IUPUI Life-Health Sciences Internship Program

Spring 2013 Poster Session

Friday, April 12, 2013
3:00 PM—5:00 PM
VanNuys Medical Science Building Atrium
Welcome to the IUPUI Life-Health Sciences Internship Program Spring 2013 Poster Session.

The Life-Health Sciences Internship Program connects IUPUI life and health sciences undergraduates with research internships on and near the IUPUI campus. This program allows students to explore their career objectives and future career pathways, while also fostering valuable professional connections between students and faculty and staff. The students belong to a community of interns and mentors who support one another throughout the research experience and beyond. This program is funded by an IUPUI Commitment to Excellence grant.

Life-Health Sciences Internship students represent 27 different majors and minors spanning seven schools on the IUPUI campus. Many of these undergraduates have career goals involving research, medicine, dentistry, occupational therapy, physical therapy, and pharmacy. These internships are an excellent stepping stone for future research and graduate study.

Mentors represent the Indiana University School of Medicine, the Indiana University School of Dentistry, the Indiana University School of Health and Rehabilitation Sciences, the Indiana University School of Nursing, Methodist Research Labs, and the pharmacy department of Indiana University hospital (Indiana University Health). These professionals are providing invaluable experiences for undergraduate students and mentoring the next generation of scientists, researchers, and health professionals.

This program includes summaries of the posters presented and work completed by our interns. Thank you for joining us today!

Brandi Gilbert
Director, Life-Health Sciences Internship Program
LIFE-HEALTH SCIENCES INTERNSHIPS

Thank you to our 2012-2013 participants:

Interns

Brandon Ball
Kiran Bassi
Kelly Biro
Corinne Blackburn
Devin Bready
Lyndsey Brown
Megan Bryant
Mark Canner
Kevin Caruana
Felix Casiano
Shannon Cook
Brittni Cox
Sandeep Dhadwal
Hardeep Dhillon
Emily Doan
Chelsea Dodge
Emily Donovan
Josh East
Christian Egly
Andrew Engle
Monica Feustel
John Fierst
Chelsea Furnish
Vicky Gichina
Amber Goad
Laura Green
Juan Guzman

Kimberly Ho-A-Lim
Trung Hua
Emily Jones
Abdul Khan
Sarah Knefelkamp
Jessica Leitzell
Nicholas Lesch
Ashley Lewis
Victoria MacLain
Stephanie Metcalf
Drew Mitchell
Kyle Moes
Natasha Morehouse
Zia Nuss
Shivani Parikshak
Bhavmik Patel
Felicia Precht
Mariam Qureshi
Victoria Rarity
Katelyn Schneider
Sydney Skopos
Jennifer Spatt
Thu-Thao Starkey
Ronne Surface
Javed Syed
Joel Tinder IV
Tyler Unsicker
David Wheaton
Eric Wolf

Vision

The Life-Health Sciences Internship Program connects talented IUPUI undergraduate students in the life and health sciences with enriching experiences in laboratories, research projects, and other professional experiences on the IUPUI campus and in campus-affiliated locations.

Mission

To educate, engage, and enlighten IUPUI life and health sciences undergraduates through on-campus internship experiences. We seek to achieve this through the following means:

1. Seeking out and arranging high quality internship opportunities in relevant fields.
2. Nurturing mentor and intern relationships through structured meetings and gatherings.
3. Providing opportunities and support to present work.

The IUPUI Life-Health Sciences Internship Program is funded by the Indiana University Commitment to Excellence Grant.
Intern: Eric Wolf  
Major: Biomedical Engineering  
Mentor: Robyn Fuchs  
Department: Physical Therapy

Investigating Novel Proteins Involved in Regulating Bone Formation

Osteoporosis is a skeletal disorder characterized by compromised bone strength and an increased risk for fracture. The aim of our work was to investigate two novel proteins preferentially expressed in cortical bone tissue that may be involved in regulating bone formation through canonical Wnt signaling. Our goal was to evaluate how bone tissue responds to mechanical loading using a novel loading technique in mice deficient in the extracellular matrix proteins periostin and sFRP4. The right forearm of 16-week old male and female mice was loaded using a 2-Hz haversine waveform, 180 cycles/day, 5 days per week for 2 consecutive weeks. The peak load applied to the forearm was 2.5N. The axial loading model creates new bone formation on medial surfaces where the bone tissue experiences the highest amount of strain. On the 4th and 10th day of loading the mice were injected with the fluorochromes calcein (green color) and alizarin (red color), which bind to regions actively undergoing bone formation. After loading was completed the ulnae were excised and prepared for dynamic histological analyses. This process involves embedding the bones in plastic, followed by cutting 6-micron thick sections that are mounted on glass slides. The bone sections were imaged using a fluorescent microscope, after which they were analyzed to determine how much bone was formed over the 2-week loading period. Findings from this study will provide insight into the molecular mechanism of how bone tissue responds to mechanical loading. We also evaluated the skeletal phenotype of a non-loaded skeletal site in these same mice. The femur was excised and imaged using small animal dual energy X-ray absorptiometry (DXA) to calculate bone mineral content, and X-ray micro-computed tomography (microCT) to evaluate bone structure and determine estimated bone strength. After imaging, the femur was mechanical testing in 3-point bending to determine bone strength.

Thank you to our 2012-2013 participants:

**Mentors**

- Dr. Matthew Aalsma  
- Dr. Imranul Alam  
- Dr. Emily Blue  
- Ms. Sara Brown  
- Dr. Angela Bruzzaniti  
- Dr. Timothy Corson  
- Dr. Jeffrey Crabtree  
- Ms. Sharon Cromer  
- Dr. Linda DiMeglio  
- Mr. Kevin Fryling  
- Dr. Robyn Fuchs  
- Dr. David Gilley  
- Dr. Richard Gregory  
- Dr. Brenda Grimes  
- Dr. Andy Hudmon  
- Dr. Leslie Hulvershorn  
- Dr. Shoji Ichikawa  
- Dr. Melissa Kacena  
- Dr. Ann Kimble-Hill  
- Dr. Komal Kochhar  
- Dr. Murray Korc  
- Dr. Tim Lahm  
- Dr. Emily Liflick  
- Ms. Nikki Mehdiyoun  
- Dr. Marc S. Mendonca  
- Ms. Elizabeth Molnar  
- Ms. Mary Ellen Nottage  
- Dr. Alexander Obukhov  
- Dr. Mary Ott  
- Ms. Pamela Perry  
- Dr. Irina Petrache  
- Dr. Lyne Racette  
- Dr. Alexander J. Radnovich  
- Dr. Jill Reiter  
- Dr. Zeynep Salih  
- Dr. George Sandusky  
- Dr. Arlene Schmid  
- Dr. Patricia Scott  
- Dr. Li Shen  
- Daniel Silva  
- Dr. Fengyu Song  
- Dr. Yuichiro Takagi  
- Dr. Hiromi Tanaka  
- Dr. Jennifer Taylor  
- Dr. Homer L. Twigg III  
- Dr. Jingyun Wang  
- Dr. Fletcher A. White  
- Dr. L. Jack Windsor
Deficits in the Medial Prefrontal Cortex in Youth at High Risk for the Development of Substance Use Disorders

Recent addictions risk neuroimaging research has suggested abnormal hyperactivation in the prefrontal cortex (PFC) and hypoactivation in the amygdala during exposure to emotional stimuli in young adults at familial high risk for the development of substance use disorders (SUDs). We hypothesized that FHR youth would also demonstrate lower amygdala and higher medial PFC activity when processing emotional faces, compared to controls. Non—substance abusing 10-14 year olds with a paternal history of an SUD and externalizing psychopathology and healthy matched comparison were tested on a facial-emotion matching task during an fMRI scan. In this task, subjects matched faces by emotions (e.g. angry, anxious) and performed a control task that involved matching shape orientation. The medial PFC is a critical structure in a neural sub-system serving risky decision-making, which is tightly linked to drug experimentation during adolescence. Hyperactivation in the medial PFC may be the result of its effort to recruit more neurons to compensate for deficient functioning. This cortical deficiency may be linked to impairments in self-regulation, affective processing and decision making, which is likely to lead to drug use and experimentation during adolescence.

