory impairments in 5xfAD mice, but do not mediate or protect from amyloid pathology.

Keywords: microglia; alzheimers; inflammation; amyloid;

Role of Microglial C5aR1 in the Arctic Alzheimer's Disease Mouse Model

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C5aR1, the main receptor for C5a, is primarily expressed on microglia in the brain. Previous work demonstrated C5aR1 antagonist, PMX205, decreased amyloid pathology and suppressed cognitive deficits in two Alzheimer Disease (AD) mouse models. However, the molecular mechanism of this protection has not been definitively demonstrated. Here we have taken advantage of the CX3CR1-GFP and CCR2-RFP reporter mice to distinguish microglia as GFP-positive and macrophages as GFP and RFP-positive. Mice were crossed with Arctic mice to yield CX3CR1+/-CCR2+/-Arctic-/- and CX3CR1+/-CCR2+/-Arctic+/-. To understand the role of microglial C5aR1 in the arctic mice, we crossed the mice with C5aR1KO mice to generate CX3CR1+/-CCR2+/-Arctic+/-C5aR1-/- and CX3CR1+/-CCR2+/-Arctic-/-C5aR1-/- mice. Mice were aged to 2, 5, 7 and 10 months to investigate the transcriptome of the microglia with age and progression of the disease. IHC analysis showed amyloid beta deposition in the Arctic mice consistent with previous results. Interestingly, no CCR2+ macrophages were seen near the plaques. The CCR2+ macrophage population was 2-6 % of the total CX3CR1+ population at all ages and genotype. Functional analysis of the top 500 genes, as sorted by p-value, from the microglia at 5 and 7 months using IPA software suggests cellular assembly and organization and molecular transport functions are decreased in the Arctic and increased in the Arctic C5aR1KO. Furthermore, at 7 months, cellular movement is the most common functional group activated in the Arctic and it is also activated in the Arctic C5aR1KO. Taken together, the data suggests CX3CR1+ microglia are key players in the Arctic mouse model, surrounding the plaques at the onset of plaque deposition. At 5 months, deletion of C5aR1 increases cellular functions in the Arctic C5aR1KO relative to Arctic. At 7mo deleting C5aR1 has less of an effect in the functional categories, suggesting 5 months may be a better age to target C5aR1 in the Arctic model.

Keywords: Alzheimer's Disease; Microglia; C5a; Complement; C5aR;

Characterizing the effects of microglial elimination and repopulation on Aß and tau pathology

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Microglia are the primary immune cells of the CNS, responsible for responding to and removing pathological insults, as well as, maintaining CNS homeostasis and synaptic plasticity. Despite these beneficial properties, several studies have implicated microglial activation in Alzheimer's disease (AD) and a variety of other CNS disorders. These findings suggest that microglia may serve as important therapeutic targets for AD as well as other neurodegenerative diseases. Our lab has discovered that microglia in the adult brain are dependent on signaling through the colony-stimulating factor 1 receptor (CSF1R) and identified a novel brain-penetrable CSF1R inhibitor. Using this CSF1R inhibitor, we can effectively eliminate >99% of microglia in the CNS and maintain cell elimination for the duration of treatment. Notably, we also discovered that upon inhibitor withdrawl, microglia fully and rapidly repopulate the CNS. These repopulated microglia are derived from CNS progenitor cells and may provide a key to resetting a chronically activated and neurodegenerative disease state. To this end, we sought to investigate the effects of a selective CSF1R inhibitor on microglia and AD pathology in triple transgenic AD (3xTg-AD) mice. In this study, 18-month-old 3xTg-AD mice exhibit elevated levels of inflammatory-related markers, specifically interferon-? signaling, which is dampened by microglial elimination and repopulation. Microglial repopulation does not lead to profound changes in plaque remodeling, but does significantly reduce small plaque deposition. Furthermore, mRNA pathway analysis indicates that repopulation upregulates signaling associated with phagocytosis. In addition, we also observed a significant increase in tau staining following microglial elimination, which was confirmed by increases in insoluble tau levels by ELISA. Together, these findings provide evidence that microglia play an important yet complex role in Aß and tau degradation.

Keywords: Alzheimer's disease; Microglia; Amyloid; Tau; CSF1R;

Hypothalamic Paraventricular Nucleus in the Actions of Acupuncture on Cardiopulmonary Responses: Responders and Non-responders

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Electroacupuncture (EA) is effective in reducing sympathoexcitatory blood pressure (BP) increases in 70% of subjects (responders). Medullary cholecystokinin (CCK) contributes to the nonresponsiveness. EA at P5-6 acupoints also modulates parasympathoexcitatory responses through actions in the brainstem. Although cardiopulmonary-induced decreases in BP and heart rate (HR) reflexes following iv. phenylbiguanide (PBG) are modulated in the medulla by acupuncture, the role of the hypothalamus is unclear. The hypothalamic paraventricular nucleus (PVN) regulates sympathetic outflow and BP. Vagal afferent stimulation activates neurons in the PVN but little is known about cardiopulmonary physiological actions in PVN during acupuncture. We hypothesized that the PVN participates in the cardiopulmonary responses and the effectiveness of EA-modulation of parasympathoexcitatory cardiovascular responses through both opioids and CCK. Rats were anesthetized, ventilated, and HR and BP were monitored. Application of PBG close to the right atrium was delivered every 10-min. Low frequency, low intensity EA was applied for 30-min during repeated PBG applications. A CCK antagonist was microinjected into the PVN of rats unresponsive to EA, and during repetitive EA, PVN opioid receptors were blocked with naloxone. PVN vagally-activated neuronal activity was examined with extracellular recording before, during and after EA with and without naloxone. Intravenous PBG induced consistent depressor and bradycardia responses. Microinjection of kainic acid or kynurenic acid in the PVN reduced the cardiopulmonary reflex responses. Bilateral EA at P5-6 acupoints reduced the depressor and bradycardia responses for over 60-min in responsive animals. Rats not responsive to EA and microinjected with PVN CCK antagonist were converted uniformly into EA-responsive rats. Subsequent inhibition with PVN naloxone reversed the EA responses. Thus, the PVN is important in processing cardiopulmonary

Keywords: Cholecystokinin; opioids; hypothalamus; non-responder; acupuncture;

From Bench to Bedside: Marizomib Activity in Malignant Gliomas - Preclinical Development and Early Clinical Trial Results

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Background: The proteasome plays a vital role in the physiology of glioblastoma (GBM), and proteasome inhibition can be used as a strategy for treating GBM. Marizomib is a second generation irreversible proteasome inhibitor which has a more lipophilic structure, suggestive of potential for penetrating the blood brain barrier (BBB). Methods: We investigated the in vitro and in vivo antiglioma activity of marizomib. Based on these results FDA approval was given to proceed to clinical trials. Preclinical Results: Marizomib inhibited the proliferation, migration and invasion of glioma cells. While marizomib induced free radical production and apoptosis, the reactive oxygen species quenching agent N-acetyl cysteine blocked these effects. In animal studies, marizomib distributed into the brain at 30% of blood levels in rats, and significantly inhibited (>30%) baseline chymotrypsin-like (CT-L) proteasome activity in brain tissue of monkeys. Encouragingly, immunocompromised mice intracranially implanted with glioma xenografts survived significantly longer ($p<0.05$) when treated with marizomib. These preclinical studies demonstrate that marizomib can cross the BBB, inhibits proteasome activity in rodent and non-human primate brain, and elicits antitumor effect in a rodent intracranial model of GBM. Early Clinical Results: We are now conducting a Phase 1 clinical trial of marizomib in recurrent GBM patients. In dose escalation, marizomib was well tolerated; most common adverse events were headache, fatigue, and nausea. Marizomib caused >70% inhibition of chymotrypsin-like activity on day 1 with 100% by day 28. Transient hyperactivation of trypsin-like (T-L) and caspase-like (C-L) activities was seen after the first marizomib dose. RANO responses were: 5/12 partial response, 5/12 stable disease and 2/12 progressive disease. Conclusions: Marizomib was well tolerated. Rapid and pronounced pan-proteasome inhibition accompanied a very promising overall response rate of 42%.

Keywords: brain cancer; proteasome inhibitors; preclinical development; clinical trials; biomarkers;

Adenosine kinase knockdown reverses radiation-induced cognitive impairments

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Clinical radiation therapy for the treatment of CNS cancers may elicit early onset or more severe cognitive dysfunction involving a range of neurodegenerative effects including a decline in neurogenesis, oxidative stress, and compromised neuronal plasticity. However, the molecular & cellular mechanisms underlying ionizing radiation (IRR)-induced cognitive decline (RCID) have not been resolved. Since IRR causes microglial and astroglial activation, we hypothesized that maladaptive changes in astrocyte function might be implicated in RCID. Among other gliotransmitters, astrocytes control the availability of adenosine, an endogenous neuroprotectant and modulator of cognition, via metabolic clearance through adenosine kinase (ADK). To understand better mechanistic regulation of astrocyte-mediated regulation of adenosine, we utilized Adk gene silencing approach (AAV8 Adk-KO) to study the CNS radiation response and its impact on cognitive function. Adk-KO vector targeted to astrocytes selectively knocks down (>80%) ADK in vivo and increase extracellular adenosine. Adult mice expose to cranial IRR (9 Gy) showed significant declines in performance of hippocampal-dependent cognitive function tasks (novel object recognition, object in place & contextual fear conditioning) 1 month post-IRR using a clinically relevant regimen. Importantly, analyses of irradiated brains showed significant elevation of ADK immunoreactivity in the hippocampus that was coincident with elevated astrogliosis. Conversely, mice implanted with Adk-KO at two days post-IRR showed significantly improved behavioral performance in all cognitive tasks 1 month post-exposure. Astrocytic Adk knockdown also attenuated radiation-induced astrogliosis and elevated ADK in the hippocampus. Analysis of adenosine signaling represents an innovative approach to define the link between purine metabolism & neuronal/astroglial alterations that are sensitive to IRR-induced changes in cognition. (Support: ICTS-KL2 award, MMA).

Keywords: Radiation; Cancer therapy; Cognition; Adenosine; Neuroprotection;

High Sensitivity and Specificity in Brain Injury Diagnostic Method Using Statistical Parametric Mapping of Positron Emission Tomography

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Traumatic brain injury (TBI) is an important health concern. Those who sustain traumatic brain injuries are at risk of developing neurocognitive and psychiatric complications. The majority of mild TBI (mTBI) patients recover within 3 to 6 months, but there are those who continue to experience post concussive symptoms and show no structural evidence of injury with computed tomography (CT) or magnetic resonance imaging (MRI). This study examines the sensitivity and specificity of functional imaging with resting positron emission tomography (PET) in distinguishing mTBI patients from controls using statistical parametric maps. Resting PET scan images from 15 controls and 10 chronic mild TBI patients were processed using the MATLAB program Statistical Parametric Mapping (SPM) to generate contrast overlays showing areas in which metabolic processes were significantly increased or decreased compared to controls ($P = 0.01$, Voxel Threshold = 30). Positive and negative Zmaps were created for each control and TBI patient by overlaying their PET scan with the contrasts. Three raters blind to all identifying information were asked to distinguish between mTBI and control Zmaps. Raters distinguished between control and mTBI subjects with a sensitivity of 97% and specifity of 100%. The high sensitivity and specificity suggest that PET imaging along with SPM can identify abnormalities in mTBI patients with chronic post concussive symptoms. Future studies should investigate the correlation between the location and amount of abnormalities and the severity of cognitive deficits and symptoms. Limitations include the small sample sizes of the controls and TBI patients and raters.

Keywords: PET; Traumatic Brain Injury;

Deletion of Fmr1 alters function and synaptic inputs in the auditory brainstem

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Fragile X Syndrome (FXS), a neurodevelopmental disorder, is the most prevalent single-gene cause of autism spectrum disorder. Autism has been associated with impaired auditory processing, abnormalities in the auditory brainstem response (ABR), and reduced cell number and size in the auditory brainstem nuclei. FXS is characterized by elevated cortical responses to sound stimuli, with some evidence for aberrant ABRs. Here, we assessed ABRs and auditory brainstem anatomy in Fmr1-/- mice, an animal model of FXS. We found that Fmr1-/- mice showed elevated response thresholds to both click and tone stimuli. Amplitudes of ABR responses were reduced in Fmr1-/- mice for early peaks of the ABR. The growth of the peak I response with sound intensity was less steep in mutants that in wild type mice. In contrast, amplitudes and response growth in peaks IV and V did not differ between these groups. We did not observe differences in peak latencies or in interpeak latencies. Cell size was reduced in Fmr1-/- mice in the ventral cochlear nucleus (VCN) and in the medial nucleus of the trapezoid body (MNTB). We quantified levels of inhibitory and excitatory synaptic inputs in these nuclei using markers for presynaptic proteins. We measured VGAT and VGLUT immunolabeling in VCN, MNTB, and the lateral superior olive (LSO). VGAT expression in MNTB was significantly greater in the Fmr1-/- mouse than in wild type mice. Together, these observations demonstrate that FXS affects peripheral and central aspects of hearing and alters the balance of excitation and inhibition in the auditory brainstem.

Keywords: fragile x; auditory brainstem; auditory brainstem response; synaptic balance;

Postnatal oxytocin treatment rescues social deficits in Fragile X model mice

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Fragile X Syndrome (FXS) is a genetic disorder caused by the silencing of the fragile X mental retardation 1 (Fmr1) gene. FXS is the most common monogenetic cause of inherited intellectual disability and autism. Both FXS and autism spectrum disorders are characterized by multiple cognitive and social deficits and currently there is no effective pharmacotherapy. Oxytocin, a neuropeptide well known for its role in parturition and social behaviors, is in clinical trials in children and adults for treatment of social deficits that occur in FXS and autism disorders. The oxytocin system is important for the normal development of functional networks involved in social behaviors. Fragile X model (Fmr1-KO) mice display similar cognitive and social deficits as humans with the genetic disorder. Thus, we used the Fmr1-KO model to test if early life oxytocin treatment has enduring effects on social behavior. Using Designer Receptor Exclusively Activated by a Designer Drugs (DREADD) to excite oxytocin-producing neurons in the hypothalamic paraventricular nucleus, we tested if endogenous oxytocin release facilitates social learning in the KO mice. We also tested if postnatal oxytocin treatment (intranasal, p7-14) has enduring effects that rescue social deficits in adulthood. We found that both acute release of endogenous oxytocin and postnatal oxytocin treatment restored social learning in adult Fmr1-KO mice Current studies are examining how postnatal oxytocin treatment alters the oxytocin system to restore cognitive function. As oxytocin is already being tested in clinical trials with children with autism and other intellectual disabilities, it is important to examine how oxytocin treatment during development effects normal development of functional networks.

Keywords: Fragile X; oxytocin; autism;

Treating facial paralysis by selective stimulation of facial muscles with a penetrating electrode array

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Objective: Permanent facial nerve injury is a difficult challenge for both patients and physicians given its potential for debilitating functional, cosmetic, and psychological sequelae. Although current surgical interventions have provided considerable advancements in facial nerve rehabilitation, they often fail to fully address all impairments. We aim to introduce an alternative approach to facial nerve rehabilitation following facial paralysis or Bell's palsy. Study design: Acute experiments in animals with normal facial function. Methods: The study included three anesthetized cats. Four facial muscles (levator auris longus, orbicularis oculi, nasalis, and orbicularis oris) were monitored with a standard electromyographic (EMG) facial nerve monitoring system with needle electrodes. The main trunk of the facial nerve was exposed and a 16-channel penetrating electrode array was placed into the nerve. Electrical current pulses were delivered to each stimulating electrode individually. Elicited EMG voltage outputs were recorded for each muscle. Results: Stimulation through individual channels selectively activated restricted nerve populations, resulting in selective contraction of individual muscles. Increasing stimulation current levels resulted in increasing EMG voltage responses. Typically, selective activation of two or more distinct muscles was successfully achieved via a single placement of the multi-channel electrode array by selection of appropriate stimulation channels. Conclusion: We have established in the animal model the ability of a penetrating electrode array to selectively stimulate restricted fiber populations within the facial nerve and to selectively elicit contractions in specific muscles and regions of the face. These results show promise for the development of a facial nerve implant system to treat individuals with facial paralysis.

