DMU Research Symposium

December 4, 2014
Des Moines University
3200 Grand Avenue
Des Moines, IA

Des Moines University's Research Vision is to be…

A cultivator of distinctive faculty and student researchers who discover and disseminate new knowledge.

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Des Moines University, Des Moines, IA

Welcome

Welcome to the fifth annual Des Moines University (DMU) Research Symposium! One of DMU's four vision statements is to become "a cultivator of distinctive faculty and student researchers who discover and disseminate new knowledge." There is no event that captures this vision better than our Symposium where the entire DMU campus comes together to recognize the efforts of our students, faculty, and our colleagues from the health care and scientific community. We celebrate their success by demonstrating the critical role research plays in the advancement of health care, providing a forum for the collaboration of ideas, and fostering the production of new hypotheses. The research presented here is multidisciplinary; it is the result of countless hours of effort and has real potential for impacting knowledge across disciplines. I continue to be impressed with the projects and research programs that are represented at the DMU symposium.

We are excited to have Dr. Michael Osterholm as our keynote speaker this year. Dr. Osterholm is a prominent public health scientist and an internationally recognized biosecurity expert. He is the McKnight Presidential Endowed Chair in Public Health at the University of Minnesota and director of the Center for Infectious Disease Research and Policy (CIDRAP). Dr. Osterholm is also a member of the Institute of Medicine (IOM) of the National Academy of Sciences and the Council of Foreign Relations. In June 2005 Dr. Osterholm was appointed to the newly established National Science Advisory Board on Biosecurity and in October 2008, he was appointed to the World Economic Forum Working Group on Pandemics. During the symposium Dr. Osterholm will be addressing the current Ebola epidemic which has rapidly altered our healthcare environment globally.

DMU is striving to become a leader with our research culture and environment; this Symposium demonstrates the strong research that is occurring on campus and in our community. While attending the oral presentations and viewing the posters, I hope you will reflect on how the discoveries we are making in research today will impact the scientific and medical community and the future of our patients.

Please enjoy the Symposium and thank you for attending!

Jeffrey T. Gray, PhD
Vice President for Research, Des Moines University

Agenda

Time		Location
9 am	Poster Viewing	SEC First Floor (Near the Bookstore)
12 pm	Lunch	SEC Auditorium
12:30 pm	The Ebola Epidemic: Where We've Been, Where We're At, and Where We're Going Michael T. Osterholm, PhD, MPH *McKnight Presidential Endowed Chair and Director of the Center for Infectious Disease Research and Policy, University of Minnesota* 1. Describe the epidemiology of the Ebola virus infection. 2. Describe current national recommendations for protecting healthcare workers from being exposed to the Ebola virus. 3. Summarize the challenges in controlling the current Ebola epidemic in West Africa.	
1:30 pm	Poster Presentations	SEC First Floor
2:20 pm	Break	
2:30 pm	Oral Presentations	SEC Auditorium
3:45 pm	Break	
3:55 pm	Poster Presentations	SEC First Floor
4:45 pm	Awards Presentation	
5 pm	Adjourn	

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Purpose

The Research Symposium aims to recognize the research efforts of those at DMU and in the surrounding medical and scientific community by providing a forum for the collaboration of ideas, the production of new hypotheses, and to demonstrate to the attendees the critical role that research plays in the advancement of health care.

Research Opportunities

Mentored Research Program for DMU students

The mentored research program is a competitive program which encourages DMU students to work in one of the wide range of research projects at DMU. Funding for this program is provided by the research and grants committee in which participants are paid $10.75 per hour. The program began in 2002 and is a robust and active research opportunity at DMU. The eight week program also includes additional learning opportunities such as research presentations from our own DMU faculty, a closing program consisting of a guest speaker, poster and power point presentations. All applications are due by January 30, 2015. Additional information can be found at http://www.dmu.edu/research/student-research-opportunities/.

Mentored Research Program for Undergraduate Students

The undergraduate mentored research program is committed to providing an array of research experiences to undergraduate students. Selection of applicants is based upon academic performance in the sciences, statement of career and academic goals and letter of recommendation from a biology or health science faculty member. Selected students will work with faculty researchers for an eight-week period usually in June and July, on projects including but not limited to microbiology, pharmacology, physiology, biochemistry, public health, and physical therapy. Students receive a stipend of $10.75 per hour, but no housing is provided. Students are required to work up to 40 hours per week. All applications are due by January 30, 2015. Additional information can be found at http://www.dmu.edu/research/student-research-opportunities/.

CME Credit

MD: This activity has been planned and implemented in accordance with ACCME® Essential Areas and Elements and Iowa Medical Society (IMS) policies. Des Moines University is accredited by the IMS to provide continuing medical education for physicians. Des Moines University designates this live education activity for a maximum of 3.75 *AMA PRA Category 1 Credits™.* Physicians should only claim credit commensurate with the extent of their participation in the activity.

DO: This activity has been planned and implemented in accordance with the guidelines from the American Osteopathic Association (AOA). Des Moines University is accredited by the AOA and approves this live activity for a maximum of 2.0 hours of AOA Category 2-A CME credits and 1.50 hour of AOA Category 2-B CME credits.

DPM: Des Moines University is approved by the Council of Podiatric Medical Education as a sponsor of continuing education in Podiatric Medicine. This program has been reviewed and approved for a maximum of 3.75 continuing education contact hours.

Nurses: Des Moines University continuing education (provider #112) is approved by the Iowa Board of Nursing as an accredited provider. This program has been reviewed and approved for a maximum of 4.50 continuing education contact hours.

Other: This live activity was designated for 3.75 *AMA PRA Category 1 Credits™.*

Keynote Speaker

Michael T. Osterholm, PhD, MPH

Dr. Michael Osterholm is the McKnight Presidential Endowed Chair in Public Health at the University of Minnesota and director of the Center for Infectious Disease Research and Policy (CIDRAP), a professor in the Division of Environmental Health Sciences, School of Public Health, a professor in the Technological Leadership Institute, College of Science and Engineering, and an adjunct professor in the Medical School, University of Minnesota. He is also a member of the Institute of Medicine (IOM) of the National Academy of Sciences and the Council of Foreign Relations. In June 2005 Dr. Osterholm was appointed by Michael Leavitt, Secretary of the Department of Health and Human Services (HHS), to the newly established National Science Advisory Board on Biosecurity. In July 2008, he was named to the University of Minnesota Academic Health Center's Academy of Excellence in Health Research. In October 2008, he was appointed to the World Economic Forum Working Group on Pandemics.

From 2001 through early 2005, Dr. Osterholm, in addition to his role at CIDRAP, served as a Special Advisor to then–HHS Secretary Tommy G. Thompson on issues related to bioterrorism and public health preparedness. He was also appointed to the Secretary's Advisory Council on Public Health Preparedness. On April 1, 2002, Dr. Osterholm was appointed by Thompson to be his representative on the interim management team to lead the Centers for Disease Control and Prevention (CDC). With the appointment of Dr. Julie Gerberding as director of the CDC on July 3, 2002, Dr. Osterholm was asked by Thompson to assist Dr. Gerberding on his behalf during the transition period. He filled that role through January 2003.

Previously, Dr. Osterholm served for 24 years (1975-1999) in various roles at the Minnesota Department of Health (MDH), the last 15 as state epidemiologist and chief of the Acute Disease Epidemiology Section. While at the MDH, Osterholm and his team were leaders in the area of infectious disease epidemiology. He has led numerous investigations of outbreaks of international importance, including foodborne diseases, the association of tampons and toxic shock syndrome (TSS), the transmission of hepatitis B in healthcare settings, and human immunodeficiency virus (HIV) infection in healthcare workers. In addition, his team conducted numerous studies regarding infectious diseases in child-care settings, vaccine-preventable diseases (particularly *Haemophilus influenzae* type b and hepatitis B), Lyme disease, and other emerging infections. They were also among the first to call attention to the changing epidemiology of foodborne diseases. Dr. Osterholm was the Principal Investigator and Director of the NIH-supported Minnesota Center of Excellence for Influenza Research and Surveillance (2007-2014) and chaired the Executive Committee of the Centers of Excellence Influenza Research and Surveillance network.

Dr. Osterholm has been an international leader on the critical concern regarding our preparedness for an influenza pandemic. His invited papers in the journals *Foreign Affairs*, the *New England Journal of Medicine*, and *Nature* detail the threat of an influenza pandemic before the recent pandemic and the steps we must take to better prepare for such events. Dr. Osterholm has also been an international leader on the growing concern regarding the use of biological agents as catastrophic weapons targeting civilian populations. In that role, he served as a personal advisor to the late King Hussein of Jordan. Dr. Osterholm provides a comprehensive and pointed review of America's current state of preparedness for a bioterrorism attack in his *New York Times* best-selling book, *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe*.

The author of more than 315 papers and abstracts, including 21 book chapters, Dr. Osterholm is a frequently invited guest lecturer on the topic of epidemiology of infectious diseases. He serves on the editorial boards of nine journals, including *Infection Control and Hospital Epidemiology* and *Microbial Drug Resistance: Mechanisms, Epidemiology and Disease*, and he is a reviewer for 24 additional journals, including the *New England Journal of Medicine*, the *Journal of the American Medical Association*, and *Science*. He is past president of the Council of State and Territorial Epidemiologists (CSTE) and has served on the CDC's National Center for Infectious Diseases Board of Scientific Counselors from 1992 to 1997. Dr. Osterholm served on the IOM Forum on Microbial Threats from 1994 through 2011. He has served on the IOM Committee on Emerging Microbial Threats to Health in the 21st Century and the IOM Committee on Food Safety, Production to Consumption, and he was a reviewer for the IOM Report on Chemical and Biological Terrorism. As a member of the American Society for Microbiology (ASM), Dr. Osterholm has served on the Committee on Biomedical Research of the Public and Scientific Affairs Board, the Task Force on Biological Weapons, and the Task Force on Antibiotic Resistance. He is a frequent consultant to the World Health Organization (WHO), the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the Department of Defense, and the CDC. He is a fellow of the American College of Epidemiology and the Infectious Diseases Society of America (IDSA). He also has been the recipient of six major research awards from the NIH and the CDC.

R*elevant to the content of this CME activity, Dr. Osteholm indicated he has no relevant financial relationships to disclose.*

Oral Presentation Schedule

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Presenting author(s) in bold.

 # = Resident

First Metatarsal Phalangeal Joint Range of Motion Following Implant Arthroplasty

Paul Dayton, DPM, MS, Mindi Feilmeier, DPM, **Nathan Coleman, DPM[#],** Ruth Ranum, BS, Rachel A. Reimer, PhD

There is a long-standing debate regarding the choice of arthrodesis or implant arthroplasty as the best surgical treatment for advanced arthritis of the first metatarsophalangeal joint (MTPJ). Both have documented high patient satisfaction rates with a decreased level of pain post procedure. In addition to the removal of the diseased joint which is accomplished in both fusion and implant arthroplasty, those in favor of implant arthroplasty cite motion preservation as the limiting factor which is key to the success of the procedure. We sought to specifically quantify expected first MTPJ range of motion values (ROM) following replacement arthroplasty. 35 studies were included in this review including 22 prospective studies that reported total preoperative and postoperative ROM without specifying dorsiflexion and plantarflexion and 13 prospective studies that reported both dorsiflexion and plantarflexion measurements. When evaluating just studies that reported preoperative and postoperative first MTPJ ROM with reported dorsiflexion and plantarflexion measurements, we calculated a pooled mean of 29.10 degrees total preoperative ROM and 46.24 degrees of postoperative ROM or a 17.4 degree increase in the pooled ROM. The amount of increased dorsiflexion in the pooled means was 16.04 degrees (18.78 pre and 34.82 post); plantarflexion increased by 4.99 degrees (9.42 pre and 14.42 post). Our findings indicate a modest increase in postoperative motion after first MTPJ implant arthroplasty is expected.

Human Neutrophil Leukocyte Elastase Activity is Inhibited by Phenol Red

Louisa B. Tabatabai[1,2], Fred Tatum[2], Robert E. Briggs[2]

[1]National Animal Disease Center, ARS, U.S. Department of Agriculture, Ames, IA; [2]Roy J. Carver Department of Biochemistry, Biophysics and Molecular Biology, Iowa State University, Ames, IA

Neutrophil elastase (NE) activity in urine, sputum and nasal mucous is used as an indicator of inflammation due to viral or bacterial infection. However, bovine nasal mucous neutrophils collected, lysed and stored in Dulbecco's minimal medium containing Phenol Red, showed no NE activity with methoxysuccinyl-ala-ala-val-pro-7-aminofluorocoumarin (MeOsuc-AAPV-AFC) as substrate, whereas the Uristix®) strip assay was positive for NE activity. Titration of 7-aminofluorocoumarine (AFC), the fluorescent leaving group, with increasing concentrations of Phenol Red showed that Phenol Red did not quench fluorescence. Dixon plots of elastase inhibition with Phenol Red using MeOsucAAPV-AFC as substrate revealed uncompetitive inhibition, suggesting that Phenol Red binds to the enzyme-substrate complex. In contrast, a different substrate, *N*-(tosyl-alanyloxy)-3-phenylpyrrole (the substrate imbedded in the Uristix® strips), revealed that Phenol Red does not inhibit NE activity, a result that is identical to that using the Uristix® strip test for NE. The inhibition constant of Phenol Red for human neutrophil elastase is 0.103 mg/ml (0.29 mM). Similarly, the inhibition constant with a known inhibitor of human neutrophils elastase, N-(methoxysuccinyl)-ala-ala-pro-val-chloromethyl ketone, is 0.27 mM. These results suggest that caution must be used when considering using Dulbecco's solution containing Phenol Red for collecting neutrophils that are to be used in subsequent enzyme assays.

Biosynthesis of MBX-2168 Triphosphate in Herpes Virus-Infected Cells

Hannah Sauer[1], Marie Nguyen[2], Brian Gentry[1]

[1]Drake University, Des Moines, IA; [2]Des Moines University, Des Moines, IA

Human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1) can have detrimental effects on patients with compromised or immature immune systems. Currently approved pharmacotherapies for these infections carry with them several problems including the development of drug resistance and high incidences of adverse effects. The methylenecyclopropane nucleoside analogs demonstrate greater efficacy against HCMV without any observed increase in cytotoxicity. A third generation compound (MBX-2168) also demonstrates an increased range of antiviral activity to other herpes viruses including HSV-1. The purpose of the present study was to characterize the biosynthesis of MBX-2168 into its active metabolite (MBX-2168-TP) in HCMV- and HSV-infected cells. Incubation of HCMV-infected cells with 4.0 μM ($5xEC_{50}$) MBX-2168 resulted in a time-dependent increase in MBX-2168-TP reaching a maximum of 48.1 ± 5.5 pmol/10^6 cells at 120 hours. HCMV-infected cells

incubated with 25 μM ganciclovir (GCV; 5xEC_{50}), the current standard of therapy for HCMV, demonstrated a similar time-dependent increase in triphosphate accumulation (42.6 ± 3.7 pmol/10^6 cells). Conversely, HSV-infected cells incubated with 33.5 μM (5xEC_{50}) MBX-2168 demonstrated a time-dependent increase in triphosphate levels reaching a maximum of 12.3 ± 1.5 pmol/10^6 cells at 24 hours. Similarly, HSV-infected cells incubated with 5.0 μM of acyclovir (ACV; 5xEC_{50}), the current standard of therapy for HSV infections, demonstrated a time-dependent increase in ACV-TP levels (11.6 ± 0.7 pmol/10^6 cells). We therefore conclude that the biosynthesis of MBX-2168-TP in HCMV- and HSV-infected cells is equal to that of their respective standard of therapy (GCV-TP and ACV-TP) under equivalently effective concentration conditions.

