CTS Scholar Presentations: Bench to Bedside

8th Annual CCTS Spring Conference
Building Teams for Translational Science

1:10 – 3:10 pm • Thoroughbred 3

Session Chair: **Karyn Esser, PhD**
Professor, Department of Physiology, College of Medicine
Director, Center for Muscle Biology

Therapeutic Targeting of Vital Cellular Interactions: Inducing Anoikis in Glial and Prostate Cancers

Patrick Hensley
Post-Sophomore Fellow, Department of Pathology and Laboratory Medicine and Department of Surgery, Division of Urology, College of Medicine
Mentor: Natasha Kyprianou, PhD

Fresh Red Blood Cells Mitigate Human T-cell Suppression seen with Stored Blood Bank Red Blood Cells

Kristin Long, MD
General Surgery Resident
Mentor: Andrew Bernard, MD

Chemokine Ligand 20 (CCL20): A regulator of leukocyte recruitment stimulated during ovulation in the human

Linah F. Al-Alem, PhD
Post Doctoral Scholar, Department of Obstetrics and Gynecology, College of Medicine
Mentor: Thomas E. Curry, PhD

Rheological Impact of Dysregulated Neutrophil Shear Stress Mechanotransduction on Hypercholesterolemia-Related Microvascular Pathophysiology

Xiaoyan Zhang, PhD
Center for Biomedical Engineering
Mentor: Hainsworth Shin, PhD

In vivo molecular bio-imaging of retinal cell death

Kabhilan Mohan, PhD
Postdoctoral Fellow, Department of Ophthalmology and Visual Sciences
College of Medicine
Mentor: Mark Kleinman, MD

Advanced Imaging of Cardiac Dysfunction in mice using DENSE MRI

Christopher M. Haggerty, PhD
Postdoctoral Fellow, Cardiac Imaging Research Laboratory
Division of Pediatric Cardiology, Department of Pediatrics, College of Medicine
Mentor: Brandon K. Fornwalt, MD, PhD

Transmural Variations in Cellular Level Contractile Function in the Left Ventricle of Patients with Endstage Heart Failure

Premi Haynes
PhD Candidate, Department of Physiology, Center for Muscle Biology
Mentor: Kenneth S. Campbell, PhD

Potential Therapeutic Effects of Sphingosine-1 Phosphate Lyase Inhibition during Ischemic Injury of the Heart

Yuri Kyliachkin, PhD
Post-doctoral Fellow, Department of Internal Medicine
Saha Cardiovascular Research Center
Mentor: Ahmed Abdel-Latif, MD, PhD

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CTS Scholar Presentations: Bedside to Community

8th Annual CCTS Spring Conference
Building Teams for Translational Science

2:10 – 3:10 pm • Thoroughbred 2

Session Chair: **Sharon Walsh, PhD**
Professor, Department of Behavioral Science, College of Medicine
Director, Center on Drug and Alcohol Research

The Association between Burn Injuries and Pseudoephedrine Sales

Amie Goodin, MPP
Institute for Pharmaceutical Outcomes and Policy
College of Pharmacy
Mentor: Karen Blumenschein, PharmD

Comparison of Surgical Treatment Modalities for Patients with Thoracic Empyema

Matthew T. Bender
MD Candidate, Class of 2015
College of Medicine
Mentor: Sibu Saha, MD

Near-infrared Diffuse Optical Monitoring of Cerebral Blood Flow and Oxygenation for the Prediction of Vasovagal Syncope

Ran Cheng
PhD Candidate, Center for Biomedical Engineering
Mentor: Guoqiang Yu, PhD

Pediatric Congenital Hearing Loss in Appalachia: Assessing and Addressing Diagnostic Delays

Matthew L. Bush, MD
Assistant Professor
Department of Otolaryngology – Head and Neck Surgery
University of Kentucky Medical Center
Mentors: Nancy Schoenberg, PhD and TJ Gal, MD

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UK UNIVERSITY OF KENTUCKY
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8th Annual CCTS Spring Conference

Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Therapeutic Targeting of Vital Cellular Interactions: Inducing Anoikis in Glial and Prostate Cancers**

Author(s): P. J. Hensley, Departments of Surgery/Urology and Pathology, U of Kentucky
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Abstract: PURPOSE: The complexity of the tumor microenvironment in progression to metastasis has confounded efforts to establish effective clinical treatment of advanced stage tumors. Our drug-discovery efforts generated a novel lead quinazoline-based Doxazosin® derivative, DZ-50, which impairs tumor growth and metastasis via induction of anoikis and targeting tumor vascularity. This study pursued identification of the molecular targets of DZ-50 in two human prostate cancer cell lines (DU-145 and PC-3) and two human glioblastoma cells lines (U-87 and LN-18). Considering the ability of the focal adhesion regulators TALIN and ILK to confer anoikis resistance, the impact of DZ-50-mediated disruption of cell-cell interactions and anoikis induction was investigated relative to variable TALIN and ILK expression. METHODS: DU-145 cells were stably transfected to overexpress TALIN (TALIN+) and knock-down expression via shRNA (shTALIN). PC-3 cells were stably transfected to knock-down expression of ILK (shILK). The prostate cancer and glioblastoma cell lines were treated with DZ-50 (5μM). Microarray analysis was performed to identify lead gene targets of DZ-50. Quantitative Real Time-PCR (qRT-PCR) was used to validate changes in gene expression in response to treatment. Protein expression of key focal adhesion regulators was profiled using Western Blotting and fluorescent immunohistochemistry. Cell viability (MTT assay), migration and adhesion to extracellular matrix components were assessed. RESULTS: Microarray and qRT-PCR analysis revealed specific genetic targets of DZ-50, with treatment resulting in transcriptional downregulation of proteins involved in tight junction formation (Claudin-11) and the focal adhesion complex (TALIN, ILK, Fibronectin). Confocal microscopy using antibodies to tight junction proteins (Claudin-11/ZO-1) and focal adhesion components (TALIN/ILK) revealed diminished co-localization of these proteins and decreased capacity for environmental cellular interactions. TALIN and ILK expression levels were significantly correlated with susceptibility to DZ-50: overexpressing cells demonstrated increased cell viability and anoikis resistance, while the opposite was observed in the TALIN and ILK silenced cells. CONCLUSIONS: Our results suggest that DZ-50 targets integrin-mediated extracellular matrix interactions and tight junctions, potentially impairing metastatic behavior. Silenced expression of focal adhesion proteins increases susceptibility to anoikis-inducing therapeutics, while overexpression of TALIN or exposing cells to an extracellular matrix rich environment imparts therapeutic resistance. Ongoing dissection of the antitumor mechanism of DZ-50 will expand our understanding of the protective role of anoikis in cancer metastasis.