Keywords: Facial paralysis; Reanimation; electrode; stimulation; facial nerve;

Parent Perceptions of Premature Infants' Physical Activity

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Background: Little is known about parent perceptions of physical activity (PA) in premature babies, a population at risk for adverse cardiovascular health profiles into adulthood. We hypothesize that 1) parents will perceive barriers to PA, and 2) parent, social and infant factors are associated with parent perceptions of PA. Objectives: 1) Explore parent perceptions of PA for premature babies, and 2) Identify associated parent, social, and infant factors. Methods: Cross-sectional exploratory study of parent-premature infant dyads in an intervention promoting exercise. Parents recruited from NICUs at five urban hospitals completed a 36-item questionnaire (Perceptions of Pediatric Physical Activity Scale (PPPAS)). Pearson's correlations and linear regression were used to explore associations between factors and PPPAS subscales (Benefits, Barriers, Personal Influence). Results: (n=73) Maternal age (mean years(SD)) 31.0(6.1), 63% Hispanic, 67% had monthly income of =$4999, 67% had some college education, 58% female infants, gestational age (mean weeks(SD)) 27.4(1.8), birthweight (mean grams(SD)) 974.9(267.4), and 50% first-born. Parents broadly perceived benefits to PA, (ex., Physical activity increases my infant's muscle strength). Greater variability was observed in perceived barriers (ex., It is dangerous for my baby to be physically active), and personal influence (ex., My attitudes about exercise will strongly impact my child's attitude towards exercise). Significant associations in bivariate analyses: Benefits, none; Barriers, birth order (r(p-value)) 0.342(0.004), income -0.380(0.001), number of children in home 0.375 (0.001), and education -0.307(0.01); Parental Influence, income 0.254(0.03). In regression, only income was associated with barriers (p-value=0.02). Conclusions: Parents of premature infants largely perceived benefits to PA. Perceived barriers varied with income. This study provides preliminary data for future studies of infant PA. NIH5R01HL110163

Keywords: physical activity; premature infants; perceptions;

FEASIBILITY OF EDUCATING PATIENTS RECEIVING PRESCRIBED OPIOID MEDICATION USING A BRIEF NOVEL MULTIMEDIA PLATFORM

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The objective of this feasibility descriptive study was to determine if a novel multimedia presentation in the Emergency Department can reduce non-medical usage of opioid analgesics by educating patients on the dangers and safe usage of opioid analgesics. The standard of care for patient discharges with opioid painkillers in the ED focuses primarily on the most alarming side effects while marginalizing the risks of addiction, safe storage and disposal or alternative methods to alleviate pain. While steps have been taken to ensure physician education and adherence to prescribing guidelines, no significant improvements have been made in the way of informing patients about their pain management. In this study, we randomized patients receiving opioid prescriptions in the ED into the Standard of Care Group, who received the verbal education by nurses at discharge, or the Intensive Education Group, who received a 6-minute video presentation on the safe usage and dangers of opioid medication. Both groups were immediately tested after education to gauge their knowledge. Data analysis on the 47 patients enrolled in the study revealed that the multimedia presentation significantly increased patient knowledge about opioids. Results from this study will clear the way for the next phase of the study, which is to implement the video throughout the ED, and test retention over the span of several weeks and months. In the long-term, it is our hope that patient education can decrease the non-medical usage of opioid analgesics and alleviate the opioid epidemic in the United States.

Keywords: Opioids; Education; Multimedia;

Children's Perception of Symptoms of Attention Deficit Hyperactivity Disorder (ADHD)

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The Strengths and Weaknesses of ADHD and Normal behavior (SWAN) rating scale provides a dimensional approach to measuring symptoms of ADHD in children (Swanson et al., 2012). The SWAN has been demonstrated to produce reliable and valid scores when utilized as a parent- or teacher-report (Lakes et al., 2011). We propose to evaluate the reliability and validity of scores derived from the SWAN as a child self-report (SWAN-SR). Fifty-four students (47 males; ages 7-14 years) enrolled in a school-based behavioral health program participated. Participants in grades 6-8 completed the SWAN-SR in a group setting and participants in grades 1-5 completed it in a one-on-one interview. Parents and teachers completed SWAN ratings of the participants. The SWAN-SR showed good internal consistency on the subscales of hyperactivity/impulsivity (H/I ; a=.85) and opposition (ODD; a=.84), and acceptable internal consistency on inattention (IA; a=.76). First, 22.2% of participants rated themselves as having slightly above average or higher symptoms of IA compared to 65.4% from parental reports and 75.9% from teacher reports. Second, 16.7% of participants rated themselves as having slightly above average or higher H/I symptoms compared to 80.8% from parental reports and 75.9% from teacher reports. Third, 37.7% of participates endorsed slightly above average or higher symptoms of ODD compared to 9.8% from parental reports and 13.0% from teacher reports. Child and teacher ratings of IA were marginally related (r=.27, p=.099) and child and parent ratings of H/I were significantly related (r=.30, p=.032). Preliminary findings indicate support the use of the SWAN-SR as a measure of children's perceptions of their symptoms. Notably, children were less likely to rate themselves as having symptoms of IA and H/I and more likely to rate themselves as having symptoms of ODD in comparison to their parents and teachers. Implications for treatment targets for children with ADHD are discussed.

Keywords: Attention deficit hyperactivity disorder; ADHD; self-report; behavioral health;

Evaluating ATP-induced calcium signaling as a promising shared functional defect and a biomarker for polygenic forms of autism.

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Autism spectrum disorder (ASD) is a complex neurobehavioral disorder characterized by social deficits, impaired language and communication skills, and repetitive tendencies. While the prevalence of autism is increasing, its etiology still remains unclear. There are currently no known molecular biomarkers underlying the autism phenotype, complicating further research for therapies and objective diagnostic assessments. The purpose of this study is to identify an initial biomarker that may be used in diagnostic screenings. We have previously observed low calcium signaling in fibroblast cells derived from patients with rare, monogenic forms of autism - fragile X and tuberous sclerosis TSC1 and TSC2 syndromes – through high throughput fluorescence imaging and single cell optical patch clamp methods. Using fibroblasts derived from patients enrolled through UC Irvine's Center for Autism Research and Translation, we analyzed IP3-mediated calcium signaling using FLIPR high-throughput imaging to measure calcium release from endoplasmic reticulum stores. We found that an overwhelmingly large proportion of fibroblasts from autistic patients had a lower response to ATP via purinergic P2Y receptors than cells from control patients. Likewise, we confirmed this difference was not due to different initial intracellular stores with ionomycin, a calcium ionophore, which induced comparable calcium liberation across all cell lines. These results strongly support the use of deficient calcium signaling in skin fibroblasts as an early diagnostic screening and provide a cell-signaling readout method for further research in potential therapeutics.

Keywords: Autism spectrum disorder; Calcium signaling; Neurobehavioral disorders;

Changes in and Correlates of Change in Inattentive, Impulsive, and Hyperactive Behavior Among Children Enrolled in a Behavioral Health Program

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This study examines how symptoms of ADHD respond to a behavioral health program and potential correlates of change over time. Archival data from fifty-three children (46 male; ages 5-12 years) enrolled in a behavioral health program was analyzed. Strengths and Weakness of ADHD Symptoms (SWAN), completed prior to and after enrollment, is a parent and teacher questionnaire measuring dimensional variation in children's strengths and difficulties in inattention, hyperactive, and impulsive behavior (Swanson et al., 2012). Lower scores indicate greater strengths. Scores from both time points and the difference between time points were used in analyses. Parenting Stress Index-Short Form (PSI-SF), completed upon enrollment, measures the level of stress associated with the role as a parent (Abidin, 1995). Higher scores indicate greater stress. Ratings of Behavioral Competencies (RBC), completed prior to enrollment, is a parent report measuring children's emotion and impulse regulation, compliance, and attention. Higher scores indicate greater behavioral competence. Findings indicate children had decreased inattention (parent report: $t(52)=5.4$, $p<.001$, $d=.73$; teacher report: $t(40)=5.7$ $p<.001$, $d=1.07$) and hyperactive/impulsive (parent report: $t(52)=4.5$ $p<.001$, $d=.72$; teacher report: $t(40)=5.7$, $p=<.001$, $d=1.08$) symptoms over time. Greater parent reported improvement in attention was associated with lower parental distress ($r=.30$, $p=.031$) and lower parent perception of the child being difficult ($r=.39$, $p=.004$). Greater parent reported improvement in hyperactive/impulsive behaviors was linked to greater behavioral competencies ($r=.28$, $p=.048$) and longer intervention duration in the behavioral health program ($r=-.30$, $p=.032$). Results suggest a behavioral health program can play a role in the improvement of hyperactive/impulsive behaviors and that parental stress significantly impacts response to intervention. Implications and directions for future research are discussed.

Keywords: ADHD symptoms; behavioral health program; parental stress;

Examining Barriers to Sports and Physical Activity in Children with ADHD and/or ASD

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Children with ADHD and ASD have specific impairments in impulsivity, inattention, and social communication (APA, 2013) that may interfere with their participation in sports. This study examines changes over time in physical activity (PA) participation and/or prosocial behavior during team PA. Parent reported barriers to their children's success in these areas is also examined. Ninety-two children (80 males) with ADHD and/or ASD aged 7-14 years and attending a behavioral health program participated. The Physical Activity and Sports Participation Questionnaire (PASP), a parent report of children's participation in various types of PA was completed twice; at the beginning and end of the school year. Compared to baseline, parents reported more engagement in recreational sports ($t(67)=-1.86$, $p=.068$), fewer social difficulties during team PA ($t(48)=2.22$, $p=.031$), greater athletic abilities ($t(51)=2.77$, $p=.008$), and fewer ADHD symptoms ($p=.049$, McNemar Test). ADHD symptoms reported to specifically interfere with participation in sports were initially reported by parents of elementary aged and middle school aged children (84% and 78%, respectively) compared to 74% and 63% at the end of the school year. Parents also reported multiple barriers to their children's success in PA participation, which they perceived to be the most remarkable factors in preventing the child from continuing in sports: (1) ADHD Symptoms (51% of parents), peer difficulty (37% of parents), non-compliance (25% of parents), and child frustration (22% of parents). Preliminary findings suggest that children enrolled in a behavioral health program demonstrate ancillary salutary benefits in PA participation and improved prosocial behavior during PA compared to their baseline. Engaging in an intensive social skills training program can reduce barriers to participating physical activities for children with ADHD and/or ASD and is likely to improve prosocial behaviors in sports participation.

Keywords: ADHD; ASD; physical activity;

Exploring Multi-Informant Discrepancies in Ratings of Social Skills and Problem Behaviors for Children with Neurodevelopmental Disorders

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There has been recent attention on research examining the disparity in ratings of social skills and problem behaviors among various informants for children with neurodevelopmental disorders including Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). Several studies have found significant relationships between these discrepancies, treatment approaches, and stress (e.g. De Los Reyes et al, 2012). The objective of this study was to quantify multi-informant discrepancies in parent-child ratings of social skills and problem behaviors for children with ADHD, ASD, and related disorders. Forty-one children (37 male), between ages 8 and 15, from a behavioral health program participated. The Social Skills Improvement System (SSIS) parent report and child self-report were used (Gresham & Elliott, 2008). Findings indicated that average child-reported standard scores (SS: M=97.49; PB: M=105.34) and parent-reported standard scores (SS: M=87.46) were within one standard deviation of the normative average range (M=100; SD=15), with the exception of the parent ratings of problem behaviors (M=118.34). For Social Skills ratings, 59% of children and 51% of parents reported scores in the average range. For Problem Behavior ratings, 76% of children and 41% of parents reported scores in the average range. Many parents reported below average ratings on Empathy (37%) and Responsibility (39%) and above average ratings on Externalizing (46%). Significant positive relationships between parent and child ratings were found across subscales: Assertion (r=.315, p=.045), Empathy (r=.391, p=.012), Engagement (r=.403, p=.009), Self-control (r=.428, p=.005), Externalizing (r=.269, p=.088), and Bullying (r=.306, p=.052). This data provides information about how children with these disorders perceive themselves, and how their assessment compares to their parents'. These findings may enhance our understanding of parent-child relationships and guide treatment approaches.

Keywords: multi-informant; social skills; problem behaviors; self-report assessment; neurodevelopmental disorders;

Pilot Testing the Impact of an Innovative School-based CBT Intervention in Partnership with El Sol Science and Arts Academy of Santa Ana

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Background: The impact of high crime rates, poor overall health status, and limited access to healthcare on mental health is profound in Santa Ana. Over the past four years, UCI's Program in Nursing Science has partnered with El Sol Science and Arts Academy, a K-8 charter bilingual school in Santa Ana with 96% Latino families, to provide health education. Together, we have observed El Sol middle school children have exhibited increasing rates of anxiety and depression. In responding to requests from El Sol teachers and administrators, UCI Program in Nursing Science developed a culturally sensitive Emotional Health Curriculum which is based on Cognitive Behavioral Therapy (CBT) Purpose: The primary objective was to examine the efficacy of the Emotional Health Curriculum; and the secondary objective was to describe parent and teacher perceptions of feasibility and acceptability of the Curriculum. Methods: This design was mixed methods with quantitative and qualitative approaches. We used Randomized Controlled Trial method to pilot test the efficacy of Emotional Health Curriculum. The trained senior Bachelor of Science in Nursing (BSN) students delivered 8-week Emotional Health Curriculum to 100 children, and also taught General Health Curriculum in 100 children in the control group. We used focus groups to collect data about parent and teacher perception of the Curriculum. Results: We will report group differences in anxiety/depression and emotion regulation between intervention and control groups. We are conducting content analysis to summarize relevant themes about feasibility and acceptability of the Emotional Health Curriculum. Discussion: Emotional Health Curriculum may lead to improvement not only in mental health but also academic achievement in children. This early prevention/intervention approach will have great potential to provide high quality services in a cost-effective manner to at-risk communities.

Keywords: anxeity and depression; health disparities; community partnership;

An Epigenetic Model of Schizophrenia

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Schizophrenia is a debilitating mental disorder that affects about 1% of the world population. It is poorly managed by current medications. The primary obstacle in developing effective antipsychotics is our lack of animal models that adequately recapitulate the human symptoms of schizophrenia in animals. Schizophrenia is a multigenic, developmental and epigenetic disorder. We devised a simple animal model that addresses these three factors. We recalled a series of studies in the sixties and seventies have reported that methionine administration to patients with schizophrenia exacerbate the psychotic symptoms. Methionine is the universal methyl donor and brings the multigenic component to our assay and is an epigenetic component that has been shown to be important in neurogenesis and synaptic transmission. We also know that the levels of DNA methylation are higher in children conceived in the energy-limited (starvation) season than in the harvest (feeding) season and thus that developmental deficits are dependent on prenatal methylation. We therefore investigated whether administration of methionine during gestational stage induces the advent of schizophrenic-like symptoms. We administered methionine to pregnant mice and studied their offspring. We show that the offspring displays behavioral phenotypes that mimic the three classes of schizophrenia-like symptoms: positive, negative and cognitive deficits. We also show that prominent changes occur in expression of five genes that have been directly implicated in the pathophysiology of schizophrenia. Finally we show that a typical and an atypical antipsychotic drug reverse the behavioral deficits differently.

Keywords: None

Sleep Disorder Impact on Efficacy of Prolonged Exposure Therapy for Post-Traumatic Stress Disorder

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There is growing evidence that sleep disturbances may impede the utility of existing therapeutic interventions for PTSD. The vast majority of individuals with PTSD report poor sleep. A meta-analysis found that patients with PTSD generally have lighter sleep, meaning more stage 1 and less stage 3 sleep, than controls. Development of PTSD symptoms following a trauma has also been associated with a more fragmented pattern of REM sleep (Mellman, 2002). In addition to disturbances in REM sleep and wakefulness following the onset of sleep, there is growing evidence for a strong association between PTSD and sleep-disordered breathing (SDB) For example 52% of a PTSD cohort reported the presence of sleep-disordered breathing, which was associated with increased severity of PTSD symptoms (Krakow, 2000). In a large study of the national VA database looking at comorbidities associated with obstructive sleep apnea (OSA) an odds ratio between 2.7 and 3.0 was found for PTSD (Sharafkhaneh, 2005). A similar study using the National Inpatient Sample, a commercial database of non-government patients found an odds ratio of 2.1 for PTSD if a patient had a diagnosis of OSA (Reist, unpublished data). Of particular intrigue are observations that treatment of SDB can have a benefit on PTSD outcome. Engdahl and colleagues (2000) reported significant improvement in PTSD symptoms with sleep treatment. More recently a retrospective study of 56 Veterans with PTSD and OSA found that CPAP (continuous positive airway pressure) therapy reduced PTSD-associated nightmares and improved overall PTSD symptoms (Tamanna, 2014). Finally, there is preliminary data that patients with both PTSD and OSA show more benefit for PTSD symptoms from combination therapy (prolonged exposure + CPAP) than for prolonged exposure alone (Amin, 2013). This retrospective review examined the hypothesis that sleep disturbance impacts the outcome of prolonged exposure therapy for PTSD. Included subjects were those treated with prolonged exposure (PE) who also had PTSD Check List (civilian version, PCL-C) scores at each therapy session (N=18). A group of subjects without SDB (n=12) was compared to a group with untreated SDB (n=6), five of which were documented by polysomnography. All subjects in the sleep disordered group received a minimum of 10 sessions and the mean number of sessions was comparable between both groups. Post treatment PTSD checklist (PCL-C) scores were significantly reduced in those without a sleep disorder (-28.25; 58.0% reduction; $F[1,11] = 59.041$, $p<.001$; $d = 2.22$) but not those with a sleep disorder (-7.17; 13.5% reduction). With the exception of one no-SDB subject, all post-treatment PCL-C scores were below 50 (one subject had a score of 50). In contrast, for the SDB group no post treatment PCL-C scores were below 50 (chi square 14.14, $p < 0 .001$). Categorizing subjects by response to PE (> 50% reduction in PCL-C score) also showed a significant effect of group (chi square = 5.72, $p = .016$). These observations support the idea that efficacy of prolonged exposure therapy is impacted by sleep quality. If these findings are replicated treatment algorithms may need to incorporate the presence or absence of sleep disorders as a factor in treatment choice. One mechanism by which exposure based PTSD treatment may be hindered in the context of sleep disturbances is through disruption of memory consolidation and generalization of extinction memory. Previous reports have found that disrupted sleep following fear conditioning blocked the consolidation of the extinction memory (Spoormaker, 2010) and generalization of an extinction memory from an extinguished stimulus to an unextinguished stimulus (Pace-Schott et al., 2009).