Investigating Presenilin-1 Functionality in Bone Mass Regulation

Many major health concerns involve the disturbance of normal bone cell regulation that leads to decreased overall bone health and causes susceptibility to osteoporosis. Alzheimer’s disease (AD) patients have been noted to have decreased bone quality when compared to healthy individuals of the same age. Our research is focused on the protein Presenilin-1 (PS1) since studies has shown activity involving PS1 and the brains of AD patients in the formation of amyloid plaques. The purpose of this project is to investigate the role PS1 has on bone mass regulation. For these studies, we are using PS1 mice harboring a single point mutation L166P in the PS1 gene, which has previously been found to be important in AD. We compared the bone mineral densities of male and female, wild-type (WT) and PS1-L166P knockin (KI) mice over several months using a Lunar PIXImus densitometer. Our results revealed a significantly lower (p<0.05) body mineral density (BMD) in female PS1-L166P mice at months 1 (0.03304 + 0.00277 SD), 3 (0.04967 + 0.00366 SD), and 4 (0.05035 + 0.00477 SD) months of age, but not of age 2 (0.04319 + 0.00615 SD) months of age, compared to female WT mice of the same ages: 1 (0.03496 + 0.00306 SD), 2 (0.04311 + 0.00856 SD), 3 (0.05482 + 0.00438 SD), 4 (0.05579 + 0.002165 SD). For males there was no significant difference in body mass density. These findings provide a foundation for future research in which we will examine the specific effects of PS1 on in-vitro osteoblast formation and osteoclast removal of bone tissues. Findings from these studies may lead to a better understanding of the overall mechanisms that regulates bone loss associated with PS1 mutations and AD.
The cardiovascular effect of Fgf23 in chronic kidney disease

Fibroblast growth factor 23 (Fgf23) is a peptide hormone essential in the regulation of phosphate homeostasis. Patients with chronic kidney disease (CKD) have reduced ability to excrete phosphate, leading to high serum phosphate levels. In turn, Fgf23 levels rise to promote phosphate excretion in the kidney. This rise in Fgf23 levels is reported to have detrimental effects on the heart by inducing left ventricular hypertrophy (LVH). This study investigates whether having a low Fgf23 level with CKD can prevent LVH from occurring. We used juvenile cystic kidney (Jck) mutant mice as a mouse model of CKD. These mice were bred with glycosyltransferase 3 (Galnt3) knockout mice, which have impaired Fgf23 secretion. This provided double knockout mice with traits of both parents, having low Fgf23 in the setting of CKD. To promote development of hyperphosphatemia, these mice along with Jck and normal control groups were placed on a high phosphate diet at three weeks of age. After nine weeks on this diet, blood was collected for analysis. Compared to normal controls, Jck mice had high serum phosphate and Fgf23 levels, as well as an increased heart mass index. In double knockout mice, Fgf23 levels were significantly low; however, the average heart mass index for this group was less than the average for the Jck mice. These results suggest that elevated Fgf23, rather than phosphate, likely contributes to the development of LVH in CKD.

The Role of RAGE and TLR-4 Signaling in Neuropathic Pain

Pain is associated with a broad range of injury and disease and can sometimes be the disease itself. Some conditions may have pain and other symptoms surfacing from a discrete cause such as postoperative pain, whereas other conditions may have pain which constitutes it as the primary problem, such as neuropathic pain. It has recently been reported that approximately 100 million Americans suffer from chronic pain which is more than those who suffer from diabetes, heart disease, and cancer combined. In past studies, it has been demonstrated HMGB-1, an intracellular DNA binding protein important in chromatin remodeling, is part of a neuronal signaling pathway which may rely on either of the two receptors, RAGE or TLR-4. RAGE has been linked to several chronic diseases, which are thought to result from vascular damage. The activation of TLR-4 leads to a downstream release of inflammatory modulators including TNF-&alpha; and interleukin-1. It has been reported that RAGE is expressed in the primary afferent neurons, satellite glial cells (SGCs) in the DRG, along with Schwann cells. Results from other studies have indicated that HMGB-1 is synthesized and secreted into the DRG, which contributes to the development of neuropathic pain after nerve injury. Thus, blocking HMGB-1/RAGE signaling pathway may be a promising therapeutic strategy for the control of neuropathic pain.
The Role of Extracellular Matrix proteins in Regulating Bone Formation

Reduced bone strength associated with aging increases an individual’s risk for suffering a fracture. Osteoporotic fractures create devastating consequences, including increased morbidity and mortality. The aim of our work was to investigate two novel proteins preferentially expressed in cortical bone tissue that may be involved in regulating bone formation through canonical wnt signaling. Mechanical loading in the form of exercise positively alters bone structure by adding bone to regions of increased stress. At this time the genetic regulation of periosteal apposition in response to mechanical stimuli is largely unknown. We performed a mechanical loading experiment in genetically modified mice deficient in periostin and sFRP4 using an ulnar axial loading model. The right forearm of 16-week old male and female mice was loaded using a 2-Hz haversine waveform, 180 cycles/day, 5 days per week for 2 consecutive weeks. The peak load applied to the forearm was 2.5 N. On the 4th and 10th day of loading the mice were injected with the fluorochromes calcein (green color) and alizarin (red color), which bind to regions actively undergoing bone formation. At the completion of loading the ulnae were removed and embedded in plastic. After loading was completed the ulnae were excised and prepared for dynamic histological analyses. This process involved embedding the bones in plastic, cutting 6-micron thick sections, and mounting the bone sections on glass slides. Bone sections were then imaged using a fluorescent microscope, after which they were analyzed to determine how much bone was formed over the 2-week loading period. Findings from this study will provide insight into our understanding of how bone tissue responds when it is mechanical loading through activities such as jumping and running, which place high loads on the skeleton. We also harvested the femurs and tibia from these mice to perform western blot analyses to identify differences in protein expression for LRP5 and SOST between our different genetically modified mouse models.
Software Tools for Genetic Analysis of Neuroimaging Phenotypes in Alzheimer’s Disease

Alzheimer’s disease (AD) is by far the most widespread type of dementia. Since there is no cure and family history is a major contributor to this disease, the best way to combat this epidemic is through preventative measures. Therefore, research in AD genetics has received a lot of attention. The purpose of this work is to search for genetic risk factors associated with AD imaging phenotypes extracted from MRI scans. Because factors such as gender, education, phenotype, and other considerable factors can also affect imaging phenotypic measures, these aspects are taken into account when analyzing the data. This study is conducted to explore various software packages for analyzing brain imaging genetic data in AD. These software packages include PLINK and Haploview, which both are open source tools for analyzing the raw data, identifying imaging genetic associations, and visualizing the data and results. In addition, web-based tools such as LocusZoom and SNAP Plots are also employed to generate various types of plots to allow a better comprehension of the raw data and the final results.

The Mitotic Kinase, MPS1, as a Therapeutic Target in Pancreatic Cancer

The purpose of this study was to test the capacity of NMS-P715, a pharmacological inhibitor of the mitotic kinase, MPS1, to limit growth of pancreatic cancer (PC) cells. The mitotic checkpoint complex (MCC), of which MPS1 is a component, ensures correct chromosomal segregation. While many cancer cells, including PC cells, have elevated chromosome mis-segregation, it has been proposed that MCC components, including MPS1, are up-regulated in cancer cells which may help to restrain chromosome mis-segregation and keep cancer cells viable. MPS1 inhibition using NMS-P715 has been shown to abrogate MCC function leading to massively elevated chromosome instability (CIN) and cancer cell death, while normal cells were markedly less affected. In the present study we demonstrate that NMS-P715 leads to a large increase in the CIN rate in human BxPC3 and PANC-1 PC cell lines using fluorescence in situ hybridization with chromosome-specific probes. Reduction in phosphorylated serine 10 on H3 (a mitosis marker) was observed in NMS-P715 treated BxPC3 and PANC-1 cells, which is consistent with MCC disruption leading to accelerated mitosis and thus fewer cells in mitosis. Further, we demonstrate that BxPC3 and PANC-1 cells are growth inhibited by NMS-P715, while normal human adipose stem cells were less affected. Our results suggest that NMS-P715 is a potent and selective inhibitor that can lead to PC cell death. Future studies will test effects of NMS-P715 in pre-clinical mouse PC models to evaluate MPS1 inhibition as a new treatment approach for this deadly malignancy.
Atypical Binding of Calcium/Calmodulin to Calcium/Calmodulin-Dependent Protein Kinase II

Calcium/Calmodulin-dependent protein kinase 2 (CaMKII) is a multifunctional serine/threonine kinase highly concentrated in brain where it is believed to be a calcium spike integrator in plasticity; a cellular correlate of learning/memory. To understand how CaMKII contributes to these processes much effort has been expended to understand the mechanisms underlying its activation and regulation. A crystal structure of CaMKII activated by calcium/CaM indicates that the regulatory domain fully displaced from the catalytic surface; presumably permitting substrate binding and the phosphotransferase reaction. This structure differs from a crystal structure of activated CaMKII obtained from Toxoplasma Gondii (CDPK1); a structure that shows that the displaced regulatory domain moves away from the catalytic surface to allow the surface of CaM to bind to the backside of the catalytic domain. To explore the potential of CaM binding in an atypical mode to mammalian CaMKII, we expressed the human form of CaMKII (deltaCaMKII) as both wild-type (dodecameric) and monomeric catalytic fragment devoid of the regulatory domain and used biochemical assays to measure calcium/CaM interactions with CaMKII. Initially, CaM was purified and fluorescently labeled with Alexa-488 to create a tool to measure CaM binding. A complex activation protocol to prevent CaM binding to the target domain of CaMKII suggests that calcium/CaM binding to a target peptide is influenced by the presence of activated wild-type CaMKII. Furthermore, fluorescently-labeled calcium/CaM was found to bind to a CaMKII protein lacking a regulatory domain with a Kd =0.642nM. The specificity of this binding is suggested by the fact it requires calcium. In summary, our data suggests CaMKII activation by CaM leads to non-traditional modes of CaM binding to the catalytic domain and we speculate that these contribute to CaMKII’s ability to decode calcium transient frequency in neurons.