Supported by: This work was supported by a grant from the National Institutes of Health (R01CA107575-6) and the National Center for Advancing Translational Sciences (UL1RR033173).

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8th Annual CCTS Spring Conference

Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Fresh Red Blood Cells Mitigate Human T-cell Suppression seen with Stored Blood Bank Red Blood Cells**

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Abstract: INTRODUCTION: Transfusion of packed red blood cells, while often necessary and life-saving, can produce a myriad of immunologic derangements. Prior studies have shown that exposure to packed red blood cells (PRBCs) will suppress the normal proliferative response of human T cells in culture. This is not a consequence of apoptosis or necrosis. PRBCs of varying ages have exhibited similar behavior. By replacing PRBCs with fresh red blood cells, proliferative capabilities of T cells are restored. METHODS: Purified human T cells are placed in culture and stimulated to proliferate with CD3/CD28. T cells were stained with CFSE (carboxyfluorescein succinimidyl ester) to measure proliferation and then exposed to either a) stored red blood cells obtained from the blood bank (average age 21 days) or b) fresh red blood cells obtained from a volunteer donor within 1 hour of culture. RBCs (both stored and fresh) were counted and placed in culture at equal concentrations. Apoptosis/necrosis studies were done by staining with Annexin V and PI after exposure to PRBCs. RESULTS: T cells exposed to PRBCs from the blood bank exhibited near-complete suppression. T cells treated with fresh RBCs, however, continued to proliferate. Negative controls using unstimulated T cells showed no independent proliferation. Additional experiments confirm that apoptosis and necrosis, seen normally in stimulated T cells, do not contribute to the suppression seen after RBC exposure. CONCLUSIONS: Transfusion of fresh human red blood cells eliminates the prohibitive effects of stored RBCs on human T cell proliferation in vitro. The handling, processing, and storage of RBCs by the blood bank alter the cell function and contribute to the witnessed immunosuppressive effect seen in T cells. Apoptosis or necrosis of the T cells is not responsible for this suppression, indicating that the PRBCs play a more direct role. Further analysis is necessary, but this offers insight into a potential mechanism for transfusion-related immunomodulation.

Supported by: The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117, and the Dean of the College of Medicine, University of Kentucky. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the University of Kentucky.

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8th Annual CCTS Spring Conference

Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Chemokine Ligand 20 (CCL20): A regulator of leukocyte recruitment stimulated during ovulation in the human**

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Abstract: The LH surge sets in motion a chain of events that culminates in ovulation. One of these events is the presence of an inflammatory reaction characterized by leukocyte influx. To determine the key regulators of leukocyte recruitment, we explored the expression of a specific chemokine, Chemokine ligand 20 (CCL20) in the human ovary. Our hypothesis is that the LH surge stimulates an increase in CCL20 resulting in the recruitment of leukocytes that impact ovulation. To address this hypothesis, the dominant follicle was collected from women undergoing tubal sterilization at the preovulatory phase or women were given rhCG and dominant follicles collected after rhCG: early ovulatory (EO, 12-18h), late ovulatory (LO, 18-34h) and postovulatory (PO, 44-70h). Follicles were processed for protein localization, or granulosa (GC) and theca cells (TC) were isolated and processed for mRNA analysis. CCL20 was induced during the EO and LO stage in GC (>10,000 fold) and TC (>4000 fold). CCL20 protein was localized to the GC cell layer and increased at the EO phase. To determine the regulation of CCL20, an in vitro model was developed using granulosa-lutein cells (GLC) from IVF patients. Administration of hCG increased CCL20 40-fold. To determine the hCG regulated pathway(s) controlling CCL20 expression, studies using specific pathway inhibitors revealed that CCL20 expression was regulated by the EGF pathway. In addition, recombinant hCCL20 used in migration transwell assays was capable of stimulating leukocyte migration. In summary, CCL20 expression is potentially a regulator of leukocyte recruitment into the ovary impacting ovulation and fertility.

