INTERSECTIONS

Summer Poster Session

August 2, 2013
9:30-11:30am
Biomedical Research Building Atrium
The 2013 Intersections Poster Session at Case Western Reserve University is comprised of seven research programs focused on the biological sciences, chemistry, and social sciences that had approximately 52 undergraduate participants not only from Case Western Reserve University but also from colleges and universities around the country. Most of the programs began on May 28 and ended with the Intersections Cooperative Poster Session on August 2. The Intersections Cooperative Poster Session is pleased to share the students’ abstracts from the poster session.

The six summer undergraduate research programs comprising the Cooperative are:

- Academic Career in Engineering and Sciences (ACES+)
- Center for AIDS Research Minority HIV Research Training Program (MHRTNP)
- CWRU’s Rising Engineers & Technological Entrepreneurs (CREATE)
- Heart, Lung, and Blood (HLB)
- Independent Research with Faculty
- Provost Summer Undergraduate Research Grant (P-SURG)
- SOURCE Summer Research Program
- Summer Program in Undergraduate Research (SPUR) in Biology

Descriptions of each summer undergraduate research program can be found within this Abstract Compilation.

The SPUR Cooperative is especially grateful to the following for providing support to make the summer seminar program:

- Center for AIDS Research
- Center for Proteomics and Bioinformatics
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ACES Summer Undergraduate Research Program
The ACES program at Case Western Reserve University is part of the National Science Foundation (NSF) ADVANCE program to develop a national science and engineering workforce that includes the full participation of women at all levels of faculty and academic leadership. Students participating in this program learn new skills and gain valuable experience by contributing to ongoing research activities. ACES funded 4 students this summer. Funding is provided by Case Western Reserve University.

Designing a multi-touch system for intuitive control of nanoscale scanning probe microscopy

Michael Eze, Department of Physics and Computer Science; Michael Wolf, Department of Physics.

Scanning Probe Microscopy (SPM) is a powerful tool which has the ability to image nanostructures, measure surface topology, and map out interactions between nanostructures and the probe. By combining SPM with optical microscopy, we simultaneously measure structural and optical properties of nanostructures, such as semiconductor quantum dots. This research is aimed at developing a multi-touch system that we can use to demonstrate an intuitive interface for the optical microscopy/SPM setup based on simple hand gestures. The multi-touch screen consists of a standard LCD screen overlaid with an infrared touch frame (PQ Labs). We are developing software in python, based on open-source multi-touch platforms pyMT and Kivy, which will then interface with the SPM software in LabView or C++. Our goal at the end is to develop a multi-touch system that we can use to control the functions of the SPM by gestures, thereby creating a natural interface between the macro and nano worlds.

Project Mentor: Professor Jesse Berezovsky, Department of Physics.

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Modeling Piezoelectric Materials for Energy Harvesting

Terrell Glenn; Dr. Daniela Calvetti¹, Dr. Erkki Somersalo¹, Edrissa Gassama¹
¹Department of Mathematics, Applied Mathematics and Statistics, Case Western Reserve University

As the world becomes more technologically advanced, researchers are looking toward better, greener energy solutions for the world to utilize. Green, or renewable, energy is a provision aiming to meet the needs of the current generation without jeopardizing the lives of future generations with the harmful effects of nonrenewable energy sources. Piezoelectricity is an electrical energy that is created when a mechanical pressure or force is applied to certain materials: since the process leaves no traces of harmful chemicals and produces no bi-products, this is in principle an ideal source of energy for the future. Mathematical methods can be utilized to design more efficient piezoelectric elements and to test different compositions and geometries to find out which are most well suited for energy harvesting. My project involves understanding the mathematical description of piezoelectric materials and understanding the governing equations. Furthermore, I familiarized myself with the mathematical software package MATLAB (Matrix Laboratory) and used it to study the pairwise relationship between the 11 parameters identifying the model of piezoelectric material to find out whether they are mutually independent or show some type of correlation, using sample of virtual parameters collected by my graduate student mentor. This analysis required me to learn some elements of data mining and to become familiar with the word processing software LaTeX, routinely used for mathematical technical writing, which was used to compile the final report.

Project Mentor: Edrissa Gassama, Department of Mathematics, Applied Mathematics and Statistics
Faculty Sponsor: Dr. Daniela Calvetti, Department of Mathematics, Applied Mathematics and Statistics
Proline, a probe to understand structure-function properties of the male development transcription factor SRY

Dalilah Reyes, Department of Biology, University of Puerto Rico; Joseph Racca, Department of Biochemistry; Paul Sequeira, Department of Biochemistry; Daniel Jang, Department of Chemistry; Nelson Phillips, Department of Biochemistry; and Michael Weiss, Department of Biochemistry.

The mammalian Y chromosome encodes male-determining factor, SRY (sex-determining region on the Y chromosome) is a transcription factor and initiates male development. SRY contains a high mobility group (HMG) box domain, required for specific DNA binding and bending. The structure of the HMG box domain contains three \( \alpha \)-helices, separated by loops, a structurally conserved domain among an entire family of transcription factors. Clinical mutations in SRY are associated with sex-reversal, which can be genetically sub-grouped. Characterization of these mutations elucidates the molecular functions governing this developmental pathway. We exploit a proline mutation in an \( \alpha \)-helix, clinically identified, as probe of the structure-function relationship in the HMG box. The amino acid proline typically attenuates helices, hence its designation as an \( \alpha \)-helical “breaker”. However, this mutation, an Arg (R) to Pro (P) in the first helix of the HMG box of SRY is tolerated. Furthermore, initial DNA binding studies suggest that this mutation does not detrimentally affect DNA binding. Therefore we sought to further characterize this mutation, focusing on various faucets of HMG box structure and function. To do this, our primary methods are spectroscopic related and include: intrinsic tryptophan fluorescence, circular dichroism, and fluorescence energy resonance transfer (FRET). Similar to previously characterized inherited mutations, the R21P mutant displays a variety of moderate defects in a broad range of HMG box functions.

*Project Mentor: Joseph Racca, Department of Biochemistry*
*Faculty Sponsor: Dr. Michael Weiss, Department of Biochemistry*

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Modeling the EV71 5’ Untranslated Region IRES Consensus Structure and Determining HnRNP A1 Protein Binding Within Stem Loop VI of the IRES

John Spooney, Department of Neuroscience, Michele Tolbert, Department of Chemistry

Enterovirus 71 is a virus belonging to the picornaviridae family that uses positive strand RNA sequences for translation and replication. It has been responsible for multiple outbreaks in the past and has most recently become a problem in South East Asia. Commonly called hand, foot, and mouth disease, the virus has the ability to give a patient rashes and/or become a severely neuro-virulent disease and cause death in people who possess a compromised immune system. Upon infection the virus uses host cell proteins as ITAFs to promote translation, including the protein HnRNP A1. HnRNP A1 has been shown experimentally to bind with stem loop VI and stem loop II of the 5’ UTR. This research focuses on the consensus structure for stem loop VI and attempts to identify the exact RNA sequence within stem loop VI that HnRNP A1 binds to. Interruption of the interaction of HnRNP A1 with SLII decreases the infectivity of the EV71 virus which suggests that interruption of this same protein with SLVI may provide another therapeutic site that would reduce the infectivity of enterovirus 71.

*Project Mentor: Dr. Blanton Tolbert, Department of Chemistry*
Center for AIDS Research Minority HIV Research Training Program (MHRTP)
The MHRTP focuses on recruiting and training underrepresented minority research trainees to expand the pool of researchers in the HIV/AIDS field. The program offers research-training opportunities to qualified minority undergraduate students who are members of an underrepresented group in biomedical and behavioral research careers. Participants in the MHRTP benefit from early exposure to HIV science, continuous research training and faculty mentoring. One student was funded.