Whole Slide Image Analysis Quantification Using Aperio Digital Imaging in a Mouse Lung Metastasis Model

Digital whole slide imaging is the technique of digitizing a microscope slide to produce a digital virtual microscope slide. This digital image can be viewed in many fields of power. Many systems have software with image analysis capability. The goal of this study was to determine if the Aperio positive pixel algorithm (image analysis) could effectively quantitate metastatic mouse lung tumors in a lung section using a HE stain. Sections from a mouse lung metastasis model of 8 mice per group were evaluated: control, 50mg/kg and 75mg/kg Carboplatin. HE and Ki67 immunostain slides were scanned using the Aperio whole slide scanning system (ScanScope CS). The standard positive pixel algorithm was altered to read the HE slides. Various slides were used to validate the altered algorithm. The immunostain (Ki67) was generated using the standard positive pixel algorithm analysis. The Aperio automated positive pixel count for a Ki67 immunostain was consistent with the HE image analysis. The values decreased with a dose dependent treatment (control vs. 50mg/kg and 75mg/kg Carboplatin) and were HE: 37%, 28%, and 22%, and Ki67: 9%, 5%, and 3%. The analysis had decreasing values for both the HE and Ki67 analysis on a dose dependent drug treatment. The metastases decreased in both treatment groups compared to controls. The Aperio image analysis positive pixel algorithm allowed large areas of the lung section to be examined and not just a single 25x or 40x field like many common image analysis systems.
Evaluation of the Evidence for Nicotine as a Treatment for Cognitive Dysfunction in Schizophrenia

Cognitive function consists of thought and mental processes including perception, reasoning, sustained attention, memory, and executive functions. In the clinical syndrome of schizophrenia, significant disruption of these processes occurs in the context of perceptual disturbances, delusions, disorganized speech, disorganized or catatonic behaviors, and negative symptoms. The population suffering from schizophrenia smoke tobacco at a rate of approximately three times that of the general population. Because tobacco contains nicotine, a substance which has been shown to enhance cognitive function in healthy subjects, some have theorized that nicotine may treat the cognitive deficits seen in schizophrenia and that smoking tobacco may be a form of self-medication. The goal of this project is to determine whether there is evidence for this in the literature and, if so, to determine the quality of that evidence. A search of the literature was conducted and yielded a small number of articles covering a subset of cognitive functions in a limited number of subjects. Data reported suggests that nicotine has effects on the brains of those suffering with schizophrenia; however, the implications of those effects remain unclear due to the methods employed. Thus, further research to elucidate the effects of nicotine in those suffering from schizophrenia is needed.

Human Adipose Stem Cells are more Resistant than Pancreatic Cancer Cells to NMS-P715, a Mitotic MPS1 Kinase Inhibitor

Current chemotherapeutics involve administering drugs to patients that target rapidly dividing cells and thus can be effective against cancer cells. However this often leads to depletion of blood stem cells resulting in anemia, poor immune responses and fatigue. Thus it is necessary to develop agents that may be more specific towards cancer cells. One such agent is the mitotic MPS1 kinase inhibitor, NMS-P715, that has been shown to be selective towards cancer cells while having markedly lower effects on fibroblasts and B-cells. The goal of this study is to test effects of NMS-P715 on normal human stem cells. Human adipose stem cells (ASCs) are an abundant source of highly proliferative multipotent stem cells that maintain a diploid content in culture. Studies suggest that cancer cells are addicted to over-expression of mitotic checkpoint components such as MPS1 to keep chromosome instability within survivable limits. Our studies showed that the human ASCs were more resistant than pancreatic cancer cells to the effects of NMS-P715 in proliferation assays. Furthermore, we demonstrate that the human ASCs do not exhibit increased chromosome segregation errors after 72h treatment with 1µmol/L NMS-P715 whereas PANC-1 pancreatic cancer cells show a large increase in such errors under the same conditions. These results provide evidence that NMS-P715 may be selective towards cancer cells while having less effect on stem cells and could therefore have a favorable therapeutic index. Our studies warrant further testing of NMS-P715 in pre-clinical models of pancreatic cancer.
Intern: Megan Bryant  
**Major:** Biomedical Engineering  
**Mentor:** Dr. Yuichiro Takagi  
**Department:** Biochemistry and Molecular Biology

**Building a Molecular Machine: Reconstitution of RNA Polymerase II from the yeast Saccharomyces cerevisiae**

Gene transcription by RNA polymerase II (Pol II) accounts for almost all biological activities. Therefore, elucidation of the structure and function of Pol II is essential to understand biology. The crystal structure of Pol II from the yeast Saccharomyces cerevisiae has revealed key mechanisms of transcription regulation. However, currently, Pol II can only be obtained from yeast cells (native source). The native form of Pol II does not permit studies of Pol II mutations of our interest because these mutations are often lethal to yeast. Clearly, for further investigation of the Pol II mechanism, the generation of recombinant yeast Pol II is essential. My LHSI project aims to reconstitute yeast Pol II using the advanced protein complex expression technology. Pol II is a large multi-protein complex, molecular machine, composed of a total of 12 subunits. So far, a total of 8 genes encoding Pol II subunits Rpb1, Rpb2, Rpb3, Rpb8, Rpb9, Rpb10, Rpb11, and Rpb12 have been cloned into transfer vectors by the SLIC cloning method, followed by the production of two individual baculoviruses expressing Rpb1 and Rpb2, as well as, one expressing 6 genes (Rpb3, Rpb8, Rpb9, Rpb10, Rpb11, and Rpb12) simultaneously. These protein complexes were expressed with these viruses in insect cells followed by Ni column affinity purification, yielding a partially reconstituted RNA polymerase II consisting of 8 subunits. The results strongly suggest that the reconstitution of the 12-subunits of yeast Pol II is within our reach.

Intern: Jennifer Spatt  
**Major:** Exercise Science/ Pre-Physical Therapy  
**Mentor:** Patricia Scott  
**Department:** Occupational Therapy, School of Health and Rehabilitation Sciences

**Establishment of the Role Checklist V2:QP as a Transnational Measure of Participation in Life Activities**

In 2011, the World Health Organization (WHO) and World Bank issued a report stating a need for international research data collection on participation of persons with disabilities. In response, five researchers from Switzerland, Norway, Japan, Sweden, and the UK have joined Dr. Patricia Scott in this pilot study to use the Role Checklist V2: Quality of Performance (RC V2: QP) to collect transnational data. The purpose of this research is to pilot the RC V2: QP: Collect data cross-culturally on the past, present, and future participation in roles; participants values of these roles; and the participants rates of quality of performance of these roles to determine patterns of role participation. This data collection is a response to the expressed need for information about participation patterns of subgroups, satisfaction with ones participation in valued roles, and rehabilitation needs to improve desired role participation. Progress includes the translation of the English version of the RC V2: QP into German, Japanese, Norwegian, and Swedish, and the Norwegian version is operational on REDCap (a research database system that is available through the Indiana Clinical and Translational Services Institute (CTSI)) and undergoing final modification for online administration. The next steps include translating the software to accommodate the five versions, loading the translated versions, establishing construct validity for translated versions, obtaining data to support online administration, and demonstrating capacity to aggregate data for within/between/and across countries. This project shows initial feasibility to meet the objective of Recommendation 8 of the World Report on Disability.
Intern: Sydney Skopos  
Major: Biology, Neuroscience  
Mentor: Dr. Shoji Ichikawa  
Department: Endocrinology

Generation of Klotho Conditional Knockout Mice

The Klotho gene encodes a co-receptor for fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate homeostasis. Klotho is expressed in the distal tubules of the kidneys and parathyroid glands. To understand the function of Klotho and its interaction with FGF23 in those tissues, we generated conditional Klotho knockout mice. Knockout mice are genetically engineered to have specific inactivated genes. Artificial DNA is inserted into the genes, causing this inactivation. The function of these inactivated genes could then be determined by studying the effects of the loss of the genes in the mouse. In this study, conditional gene knockout was utilized to inactivate the Klotho gene in specific tissues using the Cre-Lox recombination system. The conditional allele was transmitted from chimera mice to establish a stable Klotho mouse line. Subsequently, we mated our Klotho knockout mouse to a FLPe mouse in order to remove the neomycin cassette, which was used for screening of the ES cells. The resulting mice are called “floxed” mice. To test the ability of the Klotho exon to be excised by Cre recombinase, we mated these mice to an EIIa-Cre mouse, which expresses Cre in the embryo. The first pup lacking the Klotho exon was born recently. The mating is continued to obtain additional pups with inactivated Klotho for functional analysis.