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Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Rheological Impact of Dysregulated Neutrophil Shear Stress Mechanotransduction on Hypercholesterolemia-Related Microvascular Pathophysiology**

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Abstract: Neutrophils play a key role in hypercholesterolemia-related microvascular pathobiology, but the nature of their involvement remains unclear. We previously reported that pseudopod retraction responses of neutrophils to shear stress is compromised by hypercholesterolemia. For this study, we hypothesized that impaired shear mechanotransduction, due to hypercholesterolemia, alters the flow behavior of neutrophils leading to microvascular dysfunction. To address this, we first examined the shear effects on the flow behavior of human leukocytes. When subjected to shear, leukocyte suspensions, exhibited time-dependent reductions in viscosity that tracked with transient decreases in pseudopod activity. This effect was blocked by membrane cholesterol enrichment. To link this finding with in vivo microvascular flow regulation, we determined the contribution of neutrophil shear responses to reactive hyperemia. We used a novel technique based on diffuse correlation spectroscopy (DCS) to measure the relative change of blood flow (rBF) in the thigh muscles of LDLr-/- mice fed a high-fat (HFD) or normal (ND) diet for 8 weeks. A DCS probe was glued on the thighs of anesthetized mice, and rBF was continuously recorded before, during and after 5-minute arterial cuff occlusion. Adjusted peak flow (aPF) was calculated as the average of the maximum 10% of rBF measurements which occurred between 1 and 2 min after cuff release and coincided with the time when shear was expected to induce maximal pseudopod retraction by cells in the vessels. HFD mice exhibited reduced aPF compared to ND mice that was abrogated by neutropenia induction. Notably, aPF significantly ($p<0.01$) correlated with neutrophil shear responsiveness. These results provide first evidence that connects neutrophil shear responses to reactive hyperemia. Moreover, our findings support a link between defective shear mechanotransduction and hypercholesterolemia-related pathobiology.

Supported by: American Heart Association, Beginning Grant-In-Aid (09BGIA2250309) National Science Foundation, KY-EPSCoR-Bioengineering Initiative

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Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **In vivo molecular bio-imaging of retinal cell death**

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Abstract: Introduction: In this study, we evaluated the potential use of a near-infrared fluorescent (NIRF) probe to detect and inhibit caspase 1/3 activation in a mouse model of age-related macular degeneration (AMD). The overarching goal of this work is to translate a clinical imaging tool to visualize RPE cell death in vivo in dry AMD using standard ophthalmic camera equipment. Methods: Wild-type C57BL/6 mice received subretinal injections of purified Alu-derived RNA or appropriate controls. Caspase 1/3 detection was accomplished utilizing a cell permeant NIRF coupled VAD peptide sequence administered intravitreously. Fundus imaging was performed at baseline, 8 and 24 hours after intravitreous injection of the probe. RPE/choroid flatmounts and tissue sections were prepared and analyzed to co-localize caspase probe and apoptotic cells using TUNEL. Results: Live bio-imaging for active caspase 1/3 revealed large areas of NIRF signal in treated eyes, a finding which was confirmed on RPE flatmounts. Tissue sections exhibited colocalization of NIRF signal with TUNEL positive cells in RPE and the overlying photoreceptor layer. Conclusions: Non-invasive detection of caspase activation in the RPE in vivo is feasible with a custom engineered NIRF bio-probe that can be visualized using common ophthalmic imaging equipment. The bio-probe also inhibits caspase activation and thus may serve a dual purpose of detection and inhibition of RPE loss secondary to cytotoxic RNA accumulation in advanced dry AMD.

Supported by: National Eye Institute K08EY021757 Research to Prevent Blindness Career Development Award Foundation Fighting Blindness Career Development Award University of Kentucky College of Medicine Physician Scientist Award

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Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Advanced Imaging of Cardiac Dysfunction in mice using DENSE MRI**

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Abstract: Advanced measures of cardiac function, such as myocardial strains, are good predictors of mortality in patients with cardiovascular disease. Displacement encoding with stimulated echoes (DENSE) MRI provides excellent means to make these advanced assessments because it directly measures myocardial displacement with good spatial and temporal resolution. This study addresses two questions related to scanning mice with DENSE at 7T. First, how reproducible are the DENSE results? Second, can DENSE also measure ventricular volumes, mass and ejection fraction (EF)? To assess inter-test reproducibility, nine mice were imaged with DENSE on two separate days. Left ventricular (LV) strain, twist angles, torsion, and synchrony were quantified. LV strains and torsion were highly reproducible with coefficients of variation (CoV) ≤ 15%. End-systolic twist angles showed much higher variance, due to the sensitivity of slice location. Measures of synchrony showed excellent reproducibility with CoVs ≤ 3%. Next, thirteen mice were imaged with both DENSE and a cine stack of black blood (BB) images to compare LV volume, EF, and mass results. For DENSE, a novel 3D surface fitting algorithm was employed to reconstruct the LV volume. We found that the 3D surfaces from DENSE agreed well with the BB images (CoVs ≤ 11%). In conclusion, DENSE MR imaging is a powerful tool for assessing cardiac function. This study demonstrated that 1) DENSE MRI is highly reproducible; and 2) DENSE magnitude images can be used to accurately quantify cardiac volumes and mass, which greatly reduces the amount of time required to assess cardiac function using MRI.

Supported by: This work was supported by a Postdoctoral Fellowship through the Ruth L. Kirschstein National Research Service Award (5 T32 HL91812-05), the NIH Director's Early Independence Award (1DP5OD012132-01), a pilot grant from an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the NIH (8 P20 GM103527-05), the University of Kentucky Cardiovascular Research Center, grant number UL1RR033173 [TL1 RR033172, KL2 RR033171] from the National Center for Research Resources (NCRR), funded by the Office of the Director, National Institutes of Health (NIH) and supported by the NIH Roadmap for Medical Research, and contributions made by local businesses and individuals through a partnership between Kentucky Children's Hospital and Children's Miracle network.