“Effects of a Peer Educator program on perceptions of sexually transmitted infections (STIs) and uptake of testing services among Cleveland adolescents”

Sharita Hill; Brynne Presser; Robert Salata, MD; Amanda Healan, PhD
Case Western University Department of Medicine, Division of Infectious Diseases and HIV Medicine

The ID Alliance recognized the need for a local sexual health intervention, in response to escalating sexually transmitted infection (STI) prevalence data among Cleveland adolescents. In 2011 more than 70% of Chlamydia and gonorrhea infections reported in Cleveland were in individuals less than 25 years old. A comprehensive community-based Peer Education program was designed to improve the understanding of STIs and encourage STI testing among adolescents ages 9-18 in a high risk northeast Ohio neighborhood. The Glenville neighborhood was identified by the Cleveland Department of Public Health (CDPH) as an area with a high burden of adolescent STIs. In 2010 there were 434 Chlamydia and 181 gonorrhea diagnoses reported for the Glenville neighborhood, making it the third highest reported Chlamydia infected neighborhood in the city of Cleveland. According to CDPH 1 in 11 Cleveland teen’s ages 15-19 had a Chlamydia infection in 2011. Peer education is a strategy that allows adolescents to educate other adolescents about relevant issues, including STIs. The outreach program was comprised of three components, a contextualized in-school class at Glenville High School that aided training and recruitment of adolescent Peer Educators, a Teen Night initiative hosted at J. Glen Smith Health Center and led by Peer Educators which encourages teens to receive STI testing along with counseling and advice about healthy behaviors, and service learning opportunities that allowed the Peer Educators to go out in the field and teach other adolescents about STIs and their prevention. In 2012 ten African American students both male and female were selected to participate in the Peer Educator program, today four of the educators remain in the program, one male and three female. On June 20, 2013 two new female students joined the Peer Education program. Research has shown that a peer education program can benefit adolescents in particular. As the program has advanced the Peer Educators have taken on a leadership role in teaching sessions; and event planning. A survey assessing Peer Educators’ knowledgebase and self-reported behavior given to Peer Educators at the start of the program, and then one year later shows increased understanding of STIs. Adolescent use of STI testing resources in Glenville and Peer Education participation in service learning was also tracked. We expect that overtime the peer education program will provide the Peer Educators and youth with whom they interact with a stronger foundation of STI knowledge, which will lead to more responsible sexual- behaviors, including use of testing resources.

Project Mentors: Robert A. Salata, M.D., Department of Medicine, Chief, Co-director of ID Alliance & Amanda Healan, Ph.D., Department of Medicine, Co-director of ID Alliance
CREATE

CREATE involves students at all levels of engineering disciplines in the real-world engineering design process. Students work full-time on projects from companies, hospitals, and professional researchers. Simultaneously, summer students receive lectures and hands-on tutorials in order to learn the necessary concepts, software, and skills required to solve the design problems. CREATE is funded by The Case Alumni Association (CAA).

Device for Improving Neonatal Transport Incubator Maneuverability

Masih Ahmed, Case Western Reserve University, Department of Mechanical Engineering; Kyle Fedorchak, University of Rochester, Department of Biomedical Engineering; Peter Shyu, University of Illinois at Urbana-Champaign, Department of Bioengineering;

Neonatal transport incubators are used for inter- and intra-hospital transport of newborns. Such incubators are often cumbersome and difficult to maneuver. The goal of this device is to improve user control over neonatal transport incubators. The proposed design includes four caster wheels, each of which is controlled by an individual stepper motor. There are four force sensing resistors built into the handlebar of the device in order to detect the user’s intended direction of motion. The intended direction is interpreted by the Arduino Uno microcontroller and relayed to the stepper motors in order to orient the caster wheels in the desired direction. This improves the user’s control over turning and maneuvering the transport incubator and prevents unwanted caster flutter and drift. Future work might include adding drive motors to two of the caster wheels in order to provide power assist. Additionally, this device can potentially be adapted for other applications including patient transport and transport of heavy equipment.

Project Mentor: Dr. Dustin Tyler, Department of Biomedical Engineering
Project Sponsor: Dr. Qin Yao, Perinatal and Neonatal Medicine at University Hospitals

Surgical Training Simulator for Operating Room

Evan Breitsch, Allegheny College, Department of Physics; Christopher Fuqua, Case Western Reserve University, Department of Biomedical Engineering; Kenneth Gibbons, Case Western Reserve University, Department of Biomedical Engineering; Alexis Schilf, Case Western Reserve University, Department of Biomedical Engineering.

In the operating room, the scrub nurses and surgical technicians need to be knowledgeable and need to react without hesitation while assisting the surgeon. Training involves general classroom education followed by six to twelve months of apprenticeship in surgery. To shorten apprenticeship time and to increase accuracy of the passing skills of the user, a training simulator was designed. The major skills the user needs to master are instrument identification, instrument placement, speed, and sufficient force when handing the instrument to the surgeon. The simulator consists of a simulated hand controlled by the Arduino Due and Raspberry Pi. The device will have multiple modes to teach and quiz the user on the main skills needed in surgery. User progress will be stored and available for instructors to review. A prototype of the device will be implemented in the Fall 2013 University Hospitals surgical nurse and technician training program.

Project Mentors: Dr. James Rowbottom, Mary Lou Kubu, MaryAnn Domanovic
Professor Mentor: Dr. Dustin Tyler
Assistive Reaching Device for Those with Limited Use of Their Upper Extremities

Remy Niman, Case Western Reserve University, Department of Biomedical Engineering; Jessica Kleinbart, Columbia University, Department of Biomedical Engineering; and Joseph Olewinski, Case Western Reserve University, Department of Biomedical Engineering.

The inability to perform simple daily tasks that involve reaching towards the face is one of the many difficulties encountered by people with severely limited use of their upper extremities. Currently, there are many devices on the market that aid patients with traditional disabilities from cerebral palsy, spinal cord injury, and other disorders of the nervous and/or musculoskeletal systems. The patient we are working with is unique because she only has one arm with limited functionality due to a fused elbow. The main objective of our device is to enable the patient to bring items to her face. By utilizing her ability to load the machine with objects and move her body and head once the object is at her face, we have created a device to perform the action of bringing objects from her hand to her face. Our solution is a two degree of freedom, servo-powered machine comprised of 3D-printed parts, Laser-Cut parts, and raw materials that is controlled by her three fingers via a control board. The device is capable of bringing finger foods, a toothbrush, and make-up accessories such as mascara and foundation to her face. We used SolidWorks Computer Aided Drafting (CAD) software to model the device, and an Arduino UNO microcontroller to communicate the control board inputs to move the components of the machine. Extensive research and calculations were involved in choosing the materials and motors that would be capable of handling the forces applied to the machine. In the future, we plan to utilize the versatility in the machine’s user interface to adapt the device for other patients with unique cases of nervous system and/or musculoskeletal disabilities.

Project Sponsor: Meghan Price, MS, OTR/L Occupational Therapist, Cleveland Clinic Children’s Hospital for Rehabilitation
Project Mentor: Dr. Dustin Tyler, Case Western Reserve University, Department of Biomedical Engineering

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Novel Neonatal Hypothermic Therapy Device

Ethan Krokonko, Bucknell University, Department of Biomedical Engineering; Elle Marcus, Case Western Reserve University, Department of Biomedical Engineering; Rian Wendling, University of Utah, Department of Biomedical Engineering

Hypothermic therapy is an emerging treatment for infants who are born with brain asphyxia. The goal of the treatment is to minimize brain damage, the main effect of asphyxia in the womb. The first insult of asphyxiation occurs during birth, which is then followed by another insult seventy-two hours later. The therapy acts to avoid the second insult and reduce the likelihood of brain injury by inducing mild hypothermia (33.5 °C) in the infant within the first 6 hours after birth. This is maintained for the 72-hour period before gradually returning the infant’s core temperature to a normal 37 °C. The current device being used at University Hospitals Rainbow Babies & Children’s Hospital is Blanketrol®. This consists of a blanket that is laid under the baby through which temperature-controlled water is circulated, changing the infant’s temperature through conduction. The system’s drawbacks include high cost, fluctuating temperature, and the requirement of a water reservoir, which eliminates any device portability. Our design aims to improve upon these limitations by using peltier thermoelectric cooling devices that can quickly and accurately cool a surface down to 8 °C using DC power. These will adjust the temperature of a platform on which the infant will lay to receive hypothermic therapy through conduction. The infant’s core temperature will be monitored using a rectal probe and the temperature of the cooling pad will be adjusted accordingly through PID control.

Project Mentor: Professor Dustin Tyler, Department of Biomedical Engineering
Project Contact: Dr. Sreekanth Viswanathan, Rainbow Babies & Children’s Hospital
An Ergonomic Book Holder for Sports Wheelchairs

**Austin Mak**, Case Western Reserve University, Department of Mechanical Engineering; **Valay Shah**, Marquette University, Department of Biomedical Engineering; and **Amanda Tong**, Case Western Reserve University, Department of Biomedical Engineering

In the United States, there are an estimated 1.6 million wheelchair users, the vast majority of which operate manual wheelchairs. Consequently, most commercial products that carry objects are designed for manual wheelchairs with permanent handlebars and arm rests, offering few options for sports wheelchair users.