Keywords: PTSD; sleep disorder; sleep-disordered breathing SDB; prolonger exposure therapy

Biomedical Image Interpretation: An Assessment of the Comparative Sensitivity of Color Mapped versus Grayscale Imaging Display and Analysis for the Detection of Subtle Pathology

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OBJECTIVE: The objective of this study is application of advanced methods of image analysis developed for physical sciences and engineering applications, such as astrophysics and signal processing in engineering, to modern medicine to advance patient care. It seeks to develop a new paradigm for biomedical image processing and assessment, which will improve the sensitivity for detection of subtle pathology. Grayscale display is the current standard for radiological images. The human eye, however, can discriminate thousands of hues of color as opposed to only approximately 100 shades of gray [1,2]. This study looks at whether color mapping of radiographs can increase the sensitivity and efficiency for detection of entities such as subtle bone pathology and pneumothoraces. Lytic bone metastasis was taken as a heuristic model for the pilot study. RESULTS: The pilot study results show that for grayscale images, the sensitivity for detecting subtle bone lesions is 67%, with a specificity of 96% and positive predictive value of 90%. For color mapped images, the sensitivity is 87%, with a specificity of 79% and positive predictive value of 94%. The results of this study demonstrate that color mapping of radiographs can increase sensitivity and positive predictive value for detecting subtle pathology, but can decrease specificity. References: 1. Shi, X.Q., Sallstromb, P. and Welander, U. A Color Coding Method for Radiographic Images. Image and Vision Computing, 2002. 20: 761–767. 2. Kundel, H.L., Visual Cues in the Interpretation of Medical Images. Journal of Clinical Neurophysiology, 1990. 7(4): 472-483.

Keywords: Convergence Science; Biomedical Imaging; Medicine; Color mapping; Lytic Bone lesions;

Color Me Gray: Color Mapped versus Grayscale Radiographic Image Display for Detection of Pneumothorax

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Objective: Advanced methods of image analysis have been developed in fields such as astrophysics and engineering. This study applies these methods to biomedical image processing in an aim to improve sensitivity and efficiency for detection of subtle pathology. Chest radiographs (CXR) are commonly used to exclude pneumothorax (PTX). Prior studies have demonstrated 50% sensitivity for PTX detection on grayscale CXR. The human eye, however, relies heavily on color for perception with 6.5 million cones dedicated to processing the saturation, hue, and brightness of observed colors. A 2010 pilot study showed that color mapping (CM) of images improved sensitivity of bone lesion detection from 67% to 87% compared to grayscale (GS) images. Our study investigates CM of CXR as a method to improve the sensitivity and efficiency of PTX detection. Materials and Methods: Sixty CXR were selected consisting of 22 negative controls and 38 positive cases for PTX. Images were transformed from grayscale to UnionJack CM utilizing ImageJ software. Reviewers included radiology faculty, fellow, and residents. Reviewers were restricted from adjusting image contrast or brightness. Each reviewer viewed 30 GS images and 30 CM images, each image set consisting of a mix of controls and positive PTX cases. Reviewers were given 22 sec to view each image and mark the case as negative or positive with laterality for PTX but could advance to the next case once a diagnosis was reached. Results: GS images showed a PTX detection sensitivity of 78%, specificity of 86%, PPV of 91%, and FPR of 14%. CM images showed a PTX detection sensitivity of 63%, specificity of 83%, PPV of 87%, and FPR of 17%. Average reading times were 16.5+/-0.4 sec for GS images and 18.1+/-0.3 sec for CM images ($p<0.05$). Conclusion: GS imaging showed superior sensitivity and efficiency for PTX detection compared to CM. Lack of reviewer familiarity with CM images may limit the effectiveness of this technique in clinical practice.

Keywords: convergence; biomedical imaging; image processing; clinical efficiency;

Characterization of Skin Mechanical Properties Following Electrochemical Therapy

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Background and Objectives Scarring in skin arises from reformation of injured tissue from abberant wound healing propagated by excess formation of collagen. Although treatments involving ablations and heat treatments have been developed, these processes are invasive and may alter the healing process. Our group has innovated in situ redox-based electrochemical therapy (ECT), which modifies the structure and mechanical properties of the tissue, and may potentially be utilized to treat scars. The goal of our study is to assess the changes in properties of the skin following ECT treatment using Optical Coherence Elastopgraphy (OCE) and Puncture Force Characterization (PFC). Study Design/Materials and Methods ECT was performed on ex vivo porcine skin samples using voltage ranging from 3-5V, applied for 3-5 minutes. OCE and PFC were performed on each skin sample at the cathode, anode, and control site (several millimeters away from ECT regions). With OCE, 20-1000 MHz frequency was utilized to determine the resonant frequency of the tissue, from which images were obtained. With PFC, 2mm tapered needles were used to puncture the skin while force, displacement, and time were recorded. Results PFC demonstrated changes in stiffness of the post-ECT tissue due to structural changes observed by OCE. From OCE, we observed changes in optical properties of the tissue at the anode and the cathode. From PFC, we observed tissue softening at the anode by 20% compared to the control and stiffening at the cathode by 10% compared to the control. Conclusion ECT causes tissue softening at the anode and tissue stiffening at the cathode. These changes may be due to modification of the skin matrix caused by the hydrolysis and pH change in the dermis. Further ECT experiments using varying treatment parameters is warranted.

Keywords: Electrochemical Therapy; Optical Coherence Elastography; Altering Tissue Mechanics;

Colorimetric urine-dipstick test for serum albumin

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Objective: Kidneys filter waste from the human body with high selectivity to ensure maximum retention of nutrients and plasma contents. An early sign of kidney dysfunction is the excretion of essential plasma contents (glucose, amino acids, proteins, etc.) and one of these sign is the presence of serum albumin (HSA) in urine, especially for diabetics. The current urine dipstick for HSA is not sufficient in detecting the persistent excretion between 30-300 µg/mL, which is an early indication of kidney problem. To address this problem, we aim to develop a molecular biosensor for a more sensitive and specific detection of HSA using de novo selected urea-stable aptamers coupled to gold nanoparticles. The sensor will take advantage of the structure-switching aptamer and surface plasmon resonance of gold nanoparticles to generate a simple color changing sensor. In principle, in the absence of HSA, the DNA aptamer will keep the nanoparticles aggregated. However, when HSA is presence, the aptamer will bind to the target and alleviate the aggregation of the gold nanoparticles, leading to a color changing event. The end product will be a paper-based test. Results: To generate structure-switching aptamers against HSA in urea-stable conditions, the selection platform must be established. The selection platform is composed of an amino-modified oligonucleotide that is complementary to a fixed-domain on the aptamer sequence; the oligonucleotide is covalently attached to agarose beads derivatized with succinimide functionality. This allows for the immobilization of aptamer library via base-pairing, and acts as the platform for switching aptamer evolution. We have experimental evidence demonstrating the aptamer library interacts with the oligo-modified agarose beads. We have successfully completed 6 rounds of SELEX, and the aptamer pool shows enrichment for sequences with affinity towards serum albumin. We aim to sequence the pool once the selection stabilizes.

Keywords: Biosensor; Aptamer; SELEX;

Mouse Model of Uremic Cerebral Microbleeds

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Introduction: Cerebral microbleeds are more common in chronic kidney disease (CKD) and dialysis patients compared to the general population. Diminished kidney function alone appears to be a risk factor for microbleeds, independent of age and hypertension. Microbleed burden in CKD patients is associated with cognitive dysfunction and increased risk of future hemorrhagic stroke. The mechanisms that drive uremic microbleed formation are unclear. Hypothesis: We hypothesized that CKD mice are predisposed to develop cerebral microhemorrhages (the pathologic substrate of microbleeds), and that a standardized inflammatory stimulus (lipopolysaccharide, LPS) will amplify microhemorrhage burden in CKD mice compared to non-CKD controls (CTL). Methods: Animal groups included CTL (n=4), CKD (n=5), CTL+LPS (n=5) and CKD+LPS (n=5). CKD induction in male C57BL/6 mice was achieved via nephrotoxic adenine diet for 18 days; mice were re-exposed to adenine diet at 5 weeks to maintain uremia. At 8 weeks following CKD induction, CKD and control mice were treated with LPS 1 mg/kg i.p. dosed at 0, 6 and 24 hours. Brains were harvested one week after LPS injections and 40-micron sections were stained with Prussian blue to identify microhemorrhages. IHC was performed for blood-brain-barrier (BBB) tight junction proteins. Results: CKD mice had significantly elevated blood urea nitrogen and had tubulointerstitial fibrosis on kidney histology. Total number of brain microhemorrhages per cm-square was 2.3±0.5 (mean±SEM) for CTL mice, 4.8±0.5 for CKD mice, 4.2±0.7 for CTL+LPS mice, and 13.2±3.2 for CKD+LPS mice ($p<0.05$ for CKD+LPS vs. other groups). Immunostaining showed decreased occludin and ZO-1 expression in CKD mice compared to CTL. Conclusions: We have generated a mouse model that will facilitate future mechanistic studies in the field of uremic microbleeds. Our initial findings suggest that CKD alters BBB integrity and that inflammation amplifies development of microbleeds in CKD.

Keywords: microbleeds; chronic kidney disease; mouse model;

Strong, stable neuronal networks associated with hypsarrhythmia in infantile spasms

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Infantile spasms (IS) is a potentially devastating form of epilepsy that strikes in the first year of life and is classically accompanied by a chaotic, high-voltage, and asynchronous electroencephalographic (EEG) pattern known as hypsarrhythmia. Because IS and hypsarrhythmia are associated with a wide array of etiologies, we hypothesize that an assessment of brain networks will lead to a unified understanding of the generation of this rhythm. We collected 20-minute segments of awake scalp EEG data from 14 patients with IS (10 with hypsarrhythmia), before and after treatment. As a diseased-matched control, we also analyzed the awake EEG of 11 subjects with normal EEG studies who were evaluated due to clinical suspicion of epilepsy. Connectivity was measured between pairs of electrodes by identifying the maximum cross correlation within successive 1-second epochs of data. Significance was assessed by normalizing the cross correlation value by the expected variance of the calculation and comparing to a baseline distribution generated via permutation resampling (Chu et al. 2012). For each pair of electrodes, connection strength was defined as the percentage of 1-second epochs that were significant. First, our analysis showed that the EEG-based networks were stable over several minutes, even in those with hypsarrhythmia. Second, we found stronger connections in IS patients with hypsarrhythmia, as compared to controls and IS patients without hypsarrhythmia. Lastly, these strong connections decreased to control levels following treatment. These findings are contrary to the empirical clinical description of hypsarrhythmia as “chaotic.” Further, they suggest that increased connectivity underlies the pathophysiological state that generates hypsarrhythmia and IS, which carries implications for assessing treatment efficacy and predicting clinical outcome using quantitative measures.

Keywords: Epilepsy; Infantile spasms; EEG; Connectivity; Brain networks;

Direct Measurement of in vivo Ciliary Beat Frequency using Optical Coherence Tomography

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Background Cilia are responsible for maintaining mucociliary clearance in the upper airway, thus the critical component of respiratory health. Ciliary beat frequency (CBF) describes the overall function of ciliated epithelial cells. Presently, measuring CBF is via ex vivo phase-contrast microscopy (PCM) while in vivo measurement of CBF remains challenging as visualizing cilia in vivo has not been achieved. Optical coherence tomography (OCT) is minimally invasive and analogous to ultrasonography but with a higher resolution (~10 μm). Our goal is to provide a means to directly measure CBF in a post-mortem animal model using OCT, which may then be advanced for use in a clinic setting. Methods A swept-source OCT system (central wavelength: 1310 nm, scan rate: 50 kHz), acquiring images at 25 frames per second with a flexible probe (outer diameter of 0.7 mm), was used in this study. Tracheae of three freshly euthanized male New Zealand white rabbits (~4 kg) obtained from another study were imaged. Fifteen axial-lines were recorded in each trachea and processed using the fast Fourier Transform in MATLAB, and the average frequency domains were reported. The tracheae were then extracted, and CBFs were determined using PCM (control). After adding 1:2 albuterol, the samples were again observed under PCM and the OCT system. Results The means of the 3 samples were reported. Using OCT, the post-mortem CBF range was measured to be 3.61-4.25 Hz, while the ex vivo CBF range with Albuterol was 5.65-6.45 Hz. Using PCM, the CBF range of the controls and albuterol samples were 3.55-4.34 Hz and 3.99-5.78Hz, respectively. Conclusions While the OCT system does not have the ability to resolve individual cilium, it has the ability to directly measure CBF in post-mortem rabbits. In addition, drug response of cilia was also observed using the proposed method. Measuring in vivo CBF is made possible. Our future work will focus on clinical studies of the effect of chronic smoking on CBF.

Keywords: Optical Coherence Tomography; Ciliary Beat Frequency; Phase-Contrast Microscopy;

Incorporation of Nanopatterns onto Curved Artificial Cornea Devices and Testing of Durability

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We are harnessing industrially scalable nanofabrication techniques to create the first totally synthetic (plastic) artificial cornea device. Current corneal devices may have to be explanted due to lack of host cell integration (stromal melt), over-proliferation of host cells on the device (retroprosthetic membrane formation), as well as bacterial infection. Our unique nanopatterned structures can be fabricated over the corneal devices using nanoimprint lithography and dropcasting, and have been shown to be effective in improving cell-response. We aim to eventually commercialize this technology and plan to begin animal trials this year. We have developed methodology for applying the nanostructured coating to the curved artificial cornea device. While there are robust methods for applying such coatings to flat polymer surfaces, this type of curved surface process has never been developed. Additionally, we have ran experiments for the durability of these surfaces when handled by surgeons, and the durability of the coating when submerged in a warm, aqueous environment mimicking the eye.

Keywords: Artifical Cornea Device; Nanoimprint lithography; Nanotechnology;

Pharmacokinetic Analysis of Aerosol Propellant HFA-134a Elimination in the Human Breath

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The goal of the study is to model the elimination kinetics of Hydrofluoroalkane (HFA-134a) in the exhaled breath following a typical single asthma inhaler administration. HFA-134a is the most commonly used aerosol propellant in metered dose inhalers. We previously demonstrated that our technical capabilities allow us to measure breath HFA-134a levels at 24 to 48 hours post asthma inhaler administration, and thus breath HFA-134a is a promising biomarker for identifying asthma inhaler compliance (Clinical and Translational Science 2015). Exhaled breath gases were collected in evacuated electro-polished stainless steel canisters from healthy participants at baseline and at 5 min, 7 min, 10 min, 15 min, 30 min, 1hr, 2hr, 3hr, 4hr, 6hr, 8hr, 12hr. 24hr, 36hr, and 48hr -post inhaled corticosteroids administration (Flovent HFA, Glaxo Smith Kline). The corresponding ambient HFA-134a levels were also measured. HFA-134a levels in the breath and ambient air samples were quantified using gas chromatography with a quadrupole mass spectrometer detector. The Institutional Review Board at the University of California, Irvine approved the study, and informed consent was obtained from the participants. HFA elimination in the breath followed a three-exponential pharmacokinetic model. The estimated time constants (mean (SD)) for the three components were 5.45 (0.52) minutes, 62.4 (11.1) minutes, and 664 (140) minutes, with an overall mean retention time (MRT) of 71.8 (40.4) minutes. The shortest and longest half-life components comprised 66 (17) % and 9 (7) % of the total area under the curve, respectively. Breath carbon dioxide (CO2) levels were also monitored as a reference breath gas to ensure that the gas sampled was alveolar gas. The mean (SD) CO2 level was 4.7 (0.6) % of all breath samples. This study demonstrates that the breath HFA-134a elimination in healthy control humans can be described by a 3rd order exponential equation. In earlier studies, we modeled bicarbonate distribution kinetics and found similar time constants (2.2 min, 11.9 min, and 83.3 min; MRT 65 min.; Barstow et al. Am. J. Physiol. 259: R163, 1990). We speculate that the first two time constants reflect compartmental kinetics with the lung and circulation while the slowest primarily reflects distribution to body tissues. The kinetics for HFA appear to be slower than for bicarbonate. The calculated HFA-134a elimination parameters (i.e., rate constants or corresponding half-lives) may be useful in conjunction with breath HFA-134a levels for accessing asthma inhaler medication compliance and further to understand physiological complexity of the lungs that affect HFA elimination.

Keywords: asthma inhaler; compliance; HFA; pharmacokinetic analysis; human exhaled breath

A prospective, randomized, open label trial of two doses of oral betaine in patients with non-alcoholic fatty liver disease (NAFLD) and elevated alanine aminotransferase (ALT) - Preliminary Results

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the United States with an estimated prevalence of 10-46% of the population. About 20% of NAFLD patients may progress to cirrhosis, and NAFLD is projected to be the leading cause of liver transplantation by 2020. Currently there is no generally accepted treatment for NAFLD. Betaine (trimethylgycine) is a nutritional supplement which has been shown to reduce hepatic lipid accumulation and reverse insulin resistance in animal models. Preliminary studies in humans with NAFLD suggested betaine might improve ALT, too. The aim of the current study was to determine whether 12 weeks of oral betaine improved ALT in patients with a diagnosis of NAFLD and elevated ALT. Inclusion criteria included ALT>50 IU/mL, clinical diagnosis of NAFLD, and absence of other causes of liver disease. Patients were stratified based on the presence of type 2 diabetes mellitus (DM2) and were randomized into two treatment arms (low and high betaine). This study was approved by the institutional review board of the Long Beach Veterans Administration. We present preliminary results for the first 12 patients who completed 12 weeks treatment (combining the two treatment doses). All participants were male. The average age was 41 with an average BMI of 33.5. The average ALT was 112. There was only 1 patient with DM2. At week 12 of treatment ALT decreased by 30%, with ALT decreasing 40% in the low dose arm. There were no significant changes in body mass index, fasting glucose, or hemoglobin A1C. There were no significant adverse events or change in study medicines due to adverse events. In conclusion, oral betaine supplementation for 12 weeks in patients with NAFLD decreased ALT by about 30%. Enrollment is continuing with final results expected in about a year. We acknowledge financial support from ICTS for the initial clinical trial of betaine in humans.