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Building Teams for Translational Science

April 8, 2013

Bench to Bedside

Title: **Transmural Variations in Cellular Level Contractile Function in the Left Ventricle of Patients with Endstage Heart Failure**

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Abstract: As heart failure becomes more progressive, remodeling of the left ventricle occurs. Little is known about the cellular level changes across the ventricular wall during this remodeling. Our hypothesis was that the contractile properties at the cellular level become homogenous across the ventricular wall in failing hearts as compared to nonfailing hearts. To investigate this hypothesis, we procured through wall left ventricular samples from patients (n=10) undergoing heart transplants at the University of Kentucky and from nonfailing organ donors (n=5). Mechanical assays were performed on chemically permeabilized preparations that were obtained from the sub epicardial, midwall and sub endocardial regions of the ventricular wall. Maximum power output- a cellular level measure of the ability of the heart to eject blood during systole was assessed. The results showed that in the nonfailing samples, the power output was significantly higher in the midwall as compared to sub endocardium and sub epicardium (p-value < 0.05), suggesting heterogeneity in power across the wall. In contrast, transmural samples from failing hearts were not significantly different from each other indicating homogeneity across the wall. Furthermore, power decreased by ~ 30% (p-value = 0.01) in samples from patients with endstage heart failure as compared to nonfailing hearts. This decrease in power may reflect the replacement of myocyte by fibrotic tissue confirmed by increase in collagen to tissue ratio (p=0.03) by picrosirius red staining in failing midwall samples. This study suggests that there is a cellular level contractile dysfunction across the ventricular wall in endstage heart failure.

Supported by: NIH award: R01 HL090749-05 and Pilot funding from UK Center for Clinical and Translational Science

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April 8, 2013

Bench to Bedside

Title: **Potential Therapeutic Effects of Sphingosine-1 Phosphate Lyase Inhibition During Ischemic Injury of the Heart**

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Abstract: Acute myocardial infarction (AMI) brought on by ischemic heart disease is the single most prevalent cause of death and morbidity in the United States and worldwide. Currently, short of heart transplantation, there are no available treatment strategies that replace the infracted myocardium. Interestingly, cardiomyocytes undergo continuous renewal, maintained at least in part by bone marrow (BM)-derived stem/progenitor cells (SPCs) which are mobilized from the bone marrow into peripheral blood after AMI. Recent studies suggest that bioactive lipids, specifically sphingosine-1 phosphate (S1P), play an important role in BMSPC mobilization, egress, and homing to ischemic tissue. The goal of this study was to evaluate strategies to improve mobilization of BMSPCs in myocardial ischemia by modulating the activity of bioactive lipids. S1P lyase (SPL) is the essential enzyme responsible for irreversible degradation of S1P. Therefore, to better address the role of S1P in the release of BMSPCs from BM in the setting of AMI, we treated control and infarcted mice with SPL inhibitor tetrahydroxybutylimidazole (THI) at a dose of 25 mg/L + 10 g/L glucose in drinking water for 3 days (commencing at day 4 after AMI onset); and assessed plasma bioactive lipid levels and numbers of circulating BMSPCs. We observed greater than 2-fold upregulation in plasma levels of bioactive lipids S1P and ceramide-1 phosphate (C1P) at the conclusion of THI supplementation which was positively correlated with significant upregulation in mobilization of BMSPCs. This data suggests that pharmacologically elevated levels of bioactive lipids contribute to BMSPCs mobilization and may represent an attractive strategy for enhancing myocardial recovery and improved targeting during cardiac stem cell transplantation.

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Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bedside to Community

Title: **The Association between Burn Injuries and Pseudoephedrine Sales**

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Abstract: OBJECTIVES Pseudoephedrine (PSE) is used as a precursor in the illicit production of methamphetamine. Policies that restrict PSE sales have been adopted to curb burns from production. The purpose of this project is to estimate the relationship between burn injuries and PSE sales. METHODS PSE sales data from the National Precursor Log Exchange were merged with hospital discharge data from the Kentucky CHFS Office of Health Policy Public Use Data Set. Kentucky residents with a primary diagnosis of burn (ICD-9 940.0-949.5) in 2010 were included. A negative binomial regression was performed with number of burns per county as the dependent variable. The explanatory variable was PSE sales per county (in grams/100 residents). Control variables included: % high school graduates over 25, urbanicity, and unemployment. RESULTS In 2010, 340 burns were treated in Kentucky facilities with 33 counties having no burns and 94% of counties having ≤6 burns. Mean PSE sales were 49 g/100 county residents (SD=39), with a range of 0.3 to 147 g/100 residents. A 1 g/100 residents increase in PSE sales was associated with an increase of ~1.1 burns per county ($p<0.001$). Controlling for population, urban counties had more burns than rural counties ($p=0.004$) and counties with higher percentages of high school graduates had fewer burns ($p<0.001$). Results were robust to various dispersion settings. CONCLUSIONS These results suggest that PSE sales are associated with burn injuries. Limitations include missing data on cross-border sales and the inability to distinguish methamphetamine-related burn injuries from other burns. These findings suggest that additional PSE sales restrictions may reduce the number of burn-related discharges.

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8th Annual CCTS Spring Conference

Oral Presentation Abstracts

Building Teams for Translational Science
April 8, 2013

Bedside to Community

Title: **Comparison of Surgical Treatment Modalities for Patients with Thoracic Empyema**

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Abstract: Background: Historically, surgical management of empyema was predominantly done via open thoracotomy, however over the past decade the usage of video assisted thoracoscopy (VATS) as an alternative has increased. This study retrospectively compared the outcomes and management of empyema patients at the University Kentucky Medical Center who had undergone VATS versus those receiving open thoracotomy, in order to see if VATS decortication provided comparable or even superior results. Methods: 56 adult patients who had undergone open thoracotomy or VATS decortication for empyema between 2005 and 2009 were chosen for this retrospective study. Patients were sorted by procedure on an "intent-to-treat" basis. Comorbid conditions, pre-operative course, operative outcomes, and post-operative outcomes were compared. Quantitative data was analyzed with either an unpaired t test or the Mann-Whitney U test. Qualitative data was analyzed using the Fisher's exact test. Results: Of the 56 patients, 21 underwent VATS while 35 received open thoracotomy. 8 of the 21 VATS procedures (38.1%) were converted to open thoracotomy. Patients undergoing VATS had significantly shorter average length of stay (12.83 vs. 20.48 days, p=.039), operating time (93.36 mins vs. 139 mins, p=.0436) and operative blood loss (85ml vs. 322.66ml, p=.0127). The two groups did not differ significantly in overall morbidity, any individual morbidity, reoperation, mortality, or preoperative comorbidities. Conclusion: VATS offers comparable results to those of open thoracotomy, and in length of stay and operating time is actually superior. While the conversion rate of VATS to open at UK was high (38.1%) compared to studies at other institutions, the data still indicates VATS is both a safe and reliable alternative to open thoracotomy.