Intern: Mark Canner  
Major: Chemistry, Neuroscience  
Mentor: Sara Brown  
Department: Neurophysiology, IU Health Methodist Hospital

Reducing the Incidence of Skin Breakdown in Neurotelemetry Patients

Contact dermatitis and EEG electrode pressure induced wounds are a growing concern on Neurotelemetry patients (continuous real-time video EEG monitoring in the ICU) as the utility of Neurotelemetry increases nationwide. These injuries can lead to infections and increased length of hospital stays. To identify key risk factors in Neurotelemetry patients that could help reduce and prevent the incidence of contact dermatitis, skin breakdown, and EEG electrode pressure induced wounds. Once these risk factors are identified, take proactive steps to halt or minimize the skin injury process. A study of Neurotelemetry patients is being conducted to understand the method of injury. Currently, retrospective data collection is taking place with factors such as length of recording, patient description and demographics, Braden Score, nutrition information, medical history, and electrode site description being collected. Additionally, a prospective phase of the study will include daily checks of the Neurotelemetry patient electrode sites. Following analysis of data from the retrospective phase, findings will be reviewed before moving into the prospective phase. Additionally, the current categories of data may vary based upon what data elucidates possible risk factors. Lastly, upon acquiring enough data, the results of this study are intended for publication.
Study of Telomere-Dependent Genomic Instability in Sporadic Colon Cancer

Cancer is a genetic problem caused by undesirable mutations. These mutations range through hundreds of genes acting in different ways to allow for or even create the uncontrolled and destructive growth. It has been apparent that acquisition of genomic instability is a crucial feature in cancer development. In over a decade, telomere dysfunction has emerged as having a causative role in carcinogenesis by promoting genetic instability. Telomeres are a chromosomal end-cap, which function in protecting DNA from being eroded or altered, and are essential to normal function. They do however shrink with time, which would kill off fast dividing cells like cancer were they not able to find a way to replenish the telomere sequence, and thereby become dysfunctional. Alternatively, the telomere function can be impaired by loss of various telomere-capping proteins. The purpose of this study is to determine the extent of telomere-dependent genomic instability in colon cancer. As a pilot study, a total of twenty colon cancer samples, along with corresponding adjacent non-cancerous tissues were examined. This study would be unequivocally important to the understanding of colon carcinogenesis and the adjustment of potential screening and treatments. We expect that the screening of telomere dysfunction could be beneficial for high-confident cancer risk assessment.
Indiana Area Health Education Centers

The health shortage in the United States is a growing problem; especially in Indiana itself. The numbers of physicians, dentists, mental health providers, physician’s assistants, dental hygienists, and pharmacists have all been at risk with this shortage. That is one of the main reasons the Area Health Education Centers, AHEC, in Indiana and all across America have been attempting to adjust these numbers by recruiting young students to these health careers. They encourage these same students to pursue jobs in rural areas, where there is an even greater health care shortage than in other areas. Looking at previous AHEC participants and seeing if they are currently a providing health professional can show the positive effects AHEC has on young students. Being able to hear how the AHEC programs have affected those participants career choice would give a great insight to how AHEC really works and whether it is really as beneficial as claimed. Discovering the best way to learn this insight is essential to the success of future research in this area.

Relationship between the lower respiratory tract Microbiome and Alveolar chemokine and cytokine concentrations

The relationship between lung microbiome and inflammatory mediators, both at baseline and in chronic lung disorders, is an area of intense study. Its likely that resident lung bacteria influence the cytokine/chemokine milieu in the alveolar space. Analysis of the microbiome is complicated by potential contamination of specimens obtained by bronchoalveolar lavage (BAL), which may be addressable through different techniques. In this study, we compared the relationship between the microbiome and mediators in whole and acellular BAL. We hypothesized that acellular BAL was a better representative of a true lower airway microbiome and thus would have a stronger relationship with mediators found in BAL. Oral wash and BAL samples were obtained from 29 patients (20 HIV-, 9 HIV+). After setting aside an aliquot, whole BAL fluid was centrifuged to obtain the acellular fraction. Whole and acellular BAL underwent 16s ribosomal DNA analysis to determine the microbial community. BAL cytokine (IL-17a, IFN-γ, IL-6) and chemokine (IP-10, MIG, IL-8) were measured using a bead array assays. Acellular BAL was more distinct from oral wash compared to whole BAL. In general, there was a good correlation between chemokine concentrations in whole and acellular BAL, with whole containing higher levels. There were weak correlations between gram negative organisms in BAL and chemokine concentrations in normal subjects. In HIV subjects, the strongest correlation between inflammatory mediators and microbes present was with the gram positive streptococcus. The relationship between mediators and the microbial community was similar in whole and acellular BAL.
Increased Ischemic Cardiac Deaths in Central Indiana in Summer Months Compared to Winter Months

Cardiovascular diseases have been the leading cause of death in the United States for several decades. Despite sustained declines in the mortality rates from these diseases, the magnitude of the disease is still staggering. One large recent study, using data on hundreds of heart attacks documented in the National Registry of Myocardial Infarction, found that 53 percent more cases in winter than in summer. The primary culprit, many believe, is temperature. Cold weather narrows coronary arteries and raises blood pressure, stressing the heart. Physical strain and ruptured plaques caused by shoveling snow are also commonly cited. But in a recent study, two researchers, found that the risk increases even in warm climates. Analyzing death certificates in seven regions with different climates, Los Angeles, Texas, Arizona, Pennsylvania, Massachusetts and others found that cardiovascular deaths rose up to 36 percent between summer and winter, regardless of climate and temperatures. In this study we evaluated the incidence of ischemic cardiomyopathy in the Central Indiana area in the winter months compared to the summer months for the years 1998 to 2002. Approximately 5325 deaths were seen in the Marion County Morgue in central Indiana in this time period. There were 609 ischemic cardiac deaths seen in the summer (March 15th through October 15th) compared to 434 ischemic cardiac deaths seen in the winter (October 15th through March 15th). The deaths by years in the summer were 129, 131, 92, 127, and 130 and in the winter were 95, 96, 90, 96, and 57 respectively. In conclusion, this study was consistent with the outcome as the previous study done in multiple northern and southern cities in the country.

The Role of EMMPRIN in VEGF Signaling in Response to Cigarette Smoke

Emphysema is a complex and devastating pulmonary disease whose progression is enhanced by degradation of the lung matrix by metalloproteinases. Matrix metalloproteinase expression levels are regulated by a transmembrane glycoprotein called EMMPRIN, the extracellular matrix metalloproteinase inducer. EMMPRIN has been shown to be elevated in emphysema and is known to increase vascular epithelial growth factor (VEGF) signaling through modulating VEGF and VEGFR expression. We hypothesized that EMMPRIN KO (knock-out) mice would be partially protected from cigarette-smoke induced emphysema. Following 6mos cigarette smoke exposure, EMMPRIN KO mice developed significantly worsened pulmonary function compared to WT mice increase in lung compliance (p&l&;0.05), decrease in resistance (p&l&;0.05), and decrease in elastance (p&l&;0.05). To investigate this further, we analyzed VEGF signaling using IHC for VEGF receptors, VEGF-R1 and VEGF-R2, in the KO mice following cigarette smoke exposure. VEGF-R2 was decreased in the airways of EMMPRIN KO mice at baseline compared to mice exposed to ambient air (p&l&;0.05). However, VEGF-R1 was decreased at baseline in the airways of KO mice (p&l&;0.001) and was further decreased in KO mice exposed to 6mos of cigarette smoke. Differential analysis of the bronchoalveolar lavage revealed a marked increase in neutrophils in the KO mice exposed to cigarette smoke. These data suggest that airway inflammation and depressed VEGF-R1 expression in the airways may coordinate the loss in pulmonary function observed in these mice. Future experiments are designed to characterize the mechanism by which VEGF-R1 is depressed in the airways.
Effects of Nicotine on Streptococcus mutans Anaerobic Growth

The relationship between nicotine and dental carries is well known. We have previously demonstrated that nicotine increases biofilm formation. Nicotine’s half-life is two days; therefore, it is not easily found in the body after a short amount of time. Cotinine on the other hand has a similar molecular structure to nicotine and also has a longer half-life. This experiment specifically focuses on how cotinine affects nicotine and its binding to acetylcholine receptors. The aim of this study is to assess the biofilm formation that is produced with the mixture of nicotine and cotinine in various concentrations. The nicotine and cotinine concentrations that were used ranged from 0.25-4.0mg/mL. When the two were combined the concentrations that were used were the same for both molecules. If nicotine was 0.25mg/mL then so was cotinine. It was found that biofilm formation increased with increasing concentrations of nicotine but did not increase with increasing concentrations of cotinine. On the other hand there was an increase in biofilm formation observed when cotinine and nicotine were both used in equal concentration. Since there was not an increase in biofilm formation with increasing cotinine concentrations this supports that cotinine does not increase biofilm formation. The data that shows increased biofilm formation when using equal concentration of nicotine and cotinine supports that either cotinine does not bind to the same receptor as nicotine or that nicotine outcompetes cotinine for the receptors. This is being showed because if cotinine doesn’t increase biofilm formation by itself, it means that when both are used nicotine is binding to the receptor instead of cotinine.