Deciphering Pathways for C1q-Dependent Regulation of Inflammation

Sean D. O'Conner, MBS'18, Holly J. Hulsebus, Suzanne S. Bohlson

Department of Microbiology and Immunology, Des Moines University, Des Moines, IA

Efficient clearance of apoptotic cells (efferocytosis) and dampening of proinflammatory cytokine production is required for preventing inflammation and autoimmunity. Deficiency in complement component C1q is associated with a failure to clear apoptotic cells, inflammation and autoimmunity. We are investigating the mechanisms by which C1q regulates these functions in macrophages. Microarray analysis of C1q-stimulated mouse macrophages revealed that C1q upregulates expression of Mer tyrosine kinase (TK), a receptor on the membrane of macrophages that mediates apoptotic cell clearance and anti-inflammatory signaling. Pathway analysis of the microarray data led to the discovery that C1q and a related protein, adiponectin, trigger MerTK-dependent efferocytosis via activation of AMP-activated protein kinase (AMPK). Prolonged stimulation with C1q (18 hrs) resulted in MerTK-dependent efferocytosis and an inhibition of LPS-dependent TNF-α production. A more pronounced C1q-dependent inhibition of proinflammatory cytokine production was observed when macrophages were polarized to an M1 phenotype using LPS + IFN-γ. M1 polarization was confirmed by examining expression of iNOS, which was upregulated with LPS + IFN-γ treatment in the presence or absence of C1q. Furthermore, there was no detectable reduction in expression CD14 or TLR4 with C1q suggesting that the mechanism of inhibition is downstream of the LPS receptors. Future studies are aimed at evaluating the role of AMPK and downstream components of the TLR4 signaling pathway in C1q-dependent regulation of proinflammatory cytokine production.

Comparative Analysis of Methylome Profiles Using PacBio Data in *Campylobacter jejuni*

Kathy T. Mou[1], Usha K. Muppirala[2], Andrew J. Severin[2], Tyson A. Clark[3], Matthew Boitano[3], Paul J. Plummer[4]

[1]Department of Veterinary Microbiology & Preventive Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA; [2]Genome Informatics Facility, Office of Biotechnology, Iowa State University, Ames, IA [3]Pacific Biosciences, Menlo Park, CA; [4]Department of Veterinary Diagnostic and Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA

Unlike most *Campylobacter jejuni* strains that cause human gastrointestinal disease, the highly virulent *Campylobacter jejuni* subsp. *jejuni* sheep abortion clone (clone SA) is the predominant cause of *Campylobacter*-associated sheep abortions in the United States. However, recent findings of its association with human disease have led to a heightened awareness of this organism's zoonotic potential. We hypothesized that the genome-wide methylation patterns of the abortifacient clone SA would differ from other syntenic but phenotypically distinct gastrointestinal-specific *C. jejuni* strains. To test our hypothesis, we used Pacific Biosciences' Single Molecule, Real-Time sequencing technology and determined the methylome profile of IA3902, a clinical isolate of clone SA, and compared its methylation data with previously published data of phenotypically distinct, syntenic gastroenteric strains *C. jejuni* NCTC 11168 and 81-176. We discovered several differences that distinguished the methylome of IA3902 from that of 11168 and 81-176. These observations suggest a possible role of methylation in the contrasting disease presentations of these three *C. jejuni* strains. We were also interested in the hypothesis that LuxS-dependent methyl recycling is important in genomic methylation of IA3902. The LuxS system is well known for its quorum sensing and methyl recycling roles in a large number of bacterial species. This includes the important virulence role it plays in IA3902 as this isolate completely lost its abortifacient potential with the mutagenesis of LuxS. However, results showed no effect of the *luxS* mutation on the methylation profile of IA3902.

How to Read a Poster Abstract

A common approach for evaluating posters involves considering the following factors in the technical, visual and presenter categories. This tool can be used when reviewing posters at this meeting and as a helpful guide for constructing your posters in the future.

Category	Notes
Technical	
Research topic clearly described with adequate introduction and a clear hypothesis.	
Good use of the space of the poster with sections on methods, results, and discussion as appropriate.	
Conclusion section which emphasizes the relevance of the research in the field of study.	
Visual	
Title, author(s), affiliations, and contact info included.	
Poster design logical and easy to follow with appropriate visuals (methods, results, etc.).	
Text easy to read, understand and free of errors.	
Graphics clearly contribute to the overall presentation.	
Presenter	
Able to communicate in-depth technical information in an easy-to-understand manner.	
Able to interpret the data properly, and clearly answer questions related to project.	
Recognize limitations of the project's procedures.	
Courteous and professional.	

♦ 1 ♦

Des Moines University Medical Service Trip 2014: Rural Honduras

Vanessa Ross, MHA'15, Kelsey Finn, DO'17, Rebecca Shaw, MD, FACOG

Des Moines University, Des Moines, IA

In March 2014, Des Moines University (DMU) students (n=31) and health providers (n=7) participated in a medical service trip to Honduras which was sponsored by the DMU Global Health Department. Honduras is a Latin American country with a population of eight million people and the sixth highest poverty rate. With 57 physicians per 100,000 people, the life expectancy is 73.5. The mission of the service trip was to provide healthcare, education, and supplies to the underserved population in Honduras. Our primary focus was general health care, women's healthcare, and dental care/hygiene. The students and health providers visited two cities in five days. Clinic stations included: triage, general healthcare, women's healthcare, dental, kid's charla, and pharmacy. Common health issues address were: head lice, headache, arthritis, high blood pressure, foot fungus, stomachache, malnutrition and dehydration, and vaginal infections. Identified outcomes are 1,582 patients served by an interprofessional team, collaborative learning environment for students and providers, appreciation for global health needs and disparities, opportunity to apply clinical knowledge learned in the academic classroom (history, physical, diagnosis, and management), expand understanding of healthcare delivery outcomes, and an opportunity to enhance follow-up care through local specialist referrals. Recommendation for future medical service trips include: women's only charla, ability to offer contraceptive options, ability to screen for and treat sexually transmitted infections, additional medical supplies, additional medications and sunscreen, additional women's health providers, and provide further education on proper nutrition.

♦ 2 ♦

Contraceptive Accessibility in Rural Honduras

Kelsey Millonig, DPM '17, Audra Lloyd DO '16, Vanessa Ross, MHA '15, Rebecca Shaw, MD, FACOG

Des Moines University, Des Moines, IA

Background: Honduras is one of the poorest countries in Latin America with limited health coverage in rural populations. Contraception and family planning are major public health concerns in Honduras. The impact of unintended pregnancies can include increased maternal and infant mortality and decreased economic stability. Our objectives were to 1) assess the local availability and usage of female contraception and 2) to make recommendations for better continuity of care and contraception education in local health clinics.

Methods: During the Global Health Trip in March 2014, approximately 150 Honduran women were seen for women's health exams in a five day Global Brigade clinic with Des Moines University students and faculty. Patients were seen for various gynecologic concerns, well women screenings, and antenatal visits. Contraceptive methods were also observed. All data was based on conversations with the Honduran women and local healthcare providers.

Observations: Of 150 women seen, less than 10% used semi-permanent forms of contraception such as intrauterine devices and progesterone injections. Those women using oral contraceptives had variable usage due to their reliance on charitable organizations such as Global Brigades for refill medications. No implantable forms of contraception were used. Considerable lack of availability, continuity of care and documentation was observed. While there were public health education sessions presented every clinic day, no women-specific health presentation was given.

Recommendations: Contraceptive options available to Honduran women were found to be limited due to various cultural and economic factors. In the Honduran society, reproductive decisions are not solely made by the women, and at times are greatly influenced by male partners. In addition, the supply and access to contraception can be unstable, leading to ineffective usage and decreased continuity of care. Recommendations can be made for women's only education sessions, increased communication with male partners about the benefits of family planning, and more emphasis on rural health clinics as sources for contraception.

♦ 3 ♦

Sexually Transmitted Infections in Rural Honduras

Kelsey Millonig, DPM '17, Molly Olson, DO '16, Vanessa Ross, MHA '15, Rebecca Shaw, MD, FACOG

Des Moines University, Des Moines, IA

Background: Honduras is a poor Central American country where 64.5% of residents live below the poverty line. Access to health care is very limited, especially in rural areas. Sexually transmitted infections (STIs) are an important cause of morbidity in young women; some complications of STIs include cervical cancer, infertility, chronic pelvic pain, and ectopic pregnancy. In this project, our objectives were to assess the current state of STI prevention, diagnosis, and treatment in rural Honduras in order to make recommendations for future changes.

Methods: Through the Global Brigades development organization, we participated in five clinic sessions in two rural communities in Honduras. During these sessions, approximately 150 women were seen in the women's health care clinic. Women presented for various gynecologic concerns, well-woman exams, and antenatal visits. We discussed STI prevention, contraception, and other sexual health practices with patients. A charla, or public health education session, was also provided for all clinic attendees. All data was collected via observation in the clinic or through conversations with local healthcare providers.

Observations: While pelvic exams and Pap smears were provided in the rural clinics, no form of STI screening or diagnostic testing was available. Treatment for STIs was dispensed empirically. Women expressed little knowledge regarding the risk factors for STIs and little usage of contraceptive methods. Although condoms were handed out in the charla, no education was provided on how to use them properly.

Recommendations: A specific women's health charla should be provided in Global Brigades clinics to facilitate education on STI prevention. Immunization against human papillomavirus would be an important intervention to reduce rates of cervical cancer in Honduras. Point-of-care testing for chlamydia could be offered in rural health clinics. Testing for other STIs will require coordination with external diagnostic facilities.

♦ 4 ♦

Assessing Health Sector Utilization of Climate Mitigation Financing

Daniel Cole, DO'16[1], Carlos Dora, MD, PhD[2], Michaela Pfeiffer[2]

[1]Des Moines University, Des Moines, IA; [2]The World Health Organization

Objective: To investigate the extent to which climate mitigation finance is being used to support health care facility infrastructure projects and to provide insight into factors that facilitate or hinder the utilization of these resources.

Methods: Project databases from major funding sources were searched for health sector infrastructure projects related to renewable energy or energy efficiency. Next, strategy documents from these funding sources were reviewed in an attempt to better understand the factors contributing to the underutilization of climate mitigation financing by the health sector.

Results: Health sector infrastructure projects represented less than 1% of all projects receiving climate mitigation financing. Policy documents suggest a number of potential reasons for this including lack of awareness, underreporting, lack of familiarity with particular strategies, and lack of appreciation of the health co-benefits of climate mitigation in the health care sector.

Conclusion: Health sector infrastructure projects represent an underutilized target for funding sources looking to maximize the benefits of climate mitigation investments. Many potential barriers exist which limit the utilization of these funds and warrant further investigation.

♦ 5 ♦

A Stereological Investigation of the Amygdala in the Female Chimpanzee (*Pan troglodytes*)

Michael C. Conte, DO'17[1], William D. Hopkins[2], Cheryl D. Stimpson[3], Chet C. Sherwood[3], Muhammad A. Spocter[1,4]

[1]Department of Anatomy, Des Moines University; [2]Neuroscience Institute, Georgia State University; [3]Department of Anthropology, The George Washington University; [4]School of Anatomical Sciences, University of Witwatersrand

The amygdala has long been known to play a central role in the neural circuitry involved in emotion and sociality and has been the focus of attention for various studies concerned with deficits in human behavior. During the course of human evolution, the amygdala underwent significant reorganization from that observed in extant non-human primates, with several changes in complexity favoring an increase in sociality. Missing from the literature however has been a careful consideration of normal variation (sex and age) in the structure and function of the primate amygdala and the explanatory value of this variation in uniquely shaping the diversity of human socioemotional behavior. In this regard, we undertook a qualitative and quantitative investigation of the amygdala and its major subcomponents in two female common chimpanzees (*Pan troglodytes*). This included outlining and quantifying the volumes of the nuclei (lateral, basal, accessory basal and central) and estimating total neuronal counts for each region of interest using a stereological approach. Our results confirm previous findings that chimpanzees, like other great apes, have relatively higher neuronal numbers in the basal nucleus whereas humans have higher neuronal cell densities in the lateral nucleus, associated with more connections to higher level social processing areas. With sex differences in the amygdala receiving very little attention in cross species comparisons even though deficits in amygdala function are known to show marked sex differences (e.g., autism), this present study provides the preliminary steps in demonstrating the techniques necessary to continue exploring the evolution of the primate amygdala.

♦ 6 ♦

A Preliminary Description of Neuropil Distribution and Asymmetry in the North American Beaver (*Castor Canadensis*)

David Cain, DPM'16[1], Frankie Schulte[2], Kathleen Bitterman[1], Kacia Cain[2], Muhammad Spocter[1,3]

[1]Department of Anatomy, Des Moines University, [2]Biotechnology, Central Campus Des Moines Public Schools, [3]School of Anatomical Sciences, University of Witwatersrand

Beavers are a remarkable example of both a keystone species and a niche constructivist, with their ability to alter stream ecosystems. Although beavers have been the subject of several ecological studies, their comparative biology has not been studied extensively and several questions remain concerning the neuroanatomical basis for dam building behavior. Given that dam building is somewhat equivalent to nest building as seen in other rodents, and that this behavior is known to be reliant on both the limbic circuitry and on the frontal cortex, we undertook a preliminary survey of the neuropil space in the frontal and occipital lobes of the beaver (*Castor canadensis*) and rat (*Rattus rattus*) to see how these two species may differ from one another. Statistical analyses indicate the existence of significant differences in mean neuropil space between the two species (P=1.4 *10^{-17}), with beavers having greater connectivity in both the frontal and occipital lobes (P=0.002). No significant hemispheric differences in neuropil space were found between the left and right hemispheres in both rodents (P=0.649). These observations while preliminary, suggest that beavers may have anatomical specializations that are unique to their behavioral ecology and likely underlie the acquisition of skills necessary for experiential and social learning of dam building behavior. While further study is needed to expand upon these observations, we believe this data argues firmly against the notion that the beaver brain is simply a scaled-up rodent brain and encourages future study into the unique behavioral and neurological attributes of the beaver.

♦ 7 ♦

The Brain of the White-Tailed Deer (*Odocoileus virginianus*): Age, Sex and Species Differences in the Neuropil of Artiodactyls

Jeremiah Fairbanks, DO'17[1], Kathleen Bitterman[1], Amy Nguyen[2], Nina Patzke[3], Paul Manger[3], Muhammad Spocter[1,3]

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Several studies have highlighted that increased connectivity in higher-order association areas typify the Primate neocortex and have identified this as a key contributor to species differences in learning and social development. However, it is not known whether this pattern is observed in homologous regions of other mammalian species, in particular that of the Artiodactyls a group characterized by much smaller relative brain sizes and a modest behavioral repertoire.