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8th Annual CCTS Spring Conference

Oral Presentation Abstracts

Building Teams for Translational Science

April 8, 2013

Bedside to Community

Title: **Near-infrared Diffuse Optical Monitoring of Cerebral Blood Flow and Oxygenation for the Prediction of Vasovagal Syncope**

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Abstract: Background: Vasovagal syncope (VVS), the most commonly occurring syncope, has been extensively studied using the head-up tilting (HUT) test which can potentially induce VVS. Significant drops in blood pressure, cerebral blood flow (CBF) and cerebral oxygenation have been observed during VVS. This study is to determine the most sensitive parameters in predicting VVS and the final trigger of VVS. Methods: We used a finger plethysmograph and a custom-made diffuse correlation spectroscopy flow-oximeter to simultaneously monitor the relative changes of mean arterial blood pressure (rMAP), CBF (rCBF) and cerebral oxygenation (i.e., oxygenated/deoxygenated/total hemoglobin concentration: r[HbO2]/r[Hb]/rTHC) during 70° HUT. Results: Six out of the 14 subjects developed presyncope during HUT. Two-stage physiological responses during HUT were observed in the presyncope group: a slowly developing and small amplitude change in the measured variables at Stage I, followed by a rapid and large change at Stage II (i.e., rMAP/rCBF/r[HbO2]/rTHC decreased and r[Hb] increased) that eventually triggered VVS. Compared to other physiological variables, rCBF reached the break-point between the two stages earlier and had a larger change (76 ± 8% decline) during presyncope. Most importantly, a threshold of ~50% rCBF decline was determined, for the first time, from our measurements that can completely separate the subjects with or without presyncope. Conclusions: Our results suggest that rCBF has the best sensitivity for the prediction of VVS and a decrease >50% in rCBF is likely the final trigger of VVS. The 50% rCBF threshold has the potential for predicting the occurrence of VVS. In addition, simultaneous measurements of multiple cerebral hemodynamic parameters reveal that cerebral hypoperfusion is associated with cerebral hypoxia during presyncope.

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Oral Presentation Abstracts
Building Teams for Translational Science
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Bedside to Community

Title: **Pediatric Congenital Hearing Loss in Appalachia: Assessing and Addressing Diagnostic Delays**

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Abstract: Objective: Pediatric congenital hearing loss is a common problem and timely identification and intervention is paramount for the language and social development. Patients from regions of rural healthcare disparities, such as Appalachia, face barriers to timely intervention. The purpose of this study was to examine the incidence of pediatric congenital hearing loss and the timing of diagnosis in Appalachia. Methods: Data from the State of Kentucky newborn hearing-screening program was accessed to determine the incidence rate of congenital hearing loss in Kentucky. We also examined children with congenital hearing loss at our institution to determine the timing of diagnostic testing. Results: During 2009-2011, there were 6,970 hearing screening tests and the incidence of cases of permanent newborn hearing loss was found to be 1.71 out of 1000 live births (1.28/1000 in Appalachia and 1.87/1000 in non-Appalachia). Nearly one-quarter (23.8%) of Appalachian newborns compared with 17.3% of non-Appalachian children failed to obtain appropriate follow-up diagnostic testing. In our institution, children from Appalachia tended to be delayed in their initial diagnostic testing (p=0.0557) and were significantly delayed in obtaining a final diagnosis of their hearing loss (p=0.039) compared with children from non-Appalachian regions. Conclusion: Congenital hearing loss in children is a common problem and there is a significant disparity in the age of diagnosis in Appalachia, which has the potential to limit language and social development. It is vital to further assess the causative factors and develop interventions that can address this hearing healthcare issue.

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College of Public Health Research Day

Oral Presentation Abstracts

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Abstract Title: **'If There Were an Issue, You Could Bet That They Would Bring It Up': Older Patients' Interpretation of Providers' Silence Regarding Diet and Physical Activity**

Concentration:

Author(s): S.H. Bardach, Graduate Center for Gerontology, U of Kentucky

Abstract:

Rationale: Many older adults do not follow lifestyle recommendations despite the diverse benefits of healthy diet and physical activity across ages. Given that older adults frequently interact with the healthcare system and report their providers to be influential sources of health information, providers are well situated to counsel older adults to improve their health behaviors. The purpose of the present study is to better understand how patients perceive their providers' communication regarding diet and physical activity. Method: One hundred four older adults, ranging in age from 65 to 95, consented to have their routine primary care visits recorded and immediately following their visits engaged in semi-structured interviews focusing on perceptions of their providers' diet and physical activity recommendations. This analysis focuses on the interview component of this research. Interviews were transcribed verbatim, coded, and analyzed through a process of constant comparison. Results: Patients discussed how their providers supported positive behavior change by providing health motivations, alleviating concerns, and encouraging initial changes. Others, however, mentioned how vague advice left them uncertain how to proceed. A number of patients reported how their provider did not counsel them on lifestyle behaviors and that they interpreted this lack of advice as an indicator that they should just keep doing what they are doing. Implications: These findings suggest that providers should consider how their silence sends a message and identify when diet and physical activity should be discussed more deliberately. Intentional discussions of diet and physical activity should be personalized and include specific, actionable recommendations.