Sports wheelchairs are designed to be lightweight and easy to maneuver, making them an even more convenient mode of transport for the disabled. However, this design offers little room to hold an additional load such as a student’s books. The objective of this design project is to develop a lightweight, compact, and ergonomic holder that can support twenty pounds while maintaining the mobility of the wheelchair.

Our two preliminary designs included a mechanism that pivots the book holder over the right wheel and a stationary book holder attached directly to the back of the wheelchair. The first design incorporated a metal pipe frame and a swiveling TV mount arm. However, the pivoting mechanism proved to be cumbersome and unnecessarily complex. This design was ultimately simplified to a stationary metal frame attached directly to the back of the wheelchair for practicality and ease of access.

While this backpack holder was designed originally for carrying books, it can generally be used to hold various contents including groceries, lunch and clothing. We have built a functional device that the client can begin using this fall in high school.

*Project Sponsor: Dr. Anne Marie Pace, Cleveland Clinic Children’s Hospital*

*Faculty Mentor: Dr. Dustin Tyler, Department of Biomedical Engineering*
Reduced T follicular helper (TFH) cell number and function in the elderly

Osamah Zayed Badwan, Department of Biology; Dr. David Canaday, Division of Infectious Disease

It is well known that older individuals do not respond as favorably to most vaccines compared to younger subjects. According to the CDC, there are over 20,000 deaths and 200,000 hospitalizations due to influenza each year, 90% of which were in people over age 65. The seasonal trivalent inactivated influenza vaccine remains the primary public health measure recommended by the CDC; however, this vaccine has a reduced efficacy, often below 50%, in older population that needs protection most. This indicates that a better understanding of immunologic and vaccination failure is urgently needed to develop better strategies against influenza-related morbidity and mortality in older adults. T follicular helper cells (TFH) are specialized cells that provide help to B cells to make optimal antibody titers after exposure to vaccines. These are found primarily in germinal centers of B cell follicles of secondary lymphoid organs such as lymph nodes. Distinguishing features of the TFH cells are the expression of CXCR5, PD-1, SAP, IL-21, and ICOS, among other molecules. By using flow sorting methods, TFH cells were purified from the peripheral blood mononuclear cells of 17 older (ages 66-92) and 16 younger (ages 22-35) individuals. These were incubated with a common stock of naïve B cells and mitogen for 7 days. The elicited IgG was then measured with the ELISA detection method. The number of TFH cells in the blood of older individuals is reduced by 29% (p=0.02) compared to younger ones. The function of TFH cells was determined by TFH and B cell co-culture. The older subjects’ TFH cells elicited 32% lower IgG (p=0.001) than the younger group. In conclusion, there is a reduced TFH cell number and function on a per cell basis in the elderly, suggesting that this may be an important factor for the reduced efficacy of the older immune system.

Project Mentor: Dr. David Canaday, Division of Infectious Disease

Determining Ethnicities and Genotypes Through the Use of a PCR-LDR Fluorescent Microsphere Assay

Jordan W. Bailey, Chemistry; Dr. Peter Zimmerman, Global Health and Disease; Dr. Lance Vernon, Biological Sciences; Dr. Rajeev Mehlotra, Global Health and Disease; Melinda Zikursh, Global Health and Disease; Julie Rosenjack, Global Health and Disease; Binta Jalloh, Global Health and Disease

CC chemokine receptor 5 (CCR5) is a protein on white blood cells that serve as an entry cofactor for macrophage-tropic isolates of human immunodeficiency virus-1 (HIV-1). A mutation, known as CCR5-Δ32 for it’s 32 base pair deletion in the open reading frame (ORF), exists for few individuals that is capable of preventing or slowing the rate of progression to AIDS. Homozygous individuals confer resistance to HIV-1 infection, while heterozygous individuals have a slower rate of progression to AIDS. Previous studies suggest that the presence of the mutation is race dependent where it is more commonly found in Caucasians than other racial groups. A single nucleotide polymorphism (SNP), identified in the CCR5 promoter sequence at 59029-G/A, affects the rate of progression to AIDS. Individuals homozygous for the 59029-G allele exhibit decreased disease progression by limiting CCR5 expression compared to that of 59029-A homozygotes. An individual heterozygous for the CCR5-Δ32, and the 59029-G allele, express less CCR5 than an individual heterozygous for the CCR5-Δ32, and the 59029-A allele. To determine the CCR5 genotypes of different, the DNA from the blood sample was extracted. A standard PCR amplified the target DNA. A ligase detection reaction (LDR) was performed to determine the SNPs by binding allele-specific primers upstream to conserved sequence downstream. The upstream primer includes a 5’ extension of unique TAG sequences. The downstream probe anneals to a conserved sequence to and is bound to biotin on the 3’ end for fluorescence. Quantification of fluorescent beads allows determination of the genotypes of different DNA samples at the CCR5 promoter region. These genotypes can then be compared to determine the rate of occurrence based on ethnicities.

Project Mentor: Dr. Peter Zimmerman, Global Health and Disease
Mitochondrial complex 1 deficiency leads to an increase of Cystic Fibrosis signaling markers

Patricia Belle, Department of Biology; Dr. Thomas Kelley, Division of Pediatric Pulmonology; Deborah Corey, Division of Pediatric Pulmonology; Sharon Rymut, Department of Pharmacology

Cystic Fibrosis (CF) is a disease caused by mutations in the Cystic Fibrosis transmembrane conductance regulator (CFTR), a cAMP-activated chloride channel. Studies have shown that dysfunctional CFTR is associated with mitochondrial oxidative stress and reactive oxygen species (ROS) production. The source of this mitochondrial dysfunction is not yet understood. We postulate that mitochondrial complex 1 deficiency within the electron transport system (ETS) leads to cellular phenotypes associated with CF. Complex 1 is the first electron carrier in the ETS and aids with energy production. The hypothesis of this study is that inhibition of mitochondrial function in wild type cells will lead to CF signaling markers of reduced acetylated-α-tubulin, and increased β-arrestin-2 (βarr2), GRK2, and RhoA expression. The complex 3 inhibitor Antimycin A, complex 1 inhibitor Rotenone, and FCCP, which is a de-coupler of ATP synthesis from electron transport, were examined to determine what part of the ETS is likely impacted in CF. Western immunoblotting of 9HTEo (human tracheae-bronchial epithelial) cells treated with a dosage and time curve of FCCP and Rotenone showed increases in CF expression markers, whereas, Antimycin A did not. These results suggest complex 1 is key, consistent with other studies. Correction of complex 1 with Co-enzyme Q10 (CoQ10), a cofactor that regulates electron transport, in IB3 (cystic fibrosis bronchial epithelial) cells showed correction of CF signaling profiles. Using Flipin fluorescence staining, CF IB3 cells treated with CoQ10 also showed reduction in cholesterol accumulation, which is a characteristic of CF cells. These findings suggest that disruption of mitochondrial complex 1 activity is a factor of the mitochondrial dysfunction in CF cells.

Project Mentor: Dr. Thomas Kelley, Division of Pediatric Pulmonology

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HIF and Notch noncanonical pathways affect the emergence and differentiation of cardiovascular progenitor cells

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Adaptive responses to low Oxygen (O2) tension (hypoxia) are integral to embryogenesis, tumorigenesis, and tissue ischemia. Developing embryos begin to experience a hypoxic micro environment promoting the development of the cardiovascular system. Early differentiation events focus the generation of cardiovascular progenitor cells, hemangioblasts, that are Flk-1 and Brachyury double positive, which have hematopoietic, endothelial, and cardiomyocyte potential. Our model system utilizes embryonic stem (ES) cells differentiated into embryoid bodies (EBs) mimicking early development, which can be cultured under physiologic O2 conditions. Proper signaling is required temporally for the differentiation of these cells. Hypoxia Inducible Factor (HIF) is a major transcriptional player for these events. We propose that Notch signaling pathway also plays a significant noncanonical role in mediating the generation and differentiation of hemangioblasts cells. Using chemical and genetically modified mouse embryonic stem cells, differentiation experiments are being developed to explore the connection between these two pathways. Our present data demonstrate that hypoxia influences the expression of Notch receptors (Notch-1 and -4), ligands (Delta-4) and downstream Notch targets (Hrt-1 and -2).