Examining the pattern of connectivity in the artiodactyl brain is of significance not only towards contextualizing the observations seen in primates but also in helping to reconstruct the evolutionary history for cetaceans (e.g., dolphins), a group characterized by large brain sizes and complex sociality. Using the neuropil fraction as a proxy for connectivity, we evaluated age and sex differences in neuropil space of the anterior cingulate cortex of the white-tailed deer (N=5) sampled at three age cohorts (Yearling, 1.5-2.5 years and Mature). Statistical comparisons revealed no significant sex differences although males had slightly larger neuropil space than females, likely due to sexual dimorphism in brain size. A significant effect of age (P=0.0016) was observed with mature deer having enlarged neuropil space in comparison to the yearling and intermediate group. A cross species comparison indicated that the white-tailed deer had notably larger neuropil space than that observed in other artiodactyl species. This data raises the interesting suggestion that connectivity in the artiodactyl frontal lobe increases with age towards maturity, as a result of social learning and experience and may thus affect foraging behavior.

♦ 8 ♦

A Preliminary Digital MRI Brain Atlas of the Domestic Dog (*Canis familiaris*)

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There is an ever-growing interest in the canine brain as a model species for ongoing studies in translational neurology and neuroscience. In recent years a number of anatomical and functional atlases of the domestic dog brain have been created, but a caveat in the literature has been a comparative canine brain atlas, which would inform ongoing studies and foster work in evolutionary anatomy. To address this need we created a digital canine brain atlas of the domestic dog (*Canis familiaris*). Using post-mortem magnetic resonance (MR) scans obtained from two domestic dogs, acquired at 7 Tesla, post-processing of the MRI scans were undertaken using Analyze 10.0. MRI images were imported into the program and every 10th slice was image captured and saved to a workstation for labeling. Three-dimensional models of the whole brain and relevant subcortical structures were created using semi-automated segmentation as implemented in Analyze 10.0. Using existing literature anatomical structures of the domestic dog brain were labeled to form a preliminary MRI atlas and complimentary three dimensional models. These results are discussed in light of the existing literature on canid behavior and evolution.

♦ 9 ♦

Identification and Sequencing of the GSTP1 Gene and Transcript(s) in Dogs

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Glutathione-S-transferase, or GST, is an enzyme found in several mammals such as humans and dogs that detoxifies carcinogens. Natural mutations known as single nucleotide polymorphisms (SNPs) in GST genes can lead to decreased enzyme expression and/or function, which may increase the risk of canine lymphoma. The aim of this study was to optimize the amplification and DNA sequencing of specific regions of the GSTP1 gene and its transcripts(s). A bioinformatic approach was used to gather information about the structure and locus of the GSTP1 gene in dogs. Once the correct sequence of DNA had been identified *in silico*, PCR primers were designed and used to amplify, via PCR, the GSTP1 exons, promoter region, and cDNA from four different dog livers from which gDNA and total RNA had been previously isolated. Gel electrophoresis and DNA Sanger sequencing were then performed to analyze the data. Multiple polymorphisms were identified in the GSTP1 exons. The first three polymorphisms were found in the promoter region of the gene, however these polymorphisms had already been identified. The mutations that had not yet been identified were mutations in exon 1's 5' un-translated region, the I4+174 T>C, and the c.436 T>C SNP. The optimized PCR reactions obtained in this study will be used to screen dogs with and without lymphoma in an attempt to identify GSTP1 genetic polymorphisms that may be associated with an increased risk of this disease.

♦ 10 ♦

The Impact of Kir2.1 on Palate Development

Steven Rose, DO'18[1] and Emily Bates[2]

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A defect in the gene encoding an inwardly rectifying potassium channel, Kir2.1, causes Anderson-Tawil syndrome in humans, which is marked by heart arrhythmias, periodic paralysis and congenital birth defects, including cleft palate. The Bates lab previously demonstrated that a *Drosophila* Kir2.1 homolog *irk2* enables correct Bmp signaling. Using *Mus musculus* as a model, the current work sought to determine the importance of Kir2.1 in developmental signaling in mammals. Our work sought to explore the mechanism by which an ion channel could bring about the observed changes in developmental patterning.

We examined the effects of the absent ion channel on palate formation throughout the developmental process in Kir2.1 knockout mice. Palatial shelves of Kir2.1 knockout mice failed to fuse and were smaller than in wildtype and heterozygous siblings. Kir2.1 knockout mice also have a hypoplastic jaw and decreased bone formation. To determine if the palate shelves were smaller due to excessive apoptosis, we measured the percentage of TUNEL positive cells. Lastly, we tested the hypothesis that Kir2.1 is needed for correct BMP or TGF-β signaling.

We found that a lack of the ion channel Kir2.1 causes a failure of the palate to fuse, an increase in apoptosis within the palatial region, and a suggestion of downregulation of Bmp signaling and upregulation of TGF-β signaling that is to be further elucidated with qPCR.

♦ 11 ♦

Effects of Chronic Pain on Activation of Inflammatory Brain Mechanisms and Development of Depressive-Like Behaviors

Misty Carder, MBS'18, Mai Lan Leong, Michelle Lende, Matthew Dalton, Kevin Watson, Rachel Firkins, LiLian Yuan, Vanja Duric

Clinical reports indicate that many chronic pain patients also develop symptoms of mood disorders, especially major depressive disorder (MDD); however, the underlying neural mechanisms linking chronic pain conditions and depressive behaviors are still poorly understood. Our previous studies have demonstrated that rodent models of chronic pain mimic some of the stress-like alterations in intracellular signaling and cellular architecture

(e.g., decreased MAPK signaling and reduced rate of neurogenesis) within the hippocampus, a limbic brain region involved in regulation of mood. Furthermore, recent reports suggest that stress-induced activation of interlukin-1-beta (IL-1ß)-mediated inflammatory mechanisms suppress neurogenesis in the adult rat hippocampus and, therefore, may present novel factors contributing to the depressive-like effects observed in chronic stress models of depression. Thus, in this study, we examined the effects of persistent pain on activation of immune-inflammation processes in the limbic brain regions. Male rats were initially exposed to either injection of complete Freund's adjuvant (CFA; model of chronic inflammatory pain) or spared nerve injury (SNI; model of chronic neuropathic pain). Both pain models produced robust mechanical hypersensitivity over the 21 day period, accompanied by depressive-like phenotype. In parallel with the behavioral effects, exposure to pain also induced changes in expression of proteins involved in microglial pro-inflammatory signaling pathways that resemble previously observed responses to stress and depression. Preliminary results indicate that pain evoked upregulation of specific members of Nod-like receptor (NLR) family of inflammasome multiprotein complex within the hippocampus. The results of this study may ultimately contribute towards the identification of new treatment targets and the development of novel clinical strategies to diminish the mental health consequences of chronic pain.

♦ 12 ♦

Role of MKP-1 in Rapid Antidepressant Responses

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Major depressive disorder (MDD) is one of the most common psychiatric illnesses affecting approximately 17% of the world's population. The pathophysiology of MDD is complex, and the exact mechanisms involved are yet to be identified. Depression affects a variety of intracellular pathways, leading to atrophy in limbic brain regions, particularly the hippocampus and prefrontal cortex (PFC). One of the pathways implicated in MDD is the mitogen-activated protein kinase (MAPK) pathway, which plays a significant role in synaptic plasticity. Depressed subjects showed decreased MAPK activity, as indicated by decreased expression of extracellular signal-related kinases 1/2 (ERK1/2), and a reduction in volume of both the hippocampus and PFC suggests a loss of function or synaptic connections between regions.

MAPK phosphatase-1 (MKP-1) is a dual-specificity phosphatase that is inducible by stress and acts as a negative regulator of the MAPK cascade. Whole genome expression data show increased MKP-1 expression in depressed subjects, indicating dysregulation of MAPK signaling. However, the potential contribution of MKP-1 activity in treatment of depression, especially in response to fast acting antidepressants such as ketamine and D-serine (DSR), is yet to be determined. To determine the effects of ketamine and DSR treatment on the activation of MKP-1 protein and its downstream targets in the hippocampus and PFC during rapid antidepressant response, dose- and time-dependent administrations of ketamine and DSR will be given and the activation of MKP-1 protein will be determined.

♦ 13 ♦

Antidepressant-Like Actions Targeting NMDA Receptors in Glutamatergic Transmission

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Accumulating evidence suggests dysregulation of glutamatergic transmission in the brain is linked with depressive disorders. Particularly, N-methyl-D-aspartate (NMDA) receptor antagonists, such as Ketamine, have a fast-acting and long-lasting antidepressant effect in humans and in animal models. However, the downside of ketamine treatment is its abuse potential and the dissociative and psychotomimetic side-effects it induces immediately following administration. D-serine, as endogenous NMDA receptor co-agonist, also targets glutamate transmission and synaptogenesis. Furthermore, D-serine has been used in clinical trials as an effective treatment for schizophrenia suggesting that adding this drug as a pre-treatment to ketamine might combat the immediate dissociative and psychotomimetic side effects. Thus, we evaluated the therapeutic

potential of this D-amino acid in preclinical models of depression, including antidepressant dose range and duration. D-serine (2.1g/kg) administered through intraperitoneal injection produced rapid, long-lasting antidepressant actions in mice subjected to forced swim and tail suspension tests. In parallel with its behavioral effects, D-serine also induced changes in expression of synaptic signaling proteins within the prefrontal cortex and hippocampus. Preliminary results indicate that D-serine-evoked molecular signature within these brain areas significantly overlaps with that involved in ketamine-activated signaling pathways, raising the possibility that D-serine may work cooperatively with ketamine to lower its therapeutic threshold and diminish the likelihood of addiction. Further studies addressing antidepressant effects of D-serine in mice exposed to chronic unpredictable stress (CUS) are currently underway.

♦ 14 ♦

Hetero-Oligomeric Complex Between the G Protein-Coupled Estrogen Receptor 1 and the Plasma Membrane Ca^{2+}-ATPase 4b

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The circulating concentrations of estrogen are closely linked to cardiovascular health. GPER (or GPR30) is a novel G protein-coupled receptor recently shown to be sensitive to estrogen. Its discovery has rekindled interest in hormone replacement therapy (HRT), with the vision that HRT can be further tailored to target specific estrogen receptor(s). The plasma membrane Ca^{2+}-ATPase (PMCA) is essential for removal of cytoplasmic Ca^{2+} and for shaping time courses of Ca^{2+}-dependent activities. Here we show that PMCA and GPER form a hetero-oligomeric complex through which they influence each other's functions. In vascular endothelium, GPER agonist G-1 decreases cytoplasmic Ca^{2+} extrusion via PMCA. PMCA activity is decreased by GPER overexpression and is increased by GPER gene silencing. G-1 induces robust phosphorylation of the extracellular signal related kinase (ERK1/2), which was blunted by GPER gene silencing. GPER-mediated ERK1/2 phosphorylation is substantially reduced by PMCA knockdown. PMCA coimmunoprecipitates with GPER under basal condition or in cells treated with 17β-estradiol, thapsigargin and G-1. In addition, heterologously expressed human PMCA4b colocalizes with GPER. Endothelial cells robustly express the PDZ post-synaptic density protein (PSD)-95, whose knockdown reduces the association between GPER and PMCA. The association between PMCA4b and GPER is substantially reduced by truncation of either or both their C-terminal PDZ-binding motifs. These data strongly indicate that GPER and PMCA4b form a hetero-oligomeric complex via the anchoring action of PSD-95 at its PDZ domains. These interactions allow for mutual functional influences between GPER and PMCA4b, with effects on intracellular Ca^{2+} homeostasis and GPER activities.

♦ 15 ♦

Identification, Characterization and Functional Significance of Calmodulin Binding Domains in the Human Angiotensin II Receptor Type 1A

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The angiotensin II receptor type 1A (AT1R) mediates many effects of angiotensin II (AngII). Calmodulin (CaM) is essential for the functions of many proteins. We tested if signaling via AT1R involves CaM at the receptor level. AT1R constitutively forms a complex with CaM in vascular smooth muscle, which is enhanced by stimulation with AngII or thapsigargin. To identify and characterize all CaM-binding domains in AT1R, we generated new FRET biosensors (BSAT1R) in which each of the 4 sub-membrane domains (SMDs) in AT1R is flanked by ECFP and EYFP. $BSAT1R_{125\text{-}141}$, $BSAT1R_{215\text{-}242}$ and $BSAT1R_{309\text{-}327}$, corresponding to SMD2, SMD3 and the juxta-membranous segment (JM) of SMD4, display characteristic responses of direct CaM binding. K_d values of 44.7±1.0, 0.36± 0.05, and 0.51±0.01 μM, respectively, were determined for SMD2, 3, and $SMD4_{JM}$. The respective EC50(Ca^{2+}) values of these interactions were ~ 4.1±0.11, 0.13 ± 0.006, and 1.26 ± 0.09 μM, determined by concurrent monitoring responses of $BSAT1R_x$ and a Ca^{2+} indicator. These values nicely explain AT1R-CaM interactions in the conditions tested in cells. In vascular smooth muscle, AngII stimulates robust ERK1/2 phosphorylation, which is inhibited by AT1R antagonist losartan and virtually abolished by CaM

antagonist W-7. To test the functional impact of CaM-AT1R interactions, mutations were generated in SMD3 and $SMD4_{JM}$ to reduce or abolish CaM binding. Expression of these AT1R mutants in turn reduces or abolishes AngII-induced ERK1/2 phosphorylation. These data strongly indicate that CaM is involved in AngII signaling via direct interactions with multiple domains in AT1R and allow prediction of interactions between CaM and individual SMDs in AT1R under distinct physiological scenarios.

♦ 16 ♦

Calmodulin: A New Partner for the α_{1A}-adrenergic Receptor

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In addition to its role in vasoconstriction, the α_{1A}-adrenergic receptor (α_{1A}-AR) is increasingly recognized as a rescue mechanism under circumstances where β-ARs are insufficient to provide stimulus in the myocardium, such as in heart failure. Mechanisms controlling α_{1A}-AR function therefore have profound impact on cardiovascular functions. Calmodulin (CaM) is the ubiquitous transducer of Ca^{2+} signals, and has recently been demonstrated to interact with a number of G protein-coupled receptors. We have observed that in fresh ventricular tissues, α_{1A}-AR forms a complex with calmodulin in resting condition as well as under α_{1A}-AR agonism. To identify and characterize the precise interaction domains between CaM and α_{1A}-AR, we developed novel biosensors that span multiple fragments of the four sub-membrane domains (SMDs) of α_{1A}-AR, including a.a. 50-63, 123-142, 210-227, 228-256, 257-274, and 333-361, corresponding to SMD1, SMD2, SMD3a-c, and the juxta-membranous (JM) segment of SMD4. Responses of these biosensors to Ca^{2+}-saturated CaM revealed that SMD1 and SMD2 do not interact with CaM. However, SMD3b, SMD3c, and $SMD4_{JM}$ directly interact with CaM in a Ca^{2+}-dependent fashion. SMD3c and $SMD4_{JM}$ interact with CaM with relatively high affinity, K_d values being 17.17 ± 0.8 and 1.03 ± 0.03 μM, respectively. SMD3b also interacts weakly with CaM with K_d value > 100 μM. Ca^{2+} sensitivity of these interactions was determined by simultaneously monitoring biosensors and a suitable Ca^{2+} indicator. These data document CaM as a novel partner for α_{1A}-AR and provide background for on-going studies on the functional impact of these interactions in the control of cardiovascular functions.