Cost Benefit Analysis of Type 1 Diabetes Trial Net Recruitment

Type 1 diabetes (T1D) is an autoimmune disease that is occurring more often in individuals. Trial Net research conducts a series of studies to track the presence or later development of this disease in individuals. Individuals hear of the study by visiting the website, being recruited during hospital check-ups or signing up during diabetes walks that Trial Net attends. The purpose of this project was to analyze the cost and benefit of the different recruitment techniques associated with this T1D study. The Indianapolis center for Trial Net reaches a multitude of cities including those as far as Grand Rapids, MI. Trial Net pays for the Riley employees’ expenses during walks by reimbursing the center $70 for any new persons being screened as well as $45 for any returning persons that participate in rescreens. In the past 2 years, over 25,000 people have been introduced to the study. As the study grows, the effectiveness of this study must be analyzed to ensure that the locations and types of recruitment serve the best interest and provide the greatest benefit to the study. In total, recruitment cost came to a total of $25,893.00 while reimbursements totaled $20,210.00. Having screened 310 new members and rescreened 137, it cost the Indianapolis center $5,683.00. This project aimed to determine which recruitment technique is most cost beneficial.
Intra-rater and Inter-rater Reliability of the TransFACT: A Measure of Cognitive, Physical, and Sensory Transit Skills

There is a need for a reliable assessment tool that can be used to determine the paratransit eligibility of individuals across a full range of disabilities. But to date there are only two known assessment tools for paratransit eligibility of individuals with disabilities. These tools are limited in their use in that they are designed specifically to assess paratransit eligibility in individuals on the autism spectrum or individuals with cognitive impairments. A reliable assessment tool will make it easier for public transportation agencies to identify individuals who need paratransit services. The tool will also be critical for rehabilitation professionals assessing their patients for physical, sensory and cognitive impairments and develop interventions that enable their use of public transportation services. With positive reliability, test examiners can administer an assessment that has minimal errors and stability producing confident and consistent results that will be used for determining the paratransit eligibility of the test taker. To assess the inter-rater and intra-rater reliability of the TransFACT assessment, ten simulated participants with profiles of varying physical, sensory and cognitive impairments were studied. Each simulated participant represented a profile of disabling conditions that typically qualify individuals for paratransit services. Simulated participants offer consistent verbal responses to the examinee of the reviewers. The Inter-rater reliability of TransFACT was assessed by having three raters interview the same 10 simulated participant. The degree of concordance among raters was recorded. Intra-rater reliability was assessed by having a two rater’s interview the same simulated participant twice. The degree of concordance among multiple trials of the interview for the same subject was recorded. Only the research advisor and assistant had access to the simulated participant disability profiles, eliminating any bias in testing.
Delivering Bad News in Medical Education: An Evaluation of Methods and Assessment Tools

Delivering bad news is a daily occurrence in medical practice. However, no standard curriculum exists for delivering bad news in medical education. There are different methods for teaching communication skills to medical students or residents, as well as varying types of assessment tools to evaluate the effectiveness of these methods. Methods include, but are not limited to role-play, simulation, group discussions, virtual learning, and other specific communication protocols. Assessment tools include video-recordings, feedback from standardized patients (SP) and from faculty, self-assessments, and questionnaires in addition to other various evaluation tools. The goals of this meta-analysis were to 1) briefly describe the teaching methods and evaluation tools implemented by various institutions 2) evaluate the methods based on their effectiveness in improving communication skills within medical students and residents in order to provide a basis for the implementation of programs for delivering bad news in other institutions. After reviewing literature of various methods for delivering bad news, it is concluded that several methods must be combined to create an ideal program for medical students and residents, in addition to adequate feedback.

Indiana Clinical and Translational Sciences Institute (CTSI): Clinical Research Center and NuMoM2b Study

The Indiana CTSI is one of 60 Clinical & Translational Science Award-funded organizations by the National Institute of Health. The mission of the CTSI is to increase translational research that will improve the health and the economy of Indiana. The Indiana CTSI includes research being done at Indiana University, Notre Dame, and Purdue University to discover new patient treatments by integrating new ideas in the lab and moving them into clinical trials. In doing so, the CTSI provides aid for laboratory processing, patient recruitment, and the facilities where clinical research takes place. The main facility is the Clinical Research Center (CRC) located on the fifth floor of Indiana University Hospital. The CRC has research taking place in many different divisions such as: psychiatry, radiology, neurology, pulmonary, genetics, pediatrics, hematology/oncology, gastro, pathology, medicine, and pharmacy. One particular study that is very active at the CRC is the NuMoM2b study under the principle investigator, Dr. David Haas, OB/GYN. The purposes of this study are: to determine what maternal characteristics and environmental factors influence adverse pregnancy outcomes, identify specific aspects of placental development and function, and to set apart genetic, growth, and developmental parameters of the fetus that are linked with adverse pregnancy outcomes. The patients come in for three visits, one during each trimester. During these visits, patients answer unique sets of questions pertaining to their current trimester. Hence, when the first time mother has successfully completed her first pregnancy she will be more aware of what factors could affect her second pregnancy.
Identifying the Prevalence and Treatment of High Blood Pressures in Children with Type 1 Diabetes Cared for at Riley Hospital and Enrolled in the T1D Exchange Clinic Registry

This project aimed to assess the prevalence of high blood pressure (BP) in the pediatric population with type 1 diabetes (T1D) under the care of pediatric endocrinologists and adolescent medicines at Riley Children’s Hospital. All data used was collected through the T1D Exchange Clinic Registry. The T1D Exchange (T1Dx) Registry, begun in 2010, is a partnership between the Jaeb Center for Health Research and the Leona and Harry Helmsley Foundation. The T1Dx aims to improve understanding of T1D, improve care and lives of people with T1D and accelerate the search for T1D treatments and related technologies. The T1Dx Clinical Network consists of 67 US centers. Over 2 years the network enrolled over 25,000 individuals with T1D into a registry study, consisting of participant data collected through both medical records and questionnaires.

In this specific study, data from 775 patients (49% Males) enrolled into the T1Dx registry from our center was analyzed. Their mean age was 13.0 years (range 2.5-20 years). The average diabetes duration was 4.6 years (max 19 yrs). 64 had a systolic BP &gt;95% for age, sex, and height; 7 had a diastolic BP &gt;95% for age, sex, and height. 3 patients had both a systolic and diastolic BP &gt;95%. 10 patients had a diagnosis of hypertension, only one of whom had a high systolic BP. Our findings suggest that high BP in children with T1D is an area that warrants attention and intervention due to BP levels commonly being high, yet hypertension rarely being diagnosed.

The Effects of Hyperglycemia and Hyperinsulinemia on Protein Expression in Endothelial Colony-Forming Cells

Exposure to diabetes during pregnancy can lead to an increased risk of high blood pressure, diabetes, obesity, and cardiovascular disease later in life for infants of diabetic mothers. Endothelial colony-forming cells (ECFCs) are progenitor cells that play an important role in blood vessel growth and repair. They are isolated from the cord blood, and previously we have shown that ECFCs from diabetic pregnancies have reduced proliferation and reduced ability to form blood vessels. Glucose is transferred from the mother to the fetus during pregnancy through the placenta. In response, the fetus and pancreas must produce more insulin to counteract higher glucose levels from the diabetic mother. A microarray analysis demonstrated that MEOX2, PLAC8, and SM22a have higher expression at the RNA level in ECFCs from diabetic pregnancies compared to the ECFCs from normal pregnancies. Other groups previously found that hyperglycemia increased p65 expression. We hypothesize that hyperglycemia and hyperinsulinemia induce increased expression of PLAC8, MEOX2, p65, and SM22a. Normal ECFC cell lines from the cord blood of three infants were treated with high levels of glucose and/or insulin to test the hypothesis. The gene products were quantified by Western blotting after treatment. Hyperglycemia and hyperinsulinemia did not increase expressions of PLAC8, MEOX2, p65, and SM22a. When designing experiments in vitro they do not completely model diabetes during pregnancy. For example, maternal diabetes is associated with increased lipids in blood. A follow up experiment should be performed with longer treatments of higher levels of glucose and insulin, and the addition of lipids.
Indiana Medical Education Board Statewide Outcome Survey

It has become increasingly important to understand how family medicine residents decide where to practice after they complete their training. In the state of Indiana, we have not been collecting such information in a routine and comprehensive manner. This exit survey was designed by researchers from the Bowen Research Center to determine what these physicians were planning to do after graduation; where they were planning to practice; why they chose specific locations to work; and, for those leaving Indiana, why they decided not to stay in the state to practice. A cross-sectional survey of individuals completing family medicine residency training programs was conducted during late spring and early summer of 2012. A total of 78 graduates from the 11 Family Medicine residency programs were invited to participate on the survey, of which 77 responded and one declined, thereby yielding a 98.7% response rate. The top three reasons to practice at this location were: met my professional needs or preferences, liked the people, and meet my personal needs and preferences. The top three reasons given for not practicing in Indiana were: proximity to my family, proximity to my spouse or significant other, and climate. The top three reasons given for practicing in Indiana were: cost of practicing is reasonable in Indiana, proximity to my family, and salary or compensation.