Project Mentor: Dr. Diana L. Ramirez-Bergeron, Case Cardiovascular Research Institute and Case Western Reserve University School of Medicine
Structural Dynamics of the S4-S5 linker in the Activation of Voltage-Gated Sodium Channels

Annie P. Clark, Department of Chemistry; V. Sree Chalamalasetti, Department of Physiology and Biophysics; Sudha Chakrapani, Department of Physiology and Biophysics

Eukaryotic voltage-gated sodium channels (NaV) are large transmembrane proteins that regulate the electrical conduction system of the heart. NaV dysfunctions are associated with disturbances underlying cardiac arrhythmias. Understanding the relationships between the structure and functions of NaV will further enhance therapeutic treatment for cardiac dysfunctions. However, structural information availability is limited due to inherent difficulties associated with high-level expression, purification and crystallization of eukaryotic membrane proteins. NaChBac, a voltage-gated sodium channel discovered in the halophilic bacterium (Bacillus halodurans), is a homotetramer of separate 6-TM subunits. It activates in response to depolarization and shows strong homology to NaV. The ease of expression and purification makes NaChBac an ideal candidate to obtain structural and functional information in NaV channels. The goal of this project is to understand protein motions associated with channel activation, with particular emphasis on the S4-S5 linker which connects the voltage sensor to the channel pore. Upon membrane depolarization, the S4-S5 linker couples outward S4 movement to the opening of the channel pore. The study involved NaChBac protein expression, purification, site-directed spin-labeling, membrane reconstitution, and electron paramagnetic resonance spectroscopy (EPR). Presently, we found that the S4-S5 linker in the activated channel takes up a conformation at the lipid-water interface. Future studies will focus on this region in the resting state of the channel. Together, this will provide an understanding of the activation mechanism in NaV.

Project Mentor: Assistant Professor Sudha Chakrapani, Department of Physiology and Biophysics

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Correlates of withdrawing or becoming lost to follow up within Case Western’s TBRU’s Kawempe Community Study

Camille Heard, Medical Anthropology; Catherine Stein, PhD. Department of Epidemiology and Biostatistics

Whether an individual enrolled in the KC study withdraws from the study at a given point in time, or experiences difficulty with following scheduled clinical site visits in the KC clinic, is associated with whether or not that individual has a preexisting medical condition, and their classification of TB. Individuals within the study who have a preexisting medical condition such as HIV, diabetes, and hypertension, are about 1.4 times more likely to forgo following up with doctors. Within this group, HIV+ individuals have slightly higher odds ratio, which indicates they are 1.5 times more likely than HIV- individuals to forgo following up with doctors at any given point in time within the duration of the study. At 16.3%, HIV+ individuals also have the highest percentage increase in study withdrawal between the before-3-month-mark and the after-3-month-mark. This may be indicative of some difficulty faced in regiment change into the continuation period of the TB treatment regiment specifically for HIV+ individuals. Individuals with chronic TB infection have a relatively high percentage (38%) of individuals becoming lost to follow up within the study. Chronically infected individuals are thus about 1.5 times more likely to not follow up with their doctors compared to individuals that have a recent TB infection, that have TB disease, or that are totally un-infected with TB. This study also found that appetite, income, and literacy had no significant affect on an individual’s decision to withdraw or not follow up with the study.

Project Mentor: Catherine Stein, PhD. Department of Epidemiology and Biostatistics
Neonatal hyperoxic exposure leading to smooth muscle airway proliferation in mice

Evan Ingram, Department of Anthropology

Hyperoxic exposure as a treatment for neonatal lung disease may aggravate neonatal lung injury as a consequence. It is often used as a treatment in neonatal lung injury. Long term effects are seen in those patients such as asthma, airway hyperactivity and other respiratory conditions. To study the causes of the long term effects of hyperoxia, specifically on smooth muscle airway proliferation which is the muscle that surrounds the walls of the airways, neonatal mice were exposed to either mild (40% O2), severe (70% O2), or Room Air (approximately 21% O2) for seven days. We hypothesized that different levels of hyperoxic might differently affect airway smooth muscle proliferation as measured by BrdU. The synthetic nucleoside, 5-Bromo-2-deoxyuridine (BrdU) is used as it aids in the detection of proliferations cells in living tissues. Our preliminary results suggest that at 40% oxygen exposure has the greatest effect of airway smooth muscle proliferation. This has implications for the pathogenesis of airway reactivity in former preterm infants.

Project Mentors: Dr. Richard Martin, Department of Pediatrics, Rainbow Babies and Children Hospital; Anjum Jafri, Department of Pediatrics, Case Western Reserve University

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A Method of DNA Isolation from Plasma for Prolylcarboxypeptidase and Prekallikrein Exon Single Nucleotide Polymorphism Analysis

Kamari Jackson, Department of Biology, Department of Health and Rehabilitation Sciences

Collection of cell-free DNA derived from plasma is a useful means to detect genetic changes that may represent conditions that might be associated with disease. Cell-free DNA derived from plasma has been shown to be a useful marker for the detection of hepatitis B virus related hepatocellular carcinoma, other tumor tissue DNA, and can also be used for downstream single nucleotide polymorphism (SNP) studies. Healthy individuals have low concentrations of DNA in their plasma making DNA extraction from plasma a low yield effort. Currently, we have a project to isolate DNA from 1 ml plasma samples on stable patients who have a history of hypertension. The plasma samples are from two clinical trials: The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) and the Dietary Approaches to Stop Hypertension (DASH) - Sodium trial. The present study describes three methods of DNA purification from plasma samples: NucleoSpin Plasma XS kit, Epigentek FitAmp Plasma/Serum DNA Isolation kit, and the Sodium Iodide method and a method of whole genome amplification to insure adequate material for study. DNA isolated by NucleoSpin, Sodium Iodide, and Epigentek method from plasma had a mean concentration of 0.453, 0.435, and 0.122 ng/ul of DNA respectively, quantified by the Qubit dsDNA Assay. The results of this investigation may identify a prolylcarboxypeptidase and prekallikrein SNP that predicts hypertension risk and related conditions such as myocardial infarction and stroke.

Project Mentor: Dr. Alvin Schmaier, Division of Hematology and Oncology
Racial Subgroup Comparisons in the Systolic Blood Pressure Intervention Trial (SPRINT)

Crystal V. James BS, M-2, Boston University School of Medicine; Carolyn Harmon Still, Ph.D., RN, Frances Bolton School of Nursing; Jackson T. Wright, Jr, M.D. Ph.D. Division of Nephrology and Hypertension

Background: Hypertension is a major public health concern and a risk factor for multiple adverse health outcomes. It is the major cause of morbidity and mortality in African Americans; often more severe and occurring at an earlier age compared to whites, translating into a higher prevalence of disease-related complications and target organ damage at a younger age. Studies show that blood pressure control rates are lower in the black population.

Objective: The study will examine whether a lower BP target will reduce the amount of cardiovascular events (MI, stroke, non-MI acute coronary syndrome, or CVD death), renal outcomes, and changes in cognition experienced by hypertensive patients. Three high-risk groups will be the focus of this study: patients with clinical CVD other than stroke, patients with CKD, patients with a Framingham Risk Score \( \geq 15\% \), and patients \( \geq 75 \) years old. The study will also evaluate the effect of BP targets by age, race, in patients with CKD, and dementia.

Methods: The SPRINT Trial is an unmasked, open label, randomized controlled clinical trial that enrolled >9,250 non-diabetics, \( \geq 50 \) years of age with SBP \( \geq 130 \) mmHg. Patients are randomized to one of two treatment groups: standard (SBP target \( \leq 140 \) mmHg) or intensive (SBP target \( \leq 120 \) mmHg), then followed for 6 years.

Results: The study is ongoing until 2017. SPRINT has enrolled ~30% African Americans and a large number of patients with CKD and age 75.

Conclusion: The study will provide important data on the management of hypertension in Blacks.

Project Mentor: Dr. Jackson T. Wright, Jr, M.D. Ph.D. Division of Nephrology and Hypertension

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Plxn B1 and –D1 interactions with Filamin A 23, -23-24, and -24

Rocio Medellin-Solivan, General Sciences; Susmita Borthakur, Department of Physiology and Biophysics; Susan Kim, Department of Physiology and Biophysics

Plexins are transmembrane receptors for Semaphorins that control many cellular processes including growth and development of the nervous, skeletal, immune, and cardiovascular system. Both Plexin-B1 and Plexin-D1 are linked in various ways to several diseases including several types of cancer. There are four sub-families of Plexins consisting of nine different plexins; A (A1-A4), B (B1-B3), C1, and D1. All the plexins share a common modular structure including the extracellular semaphorin binding domain and intracellular Rho GTPase binding (RBD) domain among others. Plexins associate with many cytoskeletal adaptor proteins.