♦ 17 ♦

The G Protein-Coupled Estrogen Receptor 1 and Components of Ca^{2+} Entry

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The concentration of circulating estrogen is closely linked to cardiovascular health. Following menopause there is a substantial increase in the risk and incidence of cardiovascular morbidity. Nevertheless, hormone replacement therapy (HRT) has not brought about the desired effects. GPER is a G protein-coupled receptor recently identified to be sensitive to estrogen. Its discovery has rekindled interest in HRT with the vision that HRT can be tailored to target specific estrogen receptor(s). GPER has been found to participate in numerous cardiovascular functions. Store-operated Ca^{2+} entry (SOCE) is an essential mechanism required for many cell activities. We found that GPER agonist G-1 dose-dependently inhibits SOCE in endothelial cells. Heterologous expression of GPER causes a 40% decrease in the rate of SOCE. GPER antagonist G15 acutely increases rates of SOCE by 16% and when treated chronically, increases total Ca^{2+} signals by 50% in vascular smooth muscle. Consistently, GPER gene silencing increases SOCE by approximately 50%. In endothelial and ventricular tissues, GPER coimmunoprecipitates with the stromal interaction molecule 1 (Stim1) and the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), two essential molecular switchers of SOCE. In addition, Stim1-ECFP colocalizes with GPER-DsRed2 when heterologously expressed in HEK 293 cells. In addition, overexpression of GPER substantially reduces thapsigargin-induced Ca^{2+} release from the endoplasmic reticulum in vascular endothelial cells, a direct indication of reduced SERCA activity. These data indicate that GPER is an important regulatory input of store-operated Ca^{2+} entry via its interactions with key components of store-operated Ca^{2+} entry in the cardiovascular system.

♦ 18 ♦

Generation of Loss-of-Function Mutations in the Calmodulin-Binding Domains of the G Protein-Coupled Estrogen Receptor 1 (GPER/GPR30)

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The G protein-coupled estrogen receptor 1 (GPER) was recently identified as a novel receptor for estrogen, and has attracted much attention for its potential role in hormone replacement therapy. However, identification of its regulatory inputs is only beginning. Calmodulin (CaM) is the ubiquitous transducer of Ca^{2+} signals and is required for the functions of numerous proteins. We recently developed a novel approach that utilizes fluorescence resonance energy transfer (FRET) biosensor technology to identify and characterize four distinct CaM-binding domains located separately in GPER's submembrane domains (SMDs) 1-3 and the juxtamembranous (JM) segment of SMD4. Data presented here were obtained in a summer research/graduate rotation as part of a series of studies to investigate the functional roles of GPER-CaM interactions. Mutations were generated in SMD2 and $SMD4_{JM}$, two domains with higher affinity for CaM, to alter hydrophobicity and charges of the original domains. Resultant biosensors, $BSGPER_{150\text{-}175mut}$ and $BSGPER_{330\text{-}351mut}$ still display classic conformational changes upon CaM binding. However, the affinities of these interactions are drastically reduced. $BSGPER_{150\text{-}175mut}$ has a K_d value of 738.53±14 μM for CaM binding, a ~1,680-fold reduction from the wild-type value of 0.44±0.03 μM. $BSGPER_{330\text{-}351mut}$ has a K_d of 71.94±7.83 μM, a ~50-fold reduction from the wild-type value of 1.40±0.16 μM. Simultaneous measurement of biosensor response and free Ca^{2+} measurement determined the Ca^{2+} sensitivities ($EC50Ca^{2+}$ values) of the interactions between CaM and $BSGPER_{150\text{-}175mut}$ and $BSGPER_{330\text{-}351mut}$ to be 168±19 and 2.64±0.1 μM, respectively, from the 2.38±0.13 and 0.75±0.05 μM wild-type values. These values essentially render the mutant SMDs ineffective CaM binders in a cellular environment, and facilitate detailed on-going studies of the roles of GPER-CaM interactions.

♦ 19 ♦

Estrogen Enhances Linkage in the Vascular Calmodulin Network via a Feedforward at the G Protein-Coupled Estrogen Receptor 1

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Rationale: Estrogen is strongly linked to cardiovascular health. Calmodulin (CaM) is required for activation of numerous proteins, yet is a limiting factor due to insufficient expression for its targets. Whether estrogen improves vascular functions via the CaM target network is unknown.

Purpose: To determine if chronic 17β-estradiol treatment (CE_2T) improves endothelial functions by enhancing CaM expression and linkage within the network of CaM-binding proteins and identify the estrogen receptor that mediates these effects.

Methods and Results: In the endothelium, CE_2T increases total and free CaM. Pharmacological and gene silencing studies indicate that the G protein-coupled estrogen receptor 1 (GPER) mediates this effect. CE_2T increases CaM binding to different CaM target categories, including plasma membrane Ca^{2+}-ATPase (PMCA), eNOS, estrogen receptor α (ERα), and GPER itself. Novel biosensors were developed to examine the role of CaM binding on GPER function. CaM antagonism or mutations in the receptor's multiple CaM-binding domains that reduce CaM binding prevent GPER-mediated ERK1/2 phosphorylation. For PMCA, CE_2T-induced stimulation of activity through enhanced CaM binding is masked by Src-dependent phosphorylation. These effects sustain cytoplasmic Ca^{2+} for enhanced interactions between CaM and other targets. For eNOS, CE_2T doubles CaM binding. Kinetic modeling using both *in-cell* and *in vitro* data allowed comparison of CE_2T's promotion of eNOS point activity and NO accumulation via effects on determinants of eNOS function, including Ca^{2+}, CaM, and phosphorylation.

Conclusions: CE_2T improves endothelial functions via a feed-forward mechanism in which CaM expression is upregulated through GPER, leading to enhanced CaM binding and functional linkage in the network of CaM-binding proteins.

♦ 20 ♦

Inhibition of the G Protein-Coupled Receptor T1R1/T1R3 Induces Autophagy in Cardiomyocytes

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For decades researchers have pursued new means by which to limit the amount of cardiomyocyte death that occurs during progression of acute myocardial infarction. To date, the most effective approach continues to be reperfusion therapy via percutaneous coronary intervention (PCI). However, its efficacy is blunted by the fact that reperfusion itself can further damage cardiomyocytes. Results from recent studies suggest that the induction of autophagy, an ordered process by which cytoplasmic contents are degraded and recycled by lysosomes within cardiomyocytes, reduces cell death caused by ischemia and reperfusion injury. Depletion of amino acids is a potent inducer of autophagy. Induction of autophagy in this case is carried out by the inhibition of mechanistic target of rapamycin (mTOR). Recent work from this lab demonstrates that a cell surface G protein-coupled receptor (GPCR) T1R1/T1R3 relays amino acid sufficiency signals to mTOR. T1R1/T1R3 was observed to be highly expressed in cultured cardiomyoblasts and mouse heart. In this study we demonstrate that reduced expression of T1R1/T1R3 increases autophagy in both model systems. Thus, we have begun studies to test the hypothesis that T1R1/T1R3 inhibition will protect cardiomyocytes from ischemia/reperfusion injury by elevating autophagy. We demonstrate that autophagy and apoptosis are induced in H9C2 cardiomyoblasts and neonatal mouse cardiomyocytes subjected to simulated ischemia (SI). Inhibition of autophagy increased apoptosis, suggesting that autophagy is protective in our experimental conditions.

♦ 21 ♦

Role of the Calcineurin Homologous Protein-1 in Adenosine A_1 Receptor-Mediated Inactivation of the Na^+/H^+ Exchanger-3

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Adenosine is a potent autacoid that regulates Na^+ homeostasis partly through modulation of renal Na^+ transport. We previously showed that acute adenosine A_1 receptor activation by CPA (N^6-cyclopentidyladenosine) inactivates the Na^+/H^+ exchanger-3 (NHE3) via the PLC/Ca^{2+}/PKC signaling pathway and that NHE3 inhibition by CPA is dependent on a NHE3 C-terminal domain located between amino acid (aa) 462 and 552. The Calcineurin Homologous Protein-1 (CHP1) was originally identified by its ability to bind to NHE isoform 1. Now we present the following findings: 1. In yeast two-hybrid studies, CHP1 interacted directly to NHE3 (bait, NHE3 C terminus, prey, CHP1) and the minimal interacting region corresponded to the NHE3 cytoplasmic domain that mediates the CPA-induced inhibition. 2. In Opossum Kidney cells, both endogenous and transfected CHP1 co-localized with NHE3 (immunofluorescence and co-immunoprecipitation). Co-expression of CHP1 and NHE3 resulted in increased translocation of CHP1 from the intracellular pool to the apical membrane. 3. CPA (10^{-6} M, 15 min) increased the amount of NHE3 bound to total cellular CHP1 by 50% (co-immunoprecipitation). Truncation of NHE3 at aa 552 did not affect CPA-activated association of CHP1 with NHE3. 4. Transient expression of the aa 462 to 552 of NHE3 ($NHE3^{462-552}$) competed for binding of CHP1 to native NHE3. Finally, expression of $NHE3^{462-552}$ prevented CPA-induced inhibition of NHE3 and binding of CHP1 to NHE3. In summary, we demonstrate that the CHP1 is essential for CPA-mediated inactivation of NHE3.

♦ 22 ♦

Alteration in Expression of the Cardiac Gap Junction Proteins Connexin 43 and 45 Following Social and Environmental Stress in Prairie Vole Hearts

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Social stress plays a key role in the relationship between cardiovascular disease (CVD) and depression. Previous studies in animals have shown that social isolation leads to depressive like behaviors and increased incidence of arrhythmias. Alterations in the expression of the left ventricular gap junction proteins, connexin-43

(Cx43) and connexin-45 (Cx45), have been identified in the pathogenesis of cardiac arrhythmias in some forms of CVD. Prairie voles, which are socially monogamous rodents, were used to investigate the hypothesis that that long-term social isolation, combined with mild environmental stressors, would produce both depressive behaviors and altered connexin expression in the left ventricle of prairie vole hearts. Adult prairie voles were paired with or isolated from a sibling. Then, half of the paired and isolated animals were exposed to chronic mild stressors (CMS) while the other half remained undisturbed. The animals were subjected to the forced swim test (FST) as an index of depressive behavior. Social isolation, versus paired control conditions, produced significantly increased depressive behaviors. This was further exacerbated by chronic mild stress. Social isolation (alone) reduced total Cx43 expression in the left ventricle; whereas chronic mild stress (but not isolation) increased total Cx45 expression and reduced the Cx43/Cx45 ratio as measured by Western blot analysis. The present findings provide insight into possible cellular mechanisms underlying altered cardiac rhythmicity associated with social and environmental stress, depression, and cardiovascular disease.

♦ 23 ♦

IL-33 Promotes Proliferation and Inhibits Apoptosis of Colon Cancer Cells

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Background: Colon cancer causes the highest mortality among all digestive system cancers. IL-33 is a new member of the IL-1 cytokine family, and little is known about its role in tumour growth. We previously showed that IL-33 inhibited proliferation and induced apoptosis of pancreatic cancer cells, but promoted proliferation and inhibited apoptosis of ovarian cancer cells. This contrasting effect of IL-33 on different cancer cells suggests its complex role in tumour growth in different cancers. This study was performed to investigate if it has any effect on colon cancer cells.

Methods: Clonogenic survival assay, immunohistochemistry (IHC), TUNEL staining, proliferation and caspase-3 activity kits were used to evaluate the effects of IL-33 on cell survival, proliferation and apoptosis of an colon cancer cell line, HCT-116. We further investigated the possible molecular mechanisms by using RT-PCR, IHC, and Western blot.

Results: We found that the percentage of colonies of HCT-116 cells, PCNA+ cells and the OD value of cancer cells were all decreased after treatment with IL-33. TUNEL+ cells and the relative caspase-3 activity in cancer cells were increased in the presence of IL-33. The anti-proliferative effect of IL-33 on cancer cells correlated with downregulation of pro-proliferative molecules cyclin B, cyclin D and cdk2. The pro-apoptotic effect of IL-33 correlated with downregulation of anti-apoptotic molecules FLIP and Bcl-2.

Conclusions: IL-33 inhibits proliferation and promotes apoptosis of colon cancer cells by downregulation of cyclin B, cyclin D, cdk2, FLIP and Bcl-2. Thus, modulating IL-33 pathway might be a promising strategy to treat colon cancer.

♦ 24 ♦

Autophagy in Herpes Simplex Virus 1 Infected HEp-2 and hTERT-HME-1 Cells

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Herpes simplex virus 1 (HSV-1) is an enveloped DNA virus which causes common labial mucosal lesions, and, less commonly, life-threatening encephalitis. Caspase mediated apoptosis is one cellular defense against viral replication. Previous research in the Nguyen laboratory indicated that HSV-1 infected cells treated with the caspase inhibitor z-VAD-fmk are resistant to apoptosis, and produce less virus than untreated controls. Further research indicated that treatment of infected cells with the negative control for this compound, z-FA-fmk, also

led to reduced HSV-1 production. Interestingly, these cells exhibited an altered morphology different from both apoptosis and cytopathic effect. One possible explanation is that the infected, z-FA-fmk treated cells underwent autophagy. To investigate this possibility, we infected HEp-2 and hTERT-HME-1 cells with either wild-type KOS 1.1 or ICP27-null HSV-1, in the absence or presence of z-VAD-fmk and z-FA-fmk inhibitors. Immunoblotting was then performed to detect viral proteins, as well as the autophagy marker microtubule-associated protein 1A/1B-light chain 3 (LC3II). Additionally, we treated HEp-2 cells with KRBH media and performed immunoblots and plaque assays to investigate the effect of amino acid starvation-induced autophagy on viral replication. From these studies, we found that z-FA-fmk treatment induces LC3II accumulation in both cell lines, consistent with autophagy induction. Additionally, autophagy induced by amino acid deprivation significantly reduces the accumulation of late viral proteins and the amount of virus produced by HSV-1 infected, HEp-2 cells. These data lend support to our hypothesis that caspase negative inhibitor z-FA-fmk suppresses the HSV-1 lifecycle by inducing autophagy.

♦ 25 ♦

An Investigation of Pathways Involved in C1q-Dependent Efferocytosis and Inflammatory Signaling in Human Macrophages

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Complement component C1q stimulates enhanced engulfment of apoptotic cells (efferocytosis) and is important in the prevention of autoimmunity. We recently described a novel C1q-dependent pathway in mouse primary macrophages, where C1q triggers expression of the pro-efferocytic receptor Mer tyrosine kinase (Mer), and this change in gene expression was required for efficient efferocytosis. Differences between mouse and human systems can complicate the translational potential of biomedical research, so we sought to translate these findings into a human system. Human monocytes were isolated from healthy donors and differentiated to macrophages by culturing in human AB+ serum. Prolonged stimulation of human macrophages with C1q resulted in enhanced efferocytosis, and cycloheximide treatment inhibited this effect, indicating that gene expression changes were required for the phenotype. Unlike in mouse macrophages, upregulation of Mer or related receptor, Axl, was not detected on C1q-activated human macrophages; however, C1q triggered phosphorylation of AMP-activated protein kinase (AMPK) in both mouse and human macrophages. In mouse macrophages, AMPK phosphorylation is inhibited with the addition of the calcium chelator, BAPTA-AM, and we are currently investigating the role of calcium signaling in human macrophages. While C1q-treated macrophages were more efficient at efferocytosis, they were significantly impaired in producing pro-inflammatory TNFα following activation with lipopolysaccharide. This study demonstrates that C1q polarizes human macrophages towards a pro-efferocytic and anti-inflammatory phenotype, which may be important in preventing autoimmunity. Furthermore, we identified an important signaling intermediate in the pathway which may be useful in the development of targeted therapeutics for the prevention of human autoimmune diseases.