Effect of Diabetic Medication on Human Placental Cells In Vitro

Gestational diabetes is a condition when women are diagnosed with diabetes during pregnancy. This condition causes many medical complications such as large babies, which can lead to birth injuries or risk of developing type 2 diabetes later in life. Insulin, a hormone used to control blood sugar levels, is the standard treatment for diabetes; glyburide is a common alternative oral medication that is often preferred by patients. Babies born to mothers treated with glyburide versus insulin have been observed to have increased abdominal fat. The placenta is important in transferring nutrients from the mother to fetus, which raises the question whether glyburide affects placental function. The purpose of this study was to compare the effects of glyburide and insulin on glucose consumption and the proliferation of two placental cell lines that were derived from either first trimester or term placentas. Both cell lines were grown in 6 well plates with 10,000 cells per well. Cells were treated with either 1 nM insulin or 100 nM glyburide for 24 hours in the presence of physiological normal (5.5 mM) and hyperglycemic (11 mM) glucose concentration. Cell culture media supernatants were collected and used to measure glucose consumption and to analyze any change in total cell number. No significant changes in either glucose consumption or cell number were observed between cells treated with insulin or glyburide in comparison to controls. Future studies will compare the production of growth factors in treated versus control placental cells.
Natural Cardiac Deaths in Central Indiana

Cardiovascular (CV) disease has been the major cause of death in the USA for the past 50 to 60 years; CV disease consists of many subtypes that may be fatal including: ischemic cardiomyopathy, hypertrophic cardiomyopathy, congestive heart failure, hypertensive cardiomyopathy, cardiac tamponade, cardiomegaly (morbid obesity), and heart miscellaneous (arrhythmia and myocarditis). In this study, Indianapolis’s Marion County Morgue’s database was searched to ascertain the total number of deaths that occurred over the period of 2004 through 2012; and, the results were evaluated with respect to the CV disease subtypes mentioned above. There were 13,038 deaths that were sent to the Marion County Morgue during that time frame; of these, 2,946 deaths were due to CV disease. Ischemia accounted for the majority of the CV disease deaths with 1,939 cases. This was followed by hypertensive cardiomyopathy (571) and congestive heart failure (189). Hypertrophic cardiomyopathy (89), cardiomegaly (16), cardiac tamponade (11), and heart miscellaneous (131) made up the remaining cases. A previous study done at the Marion County Morgue from 1987 to 2003, focusing on hypertensive cardiomyopathy and hypertrophic cardiomyopathy, found 165 deaths and 134 deaths, respectively. Comparing these two studies, in the same population, the incidence of hypertensive cardiomyopathy was moderately increased; however, there was little difference between hypertrophic cardiomyopathy.
Pre-Operative Axial Lengths in Children with Unilateral Congenital and Developmental Cataracts

Preoperative axial length is a critical parameter for estimating eye growth and selecting intraocular lens power for surgery in children with unilateral cataracts. However, without classifying diagnosed subtypes of cataract, previous studies have failed to reach a consensus on the inter-ocular difference (IOD) of axial length between cataract eye (CE) and the fellow eye (FE). In the current study, IOD is compared in children with unilateral congenital and developmental cataracts according to previously diagnosed subtypes. Charts of otherwise healthy patients born in 1979 through 2011 with primary unilateral cataract surgery were reviewed. All axial lengths (AL) were measured with either contact or immersion A-scan prior to ocular surgery. IOD was calculated. Cataracts were classified by surgeons during surgery into one of five subtypes; posterior lentiglobus (PL, N=27), persistent fetal vasculature (PFV, N=13), posterior subcapsular (PSC, N=7), lamellar (LAM, N=7), nuclear (NUC, N=3). NUC and PFV patients have shorter CE (IOD= -0.85; 0.51; -0.16±1.64mm); PL and LAM on average have similar CE and FE (IOD=0.03;1.01; -0.04;0.28mm). Although three of seven PSC patients had a shorter CE, the axial length in CE was longer on average (IOD=0.11;0.53mm). Among subtypes of diagnosis, axial lengths are significantly different for both CE (p=0.023) and FE (p=0.008). However, there is no significantly different IOD. Subtypes of cataract may explain the variety of IOD in unilateral cataract. IOD between eyes is variable and showed different trend for subtypes of diagnosis.

Creating a Library of ACCH Mutants to Modulate Lipid Binding

Amots are adaptor proteins which coordinate signaling that controls cellular differentiation and proliferation, and their ACCH domain is able to bind lipids with specificifity which leads to membrane deformation. Understanding the biophysical mechanisms involved in lipid binding may provide pathways to modulate protein sorting and downstream signaling events inducing cellular differentiation, cancer cell proliferation, and migration. The goal of this project is to relate the ACCH structure with lipid specificity and binding. Create a library of lysine (K) to glutamate (E) and arginine (R) to glycine (G) or E mutations in the ACCH domain. This library of mutations provides a platform to study the role of each amino acid in ACCH domain lipid binding. Site-directed mutagenesis was utilized in the ACCH domain to create the lysine and arginine mutants. Template primers for each mutant were created and incorporated to make the desired mutations in the cDNA sequence. 1) Typical mutagenesis is performed by polymerase chain reaction which includes denaturation, annealing, and extension. Denaturation and annealling temperatures were optimized based off of the GC-content and melting temperature of the primer. 2) A library of 13 K to E, 4 double K to E, 23 R to G, and 3 R to E mutants were created. Transform mutated DNA into bacterial cells for in vitro protein-lipid binding assays to determine amino acids responsible for lipid binding. In addition, transform mutations into human cells to determine in vivo mutation-related changes to cell morphology and signal transduction.
Reducing the Incidence of Skin Breakdown in Neurotelemetry Patients

Contact dermatitis and EEG electrode pressure induced wounds are a growing concern on Neurotelemetry patients (continuous real-time video EEG monitoring in the ICU) as the utility of Neurotelemetry increases nationwide. These injuries can lead to infections and increased length of hospital stays. To identify key risk factors in Neurotelemetry patients that could help reduce and prevent the incidence of contact dermatitis, skin breakdown, and EEG electrode pressure induced wounds. Once these risk factors are identified, take proactive steps to halt or minimize the skin injury process. A study of Neurotelemetry patients is being conducted to understand the method of injury. Currently, retrospective data collection is taking place with factors such as length of recording, patient description and demographics, Braden Score, nutrition information, medical history, and electrode site description being collected. Additionally, a prospective phase of the study will include daily checks of the Neurotelemetry patient electrode sites.

X-ray Sensitization by Inhibition of NK-κB and Warburg Metabolism

Pancreatic cancer is the fourth leading cause of deaths associated with cancer in the United States and is estimated to have a total of 45,220 new cases of pancreatic cancer diagnosed in the United States in 2013 and 38,460 deaths will occur as a result [1]. The present treatment options include surgery, chemotherapy, radiation therapy or a combination of the three. The five-year survival rate for pancreatic cancer is approximately 6% for all stages. This study examined the efficacy of dimethylaminoparthenolide (DMAPT) and dichloroacetate (DCA) to sensitize human pancreatic cancer cells MIA PaCa2 to radiation-induced killing. We hypothesized that since these two drugs work through two distinct molecular pathways (i.e. metabolism and NF-κB regulation) that their combination could be more effective at enhancing radiation-induced cell killing than either drug on its own. The results show that the dual drug treatment alone is cytotoxic and inhibited cell growth increasing the population doubling time of MIA PaCa2 cells from 17.5; 1.2 hours for MIA PaCa2 and 20.6; 1.5 hours for DCA to 71.1; 25.9 hours for the dual treatment. The dual treatment also decreased plating efficiency from 0.47; 0.07 for MIA PaCa2 and 0.38; 0.06 for DCA to 0.28; 0.04 for dual treatment. Finally DCA and DMAPT treatment significantly enhanced radiation induced cell killing of MIA PaCa2 cells after 5 Gy from SF = 0.18; 0.01 to 0.096; 0.009. While experiments are still in progress, we have also observed similar enhancement of radiation-induced cell killing by DCA and DMAPT at other radiation doses. Our data indicates that the combination of DVA and DMAPT may have potential to enhanced radiation-induced cell killing of human pancreatic cancers.
Juvenile probation officers’ opinions regarding type of insurance and cost as barriers to mental health services for justice-involved youth

Purpose: Justice-involved youth are at high risk for mental health problems. Since most court-involved youth are involved with probation we sought to get juvenile probation officers’ opinions of cost can be a barrier to receiving mental health services for clients. Specifically, our goal was to see if insurance status, Medicaid vs. private, affected connection to appropriate care. Methods: Thirty juvenile probation officers recruited from 18 counties completed qualitative interviews. Interviews ranged from 15-67 minutes and assessed how juvenile probation officers were engaged in their work, experienced job burnout, and their connection to mental health care for their clients. We transcribed digitally recorded phone calls and then coded transcripts via qualitative coding software, Atlas. Results: Over half (56.7%) of participants stated high cost and inability to pay for mental health services were barriers to receive mental health services. Medicaid coverage was more common than private. Further, although the majority of clients were on Medicaid, it is accepted by a limited number of providers. Lastly, we found that this is easier to pay for services if the client is covered by Medicaid rather than private insurance. Conclusions: Juvenile probation officers viewed high costs and lack of insurance as major barriers for receiving mental health services. Further, Medicaid is only accepted by a few providers, which limits options for treatment. Lastly, unlike private insurance, Medicaid does not have the ability to deny coverage for treatment. These nuances may affect outcomes for justice-involved youth and has implications for their mental health and future offending.