Filamins are actin-binding proteins essential in cells. They have many cellular binding partners including enzymes, signaling intermediates, transcription factors, membrane channels and cell surface receptors. Filamin-A, for example, helps in the formation of cytoskeleton, which is vital in maintaining normal cell activity, including intracellular transport, cell division, and cell movement, that involves remodeling of the cytoskeleton and cell surface receptors. Since the function of Plexins require remodeling of the cytoskeleton, it is possible that Plexins interact with the components of the cytoskeleton, like Filamin-A. A preliminary work in the lab has observed interactions between the RBD domain of Plexin-B1 and Filamin A repeats 23-24.

Using a range of biophysical techniques, including Isothermal Calorimetry, Surface Plasmon Resonance and Nuclear Magnetic Resonance spectroscopy, this project will focus on identifying the binding regions and study the interactions of FlnA 23, FlnA 23-24 and FlnA 24 and the RBD of Plexin-B1 as well as that of Plexin-D1. It will also extend the analysis to several monomer mutants of FlnA 24. This will be done in order to understand the effect the dimerization of FlnA 24 in how it binds and interacts with other proteins, in this case, Plexins –B1 and –D1. The knowledge gained from these studies will shed novel insights into the role of Plexins and will help us understand the molecular mechanisms of Plexin signaling.

Project Mentor: Matthias Buck, M.A., D.Phil., Department of Physiology and Biophysics
Protein Purification for H-NOX Domain of the soluble guanylyl cyclase

Thao Nguyen, Department of Biochemistry; Jagamya Vijayaraghavan, Department of Biochemistry; Focco van den Akker, Department of Biochemistry

Management and treatment of cardiovascular diseases continue to be one of the big challenges for the medical field. The soluble guanylyl cyclase (sGC) is a potential drug target when certain cardiovascular processes are compromised. The heme-containing H-NOX domain of sGC is a key domain which harbors the activation site for nitric oxide and other sGC activators. In this research, we would like to determine the structure of the H-NOX domain by first expressing and purifying this domain. Different conditions were tested to have the protein folded properly (with good amount of protein structure and heme content) such that the protein can be crystallized which allows its structure to be studied using protein crystallography. This would potentially allow discovery of new ways to inhibit and activate sGC, a key cardiovascular protein factor.

Project Mentor: Dr. Focco Van den Akker, Department of Biochemistry

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Mechanistic Analysis of Akt- ERK Dual Pathway Inhibitor Using Phosphoproteomics

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Many cancers are driven by disregulation in the major cancer cell signaling pathways of Akt and/or ERK. Kinase inhibitors dominate the lung cancer drug market especially in relation to inhibition of these two pathways with upstream EGFR regulation pursued equally as well as druggable protein target. Dual pathway inhibitors can provide more efficacious therapeutic effects than a single pathway inhibitor but runs into dosing issues almost always. Tricyclic neuroleptics have been reported in select works to have antiproliferative effects through unknown mechanisms. Our team was able to modify and develop tricyclic neuroleptics into an efficacious novel anti-cancer drug, TRC 794 that is potentially applicable for multiple cancer types. Using biochemical and proteomics experimentation, we have identified a few molecular targets of the drug, especially as an activator of PP2A, a major phosphatase as well as an established tumor suppressor. Phosphoproteomics, using titanium dioxide enrichment and nano LC-MS/MS combined with bioinformatic data analysis tools, was hence pursued to evaluate the global targets of activated PP2A as well as other potential TRC 794 protein binders. A triplicate phosphoproteomic experiment was performed on H358 human bronchioalveolar non-small cell lung cancer cell line. The two experimental conditions were the control group and drug treated group with 20 micro molar TRC 794 addition with analysis done after a twelve hour lag time. LC-MS/MS quantitation based on label free approach was used to analyse the phosphorylated and unphosphorylated state of proteins in a global way. Western blot was used to validate findings from LC-MS/MS.

Project Mentor: Dr. Giri Gokulrangan, Center for Proteomics and Bioinformatics
Characterization of the in vitro and intracellular activity of a novel inhibitor of uracil DNA glycosylase (UNG)

**Giovanni Ramírez,** Department of Chemistry; **Lachelle D. Weeks,** Department of Pathology; **Stanton L. Gerson,** Case Comprehensive Cancer Center

Lung cancer is the most common cause of cancer mortality in the United States. Pemetrexed is a chemotherapy drug approved by the Food and Drug Administration (FDA) for the treatment of malignant pleural mesothelioma and nonsquamous non-small cell lung cancer (NSCLC). Pemetrexed affects the nucleotide metabolism of cells and as a result, it blocks DNA synthesis. This is toxic because cell that are not able to replicate will die. Pemetrexed inhibits thymidylate synthase (TS) and causes the accumulation of uracil in DNA. DNA base excision repair (BER) is a repair mechanism that removes damaged or incorrect bases, such as uracil from DNA and replaces them with the correct base. In the repair of uracil-DNA, BER is initiated by uracil DNA glycosylase (UNG), an enzyme that excises uracil from the DNA. Previous data has shown that cells lacking UNG accumulate uracil in DNA and are hypersensitive to pemetrexed. Additionally, we have recently shown that lung cancer cell lines with high activity of UNG are resistant to pemetrexed presumably because they efficiently remove uracil from the DNA. For these reasons, we believe that accumulated uracil is toxic to the cell during pemetrexed exposure. Based on these previous observations, we initiated an investigation of a novel class of compounds that inhibit UNG to determine if such compounds would enhance pemetrexed cytotoxicity. In vitro high throughput screening of the top 100 scoring compounds from a large in silico screen of potential UNG inhibitors yielded 11 compounds having >60% inhibition of UNG activity. Further validation using UNG cutting assays yielded 2 lead compounds. In this work, we utilize UNG cutting assays and intracellular assays to characterize the UNG inhibitory activity, intrinsic cytotoxicity and capacity to potentiate pemetrexed efficacy for 1 of these lead compounds.

**Project Mentor:** Lachelle Weeks, Graduate Student, Department of Pathology.  
**Faculty Sponsor:** Dr. Stanton L. Gerson, Director of Case Comprehensive Cancer Center and Director of National Center for Regenerative Medicine.

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Generation of nitroacetaminophen (3-N-APAP) to study its role in asthma immunopathology

**Nelki B Rivera Acosta,** B.S Biology; **Brenda Rivera Reyes,** MD, PhD, Department of Pediatric Pulmonology; **Laura Smith,** Department of Pediatric Pulmonology.

Asthma is a complex, chronic, multicellular inflammatory disease of the airways that is manifested by reversible airflow obstruction and airway hyperresponsiveness. The inflamed airway is an acidic, nitrogen rich environment where extensive nitration of endogenous proteins by the action of reactive nitrogen species (RNS) occurs. The phenol ring of tyrosine is a site of protein nitration in inflamed tissues that has been well described in the literature. Nitrotyrosine’s chemical structure is remarkably similar to the structures of dinitrophenol, dinitrochlorobenzene and other well-known potent haptons that enhance immune responses by covalently binding proteins. A positive association between the frequent use of acetaminophen (APAP) and asthma has been published in the past decade but there are almost no data that demonstrates the specific mechanism. APAP is readily nitrated by RNS produced by neutrophils to form 3-nitroacetaminophen (3-N-APAP) and possesses a chemical structure similar to the haptons mentioned before. We produced 3-N-APAP will be produced by nitration under acidic conditions, purify it by HPLC and confirm the identity by mass spectrometry and NMR spectroscopy. Our hypothesis is that APAP ring undergoes nitration by RNS under acidic conditions in the inflamed airway leading to the production of 3-N-APAP that will then act as a hapten with an allergen protein Der p1 to initiate and/or enhance the allergic response in the asthmatic airway.