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College of Public Health Research Day

Oral Presentation Abstracts

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Abstract Title: **Rural-Urban Comparison of the Use of Collaborations for Service Provision in Decentralized Rural and Urban Local Health Departments**

Concentration: Health Services Management

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Abstract:

Purpose: This study examined local health departments (LHDs), as the primary source of public health efforts, and their service provision to assess whether the number, type, and method of delivery (direct vs. contracted out) of services were associated with rurality. Methods: A secondary data analysis was conducted on the 2010 National Association of County and City Health Officials (NACCHO) questionnaire. Those LHDs from states with decentralized public health systems, as identified by the Association of State and Territorial Health Officials (ASTHO), were used for analysis (n = 1514). Independent samples t-tests and binary logistic regression models were used to examine differences between service provision in rural and urban LHDs. Findings: Rural LHDs (M = 20.32, s = 7.34) provided more services than urban LHDs (M = 18.95, s = 9.70) (t(1467) = 3.12, P = .002). Twenty of 41 services had significantly greater odds of being provided by a rural LHD than an urban LHD. The majority of service provision performed by LHD partners was contracted by urban LHDs (26 of 41 services). Conclusions: Rural LHDs provide significantly more selected core services with fewer resources than urban LHDs. However, urban LHDs utilize partnerships to provide services to a much greater extent than rural LHDs. These results suggest the need for further research to determine the types of partnerships available to rural LHDs.

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College of Public Health Research Day

Oral Presentation Abstracts

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Abstract Title: **En Mis Propias Palabras, In My Own Words: A qualitative analysis of Latino horse breeding workers' depictions of their work and health**

Concentration: Health Behavior

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Abstract:

Background Latino workers represent an increasingly large part of the labor force, yet are disproportionately represented in dangerous industries such as agriculture. Numerous factors, such as low language acquisition and lack of knowledge about resources, may increase their vulnerability to illness/injury. Although Latino workers are prominent in Kentucky's horse breeding industry, very little is known about the hazards, work organization factors, or occupational health outcomes they experience. Research objectives This study seeks to understand how Latino horse workers experience their work environment in the context of occupational safety and health. Methods/analysis Ten Latino horse breeding workers were recruited to participate in in-depth interviews with a native Spanish speaker via a community-based, purposive sampling methodology. Participants were asked for details about their work experiences and occupational health outcomes. Interviews were translated and transcribed by a medical transcription service and coded by two researchers using Atlas.ti v6. Themes were culled and collectively determined by a three-member research team. Findings Our analysis yielded five major themes: 1) work as necessity, 2) job tasks carry inherent, minimized risk, 3) language support aids training comprehension, 4) manager as power broker and gatekeeper, and 5)relationship dissonance with manager. Conclusion/implications for public health This study reveals new information about the experiences of a potentially vulnerable, yet prominent workforce in Kentucky. Communication was critical to understanding the job because training was chiefly informal and verbal. Recommendations include incorporating manager and industry perspectives in future research and creating multilayered interventions that include workers and managers in their scope.

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College of Public Health Research Day

Oral Presentation Abstracts

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Abstract Title: **The Differential Effects of Midlife and Late Life Alcohol Consumption on Cognitive Functioning and Regional Brain Volumes among Older Adults**

Concentration: Gernotology

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Abstract:

Background: Light to moderate alcohol consumption is associated with higher cognition among older adults. One hypothesis postulates that alcohol consumption contributes to preserved regional brain volumes, such as the hippocampus and frontal cortex, which are critical brain regions underlying memory and cognition. Objective: To examine the relationship between midlife (age 35-59) and late life (age > 65) alcohol consumption, regional brain volumes and cognition among older adults using longitudinal data from the Framingham Heart Study. Methods: Alcohol consumption was assessed during eight examinations from 1971-2008. Participants received a neuropsychological battery and MRI of the brain between 1999-2005. Multiple regression analysis was performed to test for associations between alcohol consumption status and both cognition and regional brain volumes. Results: Midlife alcohol consumption was not associated with cognition or regional brain volumes during late life. Light consumption (1-7 drinks/week) during late life was associated with higher mean cognition, compared to abstainers, ($P<0.005$) and larger frontal cortex volume ($P<0.05$); moderate consumption (>7-14 drinks/week) was associated with larger hippocampal volume ($P<0.01$). Neither frontal cortex nor hippocampal volumes were associated with cognitive measures after adjusting for age, education, gender and APOE e4. Younger age, female gender, and education were associated with higher cognition. Discussion: Light to moderate alcohol consumers during late life tend to have higher cognition and larger hippocampal and frontal cortex volumes. To provide appropriate recommendations on alcohol consumption, it is important to understand the effects that alcohol has on the brain and on cognitive reserve, while considering confounding factors such as age, gender and education.

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College of Dentistry Research Day

Oral Presentation Abstracts

8th Annual CCTS Spring Conference

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Abstract Title: **Extraction Socket Preservation Graft Prior to Implant Placement with Calcium Sulfate Hemihydrate and Platelet-rich Plasma: A Clinical and Histomorphometry Study in Human Subjects**