♦ 26 ♦

A Toxin-Antitoxin Pair is Responsible for Type VI Secretion System Mediated Bacterial Killing and Self-Immunity by *Acinetobacter nosocomialis* Strain M2

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Type VI secretion systems (T6SS) are a class of bacterial secretion machinery by which bacteria can inject proteins into target cells to elicit responses such as cell death. We recently demonstrated that a clinical isolate of the pathogen *Acinetobacter nosocomialis* produces a functional T6SS that is utilized to kill bacteria. Using transposon mutagenesis coupled with high-throughput sequencing we identified a gene cluster in the *A. nosocomialis* strain M2 genome that we hypothesize encodes a T6SS toxic effector (Ase1) that is used to kill other bacteria and a protein (Asi1) that confers immunity from T6SS killing. Herein, we present data that suggests Ase1 is a T6SS toxic effector that is required for strain M2 T6SS-mediated bacterial killing and that Asi1 is required to be immune to this killing. Unmarked, in-frame mutations in the *ase1* or in both *ase1* and *asi1* were generated a wild-type strain M2 background. The mutants were assessed for their ability to kill *Escherichia*

coli and survive co-incubation with wild-type M2. Both the *ase1* mutant and *ase1 asi1* double mutant were unable to kill *E. coli,* indicating that *ase1* is T6SS toxic effector. In competition with wild-type strain M2, the *ase1 asi1* double mutant was out competed while the *ase1* mutant was not. These data suggest that Asi1 acts as an anti-toxin, protecting cells from T6SS killing. In conclusion, we have identified and provided data to suggest that Ase1 acts as a T6SS toxic effector and that Asi1 is an anti-toxin that provides protection from T6SS killing.

♦ 27 ♦

Effects of Leucine Metabolism on Lymphocyte Activation and Cancer Growth: A Potential Target for Nutritional Immunotherapy in Cancer

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Both cancer cells and lymphocytes use aerobic glycolysis to maintain high levels of glycolytic intermediates to support their increased biosynthetic demands during proliferation. The mammalian target of rapamycin (mTOR), a primary regulator of cell growth and proliferation, increases glycolytic flux in both cancer and immune cells. The branched-chain amino acid leucine is a potent nutrient activator of the mTOR pathway. Intracellular leucine concentrations are regulated by the branched chain amino transferase (BCAT) isoenzymes, BCATc and BCATm. By using T lymphocytes (T cells) from global knockout BCATc and BCATm mice as well as mouse EL-4 lymphoma cells treated with leucine, we explored the role of leucine and the leucine degrading enzymes in regulating glycolytic metabolism. Our results showed that loss of BCATc and BCATm expression in activated T cells lead to increased glycolytic capacity and glycolytic reserve that correlated with increased cellular leucine concentrations and upregulation of mTOR as seen by increased phosphorylation of mTORC1 downstream target proteins, S6 and 4EBP-1. EL-4 lymphoma cells treated with different leucine concentrations also showed increased glycolytic metabolism and upregulated mTOR signaling. Our results suggest that BCATc and BCATm enzymes affect glycolysis by down-regulating mTOR pathway likely due in part by modulating intracellular leucine concentrations. Leucine activation of mTOR stimulates glycolysis, possibly triggering T cells activation or cancer cell proliferation. Understanding the role of leucine metabolism in T cell immunity and cancer will provide new strategies for nutritional cancer immunotherapy.

♦ 28 ♦

Differences Between Cerebrospinal Fluid and Blood Biomarkers of Inflammation in HIV Infection

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Background: HIV central nervous system (CNS) infection is associated with local inflammation that evolves over the course of systemic disease and impacts neurological function. To compare CNS and systemic inflammation, we assessed 10 inflammatory biomarkers in cerebrospinal fluid (CSF) and blood across a spectrum of subject groups.

Methodology: This exploratory cross-sectional study measured 10 inflammatory biomarkers (TNF-α, MMP-9, CXCL10, sCD14, sCD163, sVCAM, CCL2, IL-6, TIMP-1 and neopterin) by EIA in 9 subject groups: HIV uninfected controls (HIV-, N=20); primary HIV infection (PHI, 24); untreated neuroasymptomatic subjects in 4 blood CD4+ cell strata, >350, 200-349, 50-199 and <50 cells/μL (NA, 20 each); untreated HIV-associated dementia (HAD, 12); treated, virally-suppressed (Rx, 19) and elite controllers (EC, 8). Exploratory analysis applied nonparametric methods to *a priori* group comparisons. Relationships among CSF and blood biomarkers along with background variables across the entire sample set were explored by Spearman correlation.

Results: CSF and blood showed a broad increase in inflammatory biomarker concentrations in PHI with increases in TNFα, CXCL10, sCD14 and neopterin in both compartments, sVCAM in CSF, and sCD163 in blood. With progression of systemic disease, patterns of biomarker changes in the four NA groups diverged between CSF and blood. Whereas CSF concentrations of TNFα, MMP-9, CXCL10 decreased in the CD4 <50 group compared to one or more groups with higher CD4 counts, blood inflammatory biomarkers either increased

with falling CD4 or remained relatively stable across the four groups, CSF concentrations of all the inflammatory biomarkers except MMP-9 were higher in the HAD than the combined <200 CD4 groups. By contrast, blood concentrations did not differ between these two groups. CSF blood markers remained above HIV- levels in the Rx and EC groups including: CSF TNFα, CXCL10, sCD14, sCD163 and sVCAM in Rx and all of these except sVCAM in EC; blood sCD14, CCL2 and neopterin in Rx; and blood CXCL10, sCD163 and TIMP-1 in EC. CSF NFL showed highest correlations with CSF sCD14, sCD163, sVCAM, CCL2 and blood sCD14 and neopterin (all R>0.5).

Conclusions: Early parallel increases in CSF and blood inflammatory biomarkers diverge with evolving infection and HAD onset, and support the importance of macrophages in neural injury. Persistent CSF and blood inflammation despite viral suppression suggest incomplete—or a required 'cost' for—control of both systemic and CNS infection.

♦ 29 ♦

Pharmacological Enhancement of Anti-Viral DNA Polymerase Inhibitors via Reduction of Endogenous Nucleoside Triphosphates

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Human Cytomegalovirus (HCMV) infects the majority of the world's population. Although immunocompetent individuals present as asymptomatic, HCMV may prove detrimental for patients who are immunocompromised or immunologically immature. Complications from HCMV include retinitis, pneumonitis, and permanent neurological damage. The current standards of HCMV pharmacotherapy are nucleoside analogues (ganciclovir (GCV), cidofovir (CDV)) that directly inhibit viral DNA polymerase and/or compete with endogenous deoxynucleoside triphosphates (dNTPs) for incorporation into replicating viral DNA resulting in early chain termination. Cyclopropavir (CPV), a novel methlyenecyclopropane nucleoside analog currently in phase 1 clinical trials, elicits an anti-viral effect via the same mechanism as GCV. Life-long adherence to therapy is required due to recurrence of infection upon cessation of treatment. As such, the development of drug resistant HCMV strains is problematic. Therefore, we are exploring the use of hydroxyurea (HU) (an inhibitor of ribonucletotide reductase) to enhance the anti-viral effect of nucleoside analogs by decreasing the cellular concentration of endogenous dNTPs. We hypothesize that a reduction in endogenous dNTPs will result in increased nucleoside analog incorporation into viral DNA manifesting in a potentiation of anti-viral effect. Standard combination viral plaque reduction assays, with a 95% confidence interval, demonstrate synergy indexes of 35.74 for GCV and HU, and 65.14 for CDV and HU. These results indicate a synergistic relationship between the anti-viral nucleoside analogues and hydroxyurea. We therefore conclude that hydroxyurea synergistically enhances the anti-viral effect of nucleoside analogs used for the treatment of systemic HCMV infections.

♦ 30 ♦

DNA Polymerase Inhibitors Enhance the Anti-Viral Effect of Terminase Inhibitors When Used in Combination Against HCMV

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Human cytomegalovirus (HCMV) infects ~80% of the world's population and can prove detrimental in immunocompromised and immunologically immature individuals possibly resulting in retinitis (AIDS patients) and mental retardation (neonates). All currently approved pharmacotherapies – ganciclovir (GCV), its oral prodrug valganciclovir, cidofovir (CDV), and foscarnet (FOS) – elicit an anti-viral effect by targeting the viral DNA polymerase. Due to recurrence of infection upon cessation of therapy, lifelong adherence is necessary. Therefore, HCMV strains with decreased susceptibility are common (drug resistance). Additionally, because all currently approved therapies target the same viral enzyme, the incidence of cross-resistance is high. The benzimidazole ribonucleosides (BDCRB) and deoxyribosylindole nucleosides (Indole 1896) exert their effects late in the viral replication cycle by targeting the HCMV terminase, the enzyme responsible for cleaving and packaging viral DNA. Since these compounds exhibit a unique anti-viral mechanism but along the same replication pathway as current therapies, there is possibility for a positive pharmacodynamics drug interaction.

Therefore, we hypothesize that the combination of DNA polymerase and terminase inhibitors will result in a synergistic anti-viral effect. Combination viral plaque reduction assays, with a 95% confidence interval, demonstrated synergy indexes of 89.0 (GCV and BDCRB), 74.2 (GCV and Indole 1896), and 79.3 (BDCRB and CDV). These results indicate a highly synergistic relationship between the DNA polymerase and terminase inhibitors. Thus, we can conclude that the combination of HCMV DNA polymerase and terminase inhibitors could delay the onset of viral resistance, lower the incidence of cross-resistance, and enhance the combined anti-viral efficacy in a clinical setting.

♦31 ♦

Environmental Pesticides Induce Histones H3 and H4 Acetylation in Cell Culture Models of Parkinson's Disease: Interplay Between Mitochondrial Dysfunction and Epigenetic Modifications in Parkinson's Disease

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Persistent exposure to environmental pesticides is implicated in the etiopathogenesis of Parkinson's disease (PD). Emerging epigenetic studies show that histone acetylation is one of the key modifications that can play a role in neurodegenerative processes. In this study, we examined the effects of commonly used pesticides that target mitochondrial complex-1, including rotenone, tebufenpyrad and pyridaben, on mitochondrial dysfunction and histone acetylation. Exposure of rat dopaminergic neuronal cells (N27 cells) to tebufenpyrad and pyridaben resulted in cytotoxic cell death in a dose-dependent manner. EC_{50} for tebufenpyrad and pyridaben was determined to be 3.985 and 3.776 μM, respectively. Furthermore, N27 cells exposed to tebufenpyrad and pyridaben showed a time-dependent increase in the levels of acetylated histones H3 and H4. The classic mitochondrial complex-1 inhibitor rotenone also induced histone H3 and H4 acetylation. Measurement of ATP levels by luminescent assay showed that mitochondrial complex-1 inhibitors caused a significant reduction in ATP levels. Functional studies using the mitotracker green assay on N27 cells showed that exposure to complex-1 inhibitors caused significant damage in mitochondria. These results were also confirmed by fluorescence microscopy. Interestingly, pre-treatment with the HAT inhibitor anacardic acid (8.5uM) protected against tebufenpyrad and pyridaben–induced ATP reduction, H3 and H4 acetylation and cytotoxic cell death. Collectively, exposure to and tebufenpyad and pyridaben induced histone acetylation via mitochondrial dysfunction, which together may play a key role in dopaminergic neuronal degeneration (supported by NIH grant ES10586).

Key Words: Neurotoxicity, Pesticides, Epigenetics, Parkinson's disease, mitochondria.

♦ 32 ♦

Characterization of Antimicrobial Synergism Observed Between Aminoglycosides and Statins on the Growth of *Staphylococcus aureus*

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Staphylococcus aureus is one of the most common community- and hospital-acquired pathogens that can cause sepsis which is the 10th leading cause of death in the United States. Sepsis is frequently fatal if not diagnosed and treated properly. Treatment of *S. aureus* infections has become increasingly problematic due to the development of multidrug resistant strains that threaten the health and well-being of the population. Recent studies indicate that statins may also have antimicrobial effects and observational studies have revealed that HMG-CoA reductase inhibitors (statins) have pleiotropic effects outside their lipid lowering capabilities in sepsis disease states and can improve the outcomes of patients infected with *S. aureus.* We hypothesized that statins may have synergistic effects when combined with traditional antimicrobials. This study investigated the potential antimicrobial effects of statins in combination with aminoglycoside antimicrobials on *S. aureus* and the mechanism behind this antimicrobial phenomenon. Our data indicates that, in combination with statins, aminoglycosides demonstrate a statistically significant synergistic antimicrobial effect on the growth of *S. aureus*. Antimicrobial synergism was confirmed with a fractional inhibitory concentration index of 0.399 for the

wild type isolate and 0.113 for the gentamicin resistant mutant isolate. Utilizing an aminoglycoside resistant mutant of *S. aureus* the mechanism of action of the synergistic activity was further examined. The antimicrobial effect of inactive simvastatin on *S. aureus* has yet to be fully characterized. Revealing the mechanism by which *S. aureus* interacts with the combination of gentamicin and statins will assist in determining new treatment approaches.

♦ 33 ♦

Synergistic Effect of Aminoglycosides and Statins on Antimicrobial Resistant *Enterococcus faecalis*

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Enterococci are gram-positive bacteria that are important clinically in the hospital setting especially due to emergence of antimicrobial resistant strains. These are commensal bacterium that reside in the intestinal tract of many animal species; infection with this organism can lead to sepsis as well as fatal infections.

This research investigates the organism *Enterococcus faecalis*, measuring the phenomenon of synergism of statins and antimicrobials on inhibiting its growth. The antimicrobials evaluated include the aminoglycosides, gentamicin and kanamycin and a beta-lactam, ampicillin. To measure growth and inhibition we utilized minimum inhibitory concentration assays and growth curve analysis.

A statistically significant inhibition in growth of *Enterococcus faecalis* (ATCC 29212) was observed when the organism was exposed to simvastatin (18 ug/ml) and gentamicin (25ug/ml). The inhibition of growth was observed beginning at approximately 2 hrs after exposure and continued until a minimum of 8 hrs after exposure. However, *Enterococcus faecalis* (ATCC 51299) showed no differences between the treatment and the control groups indicating a lack of synergistic activity. Characterization of the isolate indicates the presence of a gene that makes it resistant to aminoglycosides, such as gentamicin. Minimum inhibitory concentration data of the strain also showed an MIC of > 128 µg/ml.

Due to the increasing prevalence of the antimicrobial resistant enterococci strains in nosocomial infections alternate treatments approaches are increasingly important. Many of the combinations of antibiotics that have been traditionally used are showing high level resistance, thus making new approaches appealing.

♦ 34 ♦

Boric Acid Destabilizes the Hyphal Cytoskeleton and Selectively Inhibits Invasive Growth of *Candida albicans*

Benjamin R. Pointer, MBS'18, Michael P. Boyer, Martin Schmidt

The virulence of the opportunistic fungal pathogen *Candida albicans* depends on its ability to switch from unicellular yeast growth to a hyphal morphology. The broad-spectrum anti-biological agent boric acid (BA) specifically inhibits the formation of *C. albicans* hyphae while leaving yeast growth largely unaffected. The current study demonstrates that BA exposure causes a reversible disintegration of the hyphal cytoskeleton, forcing cells to default to yeast -like growth even under hyphae-inducing conditions. Directional growth induced by genotoxic stress is not inhibited by BA.