**Project Mentor:** Dr. Benjamin Gaston, Department of Pediatric Pulmonology, Rainbow Babies and Children’s Hospital
Increase in Cytosolic $[\text{Ca}^{2+}]$ Contributes to NLRP3 Inflammasome Activation in Response to Bacterial Pore-Forming Toxins and Lysosomal Destabilization

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Abstract: Inflammasomes are multi-protein signaling complexes which mediate the production of cytokines of the IL-1β family. They consist of a member of the NOD-like receptor family (NLR), the adaptor protein ASC, and procaspase-1. Upon formation of the inflammasome complex, multiple procaspase-1 proteins are brought into close proximity and autocatalytically cleave each other to form mature caspase-1. The cytokine precursor pro-interleukin 1β (pro-IL-1β) is proteolytically cleaved by the activated caspase-1. This cleavage allows for the release of the biologically active form of IL-1β and this cytokine is an important mediator of pro-inflammatory and antimicrobial responses. IL-1β production by the NLRP3 inflammasome complex is involved in the progression of many pro-inflammatory disease states such as atherosclerosis, type II diabetes mellitus and gout. Despite its importance in the innate immune response and pro-inflammatory diseases, the molecular mechanism by which NLRP3 is activated is currently unknown. Recent studies by our lab and others have demonstrated the dependence of NLRP3 activation on the efflux of cytosolic $K^+$ into the extracellular space. We hypothesize that in addition to a decrease in cytosolic $[K^+]$, an increase in the cytosolic $[\text{Ca}^{2+}]$ modulates NLRP3 inflammasome activation. We show that stimulation of cells with NLRP3 activators nigericin (a $K^+$ specific ionophore), extracellular ATP (which activates the nonselective cation channel P2X7) and the dipeptide LLME (a destabilizer of lysosomes) cause plasma membrane disruption resulting in an increase in cytosolic $[\text{Ca}^{2+}]$. Furthermore, incubation of cells with the cytosolic Ca$^{2+}$ chelator BAPTA prior to stimulation with NLRP3 activators, results in both suppression of inflammasome activation and a reduction in $Ca^{2+}$ influx into the cytosol. The ability of high-dose thapsigargin (an inducer of noncanonical endoplasmic reticulum stress) to activate the NLRP3 inflammasome was suppressed by the absence of extracellular $Na^+$. Together our findings further emphasize the importance of cation fluxes for NLRP3 inflammasome activation.

Project Mentor: George Dubyak Ph. D, Department of Physiology and Biophysics
Independent of a Program

Buccal cortical plate thickness in premenopausal versus postmenopausal women

Christine DeBaz, Department of Biology, Christine Zhang, School of Dental Medicine

Background: Buccal cortical bone thickness plays an important role in planning immediate dental implant placement. It is well known that women lose bone after menopause, but there is no information on whether buccal cortical bone thickness changes.

Method: 59 postmenopausal women and 39 premenopausal women participated in this IRB approved study. CBCT scans were analyzed using OnDemand 3D, Cybermed Inc, Irvine, CA. Scans were oriented along the long axis of maxillary and mandibular incisors in three planes and axial scans were constructed at positions corresponding to bone crest and ½ root length of each of the 4 maxillary and each of the 4 mandibular incisors. Buccal cortical bone thickness was measured using the measurement application available in the software. Buccal cortical bone thickness of the postmenopausal group was compared to premenopausal group using t-test with a p< 0.05.

Results: When p<0.05, overall buccal cortical thickness of post and premenopausal women, in each tooth measured at the bone crest ½ the root length including the maxillary lateral incisor (1.295 ± 0.42 vs 1.752 ± 0.5, 0.976 ± 0.322 vs 1.529 ± 0.49), maxillary central incisor (1.169 ± 0.39 v. 1.534 ± 0.47, 0.938 ± 0.29 vs 1.457 ± 0.45, mandibular lateral incisors (1.167 ± 0.367 vs 1.64 ± 0.44, 0.979 ± 0.322 vs 1.476 ± 0.426), mandibular central incisors (1.00 ± 0.302 vs 1.388 ± 0.438, 0.854 ± 0.243 vs 1.389 ± 0.424) is significantly different.

Conclusion: In every tooth analyzed and in every type of tooth analyzed the buccal cortical bone thickness differs in pre and postmenopausal women. This finding may have wide reaching consequences on the way immediate dental implants are planned in pre versus postmenopausal women.

Project Mentor: Dr. Leena Palomo, Department of Periodontology, School of Dental Medicine
Faculty Sponsor: Dr. Diane Kube, Department of Biology

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Do Closely Related Plants Create Similar Soil Microbial Communities in the Rhizosphere?

Alexandra Flanigan, Department of Biology, Baldwin Wallace; Morgan MacBeth, Department of Biochemistry; Xiaoni Zhao, Department of Biology; David J. Burke, The Holden Arboretum; and Jean H. Burns, Department of Biology, Case Western Reserve University

Soil microbial communities, including fungi and bacteria, influence the health of plants, similar to the way microbes in our bodies affect nutrient acquisition and immune responses. If closely related plant species foster similar soil microbial communities, this would be consistent with niche conservatism, or the tendency of closely related species to retain environmental preferences of their ancestors. Proposed mechanisms of niche conservatism include the presence and proportional abundance of soil biota such as parasites or mutualists that affect plant growth. We collected soils from around the roots of 14 species of angiosperms at Bodega Bay, California, USA and were either gamma irradiated or live. We extracted community DNA from these soils, targeted the 16S region of the rRNA gene for bacteria and ITS for fungi, and used terminal restriction fragment length polymorphism to determine differences in soil communities. Closely related plant species fostered similar fungal communities; however, this trend was not observed among bacterial communities. Furthermore, the microbial communities were significantly different between irradiated and live soil samples. This could be because the live soil samples may have changed in composition while the irradiated soils stopped changing at the time of irradiation. Our results suggest that closely related plant species have similar fungal communities in the soil, consistent with conserved co-evolutionary processes, as might occur with mutualists such as endophytes, and that bacterial communities are less phylogenetically conserved, perhaps consistent with their shorter life spans and thus faster evolutionary dynamics.

Project Mentors: Jean H. Burns, Assistant Professor, Department of Biology, Case Western Reserve University and David J. Burke, Scientist, The Holden Arboretum
From Eugenic Foeticide to Gendercide: Slippery Slope Fallacy or Fact?

Benjamin Holvey, Departments of Philosophy and Mathematics

There is broad agreement among philosophers and ethicists, medical professionals, and the general public in the West that sex-selective abortion is ethically suspect, if not unethical. Western opposition to sex-selective abortion has been particularly visible in response to the growing practice among numerous Asian cultures of aborting female fetuses (henceforth, ‘female foeticide’) because sons are culturally regarded as preferable to daughters. There is relative neutrality, on the other hand, about disability-related abortion (henceforth, ‘eugenic foeticide’), which is fairly commonplace in the West (e.g. studies generally identify the termination rate for Down syndrome pregnancies in Europe and the United States at 91-98%).

The general effort I undertake is a moral evaluation and comparison of these two prevalent motives for abortion. The specific problem which attaches to the general effort is the plausibility of condemning female foeticide as immoral yet commending eugenic foeticide as morally permissible. Framed as a question, the specific problem becomes, “Is it rational to morally dissent from female foeticide yet morally assent to eugenic foeticide?” I assume from the outset that female foeticide is immoral but attempt to demonstrate that female and eugenic foeticide are morally equivalent. Along the way, I pursue answers to related questions such as the following: Is a healthy female fetus more valuable than a fetus with Down syndrome? Does the argument that Down syndrome diminishes quality of life justify eugenic abortion? Would an analogous argument that femininity diminishes quality of life in certain Asian cultures justify female foeticide in those cultures?

Project Mentor: Professor Shannon French, Department of Philosophy

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Glutaraldehyde Cross-linking studies of Nostoc H-NOX protein crystals

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A majority of today's medicines act via receptors, either membrane or soluble. These receptors are the communication portals for cells with mostly signals going into the cell but sometimes also signaling from the inside out. Among them, soluble guanylyl cyclase (sGC) is an important receptor for nitric oxide (NO). NO activates sGC several hundred fold to generate cGMP from GTP. Because of sGC’s roles in cardiovascular physiology, it has gained special attention as a drug target. Current research is concerned with crystallizing the homologous H-NOX domain from the Nostoc (Ns) cyanobacteria in order to gain more knowledge about the sGC and its activation sites. Multiple Solvent Crystal Structures (MSCS) of Ns H-NOX protein can be used to map the binding surface and plasticity of the protein. For MCSC studies, protein was expressed in E. coli cells, purified using gel filtration and ion exchange columns. Pure red-color protein, thus obtained, was crystallized in sodium malonate crystallization condition(s) followed by soaking the red-colored crystals in various concentrations of glutaraldehyde for several time intervals. These cross-linked crystals were tried for diffraction data collection and structure solution and refinement. After numerous combinations of glutaraldehyde concentration and soaking time points, it was observed that 0.1 % of glutaraldehyde for a time period of 20 minutes soaking was sufficient to crosslink the protein molecules in the crystal without disrupting its structure and diffraction quality. In future, the crystals generated using these conditions shall be used for MSCS method for mapping the binding surface of Ns H-NOX protein.