Author(s): A. Kutkut, Department of Oral Health Practice, U of Kentucky

Abstract: PURPOSE: The aim of this investigation was to evaluate the combination of medically graded calcium sulfate hemihydrate (MGCSH) and platelet-rich plasma (PRP) for extraction socket preservation prior to implant placement. MATERIALS AND METHODS: This study was a single-site, randomized, controlled investigation. Sixteen patients who have a nonrestorable single-tooth need to be extracted followed by implant placement were enrolled in the study. Sockets were required to have all remaining intact walls. After tooth extraction, eight patients received Medically Graded Calcium Sulfate Hemihydrate (DentoGen) mixed with Platelet-rich Plasma (PRP) in the extraction sockets (test group), and eight patients received Collagen Resorbable Plug dressing material (ACE Surgical Supply Inc.), (control group). At the time of extraction and 3 months later (at implant placement surgery), vertical and horizontal socket dimensions were measured and bone core samples were retrieved at the most center of the healed socket prior to implant placement for histomorphometric analysis. RESULTS: Independent student two samples t-test was used to process the data using Statistical Package for the Social Sciences software program (SPSS). The results indicated that there was a statistical significant difference between the two groups based on histomorphometric analysis ($p < 0.05$). New bone regeneration was greater in socket grafted with medical grade calcium sulfate hemihydrate (DentoGen) mixed with platelet rich plasma than collagen resorbable plug. After healing time of 3 months, vital bone percentage present from trephined core samples from the center of the grafted socket was higher in test group 66.5 % ± 10.4 % compared to 38.9 % ± 9.9% in control group as determined by histomorphometric analysis ($p= 0.002$). There was no statistical significant difference in amount of vertical and horizontal bone resorption ($p > 0.05$). The vertical bone regeneration in the test group at mid-buccal bone was + 0.63 mm ± 2.10 mm, mid-lingual was + 0.13 mm ± 1.25 mm, mid-mesial was - 0.13 mm ± 0.99 mm, and mid-distal was - 0.13 mm ± 1.13 mm, compared to the control group at mid-buccal was - 1.29 mm ± 3.15 mm, mid-lingual was - 1.29 mm ± 1.11 mm, mid-mesial was - 0.57 mm ± 1.40 mm, and mid-distal - 0.29 mm ± 1.11 mm based on the clinical measurements. Buccolingual width resorption was - 1.66 mm ± 1.36 mm in the test group compared to - 1.75 mm ± 0.63 mm in the control group. There was no statistical significant difference in vertical bone regeneration between groups but was more pronounced at control sites than at test sites (- 0.86 mm ± 0.73 mm amount of vertical bone resorbed in the control group versus + 0.19 mm ± 0.95 mm the amount of vertical bone gained in the test group). Radiographic measurements confirmed the mesial and distal clinical measurements in both groups with no statistically significant difference. For the test group, the amount of vertical bone resorption at the mesial site was - 0.43 mm ± 0.37 mm and at the distal site was - 0.45 mm ± 0.66 mm. For the control group at the mesial site was - 0.53 ± 0.27 mm and at the distal site was - 0.63 ± 0.40 mm. CONCLUSIONS: Medically graded calcium sulfate hemihydrate (DentoGen) mixed with platelet rich plasma showed an increased vital bone volume with accelerated bone healing process and minimizing alveolar ridge resorption in intact fresh extraction sockets. After healing time of 3 months, vital bone percentage present from trephined core samples from center of the grafted socket was higher in test group as determined by histomorphometric assessment and the amount of bone resorption was less in the test group than the control group based on clinical measurements.

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College of Dentistry Research Day

Oral Presentation Abstracts

8th Annual CCTS Spring Conference

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Abstract Title: **Global Cytokine/Chemokine Oral Epithelial Transcriptomes to Commensal and Pathogenic Bacteria**

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Abstract: A balanced cross-talk between oral epithelial cells (OECs) and bacteria is critical to elicit a protective immune response against pathogens, while simultaneously avoiding immunopathology with epithelial barrier damage. Evidence indicates that epithelial cells can discriminate between commensals and pathogenic bacteria through differential activation of cytokines/chemokines that ultimately influence the immune response. Nevertheless, a limited repertoire of cytokine/chemokine responses of OECs to oral bacteria has been previously reported. We sought to determine the global cytokine/chemokine transcriptional response of OECs in response to the oral commensal S. gordonii (Sg) and oral pathogen P. gingivalis (Pg). Human oral epithelial cells (OKF6/TERT-2) were challenged with live Sg or Pg for 16 hours. Total RNA was isolated and the abundance of transcripts for 35 cytokines and 25 chemokines was analyzed using the nCounter® analysis system. Sg enhanced transcription of a higher number of cytokines/chemokines (47/60), than Pg (17/60), however, IL-1β, IL-6, IL-18, and CCL26 were increased primarily after Pg exposure. Specific down-regulation of IL-15 and IL-20 was associated with Pg challenge. Although both bacteria up-regulated Th1/Th17 cytokines/chemokines, only Sg was effective at activating Th2/Treg cytokines/chemokines. These results suggest that oral commensal (Sg) bacteria induce a more robust OEC cytokine/chemokine transcriptional activity than pathogenic Pg. The Sg ability to activate Th2/Treg cytokines/chemokines could balance potential immuno-inflammatory responses and allow control of pathogens without tissue damage. Finally, specific bacteria-induced cytokine/chemokine profiles in OECs suggests the potential for initial epithelial barrier damage and persistent inflammation related to Pg, and potentiation of molecular features of inflammation and osteoclastogenesis induced by Sg.