♦ 35 ♦

Measuring *Candida albicans* Intracellular pH During Boric Acid Exposure

Martin Schmidt, PhD, Benjamin R. Pointer, Michael P. Boyer

Boric acid (BA) is a wide-spectrum anti-biological agent that has a remarkable effect on the morphology of a pathogenic fungus, *C. albicans.* It has been found that even at non-lethal concentrations BA suppresses the morphological transition of *C. albicans* from unicellular yeast to a hyphal mycelium. Since this morphological transition is required for virulence, the effect of BA on morphology makes it a promising agent for the treatment

of superficial yeast infections. A study of BA-sensitive deletion strains has identified the Rim101 pH-sensing signaling cascade as required for maintaining BA tolerance. The present study examines the hypothesis that BA causes a change in intracellular pH that could explain its toxicity. A *C. albicans* strain expressing a pH sensitive GFP variant (pHluorin) was constructed and shown to be a reliable reporter organism. Our data show that BA exposure does not change the intracellular pH of *C. albicans*. We conclude that sensing and counteracting changes in intracellular pH are not involved in the physiological response to BA stress.

♦ 36 ♦

Characterization of a Secreted Glucosidase from the Human Pathogen *Trichomonas vaginalis*

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Trichomonas vaginalis is a flagellated parasitic protozoan that is the causative agent of trichomoniasis, the most common non-viral sexually transmitted disease (STD) in the world. Once considered a mere 'nuisance' infection, it is now appreciated that infection with *T. vaginalis* can result in increased transmission and infection with human immunodeficiency virus and is also associated with long-term sequelae in women, including pelvic inflammatory disease, predisposition to premature rupture of placental membranes, low-birth weight infants, infertility, and cervical cancer. *T.* vaginalis secretes a variety of enzymes, some of which are thought to play important roles in virulence. Our laboratory has recently begun to characterize one such activity, a secreted glucosidase, which may be important for the pathogenesis and growth of *T. vaginalis*. We hypothesize that this enzyme helps *T. vaginalis* secure nutrients from the environment and establish infection. To investigate this hypothesis, we have begun to purify the secreted glucosidase from conditioned *T. vaginalis* growth medium, and have started analysis of its biochemical properties. Our data indicate that the secreted glucosidase activity is stable over a wide range of pH, with maximal activity occurring at an acidic pH (5.0 to 6.0). The glucosidase is also thermostable at 50°C for at least an hour, stable at 4°C for at least a week, and is stable through at least five free-thaw cycles. Polyacrylamide gel electrophoresis using amylopectin-containing substrate gels reveals that the activity migrates as a single, well-defined band. Collectively, these data support our strategies for further purification of this novel activity.

♦ 37 ♦

Expression and Purification of UDP-Glucose Pyrophosphorylase from *Trichomonas vaginalis*

Alex Davis, DO'17, Michael P. Boyer, Andrew Brittingham, Wayne A. Wilson

UDP-glucose pyrophosphorylase converts UTP and glucose-1 phosphate into UDP-glucose and pyrophosphate in a freely reversible reaction. The enzyme plays a key role in glycogen metabolism, supplying UDP-glucose for use in the synthesis of this important storage polysaccharide. The sequenced genome of the parasitic protist *Trichomonas vaginalis* contains two open reading frames, TVAG_102390 and TVAG_388260, which encode putative isoforms of UDP-glucose pyrophosphorylase. We amplified the TVAG_102390 open reading frame from *T. vaginalis* cDNA and cloned it into an *E. coli* expression vector, pET-28a. We determined that expression of the TVAG_102390 open reading frame in *E. coli* resulted in high yields of a soluble protein. The TVAG_102390 protein was purified by immobilized metal affinity chromatography and enzymatic activity was determined under various conditions. We have established that recombinant TVAG_102390 does indeed show measurable activity towards UDP-glucose, confirming its identity as a *bone fide* UDP-glucose pyrophosphorylase. We are currently in the process of cloning and expressing the TVAG_388620 open reading frame. We hope to purify recombinant TVAG_388260 and, ultimately, compare the kinetic properties of the two *T. vaginalis* UDP-glucose pyrophosphorylase enzymes.

♦ 38 ♦

Visceral Artery Aneurysm Repair: Case Report of a True Gastroduodenal Artery Aneurysm Not Amenable to Endovascular Repair

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The rarest of all visceral artery aneurysms is that of the gastroduodenal artery (GDA). These aneurysms can potentially lead to catastrophic and even fatal consequences when left untreated and the reported risk of GDA aneurysm rupture ranges from 35%-52%. Early recognition and intervention are essential to reduce the risk of rupture. Endovascular repair has become the mainstay for treatment with a reported success rate of 89.7%.

In this case report, we present a patient with chronic epigastric abdominal pain with a 4.5cm gastroduodenal artery aneurysm with primary revascularization secondary to a chronically occluded celiac artery. Pre-operative imaging showed that the proper hepatic artery was supplied via retrograde flow from the superior mesenteric artery through the aneurysm and therefore, aneurysm exclusion was not an option due to risk of end organ necrosis of the stomach, gallbladder, and spleen. This patient therefore underwent successful open repair.

Although there has been a trend toward endovascular repair of visceral artery aneurysms, certain limitations preclude endovascular repair, and these incidences should be recognized.

♦ 39 ♦

Effects of VEGF Loss on Muscle Hypertrophy and Growth Factor Responses Induced by Functional Overload in Mice

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Functional overload (FO, removal of major synergists) induces muscle hypertrophy and increases strength and endurance. Utilizing a model of FO in mice with inducible myofiber specific VEGF gene deletion (myoVEGF$^{-/-}$), we previously reported that myofiber VEGF is necessary for load-induced enhancements in force, but not increases in mass. Whether redundant or compensatory expression of growth factors regulates muscle hypertrophy in VEGF-deficient muscle is unknown. Current experiments tested the hypothesis that compensatory expression of growth factors (GF), including basic fibroblast GF (bFGF), insulin-like GF-1 (IGF-1), and hepatocyte GF (HGF), occur in VEGF-deficient muscle in response to FO. VEGF, bFGF, IGF-1, and HGF were measured by ELISA after 7 and 14d of FO or sham surgery in plantaris from wild type (WT) and myoVEGF$^{-/-}$ mice. In WT mice VEGF increased from 47±4 pg/mg (sham) to 70±8 pg/mg ($p<0.05$) after 7d, before returning to 42±4 pg/mg at 14d. Similar increases in bFGF and HGF were measured after 7d ($p<0.05$) in both WT and myoVEGF$^{-/-}$ mice. IGF-1 levels increased in both genotypes ($p<0.05$), however, greater increases were observed in myoVEGF$^{-/-}$ than WT ($p<0.05$). In WT mice IGF-1 increased from 148 ± 15 pg/mg (sham) to 372±85 pg/mg and 360±123 pg/mg after 7 and 14d, respectively. In myoVEGF$^{-/-}$ mice IGF-1 increased from 187±18 pg/mg (sham) to 670±48 pg/mg and 595±74 pg/mg after 7 and 14d, respectively. Data suggests myofiber VEGF expression is non-essential for muscle hypertrophy in response to FO and sustained increases in IGF-1 may compensate in part for inhibited myofiber VEGF expression.

♦ 40 ♦

Effects of a Pre-Exercise Supplement on Anaerobic Power and Blood Lactate Levels in Males and Females

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This study assessed the effects of a supplement containing creatine with a supplement containing creatine, beta-alanine, amino acids, caffeine, and B-vitamins (Assault™, MusclePharm) on maximal anaerobic power and blood lactate accumulation in males and females. We hypothesized that Assault™ would be associated with greater anaerobic power, increased fatigue resistance, and reduced lactate compared to creatine while both supplements would improve performance over placebo. Subjects (n=12) performed two 30-second Wingate anaerobic tests separated by five-minutes rest after the consuming the supplement in a repeated measures, blinded, placebo-controlled design. Fatigue resistance was quantified as relative power drop over the test. Blood lactate levels were measured before test 1, and after tests 1 and 2. Peak anaerobic power was not different among all conditions for test 1 or 2 (11.1±1.3 and 11.06±1.1 W/kg for males, 8.8±0.3 and 8.7±0.3 W/kg for females, respectively). Assault™ was associated with the highest fatigue resistance during the first Wingate for males and females, 39±3% and 36±2%, respectively, but was not significantly greater than creatine (43±2% and 42±4%) or placebo (43.5±4% and 42±3%). In both sexes, increases in lactate between tests 1 and 2 were lower with Assault™ (4.3±2.1 and 2.9 ±0.5 mmol/L) and creatine (3.9±1.7 and 2.8 ±2.1 mmol/L) compared to placebo (8.2±2.9 and 4.6 ±0.9 mmol/L) for males and females, respectively. Preliminary results indicate the Assault™ and creatine supplements do not significantly increase peak anaerobic power or fatigue resistance over placebo, but may buffer increases in lactate with repeated anaerobic power tests.

♦ 41 ♦

Postural Stability in Healthy Older Adults Following Tai Chi Lessons from a Novice Versus Experienced Instructor

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Tai Chi (TC) decreases fall risk and improves balance in the community dwelling older adult. Duplication of reported results and applicability in the clinic setting is difficult due to various forms, length and duration of TC studied. Tai Chi for Arthritis (TCA) is a shortened form with certified teachers to insure consistent instruction. The purpose was to determine changes in balance after TCA instruction and if there was a difference in outcomes based on experience level of the instructors.

All exercise classes were taught by TCA certified instructors, bi-weekly for 6 months. Volunteers were randomly assigned to an exercise group taught by either experienced tai chi instructors (EE) (n=15) or teachers new to tai chi (EN) (n=11). A control group (n=12) participated in test sessions only. Clinical balance measures consisting of Fullerton Advanced Balance (FAB), Four-square step test (FSST), Figure 8 walk test (Fig 8) and the Activities-specific Balance Confidence scale (ABC) were administered pre-exercise class, at 3 and 6 months, and one-month follow up.

Results of mean change scores for each group between pre and 6 month testing:

FSST (seconds): EE-1.55; EN-1.35; C-1.29
Fig 8 (seconds): EE-0.53; EN-0.59; C-1.33
FAB (points): EE-1.00; EN-0.82; C-1.64
ABC (percentage): EE-1.43; EN-2.07; C-1.33

No improvement in clinical balance measures were found following 6 months of TCA classes. Participants' anecdotally reported a decrease in pain and improved balance during daily tasks. Additional analysis will be completed on computerized postural stability data. Further study is needed to determine the effectiveness of this shortened form of Tai Chi in the well older adult population.

♦ 42 ♦

Hip Muscle Strength in Individuals with Low Back Pain

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Study Design: Descriptive, within-subject comparison.

Objective: To examine hip abduction and extension strength in individuals with low back pain (LBP).

Background: Previous research has established a link between hip strength and LBP. Extension and abduction strength deficits can be predictive of development of LBP. In contrast, other literature reports no association between hip extension or abduction strength and LBP.

Methods: Forty-two subjects with LBP were included. Mean (SD) age was 43.31 (17.72). LBP duration was 228.40 (362.85). Pain level was 4.40 (1.89) and percent disability was 26.00 (6.80). Hip abduction and extension strength were assessed using a handheld dynamometer.

Results: A significant strength difference between sides was found for hip abduction ($P<0.01$) and extension ($P<0.01$). An average of 18.03% and 14.95% difference between sides was found in hip abduction and extension strength, respectively. An association between side of weakness and side of low back pain was found for hip extension ($\chi^2 = 3.78$; $P=0.05$) but not for hip abduction ($\chi^2 = 3.27$; $P= 0.07$). There was no correlation between percent disability and strength deficit for hip abduction ($r= 0.07$; $P = 0.68$) or extension ($r= 0.03$; $P=0.87$).

Conclusion: Results of this study demonstrate that individuals with LBP present with strength differences between sides for hip abduction and extension, and that side of pain may be a factor in hip extension strength deficits. Hip strength should be examined in patients with LBP; future studies should examine whether improvements in hip strength are associated with improvements in LBP.

♦ 43 ♦

Lower Limb Dominance and Functional Task Performance

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Lower limb dominance is most often described such that the foot used to manipulate an object or to lead out (as in stepping) is the dominant leg or mobility limb, whereas the leg used for postural support is considered the non-dominant leg (Howard 2012). This pilot project evaluated individuals performing lower limb functional tasks compared to reported handedness and lower limb dominance on the Waterloo Footedness Questionnaire-Revised (WFQR).

30 healthy young adults (23.9 +/- 2.5 yrs.) participated in this project. Participants self-identified as either right-handed (N=23) or left-handed (N=7). Participant's lower limb use was noted during performance of a functional task series: opening a foot-triggered trashcan, stepping up a step stool, stepping to initiate gait, and lifting a foot for single limb stance.

74% (17/23) of right-handed participants were classified as right lower extremity dominant according to the WFQR, while 26% were classified as mixed-foot. In contrast, equal percentages of left-handers were classified as left-dominant (43%) and mixed foot (43%).

As expected for a task requiring mobility, 70% of right-handed participants used the right foot to initiate gait, while 57% of left-handed participants used the left foot. However, when performing a task focused on stability such as single-limb stance, 61% of right-handers and 57% of left-handers lifted their left leg. Both right (78%) and left-handed individuals (71%) utilized their right foot for the step-up task. In contrast, 39% of right-handers

used their left foot to open a trash can, while left-handed individuals tended to maintain use of the right foot. Right-handed individuals with mixed-foot classification did not appear to perform differently than right-foot classified individuals.

The pilot work appears to suggest an inconsistency between the lower limb dominance as classified on the WFQR and limb utilization exhibited during these functional tasks despite task mobility or stability requirements. These functional tasks may not be sufficiently challenging for young healthy participants to exhibit a lower limb preference.

♦ 44 ♦

Gait Assessment During Simulated Pregnancy

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Healthy pregnant women exhibit gait adjustments and report falls during pregnancy. Throughout pregnancy, females experience physiological changes which may lead to lumbopelvic pain and additional functional mobility challenges with sit-to-stand and stairs. The purpose of this pilot work was to evaluate the capabilities of the APDM movement monitoring system and the GAITRite instrumented walkway for capturing functional performance measures during a condition of simulated pregnancy.

Eight young healthy females (23±1 yr) participated in this pilot work. Participants donned six APDM mobility monitors and walked a distance of 25 feet, including a 14-foot section which included the GAITRite walkway. Participants performed 5 trials under a normal condition and under a simulated pregnancy condition by wearing a 13-kg Pregnancy Profile vest (RealityWorks, Inc.). Walkway data were processed via ProtoKinetics software, and APDM sensor data were obtained using Mobility Lab software. Trials were averaged per participant and paired t-tests were used for statistical comparisons.

A difference was identified in step length between the normal (73±6 cm) and simulated pregnancy condition (70±7 cm) assessed with the GAITRite ($p=0.002$). In contrast, no differences in step length were noted with the APDM system. No differences were noted in gait speed with either assessment system, although a trend of increasing cadence during the simulated pregnancy condition was identified with the APDM sensors ($p=0.06$).