Project Mentor: Dr. Vijay Kumar, Department of Biochemistry
Faculty Sponsor: Dr. Focco van den Akker, Department of Biochemistry
Global Analysis of Nonsense-Mediated mRNA Decay Provides Evidence for Translation of lncRNAs

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Nonsense-mediated mRNA decay (NMD) is a quality control mechanism in cells that monitors mRNA for the presence of nonsense or premature stop codons. In order to identify all of the targets of NMD in the cell, gene expression profiling was conducted through deep sequencing in yeast cells with and without a functional NMD pathway. Deep-sequencing data indicated that approximately 600 mRNAs showed expression level changes in the absence of the NMD-essential proteins. Unexpectedly, approximately 200 long non-coding RNAs (Inc RNAs) also expressed sensitivity to NMD.

Putative targets of the NMD pathway identified by deep sequencing were verified by northern blotting. Standard radioactive oligonucleotide probes were used to detect individual RNA in wild type cells and cells lacking an essential NMD component, UPF1. In order to distinguish RNA signals obtained from some mRNAs and IncRNAs with low abundance RNA, asymmetric PCR radioactive probes were employed. Several of the potential deep-sequencing targets were validated, while unexpectedly, some IncRNAs were sensitive to NMD. Research from this experiment suggested that the level of approximately 600 mRNAs was affected by NMD, including a number of IncRNAs. Our findings surprisingly suggest that NMD targets IncRNAs, as NMD regulation requires RNA translation.

Project Mentor: Professor Kristian E. Baker, Center for RNA Molecular Biology

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WWTR1 (TAZ) transcription is constitutively activated by fusion to CAMTA1 in Epithelioid Hemangioendothelioma

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Epithelioid hemangioendothelioma (EHE) is a rare vascular sarcoma that is typically metastatic upon detection. Recently, a balanced t(1;3)(p36,q25) translocation involving the fusion of WWTR1 (TAZ) to CAMTA1 has been identified in over 90% of EHEs, supporting its role as the disease defining genetic alteration of EHE. We found the mechanism by which the WWTR1-CAMTA1 (WC) fusion protein induces and promotes the pathogenesis of EHE in part by observing the effects of WC, WWTR1, and CAMTA1 as well as various mutants of these proteins in NIH3T3 cells. WWTR1 is a transcription factor and an important regulator of organ size. It is normally regulated by the Hippo pathway, an evolutionarily conserved serine/threonine kinase cascade that results in phosphorylation, cytoplasmic localization, and subsequent ubiquitin-mediated degradation of WWTR1 and its paralog YAP. However, Hippo regulation of WWTR1 is dampened upon fusion to CAMTA1, resulting in constitutive nuclear localization and transcription dependent upon WC binding to the transcriptional cofactor TEAD4. Since WWTR1 is naturally overexpressed in endothelial cells and the WC fusion is under control of the WWTR1 promoter, the resulting abundance of WC in the cell compounded by the inactivation of its primary regulatory pathway provides a model of pathogenesis of EHE. By understanding the pathogenesis of this rare cancer, steps can be taken to develop therapies that target the components most responsible for the progression of this lethal disease.

Project Mentor: Dr. Brian Rubin, Departments of Molecular Genetics and Anatomic Pathology
Continued Investigations into the Effects of Phenyl-Substituted Terminating Groups on the Dimerization of Germanium Phthalocyanine Systems

Evan Martin, Department of Chemistry

Phthalocyanines are cyclic, aromatic compounds that are capable of coordinating a metal atom in their centers. These compounds can often be “capped” with various functional groups on either side of the metal atom, depending on the metal’s electron valence. In previous experiments, various silanols, including triphenylsilanol and various trialkylsilanols were used via the Doris synthesis to create several different bis-siloxy capped germanium phthalocyanines. Additionally, in a related research project, it was observed that use of a triphenylsilanol reagent promoted dimerization of germanium phthalocyanines significantly more than alkyl-substituted silanols. The molar ratio of dimer to monomer compounds formed with triphenylsilanol was found to be 0.93:1 through integration of NMR spectra, as compared to 0.60:1 for triethylsilanol, and 0.16:1 for trihexylsilanol. The two methyl and phenyl-substituted silanols syntheses led to significant product decomposition during the mixing phase of the reactions. The addition of tributylamine to these reactions prevented decomposition of the reactants; however, the products from these reactions did not solubilize in any NMR solvents tested. This lack of solubility implies either asymmetric capping of products, or hydrolyzation of the caps during the work up phase of the reaction. Possible reasons for the increased dimeric yield from the triphenylsilanol synthesis include the steric hindrance of the triphenylsilanol as compared to the alkyl-substituted silanols, variations in the electron donating properties of aromatic substituents as compared to alkyl substituents, and possibly a combination of these factors. Furthermore, phthalocyanines capped with alkyl and phenyl-substituted siloxy groups appear to be unstable under standard conditions, despite the stability of triphenyl and trialkylsiloxy caps.

Project Mentor: Malcolm Kenney, Ph.D., CWRU Department of Chemistry

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Identifying the genes involved in locomotion behavior differences in Drosophila species

Shelby Snashall, Department of Biology

The identification of genes involved in locomotion behaviors in Drosophila can shed light on the evolutionary mechanisms employed to produce species-specific locomotion phenotypes. Drosophila melanogaster, Drosophila sechellia, and Drosophila simulans are three closely related species of the melanogaster subgroup. Previous work showed that these species display distinct locomotion behaviors in the larval stage. D. simulans and D. melanogaster have a similar locomotor crawling pattern, while the most recently diverged species, D. sechellia, has a lower crawling speed and display several inhibitory synaptic boutons in one of the largest neuromuscular junctions of the larval body wall. Our goal was to map the genes responsible for the D. sechellia modified locomotion behaviors. First, we made genetic crosses to distinguish maternal inheritance from X-linked inheritance, and determined that the low crawling speed of D. sechellia is due to a modification on a X-linked gene(s). Next, we made crosses between D. simulans and D. sechellia in order to produce hybrid individuals to map the gene(s) responsible for these behaviors within these Drosophila lineages. Comparisons of locomotion behaviors were analyzed through video data, as well as the presence of Type II boutons within muscles 6 and 7 of the larvae via octopamine staining. Gene mapping is performed using video data, as well as phenotypic data combined with meiotic recombination mapping with markers with known genetic positions. We will present that data that has been collected so far.

Project Mentor: Claudia Mizutani, Biology Department
Pretend play, intelligence, emotional expression and storytelling ability in preschoolers

Alaina Wodzinski, Departments of Anthropology and Psychological Sciences; Sandra Russ, Department of Psychological Sciences.

The purpose of the present study is to investigate the relationships among pretend play, intelligence, emotional expression, and storytelling ability in preschool children. Specifically, the purpose is to determine if children with better pretend play skills also have a higher IQ, express more emotion in daily life and tell more complex stories. Pretend play has been shown to relate to creativity in both elementary school age children, and preschoolers. In school age children, research has demonstrated that creativity is not related to intelligence. In preschoolers, creativity may be related to intelligence because many processes are still developing and are undifferentiated from one another. Pretend play and storytelling measures will contain an affect component that will be compared to the emotion expression measure to determine if expression emotions in play relates to expressing emotions in daily life. Fifty children will be given both the verbal and non-verbal components of the Kaufman Brief Intelligence Test to measure IQ, and the Affect in Play Scale for Preschoolers to measure creativity and pretend play. Storytelling ability will be measured by presenting the child with four pictures and asking them to tell a story about them. Emotion expression will be measured by giving the child’s teacher the teacher adapted short form of the Rothbart Child Behavior Questionnaire. By understanding the relationship among the variables new teaching methods centered on play may be developed in order to help students become more successful in the classroom and reach their full potential.