Keywords: Non-alcoholic fatty liver disease; Insulin resistance; Liver disease; Betaine; Fatty liver;

An 8 week exercise training reduces glucocorticoid receptor (GR) expression on circulating leukocyte in healthy and asthmatic adolescents

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BACKGROUND: Poor fitness in children and adolescents is associated with worsening of asthma symptoms and fitness training may improve asthma control. The mechanism linking fitness or exercise with asthma is not known. We hypothesized that in children or adolescents, repeated bouts of exercise (known to increase cortisol and other stress/inflammatory mediators) would lead to a down regulation of GR on circulating leukocytes reflecting a reduced responsiveness to stress in general. AIM: To evaluate GR expression levels in circulating leukocyte subtypes in response to an acute bout of exercise before and after exercise training program in healthy and asthmatic adolescents. METHODS: Fourteen healthy and nine asthmatic adolescents (14-17 y.o) completed an 8 week exercise training program. Pre and post-training, the participants performed an exercise challenge (ten 2-min bouts at ~75% peak VO2 with 1-min rest interspersed). Blood was drawn prior, immediately after exercise challenge and one hour into recovery. Standard flow cytometry methods were used to examine GR expression in leukocyte subtypes. Mixed models, accounting for subject inter-correlation, were run ($p<0.05$). RESULTS: Peak VO2 increased by 12±3% indicating that training had improved aerobic fitness systemically. There was a significant difference in GR expression among the leukocyte subtypes, with highest expression in eosinophils. There was a significant decrease in baseline GR expression on monocytes and NK/NKT cells with training ($p<0.05$) and a similar trend seen across the other leukocyte subtypes. There was no difference in GR expression in response to training between healthy and asthmatic adolescents. CONCLUSIONS: This is the first prospective study in adolescents to show that exercise training reduces circulating leukocyte GR expression. We speculate that exercise training downregulates the stress response in general, and was manifest by decreased GR expression.

Keywords: Exercise training; adolescents; glucocorticoid receptor; asthma;

Rise in Frequency of Sepsis Codes and Decline in Sepsis-Associated Case Fatality Rates in California between 2000-2010

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Research Objective: Hospitalizations for sepsis have more than doubled in the last decade, prompting national efforts to improve recognition and management. It is unclear whether this trend represents a true rise in sepsis cases or improved capture since the introduction of new sepsis ICD-9 codes in October, 2002. Our aim was to evaluate trends in sepsis frequency and case fatality between 2000 and 2010 in California. Study Design: We conducted a retrospective cohort study of patients admitted to all California (CA) hospitals from January 2000 to December 2010 using a comprehensive state hospitalization dataset. Sepsis was identified by ICD-9 coding and categorized as severe if organ failure was present. Admissions with more than one sepsis code were categorized according to the most severe code. Sepsis rates were calculated per 10,000 admissions. Case fatality rates were calculated for admissions with severe and non-severe sepsis diagnoses. Logistic regression models evaluated variables associated with sepsis and mortality, including comorbidity, age, race, and time. Principal Findings: The rate of all sepsis admissions tripled over the last decade, from 193 to 569 cases per 10,000 admissions, with a 4.3 and 2.0 fold increase in severe and non-severe sepsis, respectively while total annual admissions remained unchanged over the study period. A greater increase in sepsis rates occurred among patients who were septic upon admission where there was a 7.8 and 5.1 fold increase in severe or non-severe sepsis upon admission, respectively, over the 11 year period. Mean Romano comorbidity scores were highest among severe sepsis cases and increased steadily at the same rate for all patients until 2007, after which they remained nearly constant for all admitted patients and sepsis subcategories. Despite increases in comorbidity scores, crude case fatality rates decreased dramatically over a decade, from 492.4 to 269.8 severe sepsis deaths per 1,000 severely septic patients (1.8 fold drop) and from 124.2 to 34.6 non-severe sepsis deaths per 1,000 non-severe septic patients (3.6 fold drop). Findings persisted in multivariate models adjusting for comorbidity, age, race, and insurance status. Conclusion: Sepsis rates in CA have increased dramatically since the introduction of new ICD-9 sepsis codes in 2002 while case fatality for sepsis declined within the same period. Two competing explanations are improved medical care whereby sicker patients have lower mortality rates versus up-capture of sepsis and comorbidities by improving coding to include septic patients with lower mortality rates who were previously given other diagnosis codes. Prospective research is needed to better understand the genesis of higher rates of sepsis and reasons for decreasing mortality trends. Implications for Policy and Practice: Significant healthcare resources have been dedicated to improving clinical response to sepsis due to the rise in overall sepsis frequency reported by researchers and governmental agencies. Understanding whether this rise is related to surveillance bias such as up-capture of septic patients or a rising clinical problem is important given evidence suggesting stable comorbidities and declining mortality rates. Investments in surveillance, objective definitions, and epidemiologic assessments of sepsis are needed.

Keywords: sepsis; readmission; IDC-9; sepsis death

Co-morbid conditions associated with chronic kidney disease (CKD) in Nicaragua

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Background: Contrary to the conventional etiology of CKD seen in developed countries, studies on CKD in underdeveloped countries, such as in Central America, show an atypical presentation of the disease. CKD in Nicaragua is disproportionately affecting individuals without a history of chronic illness and as early as in their third decade of life. CKD rates have risen exponentially, particularly in sugarcane workers. This study assesses comorbid conditions associated with CKD in patients from an occupational health clinic in Nicaragua and examines consistencies between clinician- and patient-reports. Methods: 512 medical records (2009 to 2014) were randomly selected, translated, and transcribed onto an electronic file in REDCap. Only ID numbers were used to maintain patient confidentiality. UCI-IRB approval was obtained. Results: Of the 512 records collected, 53.7% of patients had a diagnosis of CKD, whereas 46.2% did not. Patients with CKD were younger (mean 38.5 years, p=.000), male (92%, p=.000), and work in agriculture (88.6%, p=.000). A family history of CKD was greater in CKD patients (10.2%) than in their counterparts (1.3%, p=.000). In terms of clinician diagnosis, patients with CKD showed higher rates of electrolyte/metabolic disorders (39.3%, p=.000), whereas patients without CKD showed more hypertension (16.5%, p=.048), diabetes (2.6%, p=.018), and asthma (3.4%, p=.031). Patient-reported data also showed higher rates of electrolyte/metabolic disorders, specifically azotemia (45.8%, p=.000). Patients without CKD showed higher prevalence of pulmonary diseases (2.5%, p=.008) and GI disorders (3.4%, p=.031). Conclusion: Demographic characteristics of patients from an occupational health clinic were consistent with the current CKD literature in Nicaragua. Moreover, there were consistencies between clinician- and patient-reported comorbidities. However, this study's power is limited by sample size, thus supporting more studies that assess comorbidities in CKD.

Keywords: CKD; Nicaragua; sugarcane; comorbidities;

Low Cost Optical Coherence Tomography Imaging of Oral Cancer in Third World Countries.

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Background and Objective: Worldwide, approximately 275,000 oral cancer cases are diagnosed and 125,000 deaths occur annually. Oral cancer is responsible for up to 50% of cancer deaths among Indian field workers who lack access to oral screening and care. Most oral cancer lesions are detected after metastasis resulting in very poor treatment outcomes and survival. Objective of this study is to develop and validate an e-diagnostic algorithm that provides direct triage guidance to basic level field screeners in India, using a novel, low-cost optical coherence tomography (OCT) device. Study Design/Materials and Methods: Imaging data was collected by field workers in India and transmitted via an automatic file sharing system to a de-identified database. Images from a pilot group of 79 subjects were evaluated using different diagnostic algorithmic approaches. Diagnostic accuracy was compared with the gold standard, histopathology. Results: Pixel Intensity Standard Deviation between neighboring pixels and, reflectivity and thickness ratios of superficial anatomical structures provided the most accurate diagnostic guidance, with excellent PPV (90-93%), NPV (88-92%), kappa (91-93%), diagnostic sensitivity (85-87%) and specificity (>84%). Conclusion: A simple automated diagnostic algorithm of OCT images collected in the field by basic level healthcare workers may provide an effective, simple, low-cost guidance for screening triage and decision-making.

Keywords: oral; cancer; optical coherence tomography; diagnostics; image processing;

MediCom: A multidisciplinary design project to integrate mobile health monitoring with patient-provider communication training to promote medication adherence

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More than half of patients nationwide do not take their medications as prescribed, yet a very small minority of those patients discusses the concerns about their medication to the healthcare provider. Our method to increase patient-provider communication about barriers to medication adherence is MediCom, a multi-platform experience for users to access on computers, tablets, and smartphones. Our objective was to identify a set of technologies that could collect health information. We tested health collection devices that could track information and export data as a .csv file. Our team tested step trackers, pill bottle cap counters, blood pressure monitors, blood sugar self-testing devices, and phone applications. We chose devices based on cost, convenience, size, ease of exporting, and sharing capabilities, and built a mobile software application to integrate and dynamically display the data from these devices. Following a 30 day home monitoring period where medication taking, symptoms and blood pressure are tracked, the system integrates data from the multiple sources to facilitate patient-provider discussion about barriers to adherence.

Keywords: mHealth; medication adherence; hypertension; community health; patient-provider communication;

“Mi Salud, Mi Vida” ("My Health, My Life")

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The purpose of this study, “Mi Salud, Mi Vida” or “My Health, My Life” was to examine whether sociodemographic factors such as acculturation (i.e. born in U.S., years in U.S., and English spoken), education, income, and quality of life (QOL) were associated with perceived cognitive impairment (PCI) in Latina breast cancer survivors. There were a total of 70 Latina breast cancer survivors who completed the survey. Participants’ average age was 54.9 (SD:11.1) and the average number of years since diagnosis was 5.7 (SD:3.7). The majority of participants reported having an education level of high school or less (72%), were born outside of the U.S. (86%), and spoke only Spanish or Spanish better than English (67%). With regard to relationship status, approximately 47% reported being married or living with a partner. Approximately 57% of the sample reported having an income of $14,999 or less. Of the women who had insurance, 84% had government-sponsored insurance (e.g., Medi-Cal or Cal-Optima). PCI was measured using the Functional Assessment of Cancer Treatment-Cognitive, a well validated instrument. Higher acculturation was associated with worse PCI, particularly in how others perceived the patients’ cognitive impairment ($p=0.043$). Furthermore, worse PCI was associated with lower QOL ($p=0.003$). Education and income level were not associated with PCI. Various factors such as differences in severity of treatment or work force status could contribute to these findings and will be further explored. In addition, further analyses will compare PCI and its impact on QOL among Hispanic and non-Hispanic white breast cancer survivors.

Keywords: Breast cancer; Quality of Life; Perceived Cognitive Impairment; Survivorship; Acculturation;

Clinic in the Park Goes Mobile: Connect Screen Educate

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Background: Connect •Screen •Educate. Using public space, Clinic in the Park is designed to connect, screen and educate children. The Clinic brings health care to the community for children victimized by health care disparities with limited access to traditional sources. Target population is underserved, largely Hispanic children. In the satellite communities, child poverty is over 25%. Purpose. 1. Provide free/low cost access to health services in community-based settings. 2. Compare OC Great Park Clinic to neighborhood clinics. Results In 2015, 7 Great Park Clinics (Irvine) and 7 Neighborhood Satellites in Santa Ana, Anaheim, Tustin and Costa Mesa were implemented. Comparison of venues revealed a greater number of overall visitors (2,485) at the Great Park compared to the neighborhoods (1,513). Yet, the overall services provided were greater at satellites (10,100) v Great Park (6,699). Specific services were greater at the neighborhood clinics v the Great Park – connections to resources (1,880 v. 783); dental (756 v. 59); Nutrition (1476 v. 658); early literacy & free books (2,067 v. 695); medical services (362 v 64); emotional health (825 v. 423). Services greater at the Great Park included CPR training (464 v 299); child safety education (792 v. 553); legal information (203 v. 30); child development (419 v. 170). Overall services per visitor were greater at the neighborhood clinics (6.7) v Great Park, (2.7). Surveys at Satellites revealed that 66% had incomes of less than $23,000, no high school degree and were unemployed. Health needs included dental care, 47%%; medical care, 30%; vaccines, 31%; healthy eating tools, 33%, child car seats, 30%; bicycle helmets, 43 %. Conclusions The need for Clinic in the Park services in low-income neighborhoods exceeds the needs at the Great Park Farmers Market as expected. “Clinic in the Park Goes Mobile” is our most promising new strategy to bring services to underserved neighborhoods. It is a replicable strategy.

Keywords: Clinic; Connections; Screenings; Education; underserved;

Is Consent for CT in Acute Trauma Feasible?

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Computed tomography (CT) is common for blunt trauma victims. Exposure to diagnostic radiation may increase risk of cancer. Despite this, CT is often done without informing patients of potential consequences, risks and costs. Our objective was to evaluate feasibility to provide informed consent based on Glasgow Coma Scale (GCS) score and time. At two Level I Trauma Centers in California, we timed physicians providing a sham verbal informed consent script and answering questions to patients not needing CT (sham consent time). For consecutive adult injured patients requiring CT, we recorded the duration between completion of the secondary assessment and the patient leaving the resuscitation room for CT (Trauma Gap Time, or TGT). We recorded initial and subsequent GCS score. We recorded the duration of procedures (distraction time, DT) that would have distracted the patient making CT consent infeasible. For patients with a GCS of 15, we then subtracted the DT from the total TGT, yielding Effective TGT (ETGT). Average sham consent time was 2.97 minutes (range 1.2 - 4.9 minutes, n=22). We enrolled 400 patients in the TGT analysis, 292 (73.0%) of whom had GCS 15, and could therefore comprehend consent if there were enough time. Average total TGT was 16.8 minutes between completion of secondary survey and leaving for CT. For 133/292 (45.5%) patients, there were distracting procedures during which consent would not be feasible (e.g. x-rays, foley catheter, orthopedic procedures). Average DT was 6.0 minutes. Average Effective Trauma Gap Time (Total Trauma Gap Time – Distraction Time) was 14.3 minutes (range 2.2 - 111 minutes), during which consent would be feasible. With sham consent time at minimum 1.2 minutes, all 292/400 (73.0%) patients with GCS 15 would have had time for consent, whereas with sham consent time at maximum 4.9 minutes, 276/400 (69.0%) patients would have had time for consent. Therefore, there is commonly enough time for verbal informed consent.

Keywords: consent; trauma; autonomy; CT; informed;

USING ELETRONIC QUESTIONNAIRES TO PROVIDE PATIENT-CENTRIC HEALTH CARE IN OVERACTIVE BLADDER (OAB)

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The improvements of quality of care and clinical experience for patients are some of the most important outcomes for men and women diagnosed with overactive bladder (OAB). We recently developed an electronic questionnaire system through Laborie's iList software® that allows patients to directly answer OAB-related questionnaires on an iPad, and grants healthcare providers easy access to all necessary pre and post treatment questionnaires through the iList application. An experiment was conducted to test whether patients with OAB preferred using electronic questionnaires or paper questionnaires. Forty-six patients (N=46) were randomized into two groups: one using an electronic questionnaire at the beginning of their visit, and a paper questionnaire at the end and vice-versa. At the end of the study, patients filled out a Patient Feedback Form and gave a favorability rating for electronic questionnaires (score ranging from 1-5). The results of the study show that patients significantly preferred electronic questionnaires over paper questionnaires ($p<0.05$). In addition, we found that age and familiarity using an iPad were the biggest factors in patient's preference. By studying the use of electronic questionnaires in clinical settings, we are able improve patients' clinical experiences, overall quality of life, and determine whether electronic devices would be a strong tool for future research.

Keywords: Electronic Questionnaires; Overactive Bladder; Quality of care; Clinical experience; Quality of life;

An Lành Free Clinic Model: Effective in Medical Education and Training

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A student group at the University of California, Irvine recently opened a new student run free clinic in Southern California, An Lành Clinic, and started recruiting volunteer students, residents, and faculties to staff the clinic. The purpose of this study is to keep track of the diagnoses made at this new student run clinic to assess the breadth of clinical exposures available to medical students and residents, and clinical expertise displayed by the supervising staff physicians. After each clinic visit, the final diagnoses addressed that day are collected in a database. The clinic runs on Saturday morning; however, the electronic medical record system collects data from Tuesday, Friday and Saturday clinic. The clinic on Tuesday and Friday is not student-run but the patient demographics and diagnosis are representative of the Saturday clinic. From December 14, 2014 to April 9, 2016, total 921 diagnoses were collected. Most notable are 40 cases of Diabetes Mellitus (DM) and Hypertension each, 38 cases of Hyperlipidemia, 17 cases of Anemia, 14 cases of Hemorrhoids, 12 cases of depressive disorder and numerous other isolated diagnosis covering a wide range of other organ systems. Student Run Free Clinics (SRFC) are a worthy, if not more diverse, site of medical student and resident training to expose students to a wide spectrum of medical pathologies. These data also help identify specialist volunteers for more common diagnosis, while ensuring primary physician's comfort with a wide spectrum of diseases.