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College of Dentistry Research Day

Oral Presentation Abstracts

8th Annual CCTS Spring Conference

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Abstract Title: **Spontaneous Anterior Open Lock and Multiple Sclerosis: A Case Report**

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Abstract: Aim of investigation: An edentulous 53-year old female with Multiple Sclerosis (MS) presented with bilateral recurrent temporomandibular joint dislocation (RTD). Her mandibular open lock was reduced multiple times and treatment modalities including oral muscle relaxants, analgesics, nitrous oxide sedation, local anesthesia, and general anesthesia were utilized. Uncontrolled spastic activity of her lateral pterygoid muscles following each manual reduction resulted in repeated bilateral displacement of the mandibular condyles in a sustained anterior dislocated position. This case describes a patient with forceful muscle contractions secondary to a medical history of MS, which resulted in a bilateral RTD. Methods: After reduction of the bilateral RTD under IV sedation, onabotulinum A toxin injections were performed bilaterally as follows: 25U inferior lateral pterygoid with EMG guidance, 15U masseter and 10U temporalis muscle. The patient's head was subsequently wrapped with an elastic band with her complete denture in place to discourage jaw opening. A prescription for oxycodone/acetaminophen and cyclobenzaprine was provided. Results: The patient has not experienced RTD in over one month. She was informed the effects of onabotulinum toxin A typically last 3-4 months and future injections may be necessary. Conclusions: MS is associated with episodes of global symptoms reflecting central nervous system (CNS) impairment. Patients with this demyelinating condition may develop muscle spasticity among other symptoms. This activity has been described in limbs but not masticatory muscles. Diagnosis of focal spasticity as the etiologic factor in RTD is important since other treatment modalities such as surgical options, TMJ injections with sclerosing agents, or systemic medications may not be appropriate.

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College of Dentistry Research Day

Oral Presentation Abstracts

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Abstract Title: **Gingival blood flow measurements using near-infrared diffuse correlation spectroscopy**

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Abstract: Periodontitis is currently considered as a major disease to cause the teeth loss. Previous studies demonstrated that gingival blood flow (GBF) is a prognostic marker indicating periodontitis. Laser Doppler flowmetry (LDF) has been used to non-invasively evaluate blood flow change in periodontal ligament. However, LDF detects blood flow in superficial tissues at a tiny spot, which may not reflect the blood flow in deep gingival tissues. Near-infrared (NIR) diffuse correlation spectroscopy (DCS) is an emerging method and has been used as a portable and inexpensive tool for noninvasive monitoring of blood flow in various deep/thick tissues. This study aims to adapt the DCS for the monitoring of GBF at different stages of gingival inflammation and periodontitis. We have designed a fiber-optic DCS probe consisting of source and detector fibers confined at a separation of 5.0 -7.0 mm. This separation allows NIR light penetrating to a depth of 2.5 to 3.5 mm beneath the gingivae. This probe has been tested in tissue-like liquid phantoms and blood flow index was obtained. We are currently seeking collaborators to apply this novel technique in patients with gingivitis or periodontitis. We anticipate that DCS will provide better diagnostic sensitivity than LDF as it probes blood flow close to the deep gingival tissues. It is expected that the level of GBF will be correlated with the clinical symptoms indicating the severity of gingival inflammation and periodontitis.

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Oral Presentation Abstracts

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Abstract Title: **Analysis of genetic variations within the catechol-O-methyltransferase (COMT) gene and pain perception following the placement of orthodontic separators**

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Abstract: Objective: Pain is a common side effect of orthodontic treatment and the fear of pain may be a contributing factor for the refusal of orthodontics. It is known that pain perception among individuals following a common stimulus can be genetically influenced. The purpose of this study is to determine whether genetic variation in the COMT gene is associated with pain perception following the placement of orthodontic separators. Methods: This prospective study has been approved by the UK IRB. To date, we have recruited 11 of 112 total subjects who are beginning orthodontic treatment in the UK Graduate and Faculty Practice Orthodontic Clinics. Separators are being placed in these individuals, as specified in their treatment plan, and saliva is being collected for genetic analysis. An individual's pain perception, with or without consumption of analgesics, is being measured by Visual Analogue Scale (VAS) immediately prior to the separator placement (time zero). Five additional VAS scores are being tabulated at post-separator placement times of 1 hr, 4 hrs, 24 hrs, 72 hrs and 7 days. Purified DNA will be genotyped for the COMT markers rs4633, rs4818 and rs4680 using Taqman® methodology on the Roche LightCycler480®. COMT haplotypes will be reconstructed and correlations to pain sensitivity over time determined. Results: Haplotype analysis of these particular COMT markers has been shown to correlate with both pain sensitivity and COMT enzymatic activity. When completed, this study will lend insight into what degree, if any, genetic variation in COMT is associated with pain perception following separator placement.

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College of Dentistry Research Day

Oral Presentation Abstracts

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Abstract Title: **Hypoxia Pathway Gene Expression in Aging and Periodontitis Gingival Tissues**

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Abstract: Hypoxia occurs in a diverse range of disease states and depending on the severity, permanent damage to tissues may occur. Low oxygen conditions activate the hypoxia-signaling pathway, primarily via the transcription factor hypoxia inducible factor-1 (HIF-1), which activates genes related with angiogenesis, metabolism, coagulation, among other processes to try to replenish tissues with blood and oxygen. Hypoxia signaling dysregulation also commonly occurs during chronic inflammation. This report hypothesized that gingival tissues in aging animals demonstrate enhanced expression of genes in physiologic pathways consistent with hypoxic stress in the tissues prior to a disease process. We sampled gingival tissues in health (n=23) from rhesus monkeys (M. mulatta) from 3-25 years, and naturally occurring periodontitis samples from animals 12-23 years (n=10). Total RNA was isolated and the Rhesus GeneChip (Affymetrix) used for microarray analysis. HIF-1 was significantly increased in healthy aged tissues, and both HIF-1 and HIF-3 positively correlated with aging. Multiple co-transcription factors were also increased (ARNT, COPS5). Metabolic hypoxia-inducible genes were generally increased, while angiogenesis genes were decreased in healthy aging tissues. During periodontitis, aging tissues showed decreases in metabolic gene expression, with up-regulation of hypoxia-inducible transcription genes and proliferation genes. MMP9 gene levels were significantly increased with healthy aging and up-regulated with periodontitis in both adult and aging tissues. The results supported that hypoxic stress exists in aging gingival tissues prior to clinical assessment of periodontitis. These changes might be anticipated to provide a risk for the tissues to express destructive processes in response to a pathogenic microbial challenge.

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