TRPC6 inactivation kinetic is independent from the rate of DAG decay

Transient Receptor Potential Canonical (TRPC) proteins form plasma membrane cation channels that are permeable for Ca2+ and Mn2+. TRPCs are activated by agonists of G-protein coupled receptors (GPCRs) in a PLC dependent manner. There are 7 members in the TRPC subfamily (TRPC1-7). The TRPC6 channel is widely expressed in vascular smooth muscle where it contributes to regulating vascular tone. When activated by histamine via the H1 receptor (H1R), TRPC6 activity robustly increases, but then decays over time despite the continuous presence of the agonist. It was demonstrated that the TRPC6 channel activation directly depends on diacylglycerol (DAG, (1)), a product of PLC-mediated hydrolysis of PIP2. However, the mechanisms underlying TRPC6 channel inactivation are not fully understood. We hypothesized that TRPC6 inactivation rate correlates with the rate of DAG decay. We used the human embryonic kidney (HEK) cell expression model to investigate the relationship between the intracellular DAG concentration and TRPC6 activity. We found that the histamine-induced DAG increases, assessed by a fluorescence imaging approach, were transient in H1R expressing HEK cells, suggesting that desensitization of H1R takes place in the presence of histamine. Interestingly, we observed that Ca2+ influx through TRPC6 channels persisted even after DAG was metabolized in HEK cells. We conclude that the kinetics of inactivation of Ca2+ influx through TRPC6 did not correlate with the kinetics of DAG decay. We propose that the inactivation of TRPC6 channel activity in the presence of histamine might be attributed in part to H1R desensitization. Since TRPC6 activity persists longer than DAG can be detected in the cells, we also propose that DAG surges are important for triggering TRPC6 activity, whereas only small levels of DAG, below our fluorescence system sensitivity, are required to maintain the channel activity. Understanding the molecular mechanisms underlying TRPC6 channel inactivation may be important for developing novel therapeutic approach for treating vasospasm.
Thrombopoietin: A Novel Osteoinductive Agent

Critical-size defects in bones require the use of grafts. Unfortunately, grafts have limitations. To improve bone formation, many clinicians now use bone morphogenetic proteins (BMP), particularly in critical-size defect regeneration. However, multiple side effects of BMP treatment have been uncovered. Here we show the ability of thrombopoietin (TPO), the main megakaryocyte growth factor, to heal critical-size femoral defects rodents. 5mm or 4mm segmental defects were created in the femur of Long Evans rats or C57BL/6 mice, respectively. The defects were filled with a bioabsorbable scaffold which was loaded with recombinant human TPO, BMP-2, or saline, and held stable by a retrograde 1.6 mm intramedullary Kirschner wire (rats) or 23G needle (mice). Xrays were taken every 3 weeks in rats and weekly in mice. Animal were sacrificed at 15 weeks, at which time micro-computed tomography (mCT) and histological analyses were performed. The results observed in mice and rats were similar. The saline control group lacked a bridging callus. Both the BMP-2 and TPO groups healed the defect, although bridging callus was evident at earlier times in the BMP-2 groups. However, the TPO groups showed a much more remodeled and physiologic contour on both Xray and mCT. mCT and histological analysis confirms that compared to BMP-2, TPO-treated specimens have a thicker cortex but smaller diameter and smoother contour. TPO appears to restore the original bone contour by stimulating osteoblastogenesis, allowing for periosteal bridging and stabilization to occur, while simultaneously stimulating osteoclast formation. Thus, TPO may serve as a novel bone healing agent.

Teens Having Capacity to Consent to Research (THiNCCR): A Pilot Study

Little scholarly literature exists to address the need for standardized assessment of adolescents as potential research subjects. Adolescents as a group are archetypally considered a vulnerable research population due to variation among individual cognitive developments; thus, a great need exists among clinical researchers to establish a framework that addresses needs of the individual participant. In this way, a structured interview and expectation for quality of response might bolster adolescents understanding of research protocol during the process of consent. Goals of this pilot study include: (1) to examine psychometric properties of the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) as it is adapted to evaluate adolescent research participants, (2) to compare MacCAT-CR performance among study participants, (3) to compare the MacCAT-CR with other concise competency assessment instruments including Rapid Estimate of Adult Literacy in Medicine (REALM), the UCSD Brief Assessment of Capacity to Consent (UBACC), and the Evaluation to Sign Consent (ESC) Form. Three hypothetical studies, including a biobanking study, an STD screening study, and a pharmaceutical clinical trial, serve as example research projects that involve the participation of adolescents (defined here as 14 to 21 years of age). Overall, this study serves to benefit both clinical researchers and adolescents as it supports the validity and reliability of specific research consent capacity measures, improving future consent procedures and reducing research risks for adolescents. This study correlates with previous research focused on adolescent medicine, evaluation of decision-making capacities, and community-based adolescent research in Indianapolis, Indiana.
The Effects of Aging and Radiation on Megakaryocyte-Mediated Osteoblast Proliferation

The interaction of cells of the megakaryocyte (MK) and osteoblast (OB) lineage is highly important for the formation and maintenance of bone. Common clinical problems involved with bone homeostasis include: osteoporosis due to loss of bone mass associated with aging, bone fractures or breaks, cancers, and various other bone diseases. An understanding of the relationship of cells in the MK and OB lineages involved in bone homeostasis, particularly during stress or aging, can lead to the development of innovative treatments to the aforementioned clinical problems. There were three hypotheses developed for this study. Hypotheses: A) Aged MKs are less efficient in stimulating OB proliferation and bone formation than young MKs; B) Aged OBs are less responsive to MK-induced OB proliferation than young OBs; and C) Radiation increases MK-mediated OB proliferation. To begin testing these hypotheses, we first cultured neonatal calvarial OBs alone, with fetal liver MKs, with MKs derived from the bone marrow of young (3-4 month old) mice, and MKs derived from aged (27 month old) mice and found that young MKs were significantly better at stimulating OB proliferation (p=0.0003). Next, we attempted to study the effects of radiation on OB proliferation; however, MKs expanded from irradiated mice were not viable. In future studies we will culture young and aged OB with fetal liver MKs and assess OB proliferation. Similarly, in future studies we will examine irradiated and non-irradiated OBs co-cultured in the presence or absence of fetal liver MKs and will show whether an increase in OBs in irradiated mice was due to an increase in OB responsiveness to MKs.

The Effects of Yoga Based Therapy on Balance and Posture Post-TBI: a case-study

Millions of Americans suffer from traumatic brain injuries (TBI) and subsequent disabilities resulting from TBI. The prognosis for these disabilities, even with treatment, is sometimes bleak. Recently, yoga therapy has been considered as a hopeful possibility to treat brain injuries and the accompanying disabilities. The overall goal of this particular yoga therapy case-study was to create a routine of postures and breathing exercises to facilitate post-rehabilitation life for a person with TBI. The goal of this single-subject design study was to 1) assess change in balance and balance confidence variables for one person with TBI who completed 8 weeks of yoga therapy and 2) use qualitative data to evaluate perceived changes in balance and posture. The yoga sessions consisted of 60 minute periods twice a week and were taught by a yoga therapist. The sessions took place either at the Indiana University Rehabilitation and Integrative Therapy Lab, the yoga instructor’s yoga studio, or the participant’s home depending on the transportation made available to them. Assessments for this study were completed pre and post yoga sessions and included various aspects of the patient’s medical history, orthostatic symptoms, use of devices, and common rehabilitation scales such as balance self-efficacy, balance, falls/fear of falling. The results of this single subject showed an improvement in balance and balance self-efficacy scores. Qualitative data support the change in scores. Yoga after TBI appears to have successful results for this individual and should be further explored.
**Effects of 17β-Estradiol (E2) on Gremlin 1 Expression in Pulmonary Arteries of Rats with Hypoxia-Induced Pulmonary Hypertension (HPH)**

HPH is a progressive disease characterized by high blood pressure in the lungs. If left untreated, HPH leads to right heart failure and death. Pulmonary hypertension is characterized by thickening and remodeling of pulmonary arteries. E2 exerts protective effects on pulmonary artery remodeling in HPH; however, the mechanisms of E2 action in the pulmonary vasculature have not been fully characterized. We hypothesized that E2 decreases the hypoxia-induced increase of the pro-remodeling protein gremlin 1 in the pulmonary vasculature of HPH rats. Male Sprague-Dawley rats were exposed to 2 weeks of hypobaric hypoxia (Patm = 382 mmHg) or room air. Subgroups of hypoxic rats were treated with E2 alone (75 mg/kg/d via subcutaneous osmotic minipumps) or with E2 plus the E2-receptor antagonist fulvestrant (3mg/kg/d).