Keywords: SRFC; Student-run Free Clinics; Medical Education; Residency Training;

Can neighborhood associations collaborate with school districts to promote Science Technology, Engineering, Arts and Mathematics (STEAM) awareness? A pilot program in Santa Ana, California

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OBJECTIVES/SPECIFIC AIMS Using a community-based participatory re¬search (CBPR) approach, Madison Park Neighborhood Association (MPNA) entered into a civic center agreement with the Santa Ana school district to use the facilities at James Madison Elementary (JME) for after school hours and weekend use. MPNA launched project GREEN (Getting Residents Engaged in Exercise & Nutrition) in 2012, which established educational and wellbeing programs for both children and parents in addition to exercise and nutrition. The educational programs focused on tutoring and a mobile science program that took the students out of the classroom into a teaching science laboratory. The GREEN-Science academy is a 13-week program for students in the 4th – 6th grade, that will take the student from understanding the organization of cells to the functioning organs. The aim of this study is to successfully introduce STEAM through active learning and engaging the students in a science based curriculum. GREEN Science academy hopes to encourage a lifetime interest in the sciences and promotes values that place high priority to academic achievement. METHODS/STUDY POPULATION: 50 students are selected to participate in the GREEN science academy by teachers at JME. Students, with their guardian's consent, commit to 13 consecutive Saturdays. During the program, students are introduced to a variety of STEAM topics. Each lesson begins with a 20-minute lecture followed by active learning activities led by an undergraduate mentor. At the end of the 13 week program, all students present their observations and findings using current technology platforms. RESULTS: Since the inception of the GREEN science academy a total of 350 JME students have actively participated in the program. 99% of the registered students have finished the 13 week program. SIGNIFICANCE: Our students successfully demonstrated their ability to become better critical thinkers, increase communication skills amongst their peers an

Keywords: CBPR; STEAM; work force development; Translational science education;

Implementation of Team Kid Power (KiPOW)–a school based intervention targeting pediatric dietary and physical activity behaviors

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Introduction Team Kid Power (KiPOW) was initially developed as an academic-community partnership in Washington D.C. to help implement the diet and exercise requirements of the 2010 D.C. Healthy Schools Act using face-time with mentors. In early 2016, KiPOW was piloted in one low-resource school in California to achieve a similar healthy policy. Purpose To assess the feasibility of the KiPOW program in California. To assess 5th grade students' dietary, physical activity, and sedentary behaviors. Methods Estock Elementary School was identified as KiPOW's pilot site. 5th grade students participated in 11 weekly coaching sessions with medical student volunteers during lunch and recess. Volunteers modeled healthy eating behaviors, facilitated active play, and delivered health lessons. Qualitative and quantitative measures were collected weekly according to the Reach, Effectiveness, Adoption, Implementation (RE-AIM) model. Baseline measures included the HABITS questionnaire, Body Mass Index (BMI), and blood pressure. Results Estock Elementary School in Tustin is largely comprised of low-income (92% eligible for free/reduced price lunch) and Hispanic students (90%). A total of 55 students participated in the program. 47% have BMI greater than or equal to 95th percentile; mean BMI was 74th percentile. Baseline HABITS questionnaire reveal that students consume less fruits and vegetables, and have more sedentary time than recommended. The administration feels that the program does not disrupt the flow of the school day, and that KiPOW fills the school's void in health education and physical activity and supplements the cafeteria food. Discussion While evaluation of the KiPOW pilot program is ongoing, feasibility and perceived value by school administrators and staff were identified. Next steps include: 1) full evaluation of the pilot's effect on BMI and health behaviors, 2) follow-up meetings with school staff, and 3) dissemination to other low-resource schools.

Keywords: Diet; Exercise; Obesity; School; Policy;

Emergency Medical Treatment and Labor Act (EMTALA) 2002-15: Review of Office of Inspector General Patient Dumping Settlements

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Background: The Emergency Medical Treatment and Labor Act (EMTALA) of 1986 was passed to prevent hospitals from "dumping" or refusing service to patients for financial reasons. The Office of the Inspector General (OIG) of the Department of Health and Human Services enforces the statute. Objective: To determine the scope, cost, frequency and most common allegations leading to monetary settlement against hospitals and physicians for patient dumping. Methods: Review of OIG investigation archives, including cases settled from 2002-2015 (https://oig.hhs.gov/fraud/enforcement/cmp/patient_dumping.asp). Results: There were 192 settlements (14 per year average for 4000+ hospitals in the USA). Fines against hospitals and physicians totaled $6,357,000 (averages $33,435 and $25,625 respectively). 184/192 (95.8%, $6,152,000) settlements were against hospitals and eight against physicians ($205,000). Most common settlements were for failing to screen 144/192 (75%) and stabilize 82/192 (42.7%) for emergency medical conditions (EMC). There were 22 (11.5%) cases of inappropriate transfer and 22 (11.5%) more where the hospital failed to transfer. Hospitals failed to accept an appropriate transfer in 25 (13.0%) cases. Patients were turned away from hospitals for insurance/financial status in 30 (15.6%) cases. There were 13 (6.8%) violations for patients in active labor. There were 6,035 CMS investigations during this time period, with 2,436 found to have merit as EMTALA violations (40.4%). However, only 192/6,035 (3.2%) actually resulted in OIG settlements. The proportion of CMS certified EMTALA violations that resulted in OIG settlements was 7.9% (192/2,436). Conclusion: Of 192 hospital and physician settlements with the OIG from 2002-15, most were for failing to provide screening (75%) and stabilization (42%) to patients with EMCs. The reason for patient "dumping" was due to insurance or financial status in 15.6% of settlements.

Keywords: None

Ultrasonographic Measurement of the Right Ventricular Outflow Tract Systolic Excursion to Diagnose Patients with Acute Pulmonary Embolism: A comparison to the Gold Standard

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Acute pulmonary embolism (aPE) is a fatal condition that can lead to death if not quickly identified and treated. The current standard of care in patients with suspicion for pulmonary embolism consists of a Computed Tomography scan of the Pulmonary Arteries (CTPA). Despite the accuracy of CTPA, many patients are unable to undergo this test due to renal disease, pregnancy or risk of radiation. Recently, ultrasonography has shown some promise in obtaining the tricuspid annular plane systolic excursion (TAPSE) measurements to help make the diagnosis of aPE. We assessed the right ventricular outflow tract (RVOT) by using cardiac point-of-care ultrasound (POCUS) in the evaluation of patients with suspicion for aPE. We prospectively enrolled a convenience sample of patients with suspected aPE presenting to the Emergency Department (ED) between November 2015 and March 2016, and then performed an un-paired t-test to calculate the significance in identifying patients with aPE. We enrolled 17 patients, four of which have confirmed pulmonary embolisms based on the CTPA. Based on preliminary data, our study shows that there is no statistical significance in the identification of patients with pulmonary embolisms; however, there is a trend that supports our hypothesis.

Keywords: right ventricular outflow tract; pulmonary embolism; tricuspid annular plane systolic excursion; point-of-care ultrasound; emergency department;

RELATIONSHIP BETWEEN PATIENT DEMOGRAPHICS AND ADVERSE CONSEQUENCES PERTAINING TO DRINKING HABITS: SHORTENED INVENTORY OF PROBLEMS SURVEY

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Globally, alcohol consumption has caused approximately 3 million deaths. About 88,000 people a year die due to alcohol in the United States, which correlates to the one of the highest preventable causes of death. The 88,000 people who die annually include many men as well as women, and a variety of ages, races, and levels of education. Many of these deaths are led up to by habitual consequences of peoples' drinking habits. The Emergency Department (ED) offers consistent alcohol screenings and interventions, with the hopes of minimizing alcohol-related health issues. These screenings run through the Computerized Alcohol Screening and brief Intervention program. CASI, which was developed in 2006, allows patients realize their overall alcohol dependency status, through a numerical score known as the Alcohol Use Disorders Identification Test (AUDIT). The number can allow the patient to gauge whether their drinking habits are considered healthy. A brief intervention corresponding to their AUDIT score will allow patients to explore possible reasons for their alcohol use or misuse, give suggestions on decreasing the amount of alcohol consumption, and advocate self-reflection on whether the patient is ready to cut back on drinking. Short Inventory of Problems (SIP) survey is also introduced, which is a tool that measures social, physical, emotional and other types of consequences a patient has experienced as a result of their drinking choices. Hand in hand, these surveys have been a staple in the UCI Emergency Department, and has received a significant amount of positive feedback from the patients as well as hospital staff. Demographical investigation relating to SIP score can explain the following: is there a trend of correlation between age and SIP score? Similarly, we will analyze the trends regarding gender and education level with SIP score. Lastly, mid-range AUDIT score will be compared to SIP score, to notice possible relationships between the two scores.

Keywords: ALCOHOL SCREENING; PUBLIC HEALTH; SHORTENED INVENTORY OF PROBLEMS; EMERGENCY DEPARTMENT; CASI;

Evaluation of Tmax, Thermal Spread, and Heat Dissipation of Monopolar "Short Burst" Cautery Miitigated by Ice Cold Irrigation in a Porcine Model

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INTRODUCTION AND OBJECTIVES: Cauterization has widespread usage, but elevated temperatures can produce neural trauma at 41°C, coagulation at 45-55°C., possible cell death by either denaturation at 57 to 60°C and protein coagulation at 65°C. This study observes maximum tissue temperatures, thermal spread, and heat dissipation after monopolar touch (MP) cautery and the role of ice cold irrigation to mitigate the potential thermal damage. METHODS: MP touch cautery was performed in porcine animal bowel and bladder tissues under an approved animal protocol. We performed 10-20 trials of a near one second application for two intensities of MP cautery (20W, 40W). Spatial temperature mapping including maximum surface tissue temperatures (Tmax) were captured immediately after cautery and 4-20 seconds following hemostasis using a FLIR E6 Thermal Imaging Camera, and plotted against time to generate heat dissipation curves and lateral thermal spread calculated. In the irrigation trials the ice cool saline was applied immediately after the thermal image capture of the applied cautery heat. RESULTS: The average temperature maximums immediately following 20W and 40W MP touch cautery were 87.8, 100.4°C. MP touch cautery remained above 45 °C, 8-15 seconds after application. Thermal spread was comparable between each intensity of MP cautery (5.6mm) ($p=0.86$). The immediate application of ice cold saline reduced the tissue temperatures to <40 °C within 4 seconds of cautery application. CONCLUSIONS: Even minimal amounts of electrocautery raises initial tissue temperatures to 85-100 °C. Fear of any Thermal injury led to Athermal nerve sparing techniques during radical prostatectomy. However the heat dampening capacity of ice cold saline irrigation reduced tissue temperatures to near physiologic levels within 4 seconds. These thermodynamic experiments suggest a simple method to mitigate tissue damage by electrocautery in a vast array of surgical procedures.

Keywords: electrocautery; tissue damage; thermal injury; lapascopic; surgery;

Real Time Observation of Safety and Effectiveness in the Treatment of Female Stress Urinary Incontinence (ROSE Registry)

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Stress urinary incontinence (SUI) is a debilitating, non-life threatening condition that is generally caused by a hypermobile urethra or intrinsic sphincter deficiency (ISD). A promising treatment, specifically for the latter cause, is Macroplastique, which is a type of urethral bulking agent. Even though Macroplastique has shown to be a safe, durable, and effective treatment, its long-term efficacy has not been strictly established. The purpose of this study is to contribute to the existing literature by determining the long-term safety and effectiveness of Macroplastique treatment. From 2012 to the present, 35 female patients underwent Macroplastique treatment, and the efficacy of their treatment was assessed using Stamey scores, Satisfaction scores, and Incontinence Quality of Life (IQOL) questionnaires at baseline, 3 months, and annually for up to 5 years. Analysis of baseline and 12 month assessments (n=28) showed no significant changes in Stamey score ($p > 0.05$), a mean Satisfaction score of 2 (somewhat satisfied) at 12 month, and significant improvement in IQOL score and all subsets scores ($p < 0.001$). Despite that the data regarding long-term safety and effectiveness of Macroplastique are inconclusive, this study is consistent with existing literature demonstrating that Macroplastique is a safe clinical treatment. The continuation of this study as well as future long-term studies will help establish Macroplastique as a minimally invasive, safe, and effective medical treatment for SUI due to ISD.

Keywords: None

VARIABLE CLINICAL FEATURES IN POMPE DISEASE ASSOCIATED WITH NOVEL MUTATIONS

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Pompe disease is a lysosomal storage disorder caused by the deficiency of enzyme acid alpha-glucosidase (GAA) which results in accumulation of glycogen particularly in the skeletal, cardiac, and smooth muscles. The late-onset form with symptoms presenting in childhood through adulthood, is characterized by proximal muscle weakness, respiratory insufficiency, and unlike classic or infantile-onset form typically with no cardiac involvement. We report our experience with 17 adult patients (4 F/13 M) with Pompe disease at one center, several of whom had unique findings and novel mutations. Patients ranged in ages from 18-69 y. (mean 51 y.) and were diagnosed at a range of 11-65 y (mean 37 y.) often after a history of progressive muscle disease of several years duration. Genetic sequencing revealed that 15/17 individuals had the common c.-32-13T>G mutation, and eight had 6 novel mutations: c.1594G>A, c.2431delC, c.2655_2656delCG, c. 1951-1952delGGinsT, c.525_526delTG, and c.1134C>G. A male with the c.1594G>A mutation developed an intracerebral aneurysm at the age of 43 y. treated with surgery. Another male with the c.525_526delTG developed testicular cancer and is in remission. Cardiomyopathy was noted in an adult with the c.525_526 delTG mutation, and peripheral neuropathy in a male with the c. 1951-1952delGGinsT. Two siblings with the c.2655_2656delCG developed very high antibody titers, one of whom developed a severe infusion reaction. Other clinical features included scoliosis and cardiomyopathy in an adolescent, BiPAP requirement in eleven, tinnitus in five, and one individual was born with partially developed hip and clubfoot. All patients currently receive alglucosidase alfa with different response rates in their muscle weakness, pulmonary function dynamometry, and functional studies. Our patient cohort illustrates the variable range of clinical features, and alert us to the importance of careful monitoring and early management of these complications.

Keywords: Pompe; Genotype-phenotype; enzyme therapy; Variable phenotype; novel mutations;

Pre and Post-Procedural Evaluation of Imaging Biomarkers after Radioembolization for Hepatocellular Carcinoma as an Indicator of Progression

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Purpose: The purpose of this study is to evaluate possible imaging biomarkers on contrast-enhanced CT and MRI exams that predict local progression per modified Response Evaluation Criteria in solid tumors (mRECIST) criteria post radioembolization of hepatocellular carcinoma (HCC). Methods and Materials: Among patients who underwent radioembolization for HCC between May 1, 2005 and May 1, 2015 at a single institution, 34 patients had adequate pre and at least 2 post-procedural exams. Local response to treatment was classified as progressive (PD) or stable disease (SD) using mRECIST. Imaging markers, including portal venous phase enhancement (PVE), lobulated enhancement (LE), presence of arterioportal shunting (APS), and portal vein thrombosis (PVT) were assessed in each imaging examination. Wilcoxen Rank-Sum (WRS) and log-rank analyses were performed to establish statistically significant differences in local progression free survival (LPFS). Results: The mean imaging follow-up time was 12.64 months. Local progression was seen in 25 patients (76.4%) following radioembolization. Average time to progression was 8.43 months. PVT, APS, and PVE seen on pre or post-procedural imaging were not significant predictors of LPFS. LE on immediate post-procedural imaging was a significant predictor of progression by WRS ($p=0.039$) and log-rank analysis ($p=0.035$), however LE on pre-procedural imaging was not a significant predictor. 9 patients with and 0 patients without progression showed LE on post-procedural imaging, Conclusion: PVT, APS, and portal venous enhancement were not statistically significant predictors of local progression, whereas immediate post-procedural LE demonstrated a statistically significant decrease in LPFS in patients with hepatocellular carcinoma treated with radioembolization.

Keywords: Imaging Biomarkers; modified Response Evaluation Criteria in solid tumors (mRECIST); hepatocellular carcinoma (HCC); Predictors of Local Progression; Radioembolization;

Challenging Unusual Large Pulmonary Lymphoma Mass: Correlation of Imaging and Immunostains for Tumor Markers

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Introduction: Primary Pulmonary Hodgkin’s Lymphoma (PPHL) without hilar node involvement is exceedingly rare. We report a case of a 41-year old female who presented with dry cough, and persistent lung mass in the left lung without hilar lymphadenopathy despite appropriate antibiotic treatment. Clinical differential diagnosis remains wide. CT guided transthoracic biopsy was diagnosed Hodgkin’s lymphoma, indicated by lymphocytic tumor markers. Case History: A 41-year-old woman, presented 11-month of dry cough and left thoracic rib pain, with no fevers, chills or night sweats. Chest radiograph revealed a left lung mass. She was treated with antibiotics. Repeat chest radiograph obtained later showed persistent left lung mass, suspicious for lung cancer. Initial transbronchial biopsy was inconclusive. She then came to UCI Medical Center two months later. New CT revealed no significant change in the lung mass and mediastinal lymphadenopathy. Peripheral blood smear and bone marrow were unremarkable. Radiology: CT scan revealed a large left upper lobe mass and mediastinal lymphadenopathy, but no hilar lymphadenopathy. PET-CT revealed highly FDG avid left upper lobe mass and mediastinal lymphadenopathy. CT guided core biopsy of the left upper lobe mass was performed. Pathology: Biopsy revealed bronchial mucosa with mixed inflammatory cells and scattered large atypical cells. Lymphocytic tumor markers confirmed those large atypical cells were positive for PAX5, CD15, CD30, but negative for CD45, CD3, and CD20, diagnosed as Hodgkin Lymphoma. She was then referred to chemotherapy. At extranodal location such as the lung, Hodgkin lymphoma is likely to be confused with commonly carcinomas at this site. Conclusion: PPHL rarely presents as a large lung mass. Correlation of imaging and pathologic findings is critical, as PPHL can mimic a primary lung cancer. Application of immunostains for tumor markers is useful to distinguish PPHL from conventional carcinoma.