Project Mentor: Professor Sandra Russ, Department of Psychological Sciences

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The Yeast Saccharomyces Cerevisiae Establishes Different Axes of Polarity Based on Both Ploidy and Mating Type

Kyle Wolf, Department of Biology

In S. cerevisiae, cells reproduce by a process called budding, and exhibit two general budding behaviors. The first behavior is characteristic of haploid cells regardless of whether they are of the a or α mating type, and is known as “axial.” In axial budding, subsequent budding events are immediately adjacent to the previous bud. This is contrasted with an alternate mode of budding in diploid cells that has been labeled “bipolar.” In bipolar budding, subsequent events alternate between two opposite poles of the cell. However, the budding patterns of cells of higher ploidy have not been examined in-depth. This research has focused on expanding the characterization of yeast budding patterns to higher ploidies that exist in nature and the biochemical determinants of these patterns.

Project Mentor: Dr. Alan Tartakoff, Department of Pathology and Cell Biology Program
**SOURCE Summer Undergraduate Research Program**

This summer the SOURCE Summer Undergraduate Research Program provided funding to 36 CWRU students from all disciplines. The program is funded by the University and the Case Alumni Association (CAA). SOURCE students present their research at either the December or April Intersections.

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**Dermal Wnt/Beta-catenin activity-dependent epigenetic repression in hair follicle development**

*Deepa Manjunath*, Department of Biology, Case Western Reserve University.

Hair follicles are specialized appendages of the skin that orchestrate repeated cycles of hair growth and loss. Though embryonic hair follicle development has fascinated developmental biologists for decades, many of the precise molecular mechanisms that govern the process are still unknown. β-catenin, the central transducer of the Wnt signaling pathway, is known to be required in embryonic dermis at the earliest stages of hair follicle development. Our recent studies show that when β-catenin was genetically deleted in mouse embryonic dermis, the set of upregulated genes was enriched for targets of Polycomb Repressive Complex 2 (PRC2), a molecular complex that causes epigenetic transcriptional repression through histone methylation. *We hypothesize that Wnt/β-catenin activity-dependent PRC2 target genes are repressors of hair follicle development.*

To evaluate this claim, we propose a three-part experimental approach. First, by using immunofluorescence we visualized the expression of PRC2 activity in control and β-catenin-deleted embryonic dermis. We did not find qualitative difference between these two, suggesting PRC2-mediated epigenetic repression is not universally β-catenin-dependent. Second, we will treat cells with an inhibitor of Enhancer of Zeste Homolog 2 (EZH2), the active component of PRC2 and perform qRT-PCR to quantify changes in the expression of specific targets that may be putative hair follicle inhibitor genes, such as Dickkopf 2 and Secreted frizzled-related proteins 1 and 2. We expect that inhibition of PRC2 activity will prevent the repression of these genes, resulting in higher expression levels in cells treated with the inhibitor. In our third experiment, we will treat embryonic dorsal skin explants with the inhibitor of EZH2, the active component of PRC2. We expect that if PRC2 activity is required to promote hair follicle development, then treated explants will form no hair follicles. The results of this project will shed light on the role of Wnt/β-catenin activity in Polycomb mediated epigenetic repression during hair follicle development.

*Project Mentor: Professor Radhika Atit, Department of Biology*
SPUR (Summer Program In Undergraduate Research)
This 10-week program in the Department of Biology is designed to acquaint students with all aspects of scientific research, from formulation of a question to production of a final report. Each participant is assigned to a faculty member whose research is of interest to that student. While the student’s research is expected to contribute to ongoing research in the faculty member’s laboratory, the students are encouraged to help in designing a research project. Students share in their departments’ weekly activities such as seminars and journal clubs.

Interactions between Green Frog tadpoles and freshwater snails

Laura Hill, Department of Biology; Dr. Michael Benard, Department of Biology

Interspecific interactions can strongly affect individual growth and development, for the benefit or degradation of each species. Previous studies have found evidence of both competition and facilitation between tadpoles and snails. To determine whether or not green frog (Rana clamitans) tadpoles and freshwater snails (Planorbella trivolvis) in interspecific environments differ behaviorally and developmentally from those in intraspecific environments, we manipulated the presence of both species to determine effects of interspecific interactions on growth, development, and behavior. Treatments included snails alone, tadpoles alone, snails and tadpoles together, and neither tadpoles nor snails. Behavioral assays allowed us to determine if treatments affected how often both species occupied tank walls, and if snail presence altered tadpole activity. After the experiment we compared tadpole mass and developmental (Gosner) stage across treatments. Zooplankton and chlorophyll a densities were measured to determine the effects of each treatment on abundance and primary productivity. We predicted that R. clamitans and P. trivolvis would interact through either competition or facilitation. Competition could be observed through lower survival and development for interspecific treatments, lower zooplankton abundance and primary productivity, and more snails and tadpoles on sides of mesocosms due to hiding space competition. Facilitation would result in larger, more highly developed animals in interspecific treatments, decreased zooplankton abundance due to increased consumption by tadpoles, and decreased primary productivity. Studying species interactions may reveal new information about ecological communities, but further study is needed to determine if interactions change when other species are added to the ecosystem.

Project Mentor: Dr. Michael Benard, Department of Biology

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Can Spatiotemporal Heterogeneity in Soil Moisture Affect Species Coexistence?

Angela Kaczowka, Department of Biology, Angela J. Brandt, Department of Biology, Jean H. Burns, Department of Biology

Understanding the role of environmental heterogeneity for invasibility, or the ability of a population to grow from low density, is essential for understanding plant coexistence. Early verbal theory suggested that environments with high heterogeneity would have a higher risk of invasibility. However, newer quantitative theory suggests that if heterogeneity is spatiotemporal, then high heterogeneity would result in low invasibility. In a spatially heterogeneous environment the quality of a patch in which a plant is located can change over time (i.e. high quality patches in one year might become lower quality patches in the next). In an existing experiment with heterogeneous (patches of two soil types) and homogeneous soil (patches a mixture of two soil types) we measured the soil moisture levels in each patch in each plot to determine whether differences in soil moisture across patch types changed over time, i.e. whether soil moisture exhibited spatiotemporal environmental heterogeneity. Soil patch type significantly interacted with sampling date, suggesting that soil moisture in experimental plots varies in a spatiotemporal fashion. This suggests that the effects of our spatial heterogeneity treatments depend on environmental conditions, such as precipitation. Thus the effects of environmental heterogeneity on invasibility will depend on environmental drivers, such as whether it is a dry or wet year.

Project Mentor: Dr. Angela J. Brandt, Department of Biology
Faculty Sponsor: Dr. Jean H. Burns, Department of Biology
Modification of the Dorsal Gradient across *Drosophila* Species Offers Insight into Tissue Specification Scaling

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1 Department of Biology

How tissue specification scales and morphological diversity is achieved in nature are important questions in biology. In *Drosophila*, two morphogen gradients are responsible for the dorso-ventral axis specification of the blastoderm: the ventral-to-dorsal nuclear concentration gradient of the maternally determined Dorsal (Dl) transcription factor, and dorsal-to-ventral gradient established by diffusion of the extracellular protein Decapentaplegic (Dpp) that is zygotically expressed. Based on the varying concentrations experienced by these opposing morphogens, target genes are activated leading to the specification of the mesoderm, neuroectoderm, and dorsal ectoderm. Here we focus on the formation of the Dl gradient and ask how it scales in related *Drosophila* species. Previous work determined that the Dl gradient acquired distinct distributions in three sibling species of the *melanogaster* subgroup, *D. simulans*, *D. sechellia*, and *D. busckii*, which vary in egg size, nuclei numbers, and density, leading to differences in mesoderm specification, but not neuroectoderm. Here we analyzed the Dl gradients and relevant physical parameters (e.g. nuclear size, cortical layer width, range of peak Toll signaling) of two additional species of the *melanogaster* subgroup that underwent a separate speciation event, *D. santomea* and *D. yakuba*. Similar to the separation time of *D. simulans* and *D. sechellia*, these species diverged about 0.5 MYA. *D. santomea* embryos are longer and wider than both *D. melanogaster* and *D. yakuba*, and *D. yakuba* is of similar length and width as *D. melanogaster*. *D. yakuba* has the largest number of nuclei along the DV axis, followed closely by *D. santomea*, and finally *D. melanogaster* with the smallest amount. We quantified the Dl gradient distribution and mesoderm size using an anti-Dl antibody and an *in situ* for the mesodermal marker *snail* RNA (sna), respectively. We show that the Dl gradients of *D. santomea* and *D. yakuba* are both of very similar in shape to *D. melanogaster*, despite their differences in embryo size. These data allowed us to compare *D. santomea* and *D. yakuba* with those species previously studied to determine whether similar strategies for changing the Dl gradient are deployed in these latter species.

*Project Mentor: Claudia Mieko Mizutani, Department of Biology*