Following experimentation, lungs were harvested, paraffin-embedded, and sectioned into 4 mm slides. Immunohistochemistry for gremlin 1 was performed. As expected, hypoxia-exposed rats demonstrated increases in right ventricular systolic pressure and hypertrophy. This was significantly attenuated by E2 treatment. We noted a significant increase in pulmonary artery wall thickness in hypoxic animals, consistent with hypoxia-induced pulmonary vascular remodeling and accompanied by significant increase in gremlin 1. E2-treated rats, but not E2 plus fulvestrant-treated animals, exhibited a decrease in gremlin 1-positive pulmonary endothelial cells, consistent with a receptor-dependent protective E2 effect on pulmonary artery remodeling. This effect was attenuated in rats co-treated with E2 plus fulvestrant. E2 receptor-dependent inhibitory effects on Gremlin 1 expression in pulmonary artery endothelial cells may be an underlying mechanism on E2-mediated protection from HPH.
Identifying Blood Vessels in Xenopus Laevis

The formation of blood vessels is needed by blastema tissue to provide nutrients and growth factors, which support the growth and differentiation of blastema cells. The goal of the study is to examine the formation of blood vessels in Xenopus tissue at different lengths of time post amputation. With this information, new insights into tissue regeneration may be found that provide information as to the success or amount of regeneration possible in Xenopus. Xenopus laevis was utilized in the study at a stage sixty froglet. The Xenopus samples used in the research were amputated at the level of the tibia and fibula. Tissue samples were collected at one, five, seven, and twelve days post amputation. These tissue samples were then treated with Hematoxylin and Eosin stain, Elastic Stain, and Trichrome stain. The stained slides were then qualitatively analyzed in order to observe the progress of Angiogenesis, as well as the basic structures of the blastema tissue, specifically blood vessels.

American College of Sports Medicine: American Fitness

Unhealthy lifestyles is a growing problem in the United States. The American College of Sports Medicine creates an annual report by collecting data from the top 50 metropolitan areas in the United States. From the data collected, the metropolitan areas are ranked and shown their specific strengths and areas of improvement in order to provide a good indication of the individual and community health of each area as well as the United States.
Emotional Expression Deficits in Youth at Familial High Risk for the Development of Substance Use Disorders

Recent longitudinal studies demonstrate that addiction risk may be influenced by a cognitive, affective and behavioral phenotype that emerges during childhood. Relatively little research has focused on the affective or emotional risk components of this high-risk phenotype. Non-substance abusing youth (N = 19; mean age = 12.2) with a paternal history of a substance use disorder and externalizing psychopathology and demographically matched healthy comparisons (N=18; mean age = 11.9) were tested with the Expression and Emotion Scale for Children (EESC). The EESC is a parent-report scale used to assess emotion awareness and expression differences between groups. An independent-samples t-test was conducted to compare emotion regulation for high and low-risk youth. High-risk youth scored higher (p<0.05) in all three subscales of the EESC: Positivity, Negativity: Emotional Lability and Negativity: Flatness. The most pronounced between group difference occurred in the Negativity: Flatness scale, with FHR youth (mean = 22.3, SD = 7.8) scoring much higher than the HC participants (mean 12.1, SD = 2.9; t = -5.25 p = 0.001). A parent rating scale assessing emotional expression differentiated groups of children at high and low risk for the development of substance use disorders. Further work is needed to understand the implication of emotional expression deficits on the development of addictive disorders.

Selective Bacteriophage Screening to Target Oncogenic GaqQ209L Protein

Uveal melanoma is the most common intraocular cancer in adults with 1,500 patients diagnosed every year in the United States. The cancer is highly chemoresistant and metastasizes to other parts of the body, usually the liver where it is almost universally fatal. The goal of this project is to find peptide sequences specifically binding to GaqQ209L- a mutant oncoproteindriving uveal melanoma in a 80% of uveal melanoma cases. The method of bacteriophage display was used to find peptide ligands that will bind to GaqQ209L; subtractive panning was used against Gaq Wild Type to increase specificity. The binders were tested using a phage ELISA. This screening is in progress. In the future it is hoped to find a peptide sequence that is specific to oncogenic cells and to ultimately kill the oncogenic cell without killing any other cells.
Indiana Clinical and Translational Sciences Institute: Children’s Clinical Research Center

The Indiana Clinical and Translation Sciences Institute (CTSI) is one of 60 National Institute for Health (NIH) funded centers that works to facilitate the translation of laboratory discoveries into clinical trials to aid in developing new patient treatments and enhancing the field of medicine. The CTSI supports both pediatric and adult research and partners with various public and private institutions. The newest addition to the CTSI is located in Riley Hospital for Children and is the only freestanding children’s clinical research center in the state. It is a satellite unit of the Clinical Research Center (CRC) located in University Hospital. The Children’s Clinical Research Center (CCRC) is strictly an outpatient facility. Nursing staff is not provided. There is one clinical manager onsite that is a registered nurse in the case of an emergency, but not to provide research support. Protocols accepted by the CCRC are governed by the Institutional Review Board (IRB), and follow the same approval process as protocols accepted by the CRC (approval by management, laboratory, nursing staff, and the CRC advisory committee). The CCRC can accommodate research from many different disciplines and enables researchers to process and store specimens onsite. The CCRC is set to open spring of 2013.

Reduced Central Field Sensitivity in Glaucoma Patients With Normal 10-2 Visual Fields Compared to Healthy Controls

To determine whether changes in central visual function exist in glaucoma patients who have abnormal peripheral visual fields, but who still have normal central visual fields. Patients had a diagnosis of POAG, abnormal Standard Automated Perimetry (SAP) 24-2 and normal SAP 10-2 results. Controls had healthy eyes based on a complete ophthalmological examination and normal SAP 24-2 and 10-2 results. Mean Deviation (MD), PSD, number of abnormal Total Deviation (TD) and Pattern Deviation (PD) points, and the number of TD and PD points at 1% were evaluated. POAG patients were older than controls and had lower foveal thresholds. Lower foveal thresholds may be due to the significant difference in age between the groups. POAG patients had worse MD values than controls (-1.6 &plusmn; 2.6 dB; 0.34 &plusmn; 0.9 dB; p = 0.04), higher PSD values (1.4 &plusmn; 0.1 dB; 1.1 &plusmn; 0.2 dB; p = 0.001), a higher total number of abnormal PD points (7.2 &plusmn; 2.6; 3.5 &plusmn; 3.0; p = 0.01), and a higher number of PD points at &lt;1% (1.4 &plusmn; 0.7; p = 0.02). No significant differences were found in total number of abnormal TD points (15.6 &plusmn; 24.2 dB; 0.8 &plusmn; 1.3 dB; p = 0.07) and number of TD points at &lt;1% (7.2 &plusmn; 19.5; 0.1 &plusmn; 0.3; p = 0.25). Normal 10-2 results differ in POAG patients compared to normals, showing subtle loss in central visual function in glaucoma patients.
Cannabis Use in First-Episode Psychosis: A Retrospective Review

Marijuana (cannabis) is one of many illegal and addicting drugs commonly used by individuals diagnosed with psychotic disorders. Cannabis use in those with schizophrenia has been found to have notable effects on the cognitive and social functioning of the patient as well as the presence and severity of symptoms. This retrospective review examined the prediction that individuals diagnosed with a schizophrenia spectrum disorder who use cannabis tend to perform better socially, with superior executive functioning, poorer working memory, and increased positive symptoms, as measured by various assessments. Upon conducting analyses based on the subjects' use of cannabis, it was found that the data supported the proposed hypothesis, in that the users performed better socially, with more positive symptoms, and worse than the non-users on tasks involving memory. However, these results were not statistically significant. This review revealed the potential effects of cannabis use on those diagnosed with a psychotic disorder.

Using siRNA to Knock Down a Gene and Investigate the Effects on Cell Migration

Cell migration is an important characteristic of cancer cell metastasis. Since patient mortality is frequently due to distant metastases, preventing metastasis could prolong patients’ lives. In previous experiments, MDA-MB-231 cells, a highly invasive breast cancer cell line, were treated with purified triterpene from medicinal mushroom Ganoderma lucidum (GDNT), which reduced cell migration. By the DNA microarray analysis, the genes Ezrin and Coronin 1A were identified to be down regulated by GDNT. To determine if these genes are involved in cell migration, we performed an siRNA transfection of these genes in MDA-MB-231 cells. Transfected cells were subjected to cell migration analysis in Boyden chambers and Western Blotting was performed to confirm gene knockdown. No significant inhibition of cell migration was found between Coronin or Ezrin silenced cells and control. Further studies need to be performed to optimize siRNA silencing of Coronin and proper staining and counting of transfected cells.
**Telomeres as a Function of Human Ovarian Carcinoma**

Defects in telomere maintenance have been acknowledged as a major component in many human malignancies and age related diseases. Telomere dysfunction has been marked by the presence of telomere fusions (end-to-end chromosome associations) and these fusions have been suggested to be key initiators of genomic instability associated with the development of human cancers. While genetic instability initiated by telomere dysfunction has been evidenced in human breast tumors, research has yet to determine whether defective telomere activity is a fundamental phenomenon in other human somatic cancers. To investigate this topic, a PCR based assay, termed TAR (telomere associated repeat) fusion PCR was devised to detect telomere fusion in normal, benign and tumor human ovarian tissues. We found about 45% of the tumors but not normal or benign tissues contained telomere fusions. All of the tumor tissues but not normal or benign tissues had significant telomerase activity and this activity correlated with the hTERT mRNA expression. These results obtained provide evidence for the presence of telomere fusions in human ovarian tissue and suggest that defective telomeres are a functional component behind human ovarian cancers. Further application of these methods to other human somatic cancers holds invaluable potential in devising mechanisms to evidence defective telomeres as a function of human carcinomas.