Keywords: PULMONARY MASS; HODGKIN'S LYMPHOMA; IMAGING; IMMUNOHISTOCHEMISTRY; TUMOR MARKERS;

Repurposing statins to enhance efficacy of venetoclax in lymphoma

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In this presentation we will present proof of principle for using HMG-CoA-Reductase inhibitors (statins) to enhance efficacy of ABT-199 in preclinical models of B cell cancers. ABT-199 (venetoclax) is a small molecule inhibitor of BCL-2, a key pro-survival protein that is highly expressed in many leukemias and lymphomas. ABT-199 obtained FDA breakthrough designation for chronic lymphocytic leukemia (CLL) but has not shown broad efficacy as monotherapy in aggressive B cell lymphomas. Statins are commonly used to control plasma cholesterol levels and are among the most widely prescribed medications worldwide. However, statins are also known to have anti-cancer potential. We have observed potent synergy of statins combined with ABT-199 in human cell lines derived from diffuse large B cell lymphoma (DLBCL). This synergy is also seen in murine B lymphoma cells derived from a genetically engineered mouse model. Importantly, statins do not increase killing of human lymphocyte populations from healthy donors. Mechanistic studies support the hypothesis that statins prime lymphoma cells for apoptosis by blocking prenylation of small GTPases downstream of mevalonate production. We show that RAP1a deprenylation is a robust biomarker of statin action in vitro and in vivo. Further, we present evidence that disruption of the RhoA/ROCK axis correlates with the pro-apoptotic effects of statins in lymphoma cells. Ongoing experiments aim to test the efficacy of statins plus ABT-199 in a mouse model of lymphoma.

Keywords: lymphoma; targeted therapy; apoptosis; statin; BCL2;

Small Molecule Screen in VHL-Deficient ccRCC Reveals a Synthetic Lethal Interaction with ROCK Inhibition

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Loss of the tumor suppressor von Hippel-Lindau (VHL) occurs in 80% of Renal Cell Carcinomas (RCC). The objective of this study is to identify and characterize chemotherapeutics that are synthetically lethal with this deficiency. A LOPAC chemical library screen identified seven compounds. The hit Y-27632 and another ROCK inhibitor RKI 1447 were validated using viability assays in multiple RCC lines. siRNA knockdown of ROCK1 and RhoC both resulted in synthetic lethality. ROCK inhibition by Y-27632 and RKI 1447 reduces RCC migration. Further investigation may provide insight into the molecular pathways necessary for survival/growth of RCC cancer cells and serve as new clinical treatment strategies. .

Keywords: Renal Cancer; Synthetic Lethality; Rho Kinase 1; Small Molecule Screen;

Aggressive thyroid carcinoma mimicking a benign histiocytic proliferation – utility of tumor markers by immunohistochemical analysis

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Benign and malignant tumors rarely share overlapping morphology. It is quite unusual that a malignant neoplasm has morphologic resemblance to a benign disorder which results in a delay in appropriate treatment. We are reporting an unusual clinically aggressive thyroid carcinoma that morphologically mimics a benign entity. A 58-year-old Vietnamese woman, who presented initially with neck swelling and hoarseness, was diagnosed to have 'medullary thyroid cancer' for which she underwent a partial thyroidectomy followed by radioactive iodine 131 ablation. She then developed a recurrence of the neck mass associated with dyspnea and airway obstruction. She returned to USA and was admitted to a local hospital for further treatment. Tissue samples failed to identify a thyroid carcinoma. CT scan revealed a large thyroid mass with hemorrhage encroaching the trachea and bilateral pulmonary nodules consistent with metastasis. She continued to deteriorate clinically and underwent a repeat neck exploration and hematoma evacuation. The tissue samples obtained from the neck mass showed a proliferation of benign appearing histiocytes. Immunostain for Ki-67 showed a high tumor nuclear proliferation rate of 80%, indicating malignant neoplasm. All other biomarkers based on immunohistochemical stains failed to appropriately classify the tumor. After careful examination of the tissue samples, there was a microscopic focus of thyroid follicles that merged imperceptibly into the adjacent aforementioned benign appearing histiocytes. The final diagnosis was a poorly differentiated thyroid carcinoma. Thereafter, the patient was treated with a radio sensitizer. To our knowledge, this report represents a rare case of aggressive thyroid carcinoma mimicking a benign histiocytic proliferation. To create a coordinated plan of care for patients afflicted with oncologic disorders, careful review of tissue samples and appropriate utility of biomarkers are important towards an accurate diagnosis.

Keywords: Cancer; Biomarker; Thyroid carcinoma; Immunohistochemistry; Histiocytic;

Prospective Analysis of Accessory Pudendal Artery Transection on Potency during Robot-Assisted Radical Prostatectomy (RARP)

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Background: The preservation of the erectile function / continence mechanism during radical prostatectomy (RP) is of essential priority. While preservation of erectile function depends on patient preoperative characteristics, vascular injury has rarely been discussed or cited. Objective: To assess the vasculogenic impact of transection of APAs and the subsequent effect on erectile function among men with standard preoperative erectile function and normal vascular anatomy post robot-assisted radical prostatectomy. Design, setting, and participants: We prospectively identified 881 consecutive men undergoing RARP (2007-2014) with intraoperative mapping of all APAs. Follow-up was obtained at a tertiary institution, at a median of 15 months post-op. After excluding men participating in adjuvant therapies and those with low preoperative EF, 580 men remained for assessment. Interventions: Robot assisted radical prostatectomy (RARP) Outcome Measurements and Statistical Analysis: Primary EF function was defined as IIEF-5 score > 15 or affirmative answers to two baseline SHIM items: erections are firm enough for penetration and are satisfactory. Unadjusted odds ratios were determined to compare return of potency, given APA transection (CI = 95%). Subgroup analysis further resolved increasing age, number of APAs transected and varying degrees of mild to moderate ED. Results and Limitations: Preliminary ANOVA confirmed that baseline demographics and clinical characteristics were equivalent across men with one, two or no APAs transected. Subsequently, multivariate analyses demonstrated no influence on postoperative recovery of potency, IIEF-5 scores, or fullness of erections ($p < 0.05$). Advancing age and ED did not convey an increased risk of impotence. Conclusions: APA transection does not diminish postoperative sexual function in normally pre-potent men. These results are congruent in men of advancing age, numbers of arteries transected and preoperative ED.

Keywords: Minimally-invasive; Radical prostatectomy; Sexual function; Erectile function; Accessory Pudendal Artery;

Rapid Electroencephalogramy (EEG) of Acute Stroke in the Emergency Department

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Rapid diagnosis of ischemic stroke in the Emergency Department (ED) is a challenge intensified by recent IA therapy trials that underscore the need to quickly identify patients with a large artery occlusion. EEG has established ability to immediately detect cerebral ischemia, but technical demands have limited application to acute stroke. Advances in EEG hardware and software suggest the potential for an ascendant role of EEG in the ED assessment of suspected acute ischemic stroke. Over 3.5 weeks, patients with possible acute ischemic stroke seen in the UCI Medical Center ED were consented for a 3 min resting EEG using a dense array system (256 leads, EGI, Eugene, OR), which uses saline rather than gel for lead contact, and uses an elastic cap to apply all leads at once. EEG recordings were obtained by a student once all ED assessments were done and acute interventions ordered. EEG was obtained in 15 subjects (mean age 65 yr), 4 with radiologically confirmed acute ischemic stroke. The other 11 had TIA, seizure, encephalopathy, etc; 1 had a large chronic stroke and was excluded from further analysis. Time from signed consent to EEG averaged 12.6 min and with practice was as short as 5 min. EEG was acquired as early as 2.2 hr after stroke onset, and was readily captured during IV tPA drip. Analysis focused on power in the delta range in 18 scalp leads. Despite wide-ranging infarct locations, in 7 leads, delta power was significantly ($p<0.05$ to 0.005) greater in patients with, vs. without, acute ischemic stroke. Four of these 7 leads were in the contralesional hemisphere. A 3 min dense array EEG recording at rest can be rapidly and reliably acquired in the ED in patients with possible acute ischemic stroke, without a specialized technician. Findings emphasize that a unilateral acute infarct immediately affects bilateral brain function. These findings may have the potential to be transformative for rapid diagnosis of patients with suspected acute ischemic stroke.

Keywords: Stroke; EEG; Emergency Department;

Retinal differentiation of Shef-6 human embryonic stem cells and enrichment of Crx-expressing photoreceptor progenitors

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Many forms of retinal degenerate conditions that lead to blindness are due to the loss of retinal pigmented epithelia (RPE), and ultimately loss of photoreceptors. This condition affects millions of individuals worldwide, greatly impacting their quality of life. Because the retina has no regenerative capabilities, a promising therapeutic to restore visual function is the replacement of the lost photoreceptors, the cells that transmit visual cues to the brain, with photoreceptors derived from pluripotent stem cells (PSCs). A recent 3D culture protocol has shown that human induced pluripotent stem cells (hiPSCs) could be successfully led to retinal fate and generate mature and functional photoreceptors. Importantly, this protocol used no extrinsic signaling factor or elaborate differentiation techniques. Nevertheless, use of iPSC-derived cells for clinical applications is questionable because they retain their epigenetic memory and can acquire karyotypic abnormalities during the reprogramming process. Thus, it is proposed to test whether the same protocol implemented on the human embryonic stem cell (hESC) Shef-6 cell line would result in similar findings as with iPSCs. Assays have shown that the Shef-6 cell line has normal number of chromosome, is mycoplasma contamination-free, and that the cells express the pluripotency marker SSEA4. We are trying to optimize embryoid body formation by trying various seeding densities and methods in order to obtain large numbers at approximately 0.22mm in diameter at the time of plating. It is also of interest to figure out at what time point during this differentiation process the neural retinas (NR) express the most Crx (cone rod homeobox) protein, an immature photoreceptor marker that controls their development. Studies have shown that transplantation of photoreceptor precursors expressing Crx in a defined time window is more effective in the areas of integration, maturation, and functionality.

Keywords: Stem Cells; Retina; Neurospheres; Transplantation;

Human retinal progenitor sheet transplants in immunodeficient retinal degenerate (RD) rats

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Purpose This study investigated whether human immature retinal sheets can develop normally after transplantation to blind rats that do not reject human cells (cross of rho S334ter and NIH nude). Methods: Fetal human eyes (11-15.7 weeks gestation, 5 different samples) obtained from an hSCRO-approved supplier were shipped overnight in cold hibernation medium. After dispase treatment, retina with RPE was dissected; and tissue sheets (size 0.8 x 1.3 mm) were transplanted to the subretinal space of 24-31 d old RD nude rats (n=22). Rat eyes were imaged by high-resolution spectral-domain optical coherence tomography (SD-OCT; Bioptigen Envisu R2200 SD-OIS) at 1 wk, 1 mo. and up to 7 mo. after transplant at several time points. Four rats with large transplants were recorded for visual responses in the superior colliculus (SC) at 6.7-8.6 mo. post surgery. Rats were euthanized between 0.5 and 8.6 months post surgery for histological evaluation. Results SD-OCT scan analysis showed transplant placement in the subretinal space, presence or absence of surgical trauma, and development of laminated areas or rosettes. The four 15.7 week gestation transplants all degenerated within 3 months. In 10 of 18 transplants from 11-12 week donors, large transplants developed, with clear development of plexiform layers first seen in OCT at 3 months post surgery. At 6-8 months post surgery, transplant photoreceptors developed short outer segments. Immunohistochemistry confirmed the formation of retinal layers and photoreceptor maturation of the human grafts. Two of the four SC recorded rats showed responses to bright light. Transplant cells extended processes into the host retina, and transplanted cells migrated into the host retina. Conclusions Human fetal retina (11-12 wks gestation) transplanted as sheets to the subretinal space of RD nude rats can develop mature photoreceptors and begin to integrate with the host retina. In 2 of 4 recorded animals, visual improvement could be demonstrate

Keywords: retinal transplantation; retinal degeneration; retinal imaging; superior colliculus recording; immunohistochemistry;

In Vitro Evaluation of Exosome Migration across the Blood-Brain Barrier Model

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Introduction: The delivery of therapeutics to the central nervous system (CNS) remains a major challenge in part due to the presence of the blood-brain barrier (BBB). Different nanocarrier strategies have been explored to improve delivery of therapeutic agents across the BBB. Recently, cell-derived vesicles, particularly exosomes, have emerged as an attractive vehicle for targeting drugs to the brain. However, whether and how exosomes cross the BBB, remains unclear. Objective: To elucidate the interactions between exosomes and human brain microvascular endothelial cells (BMECs) in vitro under conditions that mimic the healthy and stroke-like BBB in vivo. Methods: Exosomes were engineered to carry Gaussia luciferase (Gluc) and in vitro BMEC monolayer was established as a model system. Transwell assays and confocal microscopy were performed to examine exosome migration across the BMECs in vitro. Results: Transwell assays revealed that luciferase-carrying exosomes can cross a BMEC monolayer under stroke-like, inflamed condition (TNF-alpha activated) but not under healthy condition. Confocal microscopy suggested that exosomes are internalized by BMECs through endocytosis, co-localize with early and late endosomes and are partly exocytosed across the BMECs, in effect utilizing the transcellular route of crossing. In addition, approximately one third of the total crossing of the BMECs was due to the paracellular route of passive diffusion through the intercellular junctions between activated BMECs. Conclusion: This system can be used to examine whether or not exosomes can be utilized to deliver therapeutic agents to specific regions of the injured brain. Our study encourages further development of engineered exosomes as drug delivery vehicles or tracking tools for treating or monitoring neurological diseases in the near future.

Keywords: Exosomes; Blood-Brain Barrier; Drug Delivery; Stroke;

Histopathology and Function in a Rat Model of Retinopathy of Prematurity (ROP)

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Retinopathy of prematurity (ROP) is an important cause of blindness in premature infants and characterized by pathological angiogenesis of the retina. The oxygen induced retinopathy (OIR) rat model closely mimics the pathology present in human infants with severe ROP. Here, an in-depth assessment of this model was carried out to provide a detailed background analysis. Newborn pups were placed in a chamber to change oxygen level from 50% to 10% every 24 hours for 14 days. Electroretinography (ERG) was performed at postnatal day 18 on both OIR rats and room-air-raised controls. Oscillatory potentials (OP) and b-wave were used as measures of retinal function. To evaluate retinal vasculature and histopathology, retinas were collected as wholemounts, fixed at P18, followed by staining to label astrocytes, blood vessels, and ganglion cell bodies using GFAP, collagen IV, and gamma synuclein. Retinal mosaics of the wholemounts were collected sequentially using a laser scanning microscope from both age-matched WT control and OIR rats. ERG showed significant delay in the implicit time and decreased amplitude of OPs. b-wave amplitude was decreased across scotopic and photopic stimulus ranges. Wholemount histology shows incomplete, delayed physiologic retinal vascularization peripherally and, in addition, numerous small neovascular "tufts" in the OIR retina. By comparison, blood vessel development in WT controls appeared complete, with approximately 10 times fewer neovascular tufts compared to the OIR retina. Astrocytes in the OIR retina displayed a disorganized morphology, particularly in regions populated by neovascular tufts. There also appeared to be a decrease in the average number and average cell density of ganglion cells in the OIR eye. In conclusion, the OIR rat exhibits numerous functional and histopathological features consistent with ROP in humans and provides a useful model for therapeutic intervention in this condition.