Based on the pilot work, additional evaluation is needed prior to utilizing the APDM system for functional mobility assessments such as sit-to-stand or stair negotiation in a pregnant population.

♦ 45 ♦

Diastasis Recti Abdominis: A Narrative Review

Elizabeth Trausch, DPT, Ginger Garner, Stefanie Foster

Diastasis recti abdominis (DRA) is an area of research in postpartum maternal health lacking in both quantity and quality. At present, there are no studies that definitively guide clinicians on best practices for postpartum women with diastasis recti abdominis. High quality research is also lacking to guide peripartum clinicians, fitness professionals and individuals with DRA on safe exercise guidelines. The impetus for this narrative review is to provide a foundation for development of partnership-based (Eisler 2007), systems-based, integrated postpartum guidelines for care through a review of the literature.

The goal of this paper is to improve postpartum management of DRA and the comorbidities which often accompany it, including all types of incontinence (stress, urge, and mixed), pelvic organ prolapse (POP), postpartum depression (PPD), pelvic girdle pain (PGP) and lumbopelvic pain (LPP). Comorbid diagnoses provide a potential medical intervention point for postpartum women as they are rarely reported to be referred to specialty care like physical therapy specifically for DRA (Keeler 2012, Yuen 2013). Deeper investigation of these associations can also provide a stimulus for theorizing biomechanical factors contributing to the presence or persistence of DRA and associated postpartum diagnoses. The findings of this literature review incorporating biomechanical factors and comorbidities of DRA support the need for the development of partnership-based (Eisler 2007), systems-based, integrated guidelines for DRA and associated postpartum diagnoses.

♦ 46 ♦

Comparison of Pain Ratings Post Total Joint Arthroplasty with Regard to Body Mass Index

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Introduction: Total joint replacements are among the most prevalent and painful surgeries. Common pain management methods include general anesthesia, femoral nerve, and combined peripheral nerve blocks. With obesity on the rise and in an effort to manage pain and expedite recovery, there is an increased concern how BMI effects pain post operatively.

Research has shown that higher BMIs correlate to a higher risk of complications following total joint replacement surgery. The purpose of this study is to evaluate the effect of BMIs on VAS pain ratings when controlling for anesthesia method used during total joint replacement surgery and to determine if a type of pain management was most effective in each BMI group.

Hypothesis: Higher BMIs increase VAS pain ratings post operatively and combined sciatic and femoral anesthesia is most effective in managing pain for patients with higher BMIs in total joint replacement surgeries.

Methods: 300 patient charts were retrospectively reviewed for body mass indices, VAS pain ratings, and anesthesia method used following total hip or knee arthroplasty. The patients were randomly assigned by surgeon.

Results: The pain ratings were the highest for all of the groups when utilizing the femoral nerve block and the lowest when utilizing the combined femoral and sciatic nerve blocks. The obese group did exhibit the highest pain rating during the hospital stay in the general and combined anesthesia group.

Conclusion: The descriptive analysis demonstrates that higher BMIs do not directly correlate with higher VAS pain ratings for all types of pain management methods used.

♦ 47 ♦

Gait Deviations Associated with Plantar Heel Pain: A Systematic Review

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Introduction: Plantar heel pain (PHP) is a common foot disorder that presents with significant pain and gait-related disability. The aim of this systematic review was to identify relevant gait deviations associated with PHP.

Method: A systematic review of articles that measured gait variables in individuals with PHP was conducted using the CINAHL, MEDLINE, and Scopus databases. Methodological quality was assessed using the Downs and Black criteria and level of evidence was determined from quality estimates and compiled conclusions for each gait variable.

Results: Seventeen articles were identified for review. There was strong evidence that stance phase duration is unchanged in PHP, but there was limited evidence of decreased center of pressure (COP) duration and velocity during loading response phase. There was conflicting evidence of altered regional (rear-, mid-, forefoot) impulses in PHP, but reduced rearfoot impulse was observed if the COP method was used. Clinical observations of pronation and supination were reported, but the only quantified measure of pronation/supination included limited evidence of increased plantar flexion at initial contact and overall mobility of the medial forefoot in PHP.

Conclusion: Gait deviation is observed in individuals with PHP, but low study quality and measurement variation prevent a clear consensus on the most relevant gait deviations in PHP. Subgroups of gait deviations may be present in PHP that require further investigation with larger samples. In addition, further consensus is needed to standardize relevant gait measures for future investigation and, ultimately, to inform gait-related management considerations in PHP.

♦ 48 ♦

Inter-Rater Reliability of Ankle Plantar Flexor Isokinetic Testing

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Isokinetic testing is often considered the gold standard to assess muscle strength as an outcome of treatment because of the ability to standardize testing methods and the accuracy of the equipment. Despite the common use of isokinetic testing in outcome studies, there are sources of error that can contribute to erroneous and unreliable data. The purpose of this study was to investigate the reliability of ankle plantar flexion peak torque derived from isokinetic testing that will be used as a primary measure in an outcome study of gastrocnemius recession. A secondary purpose was to describe sources of error and measures to control error during isokinetic testing. In this study plantar flexor peak torque was measured reliably between different sets of examiners on different days using isokinetic testing at 60, 120 and 240 degrees/sec. Isokinetic testing was performed with a specified protocol by trained examiners and an appropriate sample size produced reliable results that can improve confidence in the results of our future study looking at muscle strength after a gastrocnemius recession. There were several sources of error identified that require consideration in isokinetic testing and reporting of reliability in each investigation using isokinetic measures.

♦ 49 ♦

Differences in the Kinematic Breakdown of Foot Support Pattern in Patients with Plantar Fasciitis

Jesse Wolfe, DPM'16, Julian Rivera, BSc, Shane McClinton, DPT, Vassilios Vardaxis, PhD

Foot function, in respect to the gait cycle, is important in determining the presence of an ongoing pathologic condition. Simple gait-monitoring technology has the ability to provide valuable insight into the current state of a patient's particular condition; however these diagnostic modalities remain under-utilized in the clinical setting. Plantar fasciitis (PF) provides a testable model for the application of these simple diagnostic modalities due to its known pathologic manifestation during stance phase of the gait cycle. Likewise, these modalities can assist the physician in monitoring effective treatments and outcomes in patients with plantar fasciitis (PF). The current study aims to quantify potential differences in timing between the foot and floor contact of: the heel, the foot flat (heel and forefoot), and the forefoot between PF patients and healthy controls during gait. Twelve PF patients and twenty control subjects were analyzed using 3-dimensional motion capture while walking at their preferred speed. The vertical kinematic features of the heel and toe markers were used to identify the heel strike, toe down, heel-off, and toe-off events during stance. These events were used to define the foot support pattern (in percent stance phase duration) metrics for the heel (heel support), ankle (foot-flat support), and toe (forefoot support) rockers. Our findings indicate that PF patients walk significantly slower than controls (1.16 vs 1.26 m/s, p=0.016), but with similar stance phase duration (p=0.668). The floor contact timing pattern was different in the PF patients, showing a longer heel rocker (22.7 vs 12.8%, p=000), a shorter toe rocker (32.2 vs. 40.7%, p=0.001), and a delayed heel rise (occurring at 67.8 vs. 59.3%, p=0.001), during the stance phase of gait. We concluded that the ability to recognize the presence of an altered floor contact pattern during gait in PF patients can be useful in the detection, diagnosis and rehabilitation of these patients.

♦ 50 ♦

Forefoot and Midfoot Radiographic Reliability and Structural Deformation with Respect to Load

Garrett Melick, DPM'17, Catherine Jacobs, Vasillios Vardaxis PhD

Background: Clinicians often use radiographic angular measurements to make clinical decisions, but changes in these measures as a consequence of load and their reliability are not typically established. *Objective*: We hypothesize that foot deformation due to different static weightbearing conditions has an impact on radiographic angles. In this study, we seek to assess the change in radiographic angles according to static load on the foot, and understand their potential implications for clinical considerations regarding foot pathology.

Method: Radiographic data was collected from 40 asymptomatic subjects under three static weightbearing conditions: low load, bilateral stance, and high load. Digitally converted radiographs were analyzed using an in-house software written in MATLAB®. Reliability was performed for each angle, and one-way repeated measures ANOVA followed by profile contrasts were utilized to test for load effects (a=0.05).

Results and Conclusions: Comparisons of the radiographic measures showed splay increase between the first and second metatarsals, decrease in the toe splay of the remaining metatarsals, hallux varus-directed motion, decrease in the articular coverage between the talus and the navicular, and that the perspective view of the medial cuneiform changes upon increased load. The significant change in foot posture with static load is not only informative with respect to pseudo-dynamic foot function, but it has the potential to be used for surgical intervention planning and outcome assessment.

♦ 51 ♦

Bilateral Differences in Lower Extremity Loading During Sit-to-Stand in Unilateral Hip OA Patients Before and After Total Hip Arthroplasty

Vassilios Vardaxis, PhD, Viet Nguyen, DO'16, Aaron Huegel, DPT'15, Laura Covill, DPT, John Nettrour, MD, Craig Mahoney, MD

Standing from a chair without arm assistance is a challenging task that demands high range of motion (ROM), strength and balance. The magnitude of hip motion and torque needed during chair-rising were found to be higher than stair climbing or walking. This common everyday activity is performed 65.5 (±17.3) times a day by the healthy elderly and is an essential task for independent living individuals.[1] Patients with unilateral hip osteoarthritis (OA) and post total hip arthroplasty (THA) exhibit strength and ROM deficiencies which may be critical limiting factors for this task. Therefore, the purpose of our study was to measure the bilateral differences in lower extremity loading during sit-to-stand in unilateral hip OA patients and controls and assess load discrepancies for one year post THA.

The bilateral lower extremity loading during sit-to-stand of 34 unilateral hip OA patients that subsequently had total hip arthroplasty (THA group) and of 9 healthy age matched individuals (Control group) were compared at 4 time points over a one year period (PRE – before surgery; and 3, 6, and 12 – months post-surgery). Participants were told to stand from a standard height armless/backless chair, unassisted, using only their legs. Ground reaction forces were recorded bilaterally by 2 side-by-side force plates using a symmetrical 25cm wide stance. The normalized peak vertical force and impulse were determined bilaterally and asymmetry ratios were calculated. Differences/changes over time in bilateral loading were assessed using two-way ANOVA on the asymmetry ratios and for the THA group on the bilateral impulse and normalized peak vertical force (a=0.05).

We found significant group, time and interaction effects for impulse and peak vertical force asymmetry ratios indicating that the THA patients gradually shifted (over time) the cumulative and peak load towards the surgical side, however, they remained more asymmetrical than the controls. For the THA group we found significant leg, time and interaction effects at p=0.000 level for impulse and peak force. Significant bilateral differences in impulse were found only at the pre-surgery level, while normalized peak forces displayed persistent differences 12 months post-surgery.

During standing from a standard height chair, hip OA patients learn to distribute their bodyweight load more evenly after THA; however, asymmetrical loading continues a year post-surgery. These findings add to the volume of data showing persistent favoring of the surgical side early and late post-THA with unknown implications to lower extremity pathology progression.

Reference: Egerton T, Brauer SG. 2009. Temporal characteristics of habitual physical activity periods among older adults. J Phys Activity Health 6:644–650.

♦ 52 ♦

Postural Control in Hip Osteoarthritis Patients Before and After Total Hip Arthroplasty

Vassilios Vardaxis, PhD, Dhaval Patel, DO'16, Kelsey Schultze, DPT'15, Laura Covill, DPT, John Nettrour, MD, Craig Mahoney, MD

Hip and knee osteoarthritis (OA) is a disabling pathology associated with pain, joint stiffness, limited range of motion and muscle weakness. Proprioception and postural control are diminished in individuals with knee OA when compared to controls but the literature is inconclusive regarding these limitations in subjects with hip OA.[1]. Muscle weakness and balance impairment are risk factors for falls in older adults, therefore it is important to study the dynamics of balance in advanced stage hip OA patients pre and post total hip arthroplasty (THA).

Twenty-three patients with advanced unilateral hip OA participated in the study. Postural control of all patients was evaluated over time before (Pre) and at 3, 6, and 12 months Post THA. The postural control assessment was performed in bilateral standing position (on two side-by-side force plates, 25cm wide stance) with eyes open/closed. Thirty second balance test was used, and three trials per condition were captured. The bilateral body weight (BW) distribution and the combined and unilateral center of pressure (CoP) displacement were used to evaluate changes in BW unilateral support and postural sway variables over time. Two factor ANOVA (limb x time) repeated measures design was used, followed by single factor and paired t-tests, as needed ($\alpha = 0.05$).

The percent BW supported by the OA side during the balance task was at 48.4% (±5.0) and 47.9% (±5.5) for the eyes open/close conditions, respectively. The two-way ANOVA (limb x time) showed a significant interaction effect ($p = 0.020$) indicating a change in weight distribution over time. The CoP path length decreased significantly over time under both eyes open and eyes close conditions for the combined (to 80.15%) and the unilateral (to 86.21% and 68.42% for the healthy and OA sides respectively) CoP displacement. The marked decrease in the CoP path length of the OA side was also reflected by a two-way ANOVA (limb x time) interaction effect at the $p = 0.000$ under both eye conditions. The planned comparisons between limbs at each time level showed bilateral differences until 6 months post-surgery.

The findings of this project suggest that advanced hip OA patients have significant balance deficits and these persist to at least six months post-surgery. To which extent these are associated with the physical deficits of strength or proprioception related to cartilage damage and/or surgery is unknown.

Reference: Kinds et al, (2011). A systematic review of the association between radiographic and clinical osteoarthritis of hip and knee. Osteoarthritis and Cartilage 19:768-78

♦ 53 ♦

Clinical Evaluation of Dorsal Lisfranc Ligament Deformation with Change in Load Using Ultrasound Imaging

Dalton Ryba, DPM'16, Nooreen Ibrahim, Todd Jaramillo, James Choi, MD, Vassilios Vardaxis, PhD

Preface: The use of ultrasound is a viable modality for medical imaging of ligamentous tissue. In a previous study we showed that the dorsal Lisfranc Ligament (dLL) can be reliably visualized with ultrasound and that we can potentially discern load-varying ligament deformation with the images obtained. The study was limited with respect to the artificial loads used to apply stress on the foot using a calf raise machine.

Purpose: The goal of the present study was to load the foot using physiologically relevant stresses in a clinical setting and assess the dLL deformation from the acquired ultrasound images. We expect that these results will contribute towards the development of a protocol for Lisfranc ligament injuries diagnosis.

Methods: Bilateral dLL measurements were taken from fifty healthy volunteers (25 males and 25 females), for a total of one hundred asymptomatic feet, using sonographic imaging technology under three different stress conditions (low, medium and high load). Stress load was applied using the individuals' body weight (low load – seated position; medium load – equal weight bearing standing position; and high load – single leg standing).Two floor imbedded force plates were used to measure the exact physiological load. Digital images of the dLL obtained using a 10.0 MHz linear array ultrasound transducer were analyzed to determine ligament parameters using software written in MATLAB.

Results: One-way repeated measures ANOVA revealed a statistically significant increase in the dLL length with load. The average dLL elongation, as percent change, was 7.43 ±0.98% (pooled bilaterally) between seated and single leg standing positions. Most of the dLL length change (6.02 ±1.05%) occurred between seated and bilateral standing positions.