Keywords: Retinopathy of Prematurity (ROP); Oxygen Induced Retinopathy (OIR) rat; Retinal degeneration; Retinal progenitor cells;

Molecular Characterization Of Human Embryonic Stem Cells Differentiated Into Transplantable Retinal Sheets Via 3D Neurosphere Retinogenesis

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Age-related macular degeneration and other retinal disorders affect millions of people worldwide. Current treatments can delay the degradation, but few can restore function and visual acuity. The challenge is how best to create and introduce fresh, healthy tissue to replace damaged host retinal cells. We are using human embryonic stem cells (hESC) to produce transplantable sheets of retinal and retinal pigmented epithelium (RPE). It is hoped that the new hESC derived tissue will create fresh photoreceptors for the host, generate new synaptic connections for phototransduction, and a new RPE monolayer critical for photoreceptor maintenance. hESCs were differentiated into retinal tissue by creating 3D neurospheres, following a protocol modeled after Zhong et al. 2014 (Nature Communications 5:4047) which results in laminated 3D structures (neurospheres). Quantitative polymerase chain reaction (qPCR) analysis of genes characteristic for neuronal (Pax6) and retinal development (Chx10, Rax, CRALBP, CRX, recoverin), and RPE (MITF) was performed on retinal neurospheres between d27 and d73 of differentiation and hESC-derived RPE monolayers. For comparison, d84 and d110 human fetal retina (HFR) and RPE were also analyzed and used as control tissues. In parallel, immunofluorescence (IF) experiments on fixed differentiated neurospheres looked for the expression of important neuro-retinal proteins found in the human eye (e.g. Rax, CRX, Recoverin, CRALBP, MITF). Immunohistochemical H+E staining confirmed the developing lamination and retinal maturation of the neurospheres at progressive time points. Taken together, the data demonstrates a neurosphere expression pattern similar to that seen in the developing human fetal eye with early commitment progenitor markers like PAX6 and CHX10 coming up first during the culture time course and more mature photoreceptor and RPE proteins (i.e. recoverin and CRALBP) coming up late. The 3D neurospheres are clearly undergoing retinogenesis

Keywords: Neurosphere; hESC; Retinogenesis;

Stem Cell Scaffolds to Treat Brain Trauma

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Stroke is the leading cause of long term disability nationwide and most stroke sufferers do not qualify for current FDA-approved treatments. Stem cell transplantation stands as a promising therapy for those battling to regain function after stroke and neural stem/progenitor cells (NSPCs) are good therapeutic candidates since they secrete beneficial trophic factors and differentiate into mature CNS cells. However, many NSPCs die after transplantation, creating a bottleneck in the field. Biomaterial scaffolds can taper transplanted cell death and improve stem cell-mediated recovery. We and others have shown that deformable, injectable, non-toxic scaffolds are good matches for CNS tissue, which is one of the softest in the body. Injectable scaffolds that polymerize in vivo can form tight appositions with spared tissue and promote recovery without damaging surrounding regions. We found that fibrin, a natural scaffold material generated during the clotting cascade, supports CNS cells and matches the stiffness of CNS tissue. However, implantation of fibrin in a rodent model of spinal cord injury revealed rapid scaffold degradation in vivo (~7 days), thus suggesting fibrin cannot provide long term support for transplanted cells. To mitigate this rapid degradation, we designed combination scaffolds that include hyaluronic acid (HA), in addition to fibrin. HA is utilized as an injectable transplant biomaterial that promotes NSPC survival in the stroke injured brain and persists for at least 2 months in vivo. Scaffolds embedded with human NSPCs (hNSPCs) demonstrate significantly slower degradation of combination scaffolds while retaining favorable polymerization kinetics, deformability, and support of hNSPC growth and differentiation in vitro. We are currently assessing these scaffolds in a rodent model of ischemic stroke to test whether remodeling the transplantation niche with an injectable scaffold is sufficient to significantly enhance survival of transplanted hNSPCs.

Keywords: stroke; neural stem cell; transplantation; scaffold;

Two Phase Approach to Islet Transplantation

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An estimated 1.25 million Americans suffer from type I diabetes (T1D), an incurable autoimmune disease with increasing prevalence. Currently, patients manage their disease with combined insulin administration via injection or pump and blood glucose monitoring. For severe cases, pancreatic islet transplantation into the liver via the portal vein has shown to increase patient quality of life; however, this procedure comes at the expense of lifelong immunosuppression. The risk of morbidities such as portal vein thrombosis and abdominal hemorrhage makes the procedure unsuitable for a majority of the T1D population. A bioartificial pancreas provides an attractive advantage over current treatment methods by allowing “hands-free” glucose control mediated by beta cell replacement tissue (BCRT). BCRT includes both islets from isolated donor pancreata and stem cell-derived tissue. Our primary goal is to develop a safe and effective medical device for BCRT, designed to preserve BCRT function for the reversal of T1D. Specifically, we aim to validate a two-phase approach to BCRT transplantation with a thin-sheet device perfused by the host vasculature prior to BCRT introduction. In phase one the host develops new tissue within the device that we have shown is fully integrated into the subcutaneous space, demonstrated by the infiltration of dense microvasculature and nerves. In phase two we inject oxygen-demanding BCRT into our device such that they are immediately within 50-100 microns from the dense vasculature. We have presently implanted prototype devices in diabetic athymic nude mice. Devices were allowed to vascularize for 1 week, at which point we re-accessed the inlet/outlet of the device to inject BCRT into the device channels in situ. Preliminary evidence indicates only after BCRT injection did diabetic mice achieve euglycemic conditions. Mice remained euglycemic until devices were excised, where they then returned to hyperglycemic conditions.

Keywords: islet transplantation; prevascularization; type I diabetes;

MESENCHYMAL STEM CELL BIOMARKERS PREDICT AND PREVENT BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS

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BACKGROUND: Bronchopulmonary dysplasia (BPD) is a chronic disease of preterm infants caused by multiple factors leading to arrested alveolar development. Current therapies lack effectiveness and have negative side effects. Our work using mesenchymal stem cells (MSC) and conditioned-media (MSC-CM) has shown protective effects in mouse models. Analysis identified Osteopontin (Opn) and Macrophage colony stimulating factor 1 (Csf1) as key biomarkers protecting against BPD. Our pilot study proved the feasibility of Opn and Csf1 detection in the tracheal aspirate fluid (TAF) of preterm infants. AIM: We hypothesize that low Opn and Csf1 at birth leads to BPD. Our aim is to determine the association between Opn and Csf1 and BPD by quantifying these markers in preterm infant TAF. METHOD: Infants <32 weeks or <1500g birth weight intubated within 24 hours of life were enrolled into the UCI IRB-approved study. Those with congenital anomalies or pulmonary hemorrhage were excluded. The 1st TAF sample was obtained at intubation. The 2nd was obtained at extubation or the 4th day if still intubated. Opn, Csf1 and IgA levels were analyzed using ELISA. IgA was used as control to correct for TAF volume. Infants were followed prospectively for the development of BPD. RESULTS: 22 infants have been enrolled. Subjects were similar in their baseline characteristics. Standard curves were used from the pilot study. 15 of 22 subjects developed BPD. Levels of Opn and Csf1 were much lower at birth for these infants when compared to those who did not develop BPD (Opn 15 vs 28 ng/mL; Csf1 1844 vs 4787 pg/mL). The Opn and Csf1 levels at extubation, while lower in the BPD subjects, did not reach statistical significance. CONCLUSIONS: MSC biomarkers Opn and Csf1 predict and prevent BPD at birth. Our work in progress suggests that an early surge in Opn and Csf1 at birth in the TAF of preterm infants protects against developing BPD. Further data collection is underway to reach study power.

Keywords: stem cell; bronchopulmonary dysplasia; preterm infant;

TARGETED INVESTIGATION OF NOVEL HUMAN UMBILICAL CORD MESENCHYMAL STEM CELL BIOMARKERS OF BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS

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BACKGROUND: Bronchopulmonary dysplasia (BPD) is a chronic debilitating disease of preterm infants caused by oxygen toxicity, inflammation, and ventilator use leading to arrested alveolar development. Current therapies lack effectiveness and cause undesirable side effects. Our work utilizing bone-marrow derived mesenchymal stem cell (MSC) and their conditioned-media (MSC-CM) have shown protective effects in mouse BPD models. Analysis of the MSC-CM identified Osteopontin (Opn) and Macrophage colony stimulating factor 1 (Csf1), as key biomarkers leading to protection against BPD. We hypothesized that human umbilical cord mesenchymal stem cells (hUC-MSCs) have similar growth and differentiation potential as mouse bone-marrow derived MSCs. In addition, we hypothesized that like mouse MSCs, hUC-MSCs secrete biologically active factor(s) into their conditioned media which can account for their therapeutic efficacy in BPD. OBJECTIVES: Our objectives are; 1. To isolate, culture, immunodeplete and differentiate hUC-MSCs. 2. To identify the active factor(s) / biomarkers secreted by hUC-MSCs into their conditioned media relevant to neonatal BPD, utilizing advanced proteomic analysis. Design/METHODS: The hUC-MSCs were isolated according to published methods with minor modifications. Immunodepletion was performed with negative selection of CD34, CD45, CD11b, CD19, and HLA-DR cell markers and positive selection of CD105, CD90, CD44, and CD73 markers. Following this, the differentiation potential of these cells into osteocytes and adipocytes was assessed by selective propagation in specific differentiation media. hUC-MSC and mouse MSC confluent cultures were incubated in serum-free D-MEM media for 24 hours and the conditioned media from equal numbers of cells in each culture was obtained and concentrated 10-fold and analyzed for the identification of active factors via advanced proteomics. RESULTS: The hUC-MSCs were successfully isolated, propagated in culture, immunodepleted, an

Keywords: Bronchopulmonary dysplasia; Stem cell; conditioned media;

Systemic neutrophil depletion modulates the migration and differentiation of transplanted human neural stem cells to rescue functional repair.

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The interaction of transplanted stem cells with local cellular and molecular cues in the host central nervous system (CNS) microenvironment may affect the potential for repair by therapeutic cell populations. In this regard, spinal cord injury (SCI), Alzheimer's disease, and other neurological injuries and diseases all exhibit dramatic and dynamic changes to the host microenvironment over time. Previously, we reported that delayed transplantation of CNS-derived human neural stem cells (hCNS-SCns) at 9 or 30 days post-SCI (dpi) resulted in extensive donor cell migration, predominantly neuronal and oligodendrocytic donor cell differentiation, and functional locomotor improvements. Here, we report that acute transplantation of hCNS-SCns at 0 dpi resulted in localized astroglial differentiation of donor cells near the lesion epicenter, and failure to produce functional improvement. Critically, specific immunodepletion of neutrophils (polymorphonuclear leukocytes, PMN) blocked hCNS-SCns astroglial differentiation and rescued the capacity of these cells to restore function. These data represent novel evidence that a host immune cell population can block the potential for functional repair derived from a therapeutic donor cell population, and support targeting the inflammatory microenvironment in combination with cell transplantation after SCI.

Keywords: neutrophil depletion; spinal cord injury; innate immune response; stem cell transplantation; cell-based therapy;

Optimizing label-free human neural stem cell sorting

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Human neural stem and progenitor cells (NSPCs) have therapeutic potential to treat neurological ailments as they provide neuroprotection and differentiate into astrocytes, neurons, and oligodendrocytes. However, cultures of these cells are heterogeneous, containing progenitor cells with distinct differentiation properties. Little is known regarding which types of progenitors are best for neural repair. Dielectrophoresis (DEP) uses electric fields to separate cells based on the dielectric properties of their membrane and cytoplasm. Using DEP, we've demonstrated that astrocyte progenitors (APs) and neuron progenitors (NPs) can be isolated from mouse NSPCs at select frequencies. This behavior is linked to membrane capacitance and fate potential. The DEP response of NSPCs is not always the same at a single frequency, therefore, a two-step NSPC sorting scheme is used: step 1 defines a sample specific trapping frequency, and step 2 separates cells at the trapping frequency using a DEP microwell device. Human APs were detected and separated from heterogeneous NSPCs using DEP. A trapping frequency specific to APs was defined using a 3DEP reader. Then, APs were sorted at the trapping frequency using a microwell DEP device with interdigitated electrodes. Prior to sorting, a mini-trapping curve was developed in the microwell device, confirming accuracy of the predicted trapping frequency. For post-sorting analysis, cell differentiation and 3DEP reader analysis were completed to verify AP separation, determine cell enrichment, and measure membrane capacitance values of sorted cells. Cells trapped at 1MHz and incubated in the DEP buffer solution were tested as controls. AP separation was confirmed after cell differentiation by GFAP and SOX2 and cell enrichment was found to be 1.75 fold. Effectively sorting human NSPCs to generate distinct progenitor populations enables further study of specific progenitors as treatment options for neurological diseases and injuries.

Keywords: Neural stem and progenitor cells; Dielectrophoresis; Membrane capacitance; Cell differentiation; Cell sorting;

SMAC Mimetics as a Therapeutic Approach in Myeloproliferative Neoplasm

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Myeloproliferative neoplasm (MPN) is a hematologic malignancy resulting from the somatic acquisition of a JAK2V617F mutation in a hematopoietic stem cell. The clinical consequences of MPN are elevated blood counts, thrombosis, splenomegaly, and transformation to acute leukemia. Bone marrow transplantation is the only curative option, there is a clear need for novel therapeutics that specifically target the mutant neoplastic cells in MPN. Neoplastic cells can evade death by upregulating anti-apoptotic proteins such as inhibitor of apoptosis proteins (IAPs). IAPs bind to and inhibit caspases, preventing their pro-apoptotic protease function. SMAC mimetics bind IAP proteins causing their degradation, these drugs are actively investigated as cancer therapeutics. TNF signaling induces activation of NF?B and this mediates SMAC mimetic induced apoptosis. Because JAK2V617F MPN cells have active NF?B signaling, we hypothesized that JAK2V617F mutant cells would be sensitive to SMAC mimetics in the absence of TNF whereas normal cells would only be sensitive to SMAC mimetics when TNF is present. We compared the sensitivity of JAK2V617F mutant cells to LCL-161 in four different systems: an established human cell line with a JAK2V617F mutation (HEL) versus an established cell line without the JAK2V617F mutation (K562), a mouse fibroblast cell line (L929) that we engineered to stably express JAK2V617F versus empty vector, primary bone marrow cells from JAK2V617F knock-in mice versus wild-type mice, and peripheral blood mononuclear cells from MPN patients versus normal controls. We found that in all four systems JAK2V617F cells were more sensitive to LCL-161 alone. However, when TNF was added this differential sensitivity was lost, and both JAK2V617F mutant and wild-type cells were equally sensitive to LCL-161. Based on these data, we predict that a combination of SMAC mimetic and an anti-TNF agent would be a beneficial therapeutic combination in MPN.

Keywords: hematopoietic stem cell; hematologic malignancy; myeloproliferative; TNF; apoptosis;

Microbial community characterization of fecal samples from healthy premature infants compared to those that develop late onset sepsis

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Extreme low birth weight (ELBW) infants are at very high risk for developing necrotizing enterocolitis (NEC), a common cause for morbidity and mortality among these infants. Premature birth and early feeding are both important risk factors. A majority of infants with NEC go on to develop severe late onset sepsis (LOS) requiring prolonged broad spectrum antibiotics and debilitating surgical intervention. We aim to use a systems biology approach to characterize gut microbial communities from otherwise healthy premature infants to compare them to those from ELBW infants who develop LOS (with or without NEC). Fecal samples have been collected from 37 ELBW infants, including 24 controls, 5 with NEC, and 7 septic non-NEC. Metagenomic DNA was extracted, and barcoded 16s rRNA (V3-V4 region) sequencing libraries were prepared with the NexteraXT primers followed by Illumina sequencing. Fecal samples were also analyzed for metabolites using GC-MS. Prinseq was used for quality control of the sequencing data and further analysis was performed using Qiime and the R packages Vegan and randomForest. The bacterial composition of the infant guts varies greatly from patient to patient. Because of the widespread use of antibiotics on premature infants, the gut microbial composition often varies greatly at different timepoints in a single infant. No clear indicators of disease were found but a number of metabolites correlated with dysbiosis have been identified for further study. Understanding the characteristics of normal gut microbial communities in ELBW infants will enable strategies to preserve or reconstitute healthy microbial community assembly after modification by diverse therapeutic interventions.

Keywords: human microbiota; metabolomics; genomics; necrotizing enterocolitis;

Pathological Characteristics and Prognostic Indicators of Different Histopathological Types Following Radical Cystectomy: A Large Cohort with Long-Term Follow-up

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INTRODUCTION: We identified differences in pathological features and prognostics among 4 histological types of bladder cancer: urothelial carcinoma (UC), urothelial carcinoma with metaplasia (UCM), squamous cell carcinoma (SCC) and adenocarcinoma (ADC), utilizing a large cohort of radical cystectomy (RC) patients with long term follow up METHODS: We retrospectively evaluated 1,280 patients who underwent RC between 1997-2004 at a single institution in Mansoura, Egypt. Multivariate analyses were used to evaluate the prognostic significance of tumor stage, grade, lymphovascular invasion (LVI), and lymph node involvement (LN) in patients with different subtypes RESULTS: The study included 1,238 patients with median age 58 (29-87) and a median follow up of 39 months (0-109). There were significant differences in demographics, tumor stage, grade, LVI, LN involvement and presence or absence of schistosomiasis infection between all 4 histological subtypes. Schistosmiasis was associated with SCC and ADC (76%) followed by UCM (69%) then UC (54%). Nearly all patients observed with UC and UCM had high-grade disease, in comparison with only 41% and 68% patients with SCC and ADC. Grade was an independent predictor of disease recurrence only in SCC (HR 1.6, p value = 0.023). LVI was an independent prognostic in SCC and ADC (HR 2.1, $p < 0.05$). LN involvement was most common in UCM (1/3 of cases) and was the most important independent predictor of disease recurrence (HR 2.14, p value = 0.012) CONCLUSIONS: Histopathological types of bladder cancer differ significantly in clinico-pathological features. SCC and ADC are associated with younger age, schistosomiasis, lower grade, and less LVI and LN involvement. LVI plays a greater prognostic role in SCC and ADC. LN metastasis is more common and more adversely affects oncological outcomes in UCM. Prognostic models based on independent predictors can tailor postoperative surveillance and guide future multimodal treatment approaches

Keywords: Radical cystectomy; Squamous cell carcinoma; Urothelial carcinoma; Adenocarcinoma; Schistosomiasis;

Early diagnosis and treatment of Prader Willi Syndrome: Is Newborn Screening feasible

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Background: Prader-Willi syndrome (PWS), affecting 1/15,000 individuals, is a genetic disease characterized by lack of expression of genes on the paternal chromosome 15q11-q13 region. Clinical presentation ranges from hypotonia and feeding problems in infants, short stature in children to significant morbidity and mortality from hyperphagia and morbid obesity in adolescents. Growth hormone (GH) replacement has revolutionized the stature/body composition and obesity with improvement in the morbidity and mortality in PWS individuals who have started treatment early. Despite significant diagnostic advances however the mean age for diagnosis of PWS continues to lag behind. California Newborn Screening (NBS) program allows for early diagnosis of many metabolic and genetic conditions with additional disorders are being added to the list. In this study we show that not only does PWS meets all the criteria for early NBS but it also amenable to an economical method of testing. Hypotheses: We hypothesize that our proposed genetic testing of newborns for PWS will be time and cost effective allowing for early diagnosis and treatment leading to lower morbidity and mortality and improved prognosis of PWS patients. Objectives: 1) To extract DNA from dried blood spots on NBS filter paper cards from 150 subjects (100 PWS; 50 controls) 2) To evaluate time and cost effectiveness of MS-MLPA test for PWS using fragment analysis vs. Next Generation Sequencing (NGS) Methods: DNA isolated from NBS filter paper card using modified combination of GenSolve and Qiagen DNA MicroKit. PWS testing done using MS-MLPA probe mix and fragment analysis using Sanger sequencer. Results: We were able to extract sufficient amount of DNA from dried blood spot on newborn screening filter paper on 10 samples. Preliminary data is promising that MS-MLPA can prove to be time and cost effective for PWS testing. We anticipate that NBS will significantly improve the prognosis for patients with PWS.