Conclusion: Ultrasound imaging can be used to visualize the dLL and can detect ligament elongation that reflects increase in physiological load, making ligament imaging clinically practical. These clinically practical findings may prove useful in protocol development that uses ultrasound as a clinical imaging technique to diagnose Lisfranc ligament injuries.

♦ 54 ♦

The Effects of Walking Speed on the Transverse Plane Kinematics of the Forefoot

Catherine Jacobs, DPM'17, Julian Rivera, Garrett Melick, and Vassilios Vardaxis

Statement of Purpose: Forefoot pain is a common debilitating condition and is associated with chronic impairment. Patients that experience forefoot pain present both hypo- and hyper-flexibility of the forefoot caused by different underlying mechanisms. During the stance phase of gait the magnitude and distribution of foot load changes with each step and each individual, imposing changes to the overall foot posture and motion. The present study measured splay angles medial and lateral to the second metatarsal bone during the stance phase of self-selected typical and fast gait.

Methodology: Nineteen healthy volunteers performed five walking trials per leg at self-selected typical and fast walking speeds. Heel and toe retro reflective markers attached to the foot identified heel strike, toe down, heel-off, and toe-off events. Markers on the first, second, and fifth metatarsal bases and heads quantified the medial and lateral forefoot splay angles.

Results: The medial splay angle remained around 10.8° divergence during the heel rocker, while an additional 4° deviation occurred during the ankle rocker, diverging maximally soon after heel-off. Interestingly, a small decrease in divergence (2-3°) occurred during the toe rocker, irrespective of the walking speed. The lateral splay angle was found negative (-13.3°) during heel strike, indicating convergence. The lateral splay increased rapidly during the heel rocker, reaching -3.1° during the ankle rocker. At push-off the lateral splay rapidly decreased to -9.6°.

Discussion: The measurements of the forefoot medial and lateral splay angles during the stance phase of gait provide an objective functional assessment of forefoot flexibility.

Level of Evidence: Level 2 Diagnostic Study

♦ 55 ♦

Quantification of Rotational Correction Achieved During First Metatarsal Cuneiform Joint Fusion

Paul Dayton, DPM, FACFAS, **Merrell Kauwe, DPM[#],** Lawrence DiDominico DPM, FACFAS,
Mindi Feilmeier DPM, FACFAS

Format: Scientific Format

Purpose: Recent literature has described both the pathologic valgus position of the metatarsal in a bunion deformity as well as correction of this position. The papers regarding correction do not seek to quantify the amount of rotational correction obtained with the corrective procedure; rather they focus on the qualitative direction and subsequent changes in radiographic post-operative assessment. This case series presents our observation and analysis of the degree rotational correction imparted with a Lapidus arthrodesis that addresses the third plane of deformity.

Methodology: 41 consecutive patients receiving a first tarsal metatarsal joint fusion for correction of hallux valgus from two different institutions are included in this study. During operative correction a device was used to measure the amount of correction that was imparted during a modified Lapidus arthrodesis. Intraoperative fluoroscopy was used assess correction of the rotational aspect of the deformity. Mean, standard deviation, and range were calculated.

Procedure: Modified Lapidus Arthrodesis.

Results: The mean and standard deviation of the case series is 22.3 and 5.5 respectively. The values ranged from 12-31 degrees of rotational correction.

Discussion: Though rotational correction during bunion procedures was described as early as 1956, it has not found a consistent place in correction of the deformity. Recent publications have focused on direction of rotation. The authors are unaware of any study quantifying the amount of correction obtained with procedure. Further studies should include appropriate pre-operative assessment of rotation.

Level of Evidence: IV

♦ 56 ♦

Comparison of Outcomes and Complications for Internal and External Fixation for Charcot Reconstruction: A Systematic Review

Paul Whitehouse, DPM'17, Mitchell Thompson, DPM '17, Paul Dayton, DPM, Mindi Feilmeier, DPM, Rachel Reimer, PhD

The surgical reconstruction of Charcot deformity can be a challenge for foot and ankle surgeons. There is lack of consensus among surgeons as to the best method of surgical fixation to be used in reconstruction, as well as lack of clear strong evidence in the literature. We undertook a systematic review of electronic databases and other relevant sources in an attempt to better understand the complications and outcomes associated with internal and external fixation for Charcot foot and ankle reconstruction. Twenty-three level four studies with a total of 616 procedures were identified. Of these, 12 studies with 275 procedures used internal fixation and 11 studies with 341 procedures used external fixation. The odds of a successful outcome with internal fixation = 6.86. The odds of successful outcome with external fixation = 13.20, OR = .52, 95%CI (.30, .90). The odds of success for internal fixation were .52 times as likely as the odds of success with external fixation. Because the OR does not include 1, this difference is statistically significant at the $p < .05$ level. An identified trend was that external fixation was used more often in cases deemed to be difficult by the surgeon preoperatively. These findings may prove helpful to foot and ankle surgeons when making decisions on fixation for Charcot reconstruction.

♦ 57 ♦

Community Engaged Scholarship: Research Orientation Module in Comparative Neuroanatomy

Muhammad Spocter, PhD[1], Kathleen Bitterman[1], Kacia Cain[2], Clarissa Snapper[3], Donald Matz[1], Julie Rosin[2]

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Community engaged scholarship (i.e., teaching, research and service) has become central to the academic mission of the modern university and is poised to play a key role in positioning tertiary institutions to help address economic and health disparities within their region. One such example has been the focus on improving K-12 student engagement and achievement in science, technology, engineering and math (STEM), thus not only helping individuals acquire the basic skills necessary for achieving academic goals but also ensuring that the American workforce as a collective remains competitive within the global community. Here we report on a collaborative undertaking between Des Moines Public Schools Central Campus and Des Moines University in which educators have constructed a Research Orientation Module in Comparative Neuroanatomy that familiarizes high school students (Grades 11-12) with evolutionary neuroscience and some of the research methods employed in mapping the human brain. Through the use of a mixed instructional approach this intervention has allowed students to learn science outside of the traditional classroom setting and to apply this knowledge by collaborating on a research project pertaining to the mammalian brain. So far this intervention has graduated 20 students over a two year period, 80% of which were females and all of whom have gone onto college. Through continual recommendations of accreditation and funding bodies such as the National Science Foundation, projects which engage the community and help foster achievement in STEM based opportunities are helping to transform our universities from silos of intellectual privilege to focal points for community dialogue and interaction.

♦ 58 ♦

The Relationship Between Student Traits and Attitudes Toward the Flipped Classroom Experience

Laura Covill, DPT and Jason Cook, DPT

Introduction: Educators are choosing to "flip" their classroom experience by delivering lecture material through technology and using classroom time for more active learning. The purpose of our study was to compare student's self-selected learning preferences of visual, auditory or kinesthetic learner, their traits of extrovert or introvert, and their opinion regarding the flipped classroom experience. We hypothesized that the kinesthetic, extroverted student would enjoy the experience more.

Methods: Two professors at Des Moines University delivered their lecture material in a flipped process to 1st and 2nd year Doctor of Physical Therapy students. Students responded to a survey of the experience. Likert scale data from 1 (strongly disagree) to 5 (strongly agree) was evaluated.

Results: Survey response rate was 73%. Students self-identified as visual (55%) or kinesthetic learners (45%); no student self-identified as an auditory learner. Students self-identified as extroverts (60%) or introverts (40%). Many students were undecided regarding whether the flipped classroom suited their learning style or if they enjoyed it. Both kinesthetic and visual learners felt the flipped classroom suited their learning style but kinesthetic learners with a greater percentage (57%, 49% respectively). While extroverts enjoyed the experience (45% agree or strongly agree), more introverts did not (41% disagree or strongly disagree).

Conclusion: Even with activities to address learning and personality types, the flipped classroom method seems to appeal more to extroverted students and students who are kinesthetic learners.

♦ 59 ♦

Effectiveness of Iowa Simulation Center Experience on Long-Term Learning

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SIM lab is known for being beneficial to students in that it puts the student is a real life clinical situation where decisions have consequences. It not only prepares the medical students for real patients but prepares them for stressful situations like a cardiac arrest or trauma. SIM lab also facilitates group communication and builds teamwork skills. The purpose of this study is to show that SIM lab has a direct academic benefit as well as preparing students for real life situations.

We hypothesize that students who have experienced both SIM lab and lecture will perform better on our case based exam compared to the students who only experienced lecture, for a given subject.

By testing the students and looking at how they performed when having experienced both SIM lab and lecture, and then comparing those results to the students who only had lecture, we will be able to see if SIM lab helps on an academic level. We already know that SIM has a number of benefits in regards to preparing students for real life decision making scenarios, but the aim here is to see if SIM lab helps with basic retention of medical knowledge.

This research study was conducted with the voluntary participation of the DO class of 2016. Data was gathered from an online case study based test that was developed to directly reflect the information portrayed in Simulation Lab.

After conducting the study we found that there was not a significant increase in scores for students who participated in the given Simulation lab. We did find that there was an overall increase in confidence for students that participated in the SIM lab compared to students that did not.

Is the Increasing Scope of Podiatric Medical Education and Residency Training Leading to an Increase in the Privileges Granted to Recently Graduated Podiatric Physicians?

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In 2005 the American Podiatric Medical Association (APMA) established an initiative, *Vision 2015*, with the goal of "podiatrists being defined as physicians who treat patients in the physician's specialty without restrictions." "The overall mission of Vision 2015 is to ensure that podiatrists are universally accepted and recognized as physicians consistent with their education, training, and experience." Since Vision 2015 was initiated, the podiatric medical field has made leaps and bounds in increasing the quality of student education and residency training. The purpose of this survey is to determine if this increase in scope of podiatric medical education and residency training, has led to an increase in the privileges granted to recently graduated podiatric physicians.

The data was obtained via a voluntary paper survey, which was handed out to podiatric physicians at the Iowa Podiatric Medical Society's 2014 Heartland Podiatry Conference, in Des Moines Iowa. All 66 participants were Doctors of Podiatric Medicine (DPM), coming from a wide variety of professional experience, as well as educational and residency training backgrounds. The survey questions inquired about completion and extent of medical education and training, any additional post-graduate training or certifications, type of practice setting, specific types of procedures currently performing, and reason why physicians may not be performing a certain procedure. The chosen surgical procedures ranged from less technical Class II, to more complex/invasive Class III procedures. This range in Class II/Class III procedures was utilized to draw a distinction between the individual physicians' current surgical privileges. The survey data was transferred from the paper hard copies to an excel spreadsheet to facilitate further analysis.

The results obtained were: graduation dates from a college of podiatric medicine spanning from 1969 – 2012. Residency training included: 6 physicians with no residency training, 10 physicians with "other" residency training, 18 physicians with a 12-month residency (PMSR-12), 12 with a 24-month residency (PMSR-24), and 20 with a 36-month podiatric medicine and surgical residency (PMSR-36). Respondents practiced in a variety of settings: 33% Sole Private Practice, 21% Small Private Podiatry Group (<4), 7% Large Private Podiatry Group (>4), 3% Small Multispecialty Group (>20), 14% Large Multispecialty Group, 9% Orthopedic Group, 17% Hospital employed. Trend noted: physicians with PMSR-12 training or less primarily working as sole practitioners, while physicians with PMSR-24 training or more are working mainly in physician groups or as hospital employees. The percentage of physicians, in each cohort, performing Class II and Class III procedures respectively: No Residency 70.8% & 6.7%, "Other" Residency Training 52.5% & 18%, PMSR-12 75% & 31.1%, PMSR-24 100% & 68.3%, PMSR-36 98.8% & 88%. The percentage of physicians, in each cohort, unable to perform Class III procedures due to insufficient training vs inability to perform procedures due to state scope of practice laws, despite sufficient training, respectively: No Residency 50% & 0%, "Other" Residency Training 30% & 20%, PMSR-12 50% & 5.5%, PMSR-24 33.3% & 0%, PMSR-36 0% & 10%.

These results suggest that the increase in scope of podiatric medical education and residency training is in fact leading to an increase in the privileges granted to recently graduated podiatric physicians. This is evident in the fact that as the amount of training increases, especially in those that have graduated in the last 10 years, the amount of invasive procedures able to perform also increases. The major weakness of the study is the small population size. To correct this, the survey will soon be sent nationwide to over 15,000 practicing podiatric physicians. In this upcoming survey a deeper look into why physicians are unable to perform specific procedures will be analyzed. The variable of interest is the limitation of state scope of practice laws, especially when the physician has sufficient training. The goal of this is to evaluate the effects of antiquated state scope of practice laws, and assist in the achievement of a uniformed national scope of practice for Doctors of Podiatric Medicine. This will in turn lead to better patient care provided by the best trained physicians in lower limb medicine.

References:

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Using Sheet Plastination Models to Enhance Podiatric Students Understanding of Cross-Sectional Relationships in the Lower Extremities

James Mahoney, DPM, **Noreen Anwar, DPM '17,** Morgan Mack, DPM '16, Donald Matz, PhD, Simon Geletta, PhD

Accurate MRI interpretation requires an understanding of cross-sectional anatomy. Traditional anatomical dissection may not provide enough understanding of the three-dimensional relationships of anatomical structures. For the study, 2nd year CPMS students in the classes of 2017 and 2018 who are enrolled in the Lower Limb Anatomy course will be voluntarily recruited for participation. Students will be randomized to one of two groups-those that will be exposed in a controlled environment to transverse sections of a plastinated leg model during the course and those that will not. Prior to the course, students will be administered a validated Mental Rotations Test to assess their spatial visualization abilities and a pre-test requiring identification of 10 anatomical structures on MRI. The same test will then be re-administered to both groups one week after completion of the foot and ankle component of the course and three months after completion of the course.

The research questions to be answered:

1. Will exposure to cross-sectional models of the foot and lower leg improve the accuracy of identification of anatomical structures on MRI?
2. Does accuracy relate to inherent visualization abilities of study participants?
3. Are the visualization abilities of male students better than females?

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Using the Wellness Recovery Action Plan (WRAP®) and Clubhouse Model to Educate Faculty and Students about Mental Illness and Community-Based Approaches to Holistic Treatment

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Americans spend 317.6 billion dollars a year on mental illness, according to the most recent statistics. Lost earnings due to disability account for over half of this sum. This problem is made worse by a shortage of preventive services and psychiatric care. A wellness program focused on self-management of psychiatric symptoms could be an effective replacement for difficult-to-find mental health services and reduce the number and length of psychiatric hospitalizations.

We examined how the use of the Wellness Recovery Action Plan (WRAP®), at a Clubhouse International-accredited house called Passageway, influences participant wellness. The participants' pretest results demonstrated poor utilization of mental health self-management skills – for example, having an action plan for returning to a state of wellness when symptoms worsen. Our hypothesis was that the same survey, delivered after completion of the course, would demonstrate that participants have learned how to identify triggers, understand when their illness is becoming more severe, and to implement a plan to keep them safe when they are most symptomatic. Additionally, we hypothesized that participants' overall sense of wellness would be increased after completing the WRAP®.

Posttest results demonstrated that participants did improve knowledge of their triggers, and understand when their illness is becoming more severe. There were no changes in ability to implement a plan to keep them safe when they are most symptomatic. Qualitative data were very positive regarding the perceived outcomes and the achieved outcomes of the course. Three and six month post-course data are pending.

Presenting Author Index

 # = Resident
+ = Undergraduate