Keywords: Prader-Willi Syndrome; Newborn screening; Obesity; MS-MLPA; NGS;

A metabolomics approach to study the interaction between bacterial isolates from Cystic Fibrosis sputum

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Cystic Fibrosis (CF) is a genetic disease that causes build up of thick mucus in the lungs and airways of patients, leading to prolonged infection. Before the widespread use of antibiotics later in the 20th century, patients succumbed to infections from Staphylococcus spp., Streptococcus spp., and other common members of the oral microbiota. Now, life expectancy has grown dramatically, and CF patients develop persistent infections with slow-growing, antibiotic resistant Gram-negative bacteria such as Pseudomonas aeruginosa and Burkholderia spp. Elucidating the available nutrients and the interactions between bacterial strains within the polymicrobial communities in the airways is essential for understanding persistent infections and patient outlook. We are interested in studying the metabolic interactions and nutrient flow between our clinical isolates Pseudomonas aeruginosa and Rothia mucilaginosa, dominant and long-term residents of the CF polymicrobial community. By performing gas chromatography mass spectrometry (GC-MS) on mono and co-cultures, we were able to characterize molecules present in the interaction between our two clinical isolates. R. mucilaginosa produces metabolites consumed by P. aeruginosa, and may provoke the production of toxic molecules. For example, fermentation products such as 2,3-butanedione provoke P. aeruginosa to produce more phenazines, which are toxic and can generate Reactive Oxygen Species in the presence of oxygen, and may also act as an alternative electron acceptor in a low oxygen environment. A combination of metabolomics data and hypothesis driven experiments to better understand the interaction between P. aeruginosa and R. mucilaginosa will be presented.

Keywords: Cystic Fibrosis; Metabolomics; clinical isolates;

A Stenotrophomonas story: characterizing a Cystic Fibrosis clinical isolate

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Molecular Biology and Biochemistry

Cystic fibrosis (CF) is a genetic disease that is currently affecting 30,000 people in the U.S. and 70,000 people worldwide. CF patients have a mutation in the CF transmembrane receptor (CFTR), resulting in reduced ion transport across epithelial cells and accumulation of dense mucus in the lungs. The thick mucus cannot be cleared from the airways, leading to colonization of the CF lungs with microbes. CF pathogens must adapt to complex microenvironments in the lungs that have variations in pH, oxygen levels, metabolites, and microbial composition. The use of culture-independent methods, such as genomics and transcriptomics, contributes to our knowledge of the composition and pathogenesis of bacteria that colonize the CF lungs. In order to determine virulence factors that contribute to infection of the lungs, we isolated Stenotrophomonas maltophilia from the sputum of a CF patient. S. maltophilia is a Gram-negative opportunistic pathogen that has been identified in the metagenomes from the sputum of CF patients, yet there are few studies on the role of this organism in CF bacterial pathogenesis. In order to identify genes that contribute to S. maltophilia pathogenesis, we sequenced the genome of S. maltophilia and performed a transcriptomics experiment in a gradient of pH values relevant to the CF airways. We then compared the genome of our clinical isolate to those of other S. maltophilia clinical isolates and environmental isolates. Our clinical isolate shared antibiotic-resistance and virulence genes with S. maltophilia K279a (an isolate associated with bacteremia) that were not found in the genomes of environmental isolates. The function of these antibiotic-resistance genes was confirmed in vitro in antimicrobial susceptibility tests in a range of physiologically relevant pH. Including S. maltophilia and other under-studied opportunistic pathogens in CF studies will improve diagnosis and treatment of polymicrobial infections in the CF lungs.

Keywords: Genome; Antibiotic resistance; Transcriptome; Cystic Fibrosis;

Using zebrafish to study ocular lens physiology: the Aquaporin 0 story

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Background: Cataract is the leading cause of blindness worldwide. Due to an aging population and increased incidence of diabetes, we face an impending cataract epidemic and need alternative therapies to surgery. Understanding the molecular causes of cataract will identify therapeutic targets to prevent or delay cataract formation. Aquaporin 0 (AQP0) is the most abundant lens fiber membrane protein, and mutations in human AQP0 lead to cataract. Purpose: Mammalian AQP0 has multiple functions, rendering it difficult to study these functional individually. Zebrafish (Danio rerio), however, have evolved two genes, Aqp0a and Aqp0b, with distinct functions making it an excellent model to study Aqp0 lens function. The purpose of this study was to characterize morphological changes that occur in response to Aqp0a and b knock down and to localize expression of both Aqp0s in the zebrafish lens. Methods: Wild type or Aqp0a or b-MO injected whole embryos and adult lenses were PFA-fixed and either whole-mounted or cryosectioned. C-terminal Aqp0a or Aqp0b antibodies were used for regional and cellular lens mapping and imaged using confocal microscopy. Results: 3 days old Aqp0a-deficient lenses were smaller, with cell swelling localized to the lens core, while Aqp0b-deficient lenses were larger, with cellular disruption at the cortical-nuclear interface. Aqp0a and b C-terminus labelling was evident throughout 2 day old lenses, and became restricted to the the outer cortex in the adult lens, in both, ball-and-sockets, as well as protrusion domains of lens fiber cell membranes. Conclusions: The functional difference between Aqp0a andAqp0b during lens development is not reflected in differential antibody labelling. This work highlights the similarity of the zebrafish Aqp0 expression compared to mammals with the strength of functional division of mammalian gene functions into two genes making it a powerful tool for the identification of novel anti-cataract therapies.

Keywords: Lens; Cataract; Zebrafish; Therapeutic target;

The Pivotal Role of Aldehyde Toxicity in Autism Spectrum Disorder

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Autism Spectrum Disorder (ASD) is characterized by social and communication impairments as well as by restricted, repetitive patterns of behavior and interests. Genomic studies have not revealed dominant genetic errors common to all forms of ASD. So ASD is assumed to be a complex disorder due to mutations in hundreds of common variants. Other theories argue that spontaneous DNA mutations and/or environmental factors contribute to as much as 50% of ASD. In reviewing potential genetic linkages between autism and alcoholism, it became apparent that all theories of ASD are consistent with aldehyde toxicity, in which endogenous and exogenous aldehydes accumulate as a consequence of mutations in key enzymes. Aldehyde toxicity is characterized by cell-localized, micronutrient deficiencies in sulfur-containing antioxidants, thiamine (B1), pyridoxine (B6), folate, Zn2+, possibly Mg2+, and retinol, causing oxidative stress and a cascade of metabolic disturbances. Aldehydes also react with selective cytosolic and membrane proteins in the cell of origin; then some types migrate to damage neighboring cells. Reactive aldehydes also form adducts with DNA, selectively mutating the bases and inducing strand breakage. The poster reviews the relevant genomic, biochemical, and nutritional literature, which supports the central hypothesis that most ASD symptoms are consistent with symptoms of aldehyde toxicity. The hypothesis represents a paradigm shift in thinking and has profound implications for clinical detection, treatment, and even prevention of ASD. Insight is offered as to which neurologically afflicted children might successfully be treated with micronutrients and which children are unlikely to be helped. The aldehyde toxicity hypothesis likely applies to other neurological disorders.

Keywords: Autism Spectrum Disorder; Aldehyde Toxicity; Oxidative Stress; de nova Mutations; ASD Genetics;

Models of Vemurafenib resistance in melanoma cell lines

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The biological basis for inherent and acquired drug resistance in melanoma is a prominent issue, highlighted by the recent discovery of various pathways leading to acquired resistance to the mutant BRAF inhibitor Vemurafenib (Plx4032). In order to dissect patterns of drug resistance, we treated 3 melanoma cell lines (A375, 1205Lu and SK-Mel28) under 2 diverse conditions: (1) Increasing drug concentrations over time(4 months)- Melanoma cells treated with increasing concentrations of Plx4032 (initial and increasing concentrations of 0.1, 0.5, 1 and 5 ?M PLx4032) exhibited an adaptation response. After an initial pause in proliferation, these cells proliferated in the continuing presence of the drug. Cells able to grow in the presence of 10 or 20 ?M of Plx4032 were cultured as pools. RNA-Seq profiling and system biology analysis comparing the gene expression in the parental SK-Mel28 cells and adapted A2-1 revealed three major altered pathways: the PDGF-MAPK-DUSP-HIF2???TGF-?-SMAD9-FGF1 and EDNRB-GNAI2-PLCB4-PKA-MITF pathway. Our qRT-PCR and western blot experiments have confirmed an up-regulation of PDGF which by-passed the BRAF gene and activated ERK1/2 kinases. These changes were accompanied by increase of NRAS accumulation in the adapted cells. (2) Using high initial drug concentrations of PLx4032 (>10 ?M), > 99.9 of cells were killed, but some single cells (Q/D) survived for at least 4 weeks in the continuous presence of drug. After the drug was removed cell proliferation reoccured 2-3 weeks later. These PD1 cells did not show increased IC50s to Plx4032 after 72 hour of retreatment. However, when treated with high dose of drug again, the PD1 cells produced more dormant cells (PD2 cells), suggesting inheritance of the DQ trait. RNA-Seq profiling studies of the DQ cells are underway. The drug-induced dormancy/quiescence and adaptive response represent 2 different pathways of how cells survive treatment and develop resistance.

Keywords: Melanoma drug resistance; Transcriptome analysis;

The influence of body mass index, gestational weight gain and diet on maternal plasma fatty acid profiles across pregnancy

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Improved understanding of how maternal weight status and nutrition in pregnancy influence underlying metabolic pathways may reveal optimal targets for more effective future interventions. This study investigates the associations of maternal pre-pregnancy body mass index (pBMI), gestational weight gain (GWG) and dietary intake on maternal plasma non-esterified fatty acids (NEFA) across pregnancy. Non-diabetic pregnant women (N=160) were recruited in early pregnancy and followed prospectively across gestation. Laboratory visits in each trimester obtained measured weight and height, fasting blood samples and dietary intake assessment on 3 non-consecutive days using the 24-hour recall method. Dietary data was used to assess average daily quantity (energy intake) and quality (Alternative Healthy Eating Index adapted for pregnancy (AHEI-P)) of the diet. GWG from pre-pregnancy up until each trimester was calculated and pBMI (kg/m2) was determined from self-reported pre-pregnancy weight and measured height. A targeted LC-MS/MS metabolomics platform determined 21 NEFA metabolites. Mean±SD pBMI was 25.9±6.0 Kg/m2 and GWG from pre-pregnancy to trimester 3 was 10.2±5.3 Kg. Mean AHEI-P score increased slightly between trimester 1 (54.9) and 3 (56.6). 42% of women were classified overweight or obese. pBMI was independently associated with elevated NEFA, particularly in trimester 2. Omega-3 NEFA C20:5 and C22:6 were unaffected in any trimester, while the omega-6 NEFA C20:3, 20:4 and 22:4 remained positively associated with pBMI throughout gestation. GWG, energy intake and AHEI-P were not associated with NEFA in any trimester. Raised pBMI appears to particularly drive elevated levels of omega-6 NEFA, which have been implicated in fetal programming of offspring adiposity. Pre-conception obesity may exert an over-riding influence on maternal fatty acid metabolism, regardless of variations in GWG or quality of the diet. This highlights the importance of pre-conception interventions.

Keywords: Pregnancy; Metabolomics; Non-esterified fatty acids; Maternal obesity; Prenatal nutrition;

Bariatric Surgery Attenuates DSS-Induced Colitis in an Obese Murine Model

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Background: Obesity-related clinical conditions and IBD represent chronic inflammatory diseases; as such, ulcerative colitis and obesity exacerbate each other. Bariatric surgery (BS) improves many obesity-related comorbidities and may also help mitigate Inflammatory Bowel Disease (IBD) symptoms and improve disease control. Post-surgery microbiome rearrangements may represent one possible mechanism whereby BS improves intestinal inflammation, independently of weight loss. This study is to explore the mechanisms governing the pathophysiologic patterns involved in post-surgical amelioration of intestinal inflammation. Methods: Obese mice were assigned to two bariatric procedures including Duodenojejunal Bypass (DJB) and Sleeve Gastrectomy (SG), and Sham-operated mice were (Sham) were used as a control. IBD was induced in all animals by administration of 2% Dextran Sodium Sulfate. Fecal samples were collected prior to and after IBD induction and microbiome analysis was subsequently performed. Mice were euthanized, intestinal tissues were harvested, and pathological analyses and immunohistochemical staining was performed. Results: Animals belonging to both bariatric surgical groups (DJB and SG) displayed a trend towards higher survival relative to control mice. However, only DJB mice showed a statistically significant survival advantage. Histopathological analysis revealed that DJB mice had significantly less intestinal inflammation compared to sham-operated controls. The observed histological improvements were not directly related to a difference in body weight among the groups. A statistically significant increase in the number of Lactobacillales was observed in the DJB group compared to pre-IBD induction levels. A similar trend was observed in SG animals. Conclusions: BS reduces the severity of colitis in a chemically induced-IBD murine model. This positive, anti-colitis effects of bariatric surgery may be associated with gut microbiome rearrangement.

Keywords: Inflammatory Bowel Disease; Colitis; Obesity; Bariatric surgery; Mouse;

HUMANIN G (HNG) REDUCES MITOCHONDRIAL (mt) DNA-MEDIATED APOPTOSIS AND AUTOPHAGY IN AGE-RELATED MACULAR DEGENERATION (AMD) ARPE-19 CYBRIDS; IMPLICATIONS FOR THERAPEUTICS

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PURPOSE: The effects of AMD mtDNA and HNG, a mitochondrial-derived peptide (MDP), on retinal cell death pathways have not yet been demonstrated. Therefore, in this study we tested the hypothesis that in an ARPE-19 transmitochondrial cybrid model, AMD mtDNA mediate cell death via apoptosis and autophagy, and that HNG protects the AMD cybrids against apoptosis and autophagy. METHODS: Transmitochondrial cybrids were prepared by fusing platelets obtained from AMD patients and age-matched normal (NL) subjects, with Rho0 (lacking mtDNA) human ARPE-19 cells. All cybrids had identical nuclei and varied only in mtDNA content. The MTT assay, mt-GFP staining, and Mitosox assay were used to determine the cell viability, mitochondrial number, and mt-ROS levels, respectively. qRT-PCR and Western blotting were performed to examine gene and protein expression profiles, respectively, of apoptosis (Bax, Caspase-3,-7,-9, BCL2L13), and autophagy (LC3B, ATG5, MFN1, LAMP2) markers. AMD and NL cybrids were treated with 3.2 µM of HNG. Student's t-test and ANOVA were used to measure statistical differences. RESULTS: The number of viable cells was significantly decreased ($p<0.05$) at 24 h (18%), 48 h (17%), and 72h (22%) post incubation, in AMD vs NL cybrids (n=4-7). Elevated mt ROS ($p<0.01$) and reduction in mitochondrial number were observed in AMD cybrids (n=3). Up-regulation ($p<0.05$) of BAX (Fold change (FC)=1.3), CASPASE-3 (FC=1.8), CASPASE-7 (FC=6.3), CASPASE-9 (FC=1.7), LC3B (FC=3.1), ATG5 (FC=1.5), MFN1 (FC=1.4), and LAMP2 (FC=2.5) genes was observed in AMD vs NL cybrids (n=4-7). AMD cybrids (n=4) had higher ($p<0.05$) protein levels of CASPASE-3 and LC3B. Treatment of AMD cybrids with HNG caused a significant decrease ($p<0.05$) in the gene expression of BAX (FC=0.67), CASPASE- 3 (FC=0.75), CASPASE-7 (FC=0.71), CASPASE-9 (FC=0.71), BCL2L13 (FC=0.76), LC3B (FC=0.81), ATG5 (FC=0.77) compared to untreated AMD cybrids (n=3-4). No gene expression differences were found in untreated vs HNG-treated NL cybrids. CONCLUSION: Consistent with our hypothesis, the current study indicates that AMD mitochondria are significantly damaged and may act as biomarkers for AMD. It also highlights the protective effects of HNG against apoptosis and autophagy in AMD cybrids. Therefore, HNG could be a cell survival factor and a potential therapeutic target for treatment of AMD.

Keywords: Retina; Mitochondria; Humanin; AMD; Age-related macular degeneration;